



# Heteroatom-substituted secondary phosphine oxides for Suzuki-Miyaura cross-coupling reactions



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## ABSTRACT

Several di-substituted diimines (**3a–3f**) and heteroatom-substituted unsaturated secondary phosphine oxides (HASPO, **6a–6f**) were prepared and characterized. Compounds **6a–6f** are regarded as pre-ligands because of their ability of tautomerization to heteroatom-substituted phosphinous acid (HAPA, **7a–7f**). An unexpected **3e**-coordinated palladium dibromide **8e** was observed from the reaction of compound **6e** with PdBr<sub>2</sub>. Molecular structures of pre-ligands **6a**, **6c**, and **6e**, as well as palladium complexes **8e** were determined by single crystal X-ray diffraction methods. When pre-ligand **6a** was applied to palladium-catalyzed Suzuki-Miyaura cross-coupling reactions, satisfactory yields were obtained. Density functional theory were employed to examine the electronic properties of HASPO **6a–6f** pre-ligands, their corresponding 1,3-di-*N*-substituted tautomers **7a–7f**, and the saturated counterpart **7as** of **7a**. Compound **7a** is the most effective and genuine ligand in Suzuki-Miyaura reaction that is confirmed by its higher-lying lone-pair (LP) molecular orbital (HOMO-1). The LP orbital of **7c–7f** is lower-lying HOMO-5. For each **7c–7f**, two conformational rotamers with minute energy difference were located. Hirshfeld charge and population analysis of **7c–7f** were also calculated in order to comprehend the electronic properties for these two rotamers for each HAPAs. Besides, the steric effect of HAPAs was estimated in terms of the Percent Buried Volume (%V<sub>bur</sub>). This model has shown that **7a** has similar steric property to that of PCy<sub>3</sub>, which is an effective ligand in Suzuki-coupling reactions.

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## 1. Introduction

Modern synthetic chemistry has cherished the grand triumphs concerning the utilization of transition-metal complexes in catalyzing cross-coupling reactions for making new C–X (X = C, N, O, S, etc.) bonds [1–5]. In particular, Suzuki-Miyaura cross-coupling reaction is one of the most useful means for making C(sp<sup>2</sup>)–C(sp<sup>2</sup>) bond [6]. Since its first report in 1979 [7,8], the scope of this reaction has been extensively investigated by both experimental and computational approaches [9–19]. Typically, the reaction is carried out with arylboronic acid and arylhalide, aryltriflate or alkylhalide as substrates which is combined with a ligand-assisted palladium complex and well-chosen base [20–24].

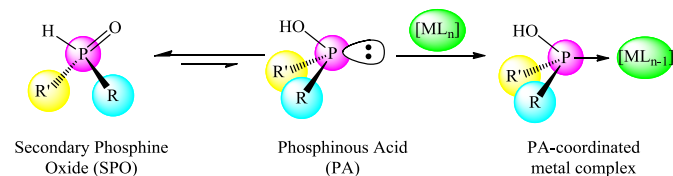
Various types and shapes of ligands play crucial roles in the success of these kinds of transition-metal catalyzed reactions [25,26]. Accordingly, searching for efficient and accessible ligands has been one of the foremost missions for synthetic chemists

[5,27–30]. Up to the present, numerous types and shapes of tri-alkyl- or triaryl-phosphines have long been favorite choices due to their tunable steric and electronic properties through delicate adjustment of the substituents on the phosphorus atom [31–34]. Nevertheless, these electron-rich organophosphines are vulnerable to oxidation and thereafter lose their coordinating abilities toward soft metals, leading to great reduction on catalytic performances. Hence, it is an undesirable property for soft phosphine ligands in terms of long-term storage. Recently, several promising alternatives such as *N*-heterocyclic carbenes, oximes, diazabutadienes, amines and imines are claimed to have advantages of low environmental impact and less sensitivity towards air [35–48]. In spite of the successes of these auxiliary ligands in catalysis, phosphines remain the most favorable choice for ligand-assisted transition-metal-catalyzed reactions, providing its inclination towards oxidation can be avoided [49].

The pentavalent secondary phosphine oxides (R'R''PH(=O), SPO) could be a solution to achieve stability desperately needed [50]. SPO is stable towards oxidation and can be converted to phosphinous acid (R'R''POH, PA) through tautomerization (Scheme 1)

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**Scheme 1.** The tautomerization of phosphinous acid (PA) and PA-coordinated metal complex.

[51–74]. With the existence of metal fragment  $[ML_n]$ , the equilibrium of SPO-to-PA is shifted to PA for ligand association. The formation of PA-coordinated palladium complexes thereafter could work for various cross-coupling reactions [75–79].

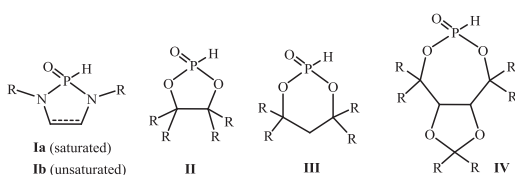
In the past few years, various kinds of SPOs were prepared and their ability as effective ligands in cross-coupling reactions have been reported [51–73,80–83]. Recently, Ackermann had demonstrated the potential application of saturated heteroatom-substituted secondary phosphine oxides (HASPO **1a**, **II–IV** in Diagram 1), which are inexpensive and ambient-stable with high steric hindrance *via* substitutions on phosphorus atom, in various palladium-catalyzed cross-coupling reactions [63,84–91]. Most of these ligands are effective even in the cases of using arylchlorides as substrates. When nickel-based pre-catalyst is loaded with saturated HASPO ligands, cross-coupling reactions with unreactive electron-deficient or steric-crowded aryl-halides can be accomplished at ambient temperature [92,93]. Particularly, in the broad field of cross-coupling reactions, many researchers show interests towards diaminophosphine oxide, which has structural resemblance to N-heterocyclic carbene [94].

Herein we report the preparation and characterization of several unsaturated diaminophosphine oxides (**1b**-type). Their capacities as efficient auxiliary ligands in palladium-catalyzed Suzuki-Miyaura cross-coupling reactions were investigated. Preliminary catalytic screening revealed that with 1,3-di-*tert*-butyl substituted HASPO **6a** a satisfactory catalytic performance was obtained. Hereby, density functional theory (DFT) and the Percent Buried Volume ( $\%V_{bur}$ ) methods were employed to examine the electronic and steric properties of saturated heteroatom-substituted phosphinous acid (saturated HAPA **7as**) and unsaturated diaminophosphine oxides (unsaturated HAPA **7a–7f**), respectively. The effectiveness of phosphinous acid HAPA **7a** (the genuine ligand, a tautomer of pre-ligand HASPO **6a**) in the Suzuki-Miyaura cross-coupling reactions is examined by DFT calculations in conjugation with its adequate steric property ( $\%V_{bur}$ ).

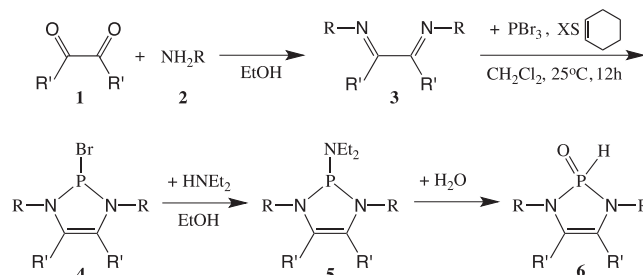
## 2. Results and discussion

### 2.1. Preparation of diimines (**3a–3f**) and heteroatom-substituted secondary phosphine oxides (HASPO) (**6a–6f**)

Six diimines (**3a–3f**) were prepared in fair to good yields from the reactions of anilines with oxalaldehyde or biacetyl (Scheme 2). Intermediates **4a–4f** could be obtained in further reactions of **3a–3f** with  $PBr_3$  in the presence of excess cyclohexene in



**Diagram 1.** Selected heteroatom-substituted secondary phosphine oxides (HASPO).



- a: R = <sup>t</sup>Bu, R' = H    c: R = 2,6-<sup>i</sup>Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R' = H    e: R = 2,6-<sup>i</sup>Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R' = Me  
b: R = Cy, R' = H    d: R = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, R' = H    f: R = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, R' = H, R' = Me

**Scheme 2.** Preparation of diimines (**3a–3f**) and heteroatom-substituted secondary phosphine oxides (**6a–6f**).

dichloromethane at 25 °C for 12 h. Subsequently, reactions of **4a–4f** with diethylamine at 25 °C for 2 h presumably yielded intermediates **5a–5f**. The targeted HASOPs **6a–6f** (Scheme 2) were obtained after the hydrolysis of **5a–5f** and thereafter workup.

All six HASPOs, **6a–6f**, were characterized by spectroscopic methods [95]. A distinctively large coupling constant ( $J_{P-H}$ ) around 650 Hz for all compounds strongly substantiates the existence of a P–H bond. Molecular structures of compounds **6a**, **6c** and **6e** were revealed by single-crystal X-ray diffraction methods and their ORTEP diagrams are depicted in Fig. 1. The existence of double bonds between P=O/alkenyl C=C on the five-membered ring of **6a**, **6c** and **6e** are reflected on their bond lengths of 1.4735(10)/1.3270(18) Å, 1.4555(18)/1.323(2) Å and 1.4746(13)/1.338(2), respectively. The five atoms on the five-membered ring of **6a**, **6c** or **6e** are roughly coplanar, a characteristic for the delocalization of  $\pi$ -electron density on the ring.

### 2.2. Unexpected results from reactions of **6c** or **6e** with palladium salts

As HAPA tautomer is the genuine auxiliary ligand in a catalytic reaction, molecular structures of **7a–7f** are illustrated in Diagram 2. Attempts to prepare HAPA-coordinated palladium complexes followed by structural determination were carried out. Monitored by <sup>31</sup>P NMR, HASPO **6e** was reacted with  $PdBr_2$  in THF at 25 °C for 2 h. The disappearance of the large coupling constant of  $J_{P-H}$  might indicate the conversion of **6e** to its phosphinous acid **7e** and presumably the formation of a **7e**-coordinated palladium complex, *trans*- $PdBr_2$ (**7e**) or *cis*- $PdBr_2$ (**7e**) (Scheme 3). Nevertheless, an unexpected **3e**-coordinated palladium complex **8e** ( $PdBr_2$ (**3e**)), was obtained while attempting to grow crystals in a THF solution. The crystal structure of **8e** was determined by single-crystal X-ray diffraction methods and the ORTEP drawing is depicted in Fig. 2. A closely related  $PdCl_2$ (**3e**) complex was reported previously [96]. The conversion of **7e** to **8e** implies that the P–N bond in **6e** is weak in the presence of trace amount of water in the duration of crystal growing process. The formation of **8e** also indicates that diimine itself having the capacity as a bi-dentate ligand towards palladium metal.

### 2.3. Palladium-catalyzed Suzuki-Miyaura reactions using **6a–6f** as pre-ligands

HASPOs **6a–6f** had been employed as ligands in palladium catalyzed Suzuki-Miyaura cross-coupling reactions of aryl halides and phenylboronic acid. To find out the optimized condition for the reaction, several factors that affect the efficiency of the reactions, including ligand/palladium ratios, solvent, base, temperature, time

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