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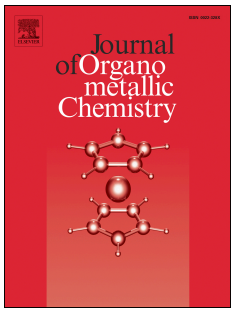

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Graphical Abstract

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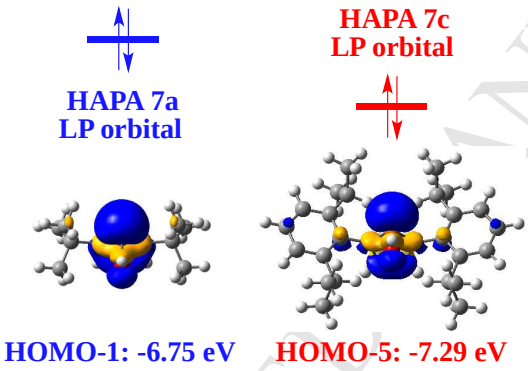

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Abstract

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 $PdBr_2$. 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 ($\%V_{bur}$). This model has shown that **7a** has similar steric property to that of PCy_3, which is an effective ligand in Suzuki-coupling reactions.

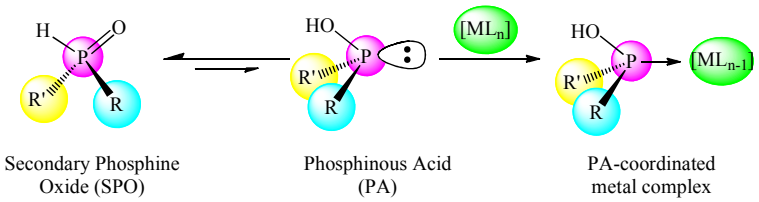
Keywords: C-C coupling; Heteroatom Substituted Secondary Phosphine Oxide (HASPO); Palladium; Density Functional Theory (DFT); Steric Effect.

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 $C(sp^2)$-$C(sp^2)$ 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 trialkyl- 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 (Scheme1).[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]



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

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 **Ia**, **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]

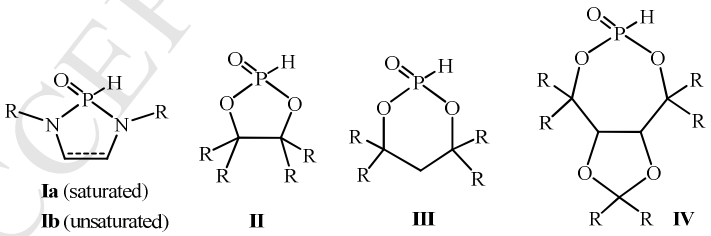


Diagram 1. Selected heteroatom-substituted secondary phosphine oxides (HASPO).

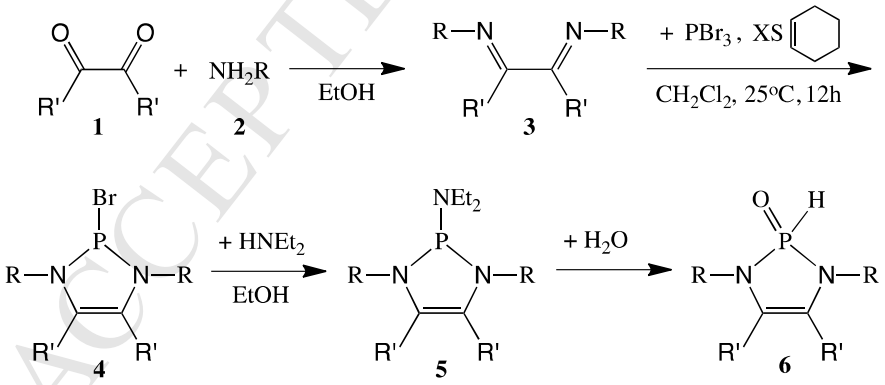
Herein we report the preparation and characterization of several unsaturated diaminophosphine oxides (**Ib**-type). Their capacities as efficient auxiliary ligands in palladium-catalyzed Suzuki-Miyaura cross-coupling reactions were investigated. Preliminary catalytic screening revealed that with 1,3-di-*tert*-butyl 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}).

Results and Discussion

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



a: R = ^{t}Bu, R' = H **c**: R = -2,6-$^{i}Pr_2C_6H_3$, R' = H **e**: R = 2,6-$^{i}Pr_2C_6H_3$, R' = Me
b: R = Cy, R' = H **d**: R = 2,4,6-$Me_3C_6H_2$, R' = H **f**: R = 2,4,6-$Me_3C_6H_2$, R' = H, R' = Me

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

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 Figure 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 π-electron density on the ring.

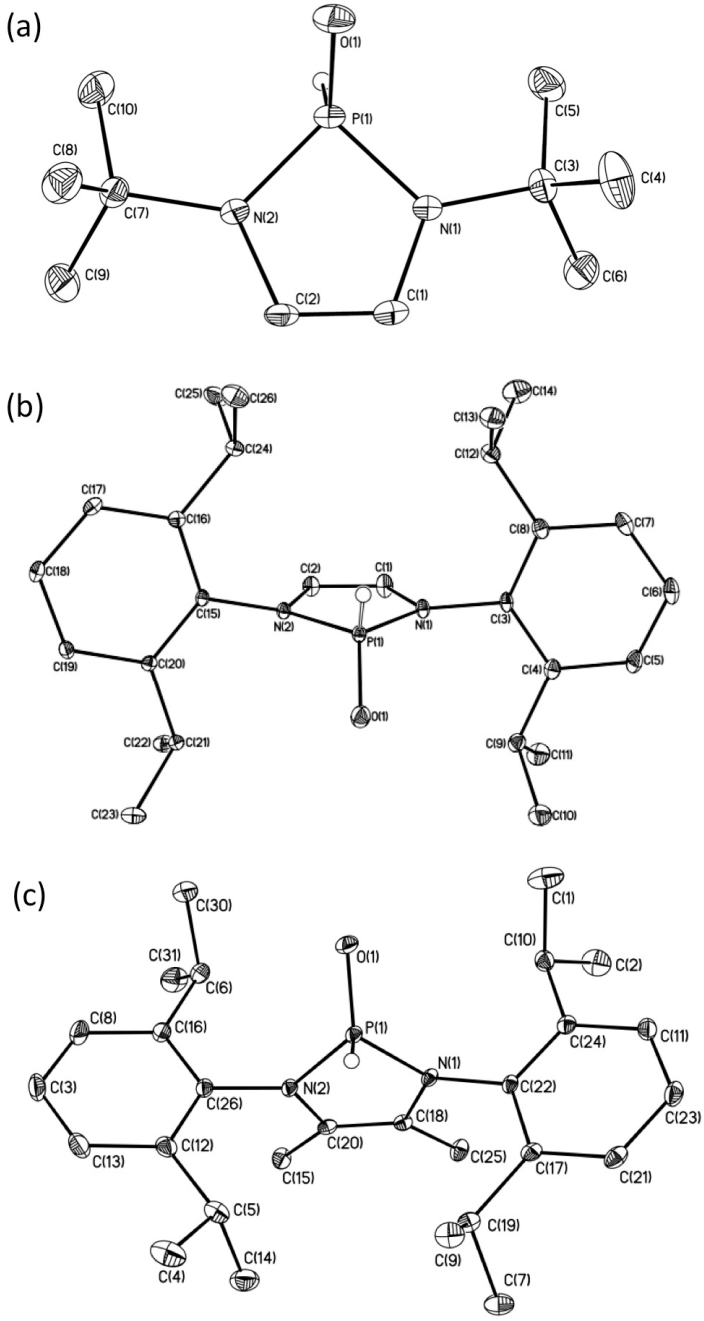


Figure 1. ORTEP plots of **6a**, **6c** and **6e**. Some hydrogen atoms are omitted for clarity.

*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 ^{31}P NMR, HASPO **6e** was reacted with $PdBr_2$ in THF at 25 °C for 2 hours. The disappearance of the large coupling constant of $J_{P\text{-}H}$ 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 Figure 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.

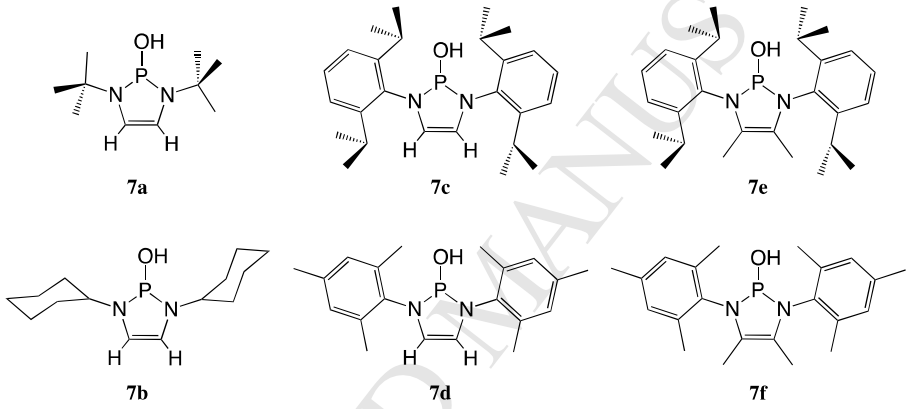
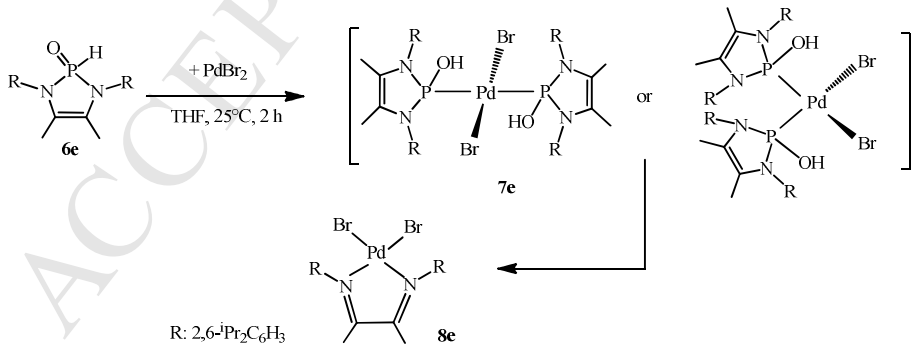


Diagram 2. Selected HAPA **7a**-**7f** (tautomers of pre-ligands HASPO **6a**-**6f**).



Scheme 3. The formation of **6e**-coordinated palladium complex **8e**.

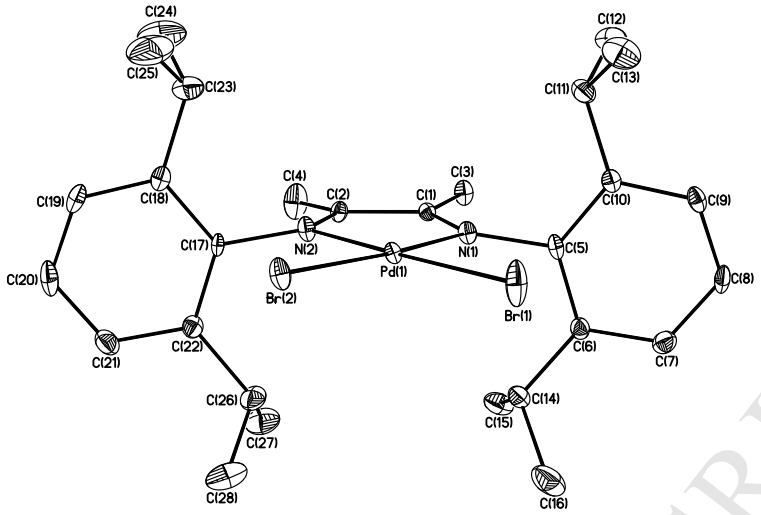


Figure 2. ORTEP diagram of **8e**. Hydrogen atoms are omitted for clarity.

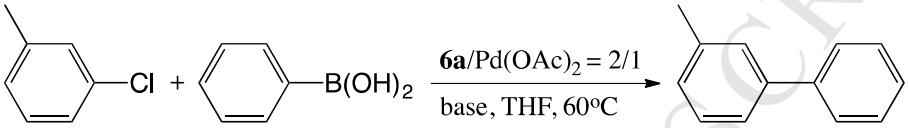
*Palladium-catalyzed Suzuki-Miyaura reactions using **6a-6f** as pre-ligands*

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 etc., had been screened. The designated procedure for the catalytic reaction is shown below. Into a 20 mL Schlenk tube was placed with 1.0 mmol of arylhalides, 1.5 mmol of phenylboronic acid, 2.0 mol% of palladium salt and 4.0 mol% of **6a-6f**, 1.0 mL of solvent, and 3.0 mmol of base. The operation was carried out under nitrogen atmosphere. The mixture was stirred at designated temperature and reaction time and then was followed by programmed work-up. Among all the six **6a-6f**, **6a** stands out as the best choice from the preliminary screening. It is consistent with the common observation that an adequately bulky ligand is favourable in Suzuki-Miyaura reactions for reductive elimination, one of the three major elementary steps in cross-coupling reactions. As known, arylchloride is less reactive than that of arylbromide due to the stronger C(sp^2)-Cl bond. The catalytic ability of **6a** in Suzuki-Miyaura reaction could be better discerned by using arylchlorides as reactant rathar than arylbromides. Therefore, **6a** is chosen as the ligand and arylchlorides as the halide sources for the optimization of reaction condition hereafter.

It was reported that rather low reactivity was observed in the absence of base for Suzuki-Miyaura reaction. The role played by base is probably the most ambiguous

and unpredictable one among all the factors that affect the catalytic efficiency.[39, 97-98] Thereby, the impact of employing different bases on the reaction yields was firstly investigated and the results are shown in Table 1. Among all the bases screened, it was found that KO^{t}Bu in THF is the most effective pair (Table 1, Entry 1); while other bases such as NaOH, Na_2CO_3, K_2CO_3, Cs_2CO_3 and K_3PO_4·nH_2O gave poor yields of product. As suspected, the cation of the base, besides its basicity, could be another key factor in this reaction with arylchlorides and using **6a** as ligand.

Table 1. Suzuki coupling reactions employing various bases[a].



Entry	Base	Conv.(%)[b][c]	Conv.(%)[b][d]
1	KO^{t}Bu	90	99
2	NaO^{t}Bu	43	46
3	KOH	-	42
4	NaOH	5	14
5	K_2CO_3	<5	11
6	Cs_2CO_3	5	9
7	Na_2CO_3	<5	<5
8	K_3PO_4·nH_2O	<5	<5

[a] Condition: 1.0 mmol 3-chlorotoluene, 1.5 mmol phenylboronic acid, 3.0 mmol base, 2 mL THF, and 2 mol % $Pd(OAc)_2$, [Pd]:**6a**=1:2, 60 ^oC; [b] Determined by NMR; [c] Reacted for 5 hours; [d] Reacted for 16 hours.

The solubility of substances and catalyst in a solvent is greatly affected by the polarity of it. As a result, a proper combination of solvent/base system is crucial to the ultimate performance of the catalytic reaction. As shown, the combination of KO^{t}Bu with THF leads to the best result (Table 2, Entry 1). In addition, the concentration of the reactant, by changing the amount of solvent, in fact affects the rate of the reaction. The more concentrated solution, the better performance it will be (Table 2, Entry 2). It was also found that higher temperature than 25 ^oC is required to reach its reasonably catalytic performance (Table 2, Entry 3). This could be a characteristic for loading

HASPO as auxiliary ligand because the HASPO-to-HAPA tautomerization is an endothermic process.

Table 2. Suzuki coupling reactions employing various solvents.[a]

Entry	Solvent	Volume (ml)	Temp (^{o}C)	Conv.(%) [b]
1	THF	2	60	85
2	THF	1	60	94
3	THF	1	25	<5
4	Toluene	2	60	78
5	1,4-dioxane	2	60	42

[a] Reaction condition is the same as in the footnote of Table 1 except using 3.0 mmol KO^{t}Bu as base and 3 hours for reaction; [b] Determined by NMR.

Subsequently, the performances of several commonly used palladium sources were screened for this reaction. As shown in Table 3, the best yield was obtained while using $Pd(OAc)_2$ as the palladium source and the ratio of **6a** to palladium salt is 2:1 (Table 3, Entries 1 & 3). It is consistent with the observations reported in the literature.[99] As known, $Pd(OAc)_2$ is more readily to be reduced to zero-valence in the presence of electron-rich phosphine than the halogenated palladium salt PdX_2 (Table 3, Entries 4-7).[95, 100-101] Unexpectedly, rather poor performance was observed for a zero-valence palladium source, $Pd_2(dba)_3$ (Table 3, Entry 8).

Table 3. Suzuki coupling reactions employing various Pd sources.[a]

Entry	Pd source	Pd : L	Time (hrs)	Conv.(%) [b]
1	$Pd(OAc)_2$	1 : 2	2	65
2	$Pd(OAc)_2$	1 : 1	2	48
3	$Pd(OAc)_2$	1 : 2	3	94
4	$Pd(COD)Cl_2$	1 : 2	2	<5
5	$PdCl_2$	1 : 2	3	<5
6	$PdBr_2$	1 : 2	3	<5
7	$[(\eta^3\text{-}C_3H_5)PdCl]_2$	1 : 2	2	5

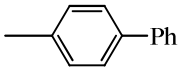
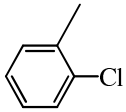
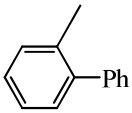
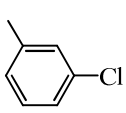
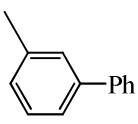
8	$Pd_2(dba)_3$	1 : 2	2	<5

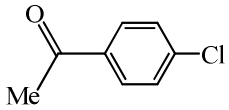
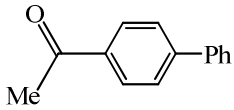
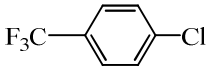
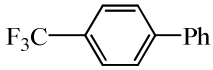
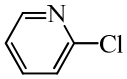
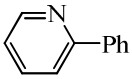
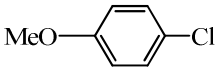
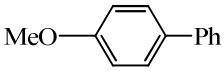
[a] Reaction condition is the same as in the footnote of Table 1 except for using different palladium sources; [b] Determined by NMR.

Further examination of the effect caused by substituent on arylhalides such as substituted arylchlorides and 2-chloropyridine were carried out (Table 4). The general observation in Suzuki-Miyaura reaction shows that a better conversion is achieved with aryl halides bearing an electron-withdrawing than an electron-donating group.[102] It is presumably held for the reaction while the oxidative addition process is the rate-determining-step. Nevertheless, other unanticipated factors might perturb this conclusion occasionally. As shown in Table 4, the catalytic performances did not obey this rule in a regular pattern as stated above. For the cases with electron-donating substituent, $-CH_3$, the best performance is found for the substituent with less steric hindrance (Entries 3 vs. 2). Relatively poor performance was observed for 1-(4-chlorophenyl)ethanone, substance with an electron-withdrawing group (Entry 4). By contrast, it performed rather effectively for 1-chloro-4-(trifluoromethyl)benzene (Entry 5). Generally, poor performance has been the result for using heterocyclic ring as halide source. Nevertheless, fair efficiency was observed for pyridyl case (Entry 6). Finally, 92 % in yield was observed for the electron-donating case of 1-chloro-4-methoxybenzene even after 24 hours in reaction (Entry 7).

In general, the performance of **6a** as a phosphine source in Suzuki-Miyaura coupling reactions for various aryl chlorides is better than that of its saturated counterpart from Ackermann's work.[84] The reactions using **7a** as a phosphine ligand took shorter time to reach better yields.

Table 4. Suzuki-Miyaura coupling reactions employing various aryl chlorides[a]

Entry	Aryl halide	Product	Time (h)	Yield(%)[b]
1			5	42
2			5	71
3			5	94

4			5	42
5			5	93
6			5	81
7			24	92

[a] Condition: 1.0 mmol arylchloride, 1.5 mmol phenylboronic acid, 3.0 mmol KO^{t}Bu, 1 mL THF, 2 mol % Pd source, [Pd]:**6c**=1:2, 60 ^{o}C; [b] Yield of isolated product.

For comparison, Suzuki-Miyaura coupling reaction for 4'-bromoacetophenone with phenylboronic acid was carried out employing selected diamines (**3e**-**3m**) and HASPOs (**6e**-**6f**). Preliminary results showed that HASPOs exhibited better catalytic efficiency than that of using diamines as ligands. It indicates that the active species in the reaction while using HASPO as pre-ligand could be different from the diamine-chelated palladium complex, although a crystal structure of this type of complex **8e** was obtained and determined from the reaction of **6e** with $PdBr_2$.

Computational Studies of electronic and steric properties

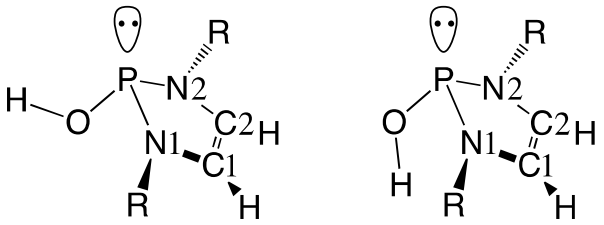
Density functional calculations (DFT)

DFT calculations were carried out to clarify the experimental observation that HAPA **7a** is superior to **7b**-**7f** as auxiliary ligand in the Suzuki-Miyaura cross-coupling reaction. Geometry optimization and frequency calculations were done with the B3LYP functional in conjugation with 6-311+(3df) for phosphorus and 6-311+(2d,p) for the other atoms. Optimized structures were confirmed to be a local minimum on the potential energy surface by all positive elements in their corresponding Hessian matrix.

*HASPO **6a**-**6f** and cis- and trans-rotamers of HAPA **7a**-**7f** and **7as***

Two rotamers of HAPA **7a**-**7f** were located on the potential energy surface during geometry optimization (Diagram 3: *cis*-rotamer **1** with -OH group pointing to the same side with phosphorus lone pair electrons, while that of *trans*-rotamer 2 points to the opposite side).[103] **7as** is the saturated HAPA counterpart of **7a**. The

relative energies of two rotamers for each HAPA **7a**-**7f** ($E = E(cis) - E(trans)$) and their corresponding Hirshfeld charges on phosphorus and two nitrogen atoms are listed in Table S1.



rotamer 1 **rotamer 2**

Diagram 3. Model molecular structures for two rotamers of unsaturated HAPA ligands.

As revealed, the rotamer **2** of HAPA **7a**-**7b**, is more stable than rotamer **1** by 1.02 and 0.63 kcal/mol, respectively. On the contrary, rotamer **1** of HAPA **7c**-**7f** is more stable by 0.60-1.10 kcal/mol. As shown in Table S1, molecular dipole moment of rotamer **2** is generally larger than rotamer **1** because of the orientation of -OH is *trans* to the lone pair (LP) of phosphorus (Diagram 3).

The Hirshfeld charge analysis shows that phosphorus atom in rotamer **1** (less positive) possesses more electron density than that in rotamer **2** (more positive). This is due to the better atomic orbital interaction between π-type atomic orbital of oxygen and σ- and π-type atomic orbitals of phosphorus in rotamer **1**, and therefore a better π-electron donating from hydroxyl group to the phosphorus atom (Table S2).[104] Additionally, the charge density on phosphorus of HAPA **7as** (0.258) is slightly larger than that of its unsaturated counterpart **7a** (0.274) Besides, all HASPO **6a**-**6f** pre-ligands are more stable than their HAPA **7a**-**7f** counterparts, which is in accordance with the previous experimental and computational observations.[105-107] With respect to rotamer 1 of **7a**-**7f**, the relative stabilized energies of **6a**-**6f** are 5.72, 5.24, 7.52, 5.97, 7.38 and 6.94 kcal/mol, respectively.

*Lone pair (LP) molecular orbital for HAPA **7a**-**7f***

Recently, Martin and Buono *et al.* investigated the σ-donating ability of acyclic HAPAs with HAPA-coordinated metalcarbonyls both by experimental and theoretical

means.[108] In their study, the LP-donating ability of dialkylphosphinous acids can actually outperform phosphines and N-heterocyclic carbenes. When two neutral saturate five-membered heterocyclic HAPAs are examined (i.e. O-P-O and N-P-N), the decreased LP-donating ability than their acyclic counterparts is observed based on the stretching frequency of metal-coordinated carbonyl ligands from DFT calculations.[109]

The HOMO and LP molecular orbitals of **7a**-**7b** and **7c**-**7f** are shown in Figure 3 and Figure 4, respectively. It was found LP molecular orbitals of **7a**-**7f** are not HOMO, which is in consistent with the Martin and Buono's computational results.[108] HOMOs of HAPA **7a**-**7f** are mostly consisted of π-type atomic orbitals from two nitrogen atoms (population > 0.13) and the two unsaturated alkenyl carbons (population > 0.21) on the five-membered ring.

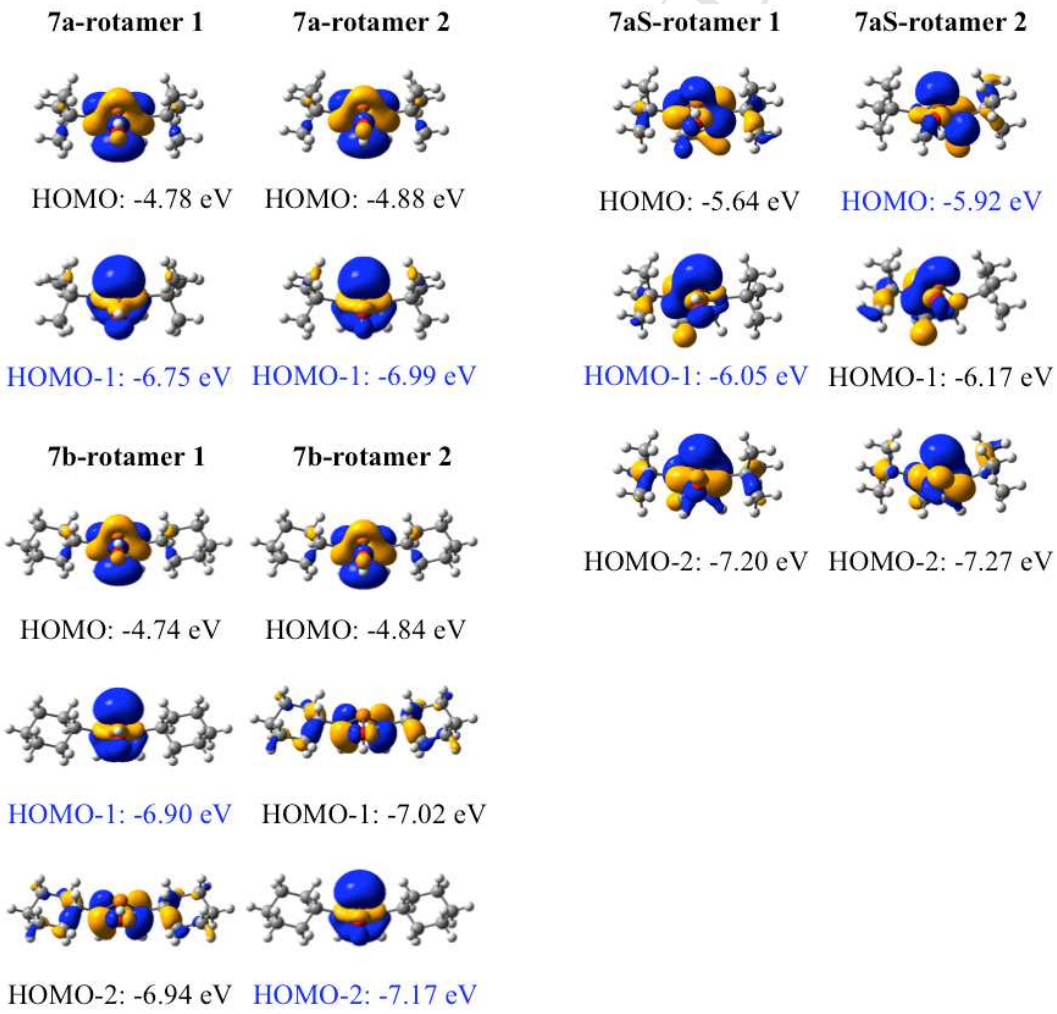
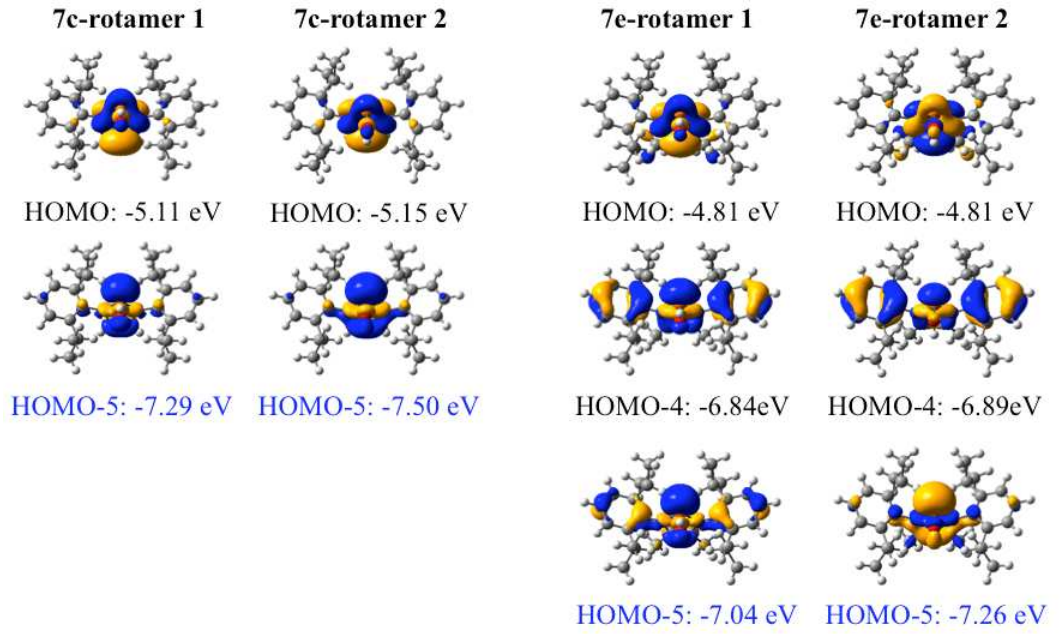


Figure 3. Selected occupied frontier molecular orbitals for two rotamers of **7a**, **7b** and **7as**. LP molecular orbitals are highlighted in blue.



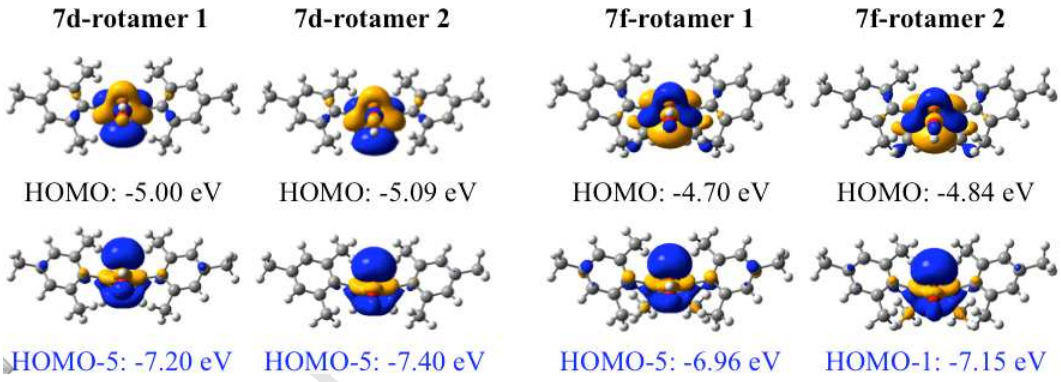


Figure 4. Selected occupied frontier molecular orbitals for two rotamers of **7c-7f**. LP molecular orbitals are highlighted in blue.

Levin had shown that phosphine with π-donating substituent has higher-lying LP orbital as a result of the lone pair-lone pair interaction between phosphorus atom and the substituent.[110] The LP molecular orbital energy of **7a-7f** is closely related to the directionality of -OH substituent because a better σ_n-π mixing between phosphorus and oxygen is observed in rotamer 1 of **7a-7f** (Table S2). In consistent with Levin's theoretical calculations, we found that the better P-O σ_n-π mixing in the higher lying the LP molecular orbital (Table S2). The *N*-alkyl substituted **7a-7b** have

LP orbitals lay at HOMO to HOMO-2 (Figure 3). LP orbital energies for HAPA **7a** are -6.75 eV (HOMO-1) in rotamer 1 and 6.99 eV (HOMO-1) in rotamer 2; for HAPA **7as** are -6.05 eV (HOMO-1) in rotamer1 and -5.92 eV (HOMO) in rotamer 2, respectively.

LP orbitals of **7c-7f** are lying even lower (HOMO-5). The low-lying LP orbitals of **7c-7f** corresponding nicely to the poor catalytic performance in Suzuki-Miyaura reactions as shown in our preliminary screening catalytic experiments, since the coordination of such phosphine ligands to soft transition metals are kinetically unfavourable. On the contrary, higher LP orbital of HOMO-1 in HAPA **7a** is the reason for its best catalytic performance among all six HAPA **7a-7f**. Although LP orbitals of **7c-7f** are very low-lying, we note that the anionic deprotonated form of **7c-7f**, i.e. monomeric $[P\text{-}O]^-$ or dimeric $[P\text{-}O^{\cdots}H^{\cdots}O\text{-}P]^-$ bi-dentate ligands,[111-112] could be a remedy and could have better performance in cross-coupling reactions.[108] The better P-O^- σ_n-π mixing can be expected in $[P\text{-}O]^-$ or dimeric $[P\text{-}O^{\cdots}H^{\cdots}O\text{-}P]^-$ because p-type atomic orbital energy on the negatively charged oxygen will be higher than that on the -OH group.[109] Hence, $[P\text{-}O]^-$ or dimeric $[P\text{-}O^{\cdots}H^{\cdots}O\text{-}P]^-$ could be equipped with higher LP molecular orbital.

Steric effects estimated with percent buried volume (%V_{bur})

Based on the definition of Clavier and Nolan,[113] the steric effect of phosphines quantified by percent buried volume (%V_{bur}) can be roughly classified into three categories when a putative metal is 2.28 Å away from phosphorus atom. It is regarded as sterically rather hindered ligand while %V_{bur} > 35.0 %; a middle or normal range for 35.0 % > %V_{bur} > 30.0 %; low steric effect for %V_{bur} < 30.0 %. Accordingly, $P(^tBu)_3$ locates at the lower limit of the large steric hindrance, while PCy_3 near the lower limit of middle range, respectively (Table S3). Note that $P(^tBu)_3$ and PCy_3 are two commonly used auxiliary phosphine ligands for Suzuki-Miyaura cross-coupling reactions.

HAPA **7c** and **7e** reveals significant steric hindrance (*%V_{bur}* > 42.0 %), much larger than $P(^tBu)_3$ and PCy_3. Although neutral **7d** (*%V_{bur}* ~ 34.0 %) and **7f** has similar quantified steric property to PCy_3 (*%V_{bur}* ~ 32.0 %), its LP orbital (HOMO-5) is too low-lying to be an effective ligand. The low catalytic performance for **7c** and **7e** as ligands can also be attributed to the same reason, while their high steric ranking could

be a merit for reductive elimination in the Suzuki-Miyaura catalytic cycle. On the contrary, the very low steric hindrance offered by **7b** ($\%V_{bur}$ ~ 24.0 %), could be one of the reasons for its lower catalytic performance than **7a** (i.e. LP orbital of **7b** lies in HOMO-1 of rotamer 1 and HOMO-2 of rotamer 2, respectively.)

Compound **7a** is the tautomer of pre-ligand **6a**, and is the best ligand for Suzuki-Miyaura reactions carried out in this study. This is due not only to HAPA **7a** ($\%V_{bur}$ ~ 32.0 %) has nearly identical steric effect as PCy_3 but also to it owns the highest-lying LP molecular orbital (i.e. HOMO-1) among **7a**-**7f**. Considering steric and electronic effects as a whole, it is rational to comment that employing **7a** as ligand shows the best catalytic yield in our screening tests. Model ligand, **7as**, is the saturated analogue of **7a**. Although **7as** may not be superior to **7a**, based on the previous two facts, we anticipate that **7as** could be as effective as **7a** in the Suzuki-Miyaura reactions at least.

Conclusion

In this study, six new HASPO **6a**-**6f** pre-ligands have been synthesized and characterized, and crystal structures for three of them (**6a**, **6c**, **6e)** have been well resolved. **6a**-**6f** can undergo tautomerization to **7a**-**7f** as genuine phosphine ligands. Diimine-coordinated (**3e**-coordinated) mono-palladium complex was obtained unexpectedly during the reaction of **6e** and $PdBr_2$. Moreover, attempting to synthesize **6c**-coordinated palladium complex was not successful. Instead, an intriguing di-palladium complex bridged by two phosphide- ligands was obtained. These two complexes were characterized by X-ray studies. In our preliminary screening of using **6a**-**6f** as pre-ligands in Suzuki-Miyaura cross-coupling reactions, only **6a** gave satisfactory catalytic performance. Therefore, further catalytic conditions were optimized for **6a**. The optimized catalytic conditions are summarized as the combination of **6a**/$Pd(OAc)_2$/KO^tBu/THF/60 ^oC. At room temperature, the poor catalytic yield could reflect that the chemical equilibrium of HASPO-to-PA tautomerization favours HASPO.

The effectiveness of **6a** and disability of **6b**-**6f** as pre-ligands are fully supported by DFT studies together with the quantified steric property. Based on the DFT calculations, the highest occupied molecular orbital of **7a**-**7c** is not LP molecular orbital. Rather, LP orbital is HOMO-1 or HOMO-2 for **7a**-**7b** and HOMO-5 for **7c**-**7f**, respectively. Notably, the steric property quantified by $\%V_{bur}$ reveals that **7a**

(tautomer of **6a**) is as bulky as PCy_3 (a useful ligand for Suzuki-Miyaura cross-coupling reactions). The higher-lying LP orbital together with adequate steric property provided by **7a** account for the satisfactory catalytic performance. To improve the catalytic performance, we suggest employing the anionic deprotonated form of **7c-7f** (i.e. monomeric $[P\text{-}O]^-$ or dimeric bi-dentate $[P\text{-}O^{\cdots}H^{\cdots}O\text{-}P]^-$ as ligands for future development of HASPO). It is because the anionic form would result in higher-lying LP molecular orbitals, which is essential for phosphines as effective auxiliary ligands in catalytic reactions, *via* better σ_n-π mixing of $P\text{-}O^-$.

Experimental Section

General Procedures

All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques or in a nitrogen-flushed glove box. Freshly distilled solvents were used. All processes of separations of the products were performed by Centrifugal Thin Layer Chromatography (CTLC, Chromatotron, Harrison model 8924) or column chromatography. GC-MS analysis was performed on an Agilent 5890 gas chromatograph (Restek Rtx-5MS fused silica capillary column: 30m, 0.25mm, 0.5μm) with an Agilent® 5972 mass selective detector. Routine ^1H NMR spectra were recorded on a Varian-400 spectrometer at 400.441 MHz. The chemical shifts are reported in ppm relative to internal standards TMS ($\delta = 0.0$). ^{31}P and ^{13}C NMR spectra were recorded at 162.1 and 100.7 MHz, respectively. The chemical shifts for the former and the latter are reported in ppm relative to internal standards H_3PO_4 ($\delta = 0.0$) and $CHCl_3$ ($\delta = 77$), respectively. Mass spectra were recorded on JOEL JMS-SX/SX 102A GC/MS/MS spectrometer. Electrospray ionization-high resolution mass spectra (ESI-HRMS) were recorded on a Finnigan/Thermo Quest Mat 95 XL mass spectrometer.

*Synthesis and characterization of **3a-3f** and **6a-6f***

Procedures for the preparations of **3a-3f** were modified from literature.[114] In the same measure, preparations of **6a-6f** were followed the modified procedures of reports elsewhere.[52, 115-116]

*Synthesis and characterization of **3a** and **3b***

Similar procedures as the previous one for the preparation of 3a and 3b were carried out. Into a 250 mL round-bottomed flask was placed 70.0 mmol (7.42 ml) tert-butylamine or tert-cyclohexylamine (100.0 mmol, 11.45 ml) in 50 mL deionized water. In ice bath, then, the solution of Glyoxal (4.01 ml, 40 wt % in H_2O, 35.0 mmol or 5.73 g, 40 wt % in H_2O, 50.0 mmol) was added slowly to the flask. White participation was observed in the bottom of the flask. The solution was stirred for 45 minutes at room temperature. It was then filtered through frit at 0 °C The collected product was washed by ethanol/H_2O mixed solution at 0 °C. A white solid **3a** (5.01 g, 29.79 mmol, 85 %) or **3b** (10.24 g, 46.50 mmol, 93 %) was obtained after solvent was removed by vacuum.

‡ *Selected spectroscopic data for **3a***, ^{1}H NMR ($CDCl_3$, δ/ppm): 1.22 (s, 18 H, CH_3), 7.90 (s, 2H, NCH); ^{13}C NMR ($CDCl_3$, δ/ppm): 157.8 (N-C), 58.1 (*ipso*-C_{tBu}), 29.3 (C_{tBu}).

‡ *Selected spectroscopic data for **3b***, ^{1}H NMR ($CDCl_3$, δ/ppm): 7.93 (s, 2 H, NCH), 3.15 (m, 2 H, NCH), 1.19-1.82 (m, 10H, CH_2); ^{13}C NMR ($CDCl_3$, δ/ppm): 160.0 (N-C), 24.5, 25.4, 33.9, 69.4 (C_{cy}).

*Synthesis and characterization of **3c** and **3d***

Into a 500 mL round-bottomed flask was placed 60.0 mmol (10.63 g) 2,6-diisopropylaniline (or 60.0 mmol 2,4,6-trimethylaniline) in 130 ml ethanol. Then, the solution of Glyoxal (4.35 g, 40 wt % in H_2O, 30.0 mmol) was added slowly to the flask which was placed in ice bath beforehand. The colour of solution changed to golden-yellow. It was then refluxed for 12 hours before cooling down to room temperature. The volume of the solution was then reduced to 100 mL under vacuum. Subsequently, the solution was filtered through frit at 0 °C. The collected product was washed with ethanol/H_2O mixed solution at 0 °C. A golden-yellow solid **3c** (6.89 g, 18.31 mmol, 61 %) or **3d** (6.87 g, 23.51 mmol, 47 %) was obtained after all solvent was removed by vacuum.

‡ *Selected spectroscopic data for **3c***, ^{1}H NMR ($CDCl_3$, δ/ppm): 1.22 (d, J_{H-H}=7.1 Hz, 24H, $CH(CH_3)_2$), 2.96 (m, J_{H-H}=6.7 Hz, 4H, $CH(CH_3)_2$), 7.20 (m, 6H, overlapping C_6H_3), 8.12 (s, 2H, NCH); ^{13}C NMR ($CDCl_3$, δ/ppm): 163.0 (N-C), 147.9 (*ipso*-C_{Mes}), 136.6 (*o*-C_{Mes}), 125.0 (*m*-C_{Mes}), 123.1 (*p*-C_{Mes}), 27.9 (^{i}Pr CH), 23.3 (^{i}Pr CH_3).

‡ *Selected spectroscopic data for* ***3d***, ^{1}H NMR ($CDCl_3$, δ/ppm): 2.15 (s, 12 H, 2,6-$(CH_3)_2$-C_6H_2), 2.29 (s, 6H, 4-CH_3-C_6H_2), 6.90 (s, 4H, C_6H_2), 8.09 (s, 2H, NCH); ^{13}C NMR ($CDCl_3$, δ/ppm): 163.3 (N-C), 147.3 (*ipso*-C_{Mes}), 126.4 (*o*-C_{Mes}), 128.9 (*m*-C_{Mes}), 134.1 (*p*-C_{Mes}), 18.1 (*o*-CH_3), 20.6 (*p*-CH_3).

Synthesis and characterization of ***3e-3f***

Into a 100 mL round-bottomed flask was placed 120.0 mmol (22.9 mL) 2,6-diisopropylaniline in 50 ml methanol. Then, formic acid (6.9 mL) was added slowly. The colour of solution changed to pale coffee. It was then added 2,3-butanedione (60.0 mmol, 5.32 mL) and stirred for 0.5~1.0 hour till yellow participation was observed. Gold-yellow solid participate was ready to be isolated after 2 hours of stirring. Firstly, the solution was cooled to 0 °C and filtered through frit at that temperature. The solvent was removed completely under vacuum. The collected product was washed with methanol/H_2O mixed solution at 0 °C. A golden-yellow solid **3e** (13.68 g, 56 %) was obtained after all solvent was removed by vacuum. Similar procedures were taken for the preparation of **3f**. The yield of the yellow product of **3f** is 58 % (11.15 g).

‡ *Selected spectroscopic data for* ***3e***, ^{1}H NMR ($CDCl_3$, δ/ppm): 1.18 (d, J = 7.2 Hz, 24H), 2.71 (septet, J=6.4 Hz, 4H), 7.17 (m, 6H), 2.07 (s, 6H); ^{13}C NMR ($CDCl_3$, δ/ppm): 16.57, 22.69, 22.97, 28.47, 122.97, 123.71, 135.04, 146.13, 168.16.

‡ *Selected spectroscopic data for* ***3f***, ^{1}H NMR ($CDCl_3$, δ/ppm): 1.98 (s, 12H), 2.00 (s, 6H), 2.27 (s, 6H), 6.87 (4H); ^{13}C NMR ($CDCl_3$, δ/ppm): 15.82, 17.79, 20.78, 124.55, 128.64, 132.41, 145.95, 168.37.

Synthesis and characterization of ***6a-6f***

A 100 mL round-bottomed flask contained 2 mmol of corresponding diimine **3a**-**3f**, 5 mL dichloromethane and 6 mmol cyclohexene. Another flask in Glove box was placed with 2 mmol PBr_3 and 5 mL dichloromethane; it was then placed in ice bath till reached 0° C. The solution of the first flask was transferred slowly into the second one and stirred at room temperature for 12 hours. Presumably, **4a**-**4f** were formed by judging from their large down-fielded shift in ^{31}P NMR, ranges from 170~200 ppm around. Without further purification, 1.00 molar equivalent of $HNEt_2$ was subsequently added into the flask. The color of solution changed to yellow. Then,

the solvent was removed completely after stirring at room temperature for 2 hours. Presumably, the corresponding **5a**-**5f** were formed. The residue was extracted twice by ethylacetate and separated by column chromatography. The hydrolyzed products (**6a**, **6b**, **6c**, and **6d**) are in the yield of 39 % for **6a** (0.17 g, 0.78 mmol), 30 % for **6b** (0.16 g, 0.60 mmol), 29 % for **6c** (0.25 g, 0.59 mmol), 35 % for **6d** (0.24 g, 0.70 mmol), 35 % for **6e** (1.27 g, 2.22 mmol), 30 % for **6f** (0.88 g, 2.39 mmol).

‡ *Selected spectroscopic data for* ***6a***, ^{1}H NMR ($CDCl_3$, δ/ppm): 8.67 (d, J_{P-H}=648.0 Hz, 1H), 7.34-7.18 (m, 6H), 5.93 (dd, 2H), 3.68 (m, J_{H-H}=6.7 Hz, 1H), 3.18 (m, J_{H-H}=6.7 Hz, 2H), 1.34 (d, J_{H-H}=6.3 Hz, 6H), 1.27 (d, J_{H-H}=7.1 Hz, 6H), 1.25 (d, J_{H-H}=7.1 Hz, 6H), 1.24 (d, J_{H-H}=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, δ/ppm): 117.1/117.2 (N-C), 123.8/124.5/128.9/132.3/147.9/149.8 (arene), 28.3/28.6 (^{i}Pr CH), 24.0/24.0/24.9/25.2 (^{i}Pr CH_3); ^{31}P NMR ($CDCl_3$, δ/ppm): 4.8 ppm (J_{P-H} = 648.0 Hz).

‡ *Selected spectroscopic data for* ***6b***, ^{1}H NMR ($CDCl_3$, δ/ppm): 2.29/2.27 (s, 12H, *o*-CH_3), 2.4 (s, 6H, *p*-CH_3), 6.92/6.96 (s, 4H, C_6H_2), 5.90 (d, J_{H-H}=16.39, 2H, NCH), 8.73 (d, 1H, J_{P-H} = 649.2, PH); ^{13}C NMR ($CDCl_3$, δ/ppm): 115.7/115.9 (N-C), 128.9/129.6/132.4/136.8/138.0/139.0 (arene), 18.3/18.5 (*o*-CH_3), 20.9 (*p*-CH_3); ^{31}P NMR ($CDCl_3$, δ/ppm): 1.3 ppm (J_{P-H} = 649.2 Hz).

‡ *Selected spectroscopic data for* ***6c***, ^{1}H NMR ($CDCl_3$, δ/ppm): 1.43 (s, 18 H, CH_3), 5.95 (dd, J_{H-H}=16.01, 2H, NCH), 8.60 (d, 1H, J_{P-H}=647.91, PH); ^{13}C NMR ($CDCl_3$, δ/ppm): 110.2/110.3 (N-C), 53.3 (*ipso*-C_{tBu}), 29.9 (C_{tBu}); ^{31}P NMR ($CDCl_3$, δ/ppm): 4.0 ppm (J_{P-H} = 647.91 Hz).

‡ *Selected spectroscopic data for* ***6d***, ^{1}H NMR ($CDCl_3$, δ/ppm): 5.84 (dd, 2 H, NCH), 1.07-2.01 (m, 11 H, C_6H_{11}), 8.64 (d, 1H, J_{P-H}=640.4, PH); ^{13}C NMR ($CDCl_3$, δ/ppm): 111.1/111.2 (N-C), 25.5/33.2/33.9/54.5 (C_{cy}); ^{31}P NMR ($CDCl_3$, δ/ppm): 6.1 ppm (J_{P-H} = 640.4 Hz).

‡ *Selected spectroscopic data for* ***6e***, ^{1}H NMR ($CDCl_3$, δ/ppm): 1.24 (d, J = 6.80, 12H), 1.25 (d, J = 7.20, 6H), 1.61 (s, 6H), 3.16 (septet, 2H), 3.55 (septet, 2H), 7.18 (d, J = 7.60, 2H), 7.25 (d, J = 8.39, 2H), 7.35 (t, 2H), 8.54 (d, J = 635.2, 1H); ^{13}C NMR ($CDCl_3$, δ/ppm): 11.07, 24.21, 24.31, 25.09, 25.27, 28.20, 28.37, 117.48, 117.59, 123.79, 124.58, 128.82, 130.37, 148.53, 150.80; ^{31}P NMR ($CDCl_3$, δ/ppm): 5.23 ppm, J_{P-H} = 635.2 Hz.

‡ *Selected spectroscopic data for* ***6f***, ^{1}H NMR ($CDCl_3$, δ/ppm): 1.57 (s, 6H), 2.21 (s, 6H), 2.29 (s, 6H), 2.43 (s, 6H), 6.90 (s, 2H), 6.95 (s, 2H), 8.57 (d, J = 637.22, 1H); ^{13}C NMR ($CDCl_3$, δ/ppm): 10.63, 18.25, 18.95, 20.98, 116.53, 116.65, 128.86,

129.52, 130.88, 137.61, 137.78, 140.10; ^{31}P NMR ($CDCl_3$, δ/ppm): 0.57 ppm, J_{P-H} = 637.22 Hz.

General procedure for the Suzuki-Miyaura cross-coupling reactions

Suzuki-Miyaura cross-coupling reactions were performed according to the following procedures. The four reactants, palladium source, ligand, boronic acid and base, were placed in a suitable oven-dried Schlenk flask. It was evacuated for 0.5 hour and backfilled with nitrogen gas before adding solvent and aryl halide through a rubber septum. The aryl halides being solids at room temperature were added prior to the evacuation/backfill cycle. The flask was sealed with a rubber septum and the solution was stirred at the required temperature for designated hours. Then, the reaction mixture was diluted with ethyl acetate (3 mL) and the cooled solution poured into a separatory funnel. The mixture was washed with aqueous NaOH (1.0 M, 5 mL) and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layer were washed with brine and dried with anhydrous magnesium sulfate. The dried organic layer was concentrated *in vacuo*. The residue was purified by column chromatography to give the desired product.

X-ray crystallographic studies

Suitable crystals of **6a**, **6c**, **6e**, and **8e** were sealed in thin-walled glass capillaries under nitrogen atmosphere and mounted on a Bruker AXS SMART 1000 diffractometer. Intensity data were collected in 1350 frames with increasing ω (width of 0.3° per frame). The absorption correction was based on the symmetry equivalent reflections using SADABS program. The space group determination was based on a check of the Laue symmetry and systematic absences, and was confirmed using the structure solution. The structure was solved by direct methods using a SHELXTL package.[117] All non-H atoms were located from successive Fourier maps and hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H atoms.[118] Crystallographic data for the structural analysis have been deposited in the Cambridge Crystallographic Data Center, CCDC no. 900104, 900105, 900106, and 900107 for **6a**, **6c**, **6e**, and **8e**, respectively.

Computational Details

All calculations were performed with *Gaussian 09* quantum-chemistry packages.[119] Geometry optimizations (*Gaussian* keyword: opt) were carried out with the B3LYP density functional in conjugation with 6-311+(2d,p) for oxygen, nitrogen, carbon and hydrogen atoms and 6-311+(3df) for phosphorus atom. All optimized geometries were confirmed to be local minima by frequency calculations (*Gaussian* keyword: freq=noraman). Hirshfeld charge analysis was used to analyse the population of electron density (*Gaussian* keyword: pop=hirshfeld).[120] In addition, orbital analysis was done to identify the atomic orbital contributions to HOMO and LP molecular orbitals (*Gaussian* keyword: pop=(orbitals,threshorbitals=3)). Contributions from atomic orbitals greater than 3 % will be printed out, and the threshold value is adequate for our purposes.

Percent Buries Volume (%V_{bur})

Due to the success of the percent buried volume (%V_{bur}) in addressing the steric hindrance of NHC and phosphine ligands,[113, 121] we employed this approach to access the bulkiness of the HAPA ligands for qualitative mutual comparison. Cartesian coordinates of HAPA are obtained from the DFT-optimized geometries. Noteworthy, %V_{bur}s are linearly proportional to the values estimated with the definition of Tolman cone angle for commonly used phosphine ligands.[113] Samb*V*ca is a web application for such purpose established by Cavallo *et al.*[122-123] %V_{bur} is estimated from the percent ratio between the ligand occupied space and the sum of ligand unoccupied free space and ligand occupied space in a hemisphere centered on a putative metal center (TM) (sphere radius is fixed as 3.5 Å). In our study, the TM-Lignad bond lengths were set to 2.00 and 2.28 Å, respectively, along the axis including phosphorus and the center of the three atoms (N, N and O) bonded to phosphorus. Hydrogen atoms are excluded in our calculations. More computational details regarding how to estimate %V_{bur} can be found in the original paper and the Samb*V*ca website.

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Appendix A.

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Highlights

- Several di-substituted diimines and heteroatom-substituted unsaturated secondary phosphine oxides (HASPO pre-ligands) have been prepared and characterized.
- Four crystal structures were presented.
- Computational studies were pursued to evaluate the relative effectiveness of heteroatom-substituted phosphinous acids (HAPAs), which are in genuine ligand format of their corresponding HASPOs, as auxiliary ligands in Suzuki reactions.
- Pre-ligand of HASPO **6a**/ligand of HAPA **7a** was found to give satisfactory catalytic performances in cross-coupling reactions.