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Fast Suzuki–Miyaura Cross-Coupling Reaction with Hexacationic Triarylphosphine Bn-*Dendriphos* as Ligand

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Abstract: The application of hexa[(dimethylamino)-methyl]-functionalized triphenylphosphine (**1**) and its benzylammonium salt, Bn-*Dendriphos* (**2**), in the Suzuki–Miyaura cross-coupling of aryl bromides with arylboronic acids is described. The 3,5-bis[(benzyldimethylammonio)methyl] substitution pattern in **2** leads to a rate enhancement compared to both the non-ionic parent compound **1** and triphenylphospine (PPh_3) itself. At the same time, the resulting catalytic species are stable towards palladium black formation, even at a phosphine/palladium ratio of 1. These observations are attributed to the presence of a total of six ammonium groups in the backbone of the phosphine ligand, which presumably leads to an unsaturated phosphine-palladium complex.

Keywords: C–C coupling; *Dendriphos*; palladium; phosphine; Suzuki–Miyaura reaction

Introduction

Recently, we developed a novel class of hexaionic phosphines derived from the hexa[(dimethylamino)-methyl]-functionalized triarylphosphine core molecule **1** [$P(NCN)_3$, Figure 1], for which we coined the name *Dendriphos* {$[P(NCN)_3{\cdot}R_6]X_6$, R = Me, Bn or Fréchet wedge and X = Br or I}.[1] These novel ligands combine a triarylphosphine core with a shell of six ammonium groups. The latter feature makes this series of dendritic ligands very versatile, as it enables them to act as phase-transfer agents and opens the way for catalyst recovery by means of a biphasic work-up or *via* nanofiltration. Both NMR and molecular modelling experiments suggested the use of these hexacationic phosphines as bulky ligands.[1] At the same time, based on the solubility range of these ligands, applications in both H_2O and MeOH, as well as in organic solvents, can be envisioned.

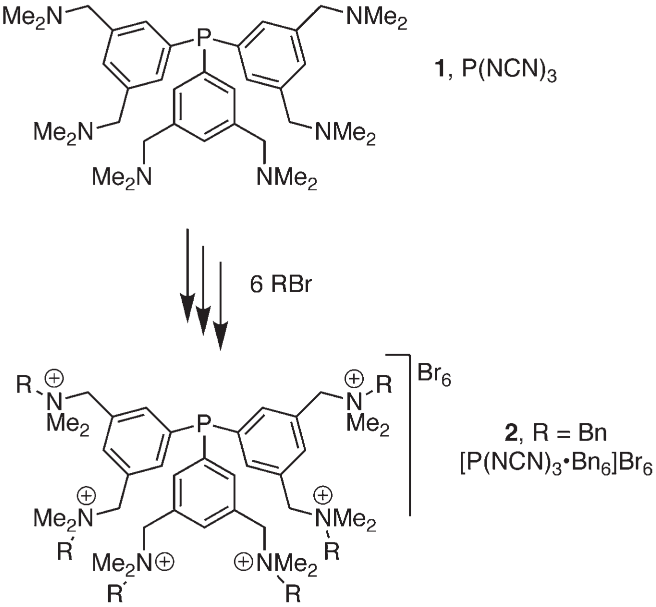
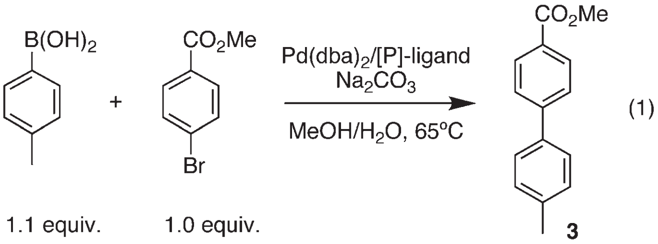


Figure 1. Hexaamino- and hexaammonium-functionalized triarylphosphines **1** and **2**.

As our first investigation into the use of this class of ligands in homogeneous catalysis, we applied Bn-*Dendriphos* (**2**, R = Bn, soluble in MeOH) in the Suzuki–Miyaura reaction, which is a widely used, Pd-mediated C–C coupling method, tolerating numerous functional groups.[2] The latter feature makes this reaction feasible for the preparation of, e.g., natural products or pharmaceuticals.[3] Most of these reactions apply aryl halides and boronic acids; boronic acids being much less toxic and easier to handle than (main group) organometallic compounds used in other cross-coupling reactions.[4] Among the successful examples of catalysts for this reaction are ligand-free Pd species[5] and Pd complexes using various types of ligands, such as N-heterocyclic carbenes[6] and sterically constrained and electron-rich monodentate phosphine ligands, such as bulky trialkylphosphines,[7] biarylphosphines[8] and ferrocenylphosphines.[9] In this report, we present our first results concerning the application of hexacationic triarylphosphine Bn-*Dendriphos* (**2**) in this reaction and the remarkable rate-enhancing effect of the 3,5-bis[(benzyldimethylammonio)methyl] substitution pattern in its ligand structure.

Results and Discussion

As model reaction we selected the coupling of 4-tolylboronic acid and methyl 4-bromobenzoate giving methyl 4-tolylbenzoic ester **3** [Eq. (1)]. Pd(dba)$_2$ was used as palladium source and Na_2CO_3 (2 equivs. with respect to the aryl bromide) as base in a mixture of methanol and water (9/1, v/v) at 65 °C. The hexaionic phosphine $[P(NCN)_3{\cdot}Bn_6]Br_6$ (**2**, Bn-*Dendriphos*) was tested as donor ligand at 3, 1, 0.1, and 0.01 mol% of Pd loading. The number of equivalents of phosphine per palladium center was varied from 4 down to 1. Furthermore, hexaionic **2** was compared to the parent phosphine $P(NCN)_3$ (**1**) as well as to PPh_3. Control reactions were run in the absence of phosphine, base or palladium source. The catalyst performance is expressed as the time at which the coupling yield reached 50%, as well as the maximum obtained yield and the required reaction time (Table 1).



These experiments show that **2** exhibited a behaviour that is dramatically different from that of the benchmark ligand PPh_3. For example, when four equivalents of **2** were applied at 1 mol% Pd loading, a quantitative yield was reached within ten minutes, whereas in the case of PPh_3 this took up to seven hours. Neutral ligand **1** also gave a lower rate than that found for hexaionic **2** (Figure 2), but performed better than PPh_3.[10]

Importantly, due to the activated nature of the aryl bromide employed, the present benchmark reaction is extremely fast. In fact, in the absence of any ligand, a quantitative yield is obtained after 90 min at 3 mol% Pd, even though rapid Pd black formation is observed. At 0.01 mol% Pd, the ligand-free process resulted in a similar activity, reaching a maximum yield of 90% after 20 min. These results are in line with those found by Bumagin et al., who reported a ligand- and stabilizer-free, Pd-catalyzed Suzuki reaction in water.[5a,b] Similar results at very low catalyst loadings were reported by de Vries et al.[5c,d] The use of a phosphine ligand stabilizes the catalyst and can prevent the formation of Pd black. Due to the inhibitory role played by the phosphine ligand in the case of PPh_3,[4] the reaction is slowed down dramatically. Remarkably, the use of an equal amount of hexaionic **2** does not show any decrease in reaction rate, while still preventing Pd black formation. As a result of high activity combined with high stability, quantitative yield is obtained within 10 min, even at 0.1 mol% Pd loading.

Table 1. Selected catalytic data for the reaction of Eq. (1).

Entry	Pd(dba)$_2$ [mol%]	Phosphine	Phosphine/Pd Ratio	Time [min][a]	Yield [%][b] (Time [min])
1	3	**2**	4	2 – 4	100 (10)
2	3	PPh_3	4	180	88 (420)
3	3	–	0	5[c]	99 (90)[c]
4	1	**2**	4	3 – 5	100 (10)
5	1	**1**	4	15 – 20	100 (130)
6	1	PPh_3	4	120	96 (420)
7	0.1	**2**	4	4	100 (10)
8	0.01	**2**	4	20	96 (60)
9	0.01	**2**	2	10	99 (60)
10	0.01	**2**	1	4	98 (60)
11	0.01	–	0	5[c]	90 (20)[c]
12	–	**2**	–	–	0 (120)
13	3	**2**	4	–	0 (120)[d]

[a] Time at which the GC yield reached 50%.

[b] Yield of the cross-coupled product, determined by GC.

[c] Pd black was formed.

[d] No base was used.

To test the lower limit of catalyst concentration, the Pd concentration was lowered from 3, *via* 1 and 0.1 to 0.01 mol% using each time four equivalents of **2** (Table 1, entries 1, 4, 7 and 8). These experiments show that only at a concentration of 0.01 mol% Pd does the reaction rate start to drop. When the ratio of ligand **2** to Pd was decreased from 4:1 to 2:1 and 1:1 at a Pd loading of 0.01 mol%, a slight increase in re-

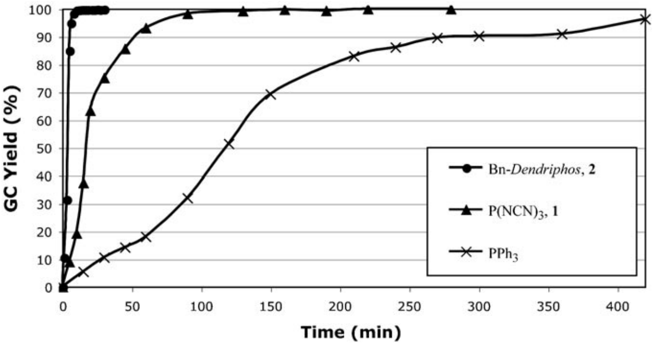


Figure 2. The effect of the ligand on the reaction of Eq. (1) at 1 mol% Pd loading. In each case a phosphine/palladium ratio of 4 was used.

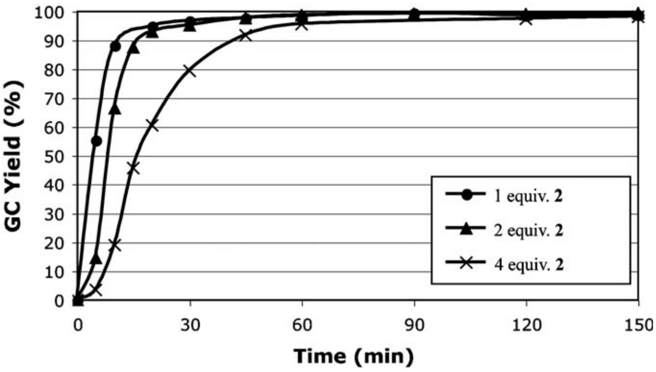
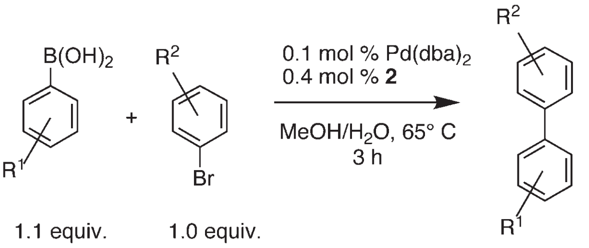


Figure 3. The effect of ligand/Pd ratio on the reaction of Eq. (1) at 0.01 mol% Pd loading using Bn-*Dendriphos*.

action rate was seen, while at the same time still no Pd black formation was observed (Figure 3).

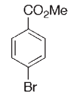
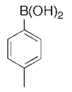
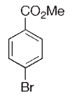
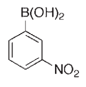
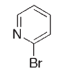
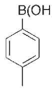
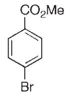
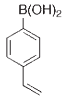
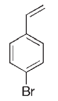
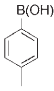
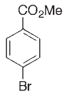
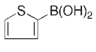
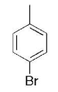
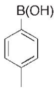
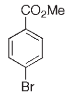
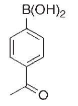
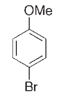
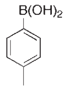
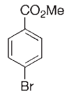
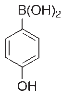
To investigate the influence of the ammonium groups in Bn-*Dendriphos* on the reaction, **2** was tested in the absence of Pd (Table 1, entry 12). Ammonium salt-promoted C–C coupling reactions with[11b] and without[11a] Pd were reported before. The reported activities in the 'absence' of Pd were recently rationalized by the presence of trace amounts of metal in the applied base.[11c] In our case, however, no conversion was observed in the absence of added Pd. Therefore we believe that the activity observed originates from a homogeneous Bn-*Dendriphos*-Pd complex. In previous studies it was noted that aryl halides can be reduced by primary and secondary alcohols in the presence of a Pd(0) source and a base.[8c,12] In our experiments, however, no detrimental effect of the use of MeOH was observed.

The performance of our catalytic system was further probed by performing the reaction with several non-activated and deactivated aryl bromides, as well as with some challenging arylboronic acids [Eq. (2) and Table 2].



(2)

Table 2. Catalytic data for the reaction of Eq. (2).

Entry	Aryl Bromide	Aryl Boronic acid	Yield [%][a]	Entry	Aryl Bromide	Aryl Boronic acid	Yield [%][a]
1			100	6			100
2			76	7			99
3			68	8			98
4			58	9			82
5			57	10			57

[a] Yield of the cross-coupled product, determined by GC after 3 h of reaction time.

The results in Table 2 show that several aryl boronic acids can be coupled with the same efficiency as observed for 4-tolylboronic acid. Changing the aryl bromide, however, leads to a decrease in the observed reaction rate. After 3 h of reaction time, moderate yields were obtained for most aryl bromides. Even though Pd black was never observed, the yield increased only marginally by letting the reactions run for an additional 3 h. This suggests that our reaction conditions need further optimization for coupling of more challenging substrates. We are currently performing these investigations.

Our results clearly indicate that hexaionic phosphine **2** can stabilize a Pd(0/II) center, without leading to inhibition of the reaction rate, as seen with the benchmark ligand PPh_3. It can thus be concluded that **2** has a very low inhibition factor.[13] This indicates that **2** leads to a preferential formation of coordinatively unsaturated phosphine Pd(0) species. The relatively small observed difference in activity between high and low L:Pd ratios (Figure 3) supports this view. Similar behaviour has been described for bulky[7b] or bowl-shaped[14] phosphine ligands, but never for phosphine ligands based on a triarylphosphine having a shell of ionic groups. Recently, an *m*-carboxylic acid-functionalized triphenylphosphine ligand (*m*-TPPTC) was reported, which showed increased reactivity in Sonogashira cross-couplings compared to its sulfonated analogue (TPPTS).[15] In this case however, the authors rationalize the results by the increased basicity of the ligand. The results for **1** and **2** are in line with the molecular modelling and coordination experiments on these ligands, reported elsewhere.[1,16] Based on these studies we predicted enlarged cone angles and a bulky behaviour for **2**. We believe that in our case the Coulombic repulsion between neighbouring phosphine ligands acts as a 'pseudo-bulk' and facilitates dissociation of **2** from the Pd center, allowing *in situ* formation of coordinatively highly unsaturated and catalytically active phosphine Pd(0) species.

Conclusions

The monodentate, hexacationic triarylphosphine ligand **2** leads, in combination with Pd(dba)$_2$, to an efficient catalytic system for the Suzuki–Miyaura cross-coupling reaction. From the comparison with the non-ionic parent compound as well as the benchmark ligand PPh$_3$, the beneficial effect of the six ammonium groups on the reaction rate is apparent. Lowering the **2**/Pd(dba)$_2$ molar ratio from 4 to 1 resulted in a slight increase of activity, without noticeable effect on the stability of the palladium site in the complex. This indicates a preferential formation of coordinatively unsaturated Pd complexes, which is a property that could be beneficial in a wide range of catalytic applications. Currently, we are further investigating the application of **2** and other *Dendriphos* ligands[1] for the catalytic conversion of more challenging substrates such as aryl chlorides. Application of these ligands in other metal-catalyzed transformations, are also envisaged.

Experimental Section

General Remarks

All catalytic runs were carried out in a parallel reactor set-up, using degassed solvents. Pd(dba)$_2$,[17] P(NCN)$_3$ (**1**),[16] and Bn-*Dendriphos* (**2**)[1] were prepared according to previously reported procedures. Aryl bromides and arylboronic acids were obtained from Acros Chimica and used without further purification. GC measurements were performed on a Perkin–Elmer AutoSystem XL gas chromatograph using pentadecane as an internal standard.

Synthesis of 4-Tolylboronic Acid

To a solution of 4-bromotoluene (5.0 mL, 40.62 mmol) in dry, degassed THF *n*-BuLi (30.0 mL, 1.6 M, 48.00 mmol) was added dropwise at –100 °C. The mixture was stirred for 15 min, B(O-*i*-Pr)$_3$ (9.0 mL, 39.00 mmol) was added dropwise and the mixture was allowed to warm up to room temperature. The product was extracted with NaOH (1 M, 3× 30 mL). The aqueous layer was acidified with concentrated HCl and extracted with ethyl acetate (3×30 mL). The organic layer was dried on MgSO$_4$, filtered and evaporated to dryness. The resulting crude product was purified by recrystallization from H$_2$O. Yield: 3.81 g (72%). ^{1}H NMR (300 MHz, acetone-d_6): $\delta = 7.76$ (d, 2H, $J_{H,H} = 7.8$ Hz, ArH), 7.16 (d, 2H, $J_{H,H} = 7.2$ Hz, ArH), 7.03 (s, 2H, OH), 2.32 (s, 3H, CH$_3$); ^{13}C NMR (300 MHz, acetone-d_6): $\delta = 141.5$, 135.7, 129.7 (Ar*C*), 22.20 (CH$_3$).

General Procedure for the Suzuki–Miyaura Reaction

Arylboronic acid (2.57 mmol), aryl bromide (2.33 mmol), Na$_2$CO$_3$ (0.49 g, 4.6 mmol), Pd(dba)$_2$ (3, 1, 0.1, or 0.01 mol% with respect to the aryl bromide) and phosphine ligand **1**, **2** or PPh$_3$ [4, 2 or 1 equivalents with respect to the Pd(dba)$_2$], were placed in a vial under nitrogen. H$_2$O (1.0 mL) and MeOH (9.0 mL) were added and the vials were placed in a pre-heated oil bath. At appropriate intervals, samples (0.1 mL) were taken and worked-up by adding 1 M NaOH (1.0 mL) and CH$_2$Cl$_2$ (1.5 mL) with thorough mixing. The organic layer was used for GC-analysis, using pentadecane as an internal standard. The aryl bromide, the cross-coupled product and the internal standard were detected by GC. No other (side) products were observed.

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