Silica-supported Tripod Triarylphosphines: Application to Palladium-catalyzed Borylation of Chloroarenes

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Silica-supported tripod triarylphosphines that have a Ph₃Ptype core tripodally immobilized on a silica surface enabled the Pd-catalyzed borylation of chloroarenes with bis(pinacolato)diboron under mild conditions. The immobilization in tripod was crucial for the excellent performance of the Ph₃P-based ligands.

Arylboronic acids and their derivatives are versatile intermediates in organic synthesis because of their applicability and broad functional group compatibility in many reactions, less toxicity, and air- and moisture stability.¹ The Pd-catalyzed borylation of aryl halides with boron reagents (Miyaura borylation) offers a method for synthesizing arylboronates with excellent functional group compatibility.^{2–8} Recently, we reported that a heterogeneous Pd catalyst system based on a silicasupported monodentate trialkylphosphine ligand Silica-SMAP shows an excellent performance for this catalytic reaction allowing the use of a broad range of chloroarenes as substrates.⁹

We proposed that this catalytic performance of the Pd-Silica-SMAP system originated from the novel characteristic of the Silica-SMAP monodentate phosphine to favor monoligation to the Pd atom and that this is due to the immobilization of the phosphine molecule with restricted mobility and with a high degree of directionality.¹⁰ In addition, we introduced other immobilized phosphine ligands Silica-TRIP,¹⁰ Silica-3p-TPP,¹¹ and PS-Ph₃P,¹² which are based on a common design concept but have a triarylphosphine core in contrast to the Silica-SMAP trialkylphosphine, and demonstrated these immobilized triarylphosphines to be useful for the Pd-catalyzed Suzuki–Miyaura coupling,^{11–13} the Buchwald–Hartwig amination,¹² or Ir (Rh)catalyzed directed sp³-C–H borylation reactions.^{10h,10j}

Herein, we report that silica-supported tripod triarylphosphine ligands such as Silica-3p-TPP enabled Pd-catalyzed borylation of chloroarenes under mild conditions. The heterogeneous Pd system based on Silica-3p-TPP was applicable to one-pot biaryl synthesis via the Miyaura borylation–Suzuki– Miyaura coupling sequence.

Various immobilized phosphines were evaluated for the ligand performance in the Pd-catalyzed borylation of *p*-chlorotoluene (**1a**, 0.5 mmol) with bis(pinacolato)diboron (**2**, 0.55 mmol) at 25 °C for 10 h in the presence of KOAc (1.5 mmol) as a base. Pd catalysts were prepared in situ from [PdCl(η^3 -cinnamyl)]₂ (0.5 mol % Pd) and the phosphine ligands (Pd/P 1:2). The results are summarized in Figure 1. Notably, 4,4'-dimethylbiphenyl, a potential by-product due to the coupling between **1a** and borylation product **3a**, was not formed under the conditions using the mild base KOAc. Interestingly, the triptycene-type ligand Silica-TRIP was more effective than Silica-SMAP inspite of its lower electron-donating ability as a triarylphosphine (98% yield).¹⁴ Among the silica-supported tripod triarylphosphines with different backbone structures



Figure 1. Ligand effects in Pd-catalyzed borylation of 1a with 2. Conditions: 1a (0.5 mmol), 2 (0.55 mmol), [PdCl(η^3 -cinnamyl)]₂ (0.00125 mmol, 0.5 mol % Pd), ligand ([P] 0.07–0.11 mmol g⁻¹, 0.005 mmol, 1 mol % P), KOAc (1.5 mmol), benzene (1 mL), 25 °C, 10 h. Yields were determined by ¹H NMR analysis. The isolated yield is given in parenthesis.

(Silica-3p-TPP, Silica-3m-TPP,¹⁵ and Silica-3p-TBP¹⁵), Silica-3p-TPP was the most efficient, causing a high conversion of **1a** into **3a**.^{16,17} The mono-P-ligating features of the silica-supported ligands would assist oxidative addition of the C–Cl bond to the Pd⁰–P species. The enhanced ligand performances of the Silica-TRIP and Silica-3p-TPP triarylphosphines over the Silica-SMAP trialkylphosphine suggest the importance of transmetalation and reductive elimination steps in these catalytic systems. Silica-3p-TPP is advantageous over Silica-TRIP in terms of the ease in preparation.

The heterogeneous catalysts were easily separated from the products by filtration, and inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis of the filtrate

Table 1. Borylation of various chloroarenes 1 with 2^{a}



^aConditions: **1** (0.5 mmol), **2** (0.55 mmol), [PdCl(η^3 -cinnamyl)]₂ (0.00125 mmol, 0.5 mol % Pd), Silica-3p-TPP ([P] 0.11 mmol g⁻¹, 0.005 mmol, 1 mol % P), KOAc (1.5 mmol), solvent (1 mL), 25–90 °C, 10 h. ^bYields were determined by ¹H NMR analysis. The isolated yields are given in parentheses. ^c[PdCl(η^3 -cinnamyl)]₂ (0.0025 mmol, 1 mol % Pd). ^d1,3,5-Triethylbenzene (17%) was detected in the crude mixture.

indicated that the Pd leaching was below the detection limit (0.02% of the loaded Pd). Unfortunately, attempts to reuse the catalyst were unsuccessful.

The bipod and monopod phosphines (Silica-2p-TPP,¹¹ Silica-1p-TPP,¹¹ and Silica-1-EtTPP¹¹) were also effective, but were significantly less efficient than the tripod phosphines, affording **3a** in only 70%, 48%, and 16% yields, respectively (Figure 1). No reaction occurred with the soluble phosphine ligands such as 3p-TPP¹¹ and Ph₃P or under the phosphine-free conditions.

The borylation protocol using the Pd-Silica-3p-TPP catalyst system was applied to the reaction of various chloroarenes. Results are summarized in Table 1. *p*-Chloroanisole (1b), which has an electron-donating MeO substituent, was somewhat less reactive than the electronically unbiased substrate 1a, but the borylation of 1b with 1 mol% catalyst loading proceeded smoothly at 25 °C to afford 3b in 91% yield (Entry 1). The chloroarenes with electron-withdrawing *para*-substituents such as CF₃ (1c), MeCO (1d), and MeO₂C (1e) groups were



Scheme 1. One-pot biaryl synthesis combining Miyaura borylation and Suzuki–Miyaura coupling.

quantitatively borylated at 25 °C with 0.5 mol % catalyst loading (Entries 2–4). Pd catalysis (1 mol % Pd, 60 °C) was applicable to the borylation of heteroaryl chlorides **1f** and **1g** to afford the corresponding heteroaryl boronates **3f** and **3g** in good to high yields (Entries 5 and 6). *o*-Chlorotoluene (**1h**) reacted at 60 °C to give **3h** in quantitative yield (Entry 7). The Pd-Silica-3p-TPP system was capable of converting the more challenging substrates 2,6-dimethylchlorobenzene (**1i**) and 2,4,6-triethyl-chlorobenzene (**1j**) into sterically congested arylboronates **3i** and **3j**, respectively, under relatively mild conditions with reasonable catalyst loading (Entries 8 and 9). However, the reaction of these sterically demanding substrates proceeded under milder conditions with the more compact Silica-SMAP ligand.⁹

The efficacy of the tripod phosphine-based catalyst systems for the Miyaura borylation and the Suzuki–Miyaura coupling with chloroarenes allows the one-pot synthesis of an unsymmetrical biaryl from two different chloroarenes as shown in Scheme 1. The substrates for the borylation reaction **1a** and **2** were mixed together in benzene with KOAc (**1a/2**/KOAc 1:1:3) in the presence of the Pd-Silica-3p-TPP catalyst (1 mol % Pd, Pd/P 1:2), and the mixture was stirred at 25 °C for conversion to **3a** (10 h). To this mixture, chloroarene **1d** (1 equiv) dissolved in benzene and aq. K₃PO₄ (3 equiv) were added, and the mixture was stirred at 60 °C for 10 h. After removal of solids, silica gel chromatography afforded the unsymmetrical biaryl **4** in 74% yield.

In summary, a silica-supported tripod triarylphosphine (Silica-3p-TPP) having a Ph₃P-type core tripodally immobilized on silica gel enabled the Pd-catalyzed borylation of chloroarenes under mild conditions inspite of the moderate electron-donating and steric properties. Various chloroarenes substituted with electron-donating and electron-withdrawing groups were successfully converted into the corresponding arylboronates in high yields. The heterogeneous Pd catalyst system is applicable to one-pot biaryl synthesis from a pair of chloroarenes through the Miyaura borylation–Suzuki–Miyaura coupling sequence. Further catalytic application of silica-supported tripod triaryl-phosphines as a ligand is currently under investigation.

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