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## A Polystyrene-Cross-Linking Tricyclohexylphosphine: Synthesis, Characterization and Applications to Pd-Catalyzed Cross-Coupling Reactions of Aryl Chlorides

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**Abstract:** A polystyrene-cross-linking tricyclohexylphosphine (PS-TCP) was synthesized through radical emulsion polymerization of 4-*t*-butylstyrene as a monomer and tris(*trans*-4-styrylcyclohexyl)phosphine as a three-fold cross-linker. The PS-TCP showed enhanced ligand performance compared to the corresponding polystyrene-triphenylphosphine hybrid PS-TPP and tricyclohexylphosphine in Pd-catalyzed Suzuki–Miyaura and Buchwald–Hartwig reactions of aryl chlorides.

Trialkylphosphines are widely used as ligands in transition metal catalysis, and are more effective than triarylphosphines for increasing the electron density of the metal center.<sup>[1]</sup> In particular, the role of sterically demanding trialkylphosphines is well-established in Pd-catalyzed cross-coupling reactions of aryl chlorides,<sup>[2]</sup> which are generally less reactive compared to the corresponding bromides and iodides.

Recently, a new type of polystyrene-triphenylphosphine hybrid PS-TPP (Figure 1, left), which contains a phosphine unit triply linked between polystyrene chains, was developed.<sup>[3]</sup> Due to spatial isolation of the P center in the polymer matrix, PS-TPP allowed selective mono-P-ligation to transition metals. As a result, PS-TPP enabled Pd-catalyzed cross-coupling reactions of aryl chlorides, regardless of its moderate electron-donating ability. Thus, the three-fold cross-linking strategy was expanded to the use of a trialkylphosphine as a cross-linker core.<sup>[4,5]</sup>



Figure 1. Polystyrene cross-linking phosphines.

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The present report describes the synthesis of a polystyrenecross-linking trialkylphosphine PS-TCP (Figure 1, right) that has a tricyclohexylphosphine core. The preferred mono-P-ligation of transition metals was indicated by <sup>31</sup>P CP/MAS spectroscopy. The PS-TCP possessed enhanced ligand performance compared to PS-TPP and tricyclohexylphosphine in Pd-catalyzed crosscoupling reactions of aryl chlorides.

For the synthesis of the desired three-fold cross-linking phosphine (PS-TCP), a cross-linked polymer was constructed in the form of a phosphine-borane adduct (PS-TCP-BH<sub>3</sub>) because trialkylphosphines are prone to oxidation in air (Scheme 1).<sup>[6]</sup> Thus, commercially available 4-phenylcyclohexanone (1) was converted to alkyl chloride 3 through reduction with NaBH4 followed by chlorination with CCl<sub>4</sub> and PPh<sub>3</sub>.<sup>[7]</sup> Formylation at the para position of the benzene ring of 3 using TiCl<sub>4</sub> and Cl<sub>2</sub>CHOCH<sub>3</sub> gave aldehyde 4 along with trace amounts of isomers. Silica gel column chromatography followed by recrystallization from hexane yielded analytically pure 4 in 39% yield based on 2. Subsequent Wittig reaction afforded 4-styryl-substituted cyclohexyl chloride 5. Magnesiation and reaction with PCI<sub>3</sub>, followed by treatment with BH3. THF, furnished TCP-BH3. Although the crude product contained small amounts of isomers from stereochemistry of the cyclohexane ring, isomerically pure TCP-BH<sub>3</sub> with an allequatorial configuration was obtained by silica gel column chromatography and reprecipitation from CH<sub>2</sub>Cl<sub>2</sub>/hexane. The allequatorial configuration of three 1,4-disubstituted cyclohexane rings was assigned by analogy to the corresponding  $\alpha$ derivative  $\alpha$ -Me-styrene-TCP-BH<sub>3</sub>, methylstyrene the stereochemistry of which was determined by single-crystal X-ray diffraction analysis (Figure 2).<sup>[8]</sup> This molecular structure was expected to be suitable for effective spatial isolation of the P center of the tricyclohexylphosphine-based ligand after crosslinking the polystyrene chains at the 4-position of the cyclohexyl rings.

The radical emulsion polymerization of 4-*t*-butylstyrene (**6**) in the presence of TCP-BH<sub>3</sub> as a three-fold cross-linker (**6**/TCP-BH<sub>3</sub> ~60:1, Scheme 1) gave the polystyrene-phosphine hybrid PS-TCP-BH<sub>3</sub>. Subsequently, BH<sub>3</sub>-deprotection with piperidine in refluxing toluene afforded the free phosphine PS-TCP. Upon BH<sub>3</sub>deprotection, the <sup>31</sup>P CP/MAS NMR signal shifted upfield from 29 to 7 ppm, indicating efficient deprotection in the polymer matrix (Figure 3). The PS-TCP in dry form was stable against P-oxidation in air and showed swelling properties similar to PS-TCP.<sup>[9]</sup> The P loading of PS-TCP (**6**/TCP-BH<sub>3</sub> 62:1) in the polystyrene resins

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was estimated to be 0.16 mmol/g based on combustion elemental analysis for P. This value, designated as  $[P]_{anal}$  (0.16 mmol/g), was larger than expected from the value  $[P]_{calcd}$ , which was calculated on the basis of the monomers used (0.095 mmol/g).





**Figure 2.** ORTEP drawing of  $\alpha$ -Me-styrene-TCP-BH<sub>3</sub> (30% probability level, H atoms, except for the BH<sub>3</sub> moiety, and disordered sections are omitted for clarity).

The coordination properties of PS-TCP toward transition metals were investigated using <sup>31</sup>P CP/MAS NMR spectroscopy. Reaction with an excess amount of [RhCl(cod)]2 was conducted in benzene at room temperature (P/Rh 1:2 based on [P]calcd). The resulting yellow beads were collected by filtration. The <sup>31</sup>P CP/MAS NMR spectrum showed a new peak at 26 ppm (Figure 4), indicating clean formation of a mono-P-ligating complex [RhCl(cod)(PS-TCP)] assigned by comparison with the corresponding soluble complex [RhCl(cod)(PCy<sub>3</sub>)] (<sup>31</sup>P NMR in C<sub>6</sub>D<sub>6</sub>; 27.3 ppm).<sup>[10]</sup> The spectrum also indicated that all of the polymer-embedded P atoms participated in metal complexation. Measurement of the amount of unreacted [RhCl(cod)]<sub>2</sub> allowed estimation of Rh loading in the polystyrene resin, which was calculated to be 0.15 mmol/g. This value was comparable to the [P]anal value (0.16 mmol/g), determined by combustion elemental analysis, and can be defined as effective P loading [P]eff for metal complexation.







Figure 4.  ${}^{31}$ P CP/MAS NMR spectrum obtained from PS-TCP and [RhCl(cod)]<sub>2</sub> (P/Rh 1:2 based on [P]<sub>calcd</sub>).

Next, reactions of PS-TCP with [PdCl<sub>2</sub>(PhCN)<sub>2</sub>] were conducted in benzene at room temperature at different P/Pd ratios (P/Pd 1:2, 1:1 and 2:1 based on [P]eff, 0.15 mmol/g). The <sup>31</sup>P CP/MAS NMR spectra indicated that PS-TCP preferentially formed a 1:1 P/Pd complex [Pd(II)-(PS-TCP)] (53-57 ppm) over a P/Pd 2:1 complex [Pd(II)-(PS-TCP)2] (24-27 ppm), irrespective of P loading relative to Pd (Figure 5). With excess P atoms (P/Pd 2:1, Figure 5c), the free PS-TCP remained uncoordinated.<sup>[11]</sup> In contrast, the corresponding soluble ligand tricyclohexylphosphine was completely consumed during reaction with [PdCl<sub>2</sub>(PhCN)<sub>2</sub>] in C<sub>6</sub>D<sub>6</sub> at the same P loading ratios (P/Pd 1:2, 1:1 and 2:1; Figure S6 in SI). When 2 equivalents of tricyclohexylphosphine relative to Pd were used (P/Pd 2:1, Figure S6c), a bis-P-ligating complex [PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>] (<sup>31</sup>P NMR in C<sub>6</sub>D<sub>6</sub>; 25.6 ppm) was formed exclusively. These results indicate that polystyrene-cross-linking is effective for realizing effective mono-P-ligation of the tricyclohexylphosphine-based ligand. The NMR studies also suggested that the 4-phenyl-cyclohexane linkers between the P

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center and cross-linking points of PS-TCP may be too long to cause complete inhibition of the bis-P-ligation in the polymer matrix.



Figure 5. <sup>31</sup>P CP/MAS NMR spectra obtained from PS-TCP and  $[PdCl_2(PhCN)_2]$  [P/Pd at a ratio of (a) 1:2, (b) 1:1, and (c) 2:1 based on [P]<sub>eff</sub>].

The preferred mono-P-ligation of PS-TCP supported by NMR analysis for P–Pd coordination promoted its use as a coordinating ligand in Pd-catalyzed Suzuki–Miyaura coupling of aryl chlorides,<sup>[12]</sup> in which the utility of bulky trialkylphosphines has been established.<sup>[2]</sup> Reaction between 4-chloroanisole (**7a**), as an example of an electronically deactivated aryl chloride, and phenylboronic acid (**8a**) was conducted with 1 mol% Pd catalyst prepared *in situ* from [PdCl<sub>2</sub>(PhCN)<sub>2</sub>] as a Pd precursor (P/Pd 2:1 based on [P]<sub>calcd</sub>, 0.095–0.098 mmol/g, **6**/TCP-BH<sub>3</sub> 60–62:1) with KF as a base in THF at 25 °C for 18 h.<sup>[13]</sup> The results are summarized in Table 1.

The PS-TCP induced the coupling reaction, giving the desired product **9a** in 96% yield (Table 1, entry 1). Its catalytic activity was significantly greater than that with PS-TPP, which is known to be useful in the Pd-catalyzed cross-coupling reactions

of aryl chlorides (65%, entry 2).<sup>[3a,b]</sup> A single-point-grafted polystyrene-tricyclohexylphosphine hybrid PS-monopod-TCP (5%, entry 3) and a soluble counterpart tricyclohexylphosphine (<1%, entry 4) were much less effective, indicating that the three-fold cross-linking is essential. Under the present conditions, PS-TCP showed better ligand performance than did Buchwald's (dicyclohexylphosphino)biphenyl-type ligands such as XPhos (80%, entry 5), SPhos (57%, entry 6), or RuPhos (76%, entry 7), which are widely used in cross-coupling reactions of aryl chlorides.<sup>[14]</sup> The (PS-TCP)-Pd catalyst system was easily recovered and could be reused at least three times, although with gradually decreasing yields (1<sup>st</sup> run, 97%; 2<sup>nd</sup> run, 96%; 3<sup>rd</sup> run, 89%; 4<sup>th</sup> run, 86%).

I	MeO-CI + 7a (0.25 mmol)	PhB(OH) <sub>2</sub> 8a (1.5 eq)	[PdCl <sub>2</sub> (PhCN) <sub>2</sub> ] (1 mol%) Ligand (2 mol%) KF (3 eq) THF (1 mL), 25 °C, 18 h	MeO-Ph 9a
	Entry		_igand	Yield [%] <sup>[b]</sup>
	1	P	S-TCP	96 (96)
	2	2 PS-TPP 3 PS-monopod-TCP		65
	3			5
	4		PCy <sub>3</sub>	<1
	5 XPhos		XPhos	80
	6	SPhos		57
	7	RuPhos		76

[a] Conditions: **7a** (0.25 mmol), **8a** (0.375 mmol),  $[PdCl_2(PhCN)_2]$  (1 mol%), ligand (2 mol% based on  $[P]_{calcd}$ , 0.095–0.098 mmol/g), KF (0.75 mmol), THF (1 mL), 25 °C, 18 h. [b] Yields determined by <sup>1</sup>H NMR analysis. Isolated yield shown in parentheses.



Within the (PS-TCP)-Pd system, several aryl chlorides and arylboronic acids participated in the coupling reactions (Scheme 2). Notably, *p*-chloro-*N*,*N*-dimethylaniline, which was strongly deactivated electronically by the NMe<sub>2</sub> group, successfully coupled with **8a** to give biaryl **9b**. The reactions of electron-deficient and heteroaryl chlorides occurred smoothly at 25 or 60 °C (**9c** and **9d**). Electron-rich and -poor arylboronic acids served as suitable substrates (**9e** and **9f**).

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Scheme 2. Scope of the (PS-TCP)-Pd system in Suzuki–Miyaura coupling. Conditions: ArCl (7, 0.25 mmol), ArB(OH)<sub>2</sub> (8, 0.375 mmol), [PdCl<sub>2</sub>(PhCN)<sub>2</sub>] (1 mol%), PS-TCP (2 mol% based on [P]<sub>calcd</sub>, 0.095–0.098 mmol/g), KF (0.75 mmol), THF (1 mL), 25 °C, 18 h. Isolated yield is shown.

In addition, PS-TCP was applied to Pd-catalyzed Buchwald– Hartwig amination of aryl chlorides.<sup>[15]</sup> In the reaction between **7a** and aniline **10a** (1 mol% Pd, with NaO*t*Bu, in toluene, 100 °C, 20 h) (Table 2), PS-TCP also showed better performance than PS-TPP, PS-monopod-TCP, and tricyclohexylphosphine (entries 1–4), and reaction efficacy with PS-TCP was comparable to those with XPhos, SPhos, and RuPhos (entries 5–7). As shown in Scheme 3, the (PS-TCP)-Pd system allowed efficient coupling of electronically and/or sterically demanding aryl chlorides with **10a**, giving the corresponding secondary amines **11b** and **11c** in good yields. Diphenylamine severed as a suitable substrate to afford triarylamine **11d**.

 Table 2. Pd-catalyzed Buchwald–Hartwig amination of 7a and 10a<sup>[a]</sup>

	L DENUL	-igand (2 mol%)	<sup>%)</sup> Ph
7a (0.25 mmol)	+ PhNH <sub>2</sub> N 10a (1.2 eq) <sup>tr</sup>	VaO <i>t</i> Bu (1.4 eq) oluene (1 mL), 100 °C, 20	0h 11a
Entry		Ligand	Yield (%) <sup>b</sup>
1		PS-TCP	89 (78)
2		PS-TPP	57
3	PS-m	nonopod-TCP	2
4		PCy <sub>3</sub>	13
5		XPhos	93
6		SPhos	97
7		RuPhos	92

[a] Conditions: **7a** (0.25 mmol), **10a** (0.30 mmol), [PdCl( $\pi$ -allyl)]<sub>2</sub> (Pd: 1 mol%), ligand (2 mol% based on [P]<sub>calcd</sub>, 0.095–0.098 mmol/g), NaO*t*Bu (0.35 mmol), toluene (1 mL), 100 °C, 20 h. [b] Yields determined by <sup>1</sup>H NMR analysis. Isolated yield shown in parentheses.



**Scheme 3.** Scope of the (PS-TCP)-Pd system in Buchwald–Hartwig amination. Conditions: ArCl (**7**, 0.25 mmol), ArNH<sub>2</sub> (**10**, 0.30 mmol), [PdCl( $\pi$ -allyl)]<sub>2</sub> (Pd: 1 mol%), PS-TCP (2 mol% based on [P]<sub>calcd</sub>, 0.095–0.098 mmol/g), NaOtBu (0.35 mmol), toluene (1 mL), 100 °C,

20 h. Isolated yield is shown. [a] A material purified by silica gel column chromatography was contaminated with a small amount of the N,N-diarylation product (97:3).

summary, polystyrene-cross-linking In а PS-TCP, trialkylphosphine which has а tricyclohexylphosphine core, was synthesized through radical emulsion polymerization of 4-t-butylstyrene and the tricyclohexylphosphine-based BH<sub>3</sub>-protected three-fold cross-linker followed by BH<sub>3</sub>-deprotection. The <sup>31</sup>P CP/MAS NMR studies on coordination behavior toward Rh(I) and Pd(II) complexes showed a significant tendency toward mono-P-ligation. As a result, PS-TCP exhibited improved ligand performance compared to the corresponding polystyrene-triphenylphosphine hybrid PS-TPP, and it outperformed the parent ligand tricyclohexylphosphine in Pdcatalyzed Suzuki-Miyaura coupling and Buchwald-Hartwig amination reactions of aryl chlorides. Further investigation on the application of PS-TCP and its derivatives is ongoing.

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**Keywords:** trialkylphosphine • polystyrene • heterogeneous catalyst • palladium • cross-coupling

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polymerization between 4-*t*-butylstyrene and  $\alpha$ -Me-styrene-TCP-BH<sub>3</sub> as the threefold cross-linker gave an unorganized polystyrene-phosphine hybrid due to different reactivities between  $\alpha$ -methylstyrene- and styrene-type monomers.

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А polystyrene-cross-linking tricyclohexylphosphine (PS-TCP) was synthesized through radical emulsion polymerization of 4-t-butylstyrene as a and monomer tris(trans-4styrylcyclohexyl)phosphine as a threefold cross-linker. The PS-TCP showed performance enhanced ligand the corresponding compared to polystyrene-triphenylphosphine hybrid PS-TPP and tricyclohexylphosphine in Pd-catalyzed Suzuki-Miyaura and Buchwald-Hartwig reactions of aryl chlorides.



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