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## COMMUNICATION

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## Phenylphosphinacalix[3]trifuran: synthesis, coordination and application in the Suzuki-Miyaura cross-coupling reaction in water†

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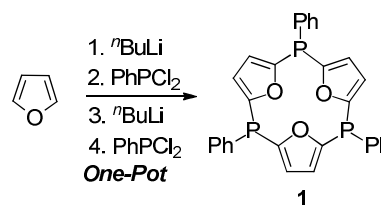
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Phenylphosphinacalix[3]trifuran and supramolecular assemblies with palladium have been synthesized. Phenylphosphinacalix[3]trifuran affords turnover numbers as high as  $3.05 \times 10^7$  in Suzuki-Miyaura cross-coupling reactions in pure water.

The development of methods for construction of supramolecular architectures offers chemists the ability to synthesize many potentially useful species. Ultimately, control over the synthesis of compounds containing well-defined cavities enables the design of species that can arrange molecules in a specific and predictable fashion for catalysis.<sup>1</sup> Indeed, chemists are now beginning to utilize supramolecular chemistry as a tool toward the realization of catalytic systems with enzyme-like properties.<sup>2</sup> Acyclic phosphine compounds play an important role in catalysis<sup>3</sup> and supramolecular chemistry. However, studies on phospho macrocycles are relatively limited.<sup>4</sup> Recently, Edwards established a metal-template hydrophosphination method to construct a cyclic structure on a metal center by a self-coupling reaction of primary or secondary alkenylphosphines. Using this ingenious template method, a dozen phospho macrocycles were prepared.<sup>5</sup> Herein, we report the preparation of phenylphosphinacalix[3]trifuran, the construction of supramolecular assemblies via metal coordination chemistry, and application in palladium-promoted Suzuki cross-coupling reactions using pure water as solvent.

The facile deprotonation of thiophene or furan by a strong base such as <sup>n</sup>BuLi is a well-known process. A wide variety of bis-electrophiles react with these anions to give bis-substituted compounds in high yields, and extension of this reaction to dianions allows the synthesis of cyclic compounds.<sup>6</sup> Using this procedure, compound **1**, a white solid, was obtained as the main product from a one-pot synthesis (Scheme 1). TLC on silica showed that there were three minor by-products in the reaction mixture, but the yields were too low for them to be isolated. The essential absence of larger cyclic oligomers suggests that

the trimeric macrocycle may be the thermodynamically favored product.

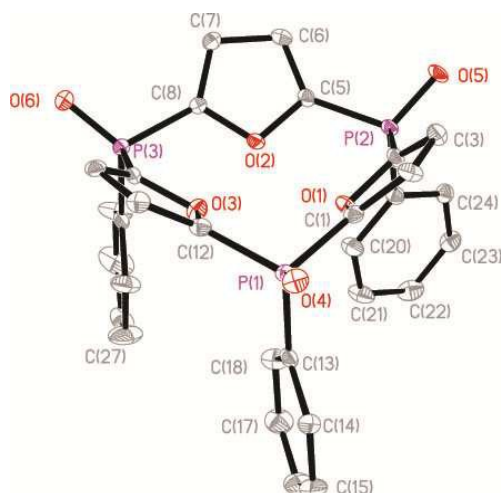
Scheme 1 One-pot four-step synthesis of **1**.

The proposed mechanism for the formation of phenylphosphinacalix[3]trifuran (**1**) is shown in Scheme 2. The reaction between 2-furyllithium and phenylphosphorus dichloride should yield the di(2-furyl)phenyl phosphine (**A**). Reaction of **A** with <sup>n</sup>BuLi would then provide intermediate **B**. Diphosphine intermediate **C** would then be produced by the reaction of **B**, 2-furyllithium and phenylphosphorus dichloride. **C** would react with <sup>n</sup>BuLi to give the dianion **D**. Finally, **1** would be generated by the reaction between dianion **D** and phenylphosphorus dichloride. To confirm the reaction mechanism, <sup>31</sup>P NMR spectra of the reaction mixture at every step were studied. In addition, 2,4-bis(2-furylphenylphosphino)furan (**C**) was isolated from the reaction mixture (see ESI†).

Compound **1** is stable in air, so no special precautions are required to handle it under ordinary laboratory conditions. It is also sufficiently soluble in common organic solvents (e.g., dichloromethane, chloroform, benzene, and THF) to permit routine spectroscopic analysis. In <sup>1</sup>H NMR and <sup>31</sup>P{<sup>1</sup>H} NMR spectra, only one furan proton signal and a sharp phosphorus signal were observed, indicating that **1** has a symmetric cyclic structure.

The corresponding trioxide (**2**) of compound **1** could be produced by reaction of **1** with H<sub>2</sub>O<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>. **1** could also be

converted cleanly to the corresponding trisulfide (**3**) by reaction with elemental sulfur or to triselenide by reaction with elemental selenium in 91% and 92% yield, respectively. The molecular structures of **2**, **3** and **4** were initially elucidated based upon  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra. The  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra of **2** and **3** contained singlets at 2.62 and 9.01 ppm, respectively. The  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra of **4** displayed one major signal with selenium satellites at  $-5.17$  ppm, due to the P atoms bonded to magnetically inactive Se nuclei, and a doublet ( $J_{\text{P-Se}} = 821$  Hz) stemming from the P nucleus bonded to  $^{77}\text{Se}$  (7.5% natural abundance,  $I = 1/2$ ).<sup>7</sup>



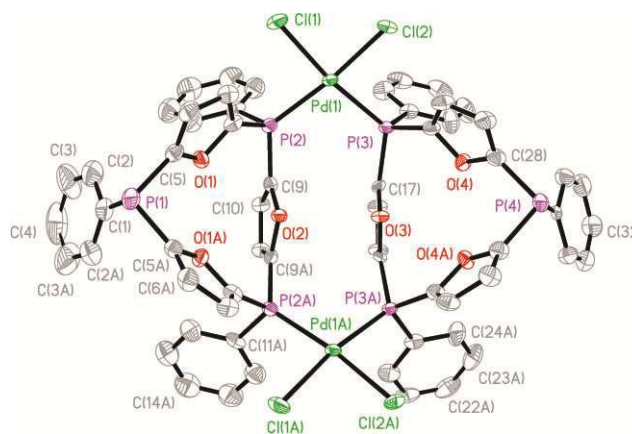
**Figure 1** Molecular structure of **2** with 30% probability level ellipsoids.

The structure of **2** was confirmed by X-ray crystallographic analysis (Figure 1). Compound **2** is  $C_{3v}$  symmetric, and looks like a type of three-legged Chinese Bronze Tripod (an ancient cauldron) (see ESI†), wherein three furan units and three Ph–P groups are alternately linked to form a conical framework. Atoms C(2), C(3), C(6), C(7), C(10) and C(11) form the upper rim, and all six atoms are nearly coplanar with a mean deviation of 0.0225 Å. The three oxygen atoms bonded to phosphorus atoms are all directed to the upper rim of the cone. The P(1)–C(13), P(2)–C(19) and P(3)–C(25) bonds are almost perpendicular to the plane mentioned above, so the three benzene rings bonded to the phosphorus atoms form three legs.

The molecular structures of **3** and **4** were also confirmed by X-ray crystallography (see ESI†). The structures of **3** and **4** are very similar to that of **2**. For example, (i) they also look like Chinese Bronze Tripods, (ii) the average distance between the two O atoms of the furan rings is about 2.87 Å for **2**, 2.80 Å for **3** and 2.81 Å for **4**, and the three O atoms of the furan ring form an equilateral triangle, (iii) the P atoms in **3** and **4** possess a tetrahedral configuration with comparable C–P–C bond angles, and (iv) P=O, P=S and P=Se bonds are directed to the upper rim of the cone, and O, S or Se, together with the 3- and 4-position carbons of the furan ring form the upper rim of the cone.

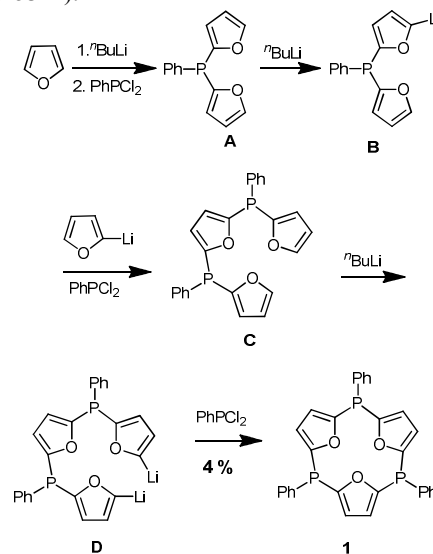
The propensity of **1** toward chelation was tested through its reaction with  $\text{PdCl}_2(\text{NCCH}_3)_2$ . The single product was assigned as dinuclear  $[\text{cis-PdCl}_2(\mathbf{1})]_2$  (**5**) on the basis of (i) broken  $C_3$  symmetry

of the cyclophane fragment (indicated by  $^1\text{H}$  NMR); (ii) observed shift in the  $^{31}\text{P}$  NMR from  $-61.95$  ppm to  $-5.19$  and  $-63.46$  ppm; (iii) a single crystal X-ray diffraction study (Figure 2).








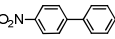





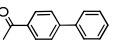





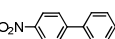





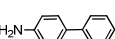




















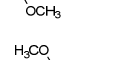


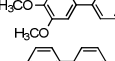





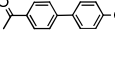


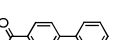


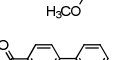
**Figure 2** Molecular structure of **5** with 30% probability level ellipsoids.

Compound **5** is  $C_2$  symmetric, and looks like a Si Muwu square vessel (an ancient cauldron with four legs) (see ESI†). Four benzene rings bonded to the coordinated phosphine atoms form four legs. The palladium atom is coordinated in a distorted square planar geometry with a *cis* arrangement of two P-donors and two Cl atoms. The average Pd–Cl and Pd–P bond lengths are comparable with those observed in other phosphinopalladium(II) chloride complexes.<sup>8</sup> A pseudo-rectangular geometry, where the four corners are occupied by coordinated P atoms, has dimensions of approximately  $5.50 \times 3.53$  Å. The internal geometry of the cyclophane ligands in **5** is different from that in **1**. The two furanyl moieties in the metallamacrocycle are almost parallel and separated by 3.385 Å, similar to other compounds that contain  $\pi$ – $\pi$  stacking interactions.<sup>8</sup> Both furanyl oxygen atoms point towards the cavity of the metallamacrocycle. Structural effects due to the formation of the metallamacrocycle also result in different P–P distances (P(1)–P(2) = 5.512 Å, P(2)–P(2A) = 5.453 Å).



**Scheme 2** Possible mechanism for the formation of **1**.

**Table 1** The Suzuki-Miyaura coupling of various aryl halides with arylboronic acid in the presence of **1**/Pd(OAc)<sub>2</sub> in water<sup>a</sup>

Entry	Halide	Boronic acid	Product	Yield <sup>b</sup>
1				90
2				92
3				94
4				98
5				61
6				21
7				0
8				85
9				82
10				65
11				81
12				87
13				87
14				89
15				91
16				93
17				63
18				72
19				87
20				97

<sup>a</sup>Reaction conditions: 1.0 mmol of aryl halide, 1.2 mmol of boronic acid, 0.5 mol% Pd(OAc)<sub>2</sub>, 1.5 mol% **1**, 3.0 mmol of K<sub>3</sub>PO<sub>4</sub>·3H<sub>2</sub>O, 2.0 mL H<sub>2</sub>O, 100°C, reaction time 8 h. <sup>b</sup>Isolated yield (%).

Since the original discovery and development of Pd-catalyzed coupling reactions that led to the recent chemistry Nobel Prize being awarded to Heck, Suzuki and Negishi, a great deal of attention has focused on the development of catalytic systems that would improve their efficiency.<sup>9</sup> The use of phosphine ligands allows very high turnover numbers (TONs) to be reached in Suzuki-Miyaura couplings, and the search for catalytic systems allowing ultra-low loadings is an ongoing field.<sup>10</sup> In addition, there has been increasing interest in the use of water as a solvent for many homogeneously catalyzed reactions. Cost, environmental benefits, and safety are among the reasons most often used to justify the replacement of organic solvents by water in organic transformations.<sup>11</sup>

Recently, cavity-shaped ligands have been shown to add value to the efficiency of the Suzuki-Miyaura coupling reaction.<sup>12</sup> With compound **1** in hand, we then studied the scope and limitations of **1**/Pd as a catalyst in Suzuki-Miyaura coupling in water at low loadings. We applied similar conditions to those reported for the  $\alpha$ -Cytep tetraphosphine. Using Pd(OAc)<sub>2</sub> as a palladium precursor together with compound **1** in a 3:2 ratio, but at a slightly higher (2×10<sup>-8</sup>%) loading than the lowest used with  $\alpha$ -Cytep, and K<sub>3</sub>PO<sub>4</sub>·3H<sub>2</sub>O in refluxing water for 3 days led to TONs of up to 3.05 × 10<sup>7</sup>. While the TONs is up to 2.55 × 10<sup>7</sup>, using bromobenzene and 2-methoxyphenylboronic acid as reactant. The TONs is just 1.50 × 10<sup>7</sup>, using Pd(OAc)<sub>2</sub> and phenyldifuranphosphine as catalyst to the reaction of bromobenzene with phenylboronic acid (see ESI†). However, this catalytic system is not as efficient as Buchwald's ligand for aryl chlorides. This observation suggests that these high TONs are not due to a facilitated oxidative addition step but, as previously noted, longevity of the catalyst can be a key to reach high TONs.<sup>13</sup>

Under the optimized reaction conditions, a wide array of aryl bromides reacted smoothly with phenylboronic acid to provide the corresponding products (see ESI†). For example, bromobenzene reacted efficiently with phenylboronic acid within 8 h, providing a 90% yield of the desired product (Table 1, entry 1). The reaction of aryl bromides bearing electron-withdrawing groups, such as -NO<sub>2</sub>, -CHO, and -COCH<sub>3</sub>, with phenylboronic acid also gave the required products in good to excellent yields (Table 1, entries 2–4). It is also noteworthy that the present protocol is applicable to the cross-coupling reaction of 2-bromothiophene with phenylboronic acid, providing the desired heterocyclic product in 61% yield (Table 1, entry 5). Furthermore, cross-coupling reactions of aryl chlorides with phenylboronic acid resulted in low yields (Table 1, entries 6, 7). The reaction of phenylboronic acid with aryl bromides bearing electron-donating substituents such as -NH<sub>2</sub>, -CH<sub>3</sub>, -OCH<sub>3</sub> gave the desired products in moderate to high yields (Table 1, entries 8–16). This catalyst system can also be used in the coupling reactions of moderately hindered aryl boronic acids with aryl bromides. For example, the reaction of 2-methoxyphenylboronic acid with 4'-bromoacetophenone proceeded smoothly to give the biaryl product in 72% yield (Table 1, entry 18). 2-methylphenylboronic acid and 2-naphthylboronic acid also reacted efficiently with 4'-bromoacetophenone to give the desired products in good yields (Table 1, entries 19, 20).

In summary, we have developed a one-pot synthesis of phenylphosphinacalix[3]furan (**1**), representing the first example of a P-bridged heteracalix[3]arene and expanding the range of heteracalixarenes. The reaction of **1** with PdCl<sub>2</sub>(NCCH<sub>3</sub>)<sub>2</sub> gives

the binuclear trimacrocyclic system **5**. Compound **5** represents the first example of a metallamacrocycle containing a P-bridged cavity-shaped ligand. Compound **1** does not display exceptionally high yield. The complex generated with Pd(OAc)<sub>2</sub> and ligand **1** that exhibit high activities in Suzuki-Miyaura cross-coupling. This property could be associated with its ability of the ligand in stabilizing the catalytic species by coordination through multiple binding sites. We have therefore shown that P-bridged heteracalixarenes can serve as interesting platforms for catalysis under aqueous conditions.

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## Graphic Abstract

**Phenylphosphinacalix[3]trifuran: synthesis, coordination and application in the Suzuki-Miyaura cross-coupling reaction in water**

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Phenylphosphinacalix[3]trifuran and supramolecular assemblies with palladium have been synthesized. Phenylphosphinacalix[3]trifuran affords turnover numbers as high as  $3.05 \times 10^7$  in Suzuki-Miyaura cross-coupling reactions in pure water.

