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Preparations of Saturated N-P-N Type Secondary Phosphine Oxides and their Applications in Cross-Coupling Reactions

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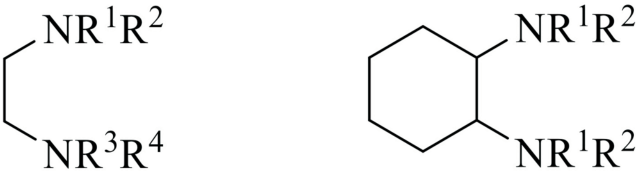
A series of cyclohexane-1,2-diamine (**3a**-**3d**) and benzene-1,2-diamine derivatives (**3e**-**3h**) were prepared. Followed by hydrolysis, the reaction of **3a**-**3c** with PCl_3 successfully led to the formation of corresponding metastable saturated heteroatom-substituted secondary phosphine oxides (HASPO **4a**-**4c**), a tautomer of the saturated heteroatom-substituted phosphinous acid (HAPA). Whereas ambient-stable diamine-coordinated palladium complexes were obtained, HAPA-coordinated palladium complexes were not successfully synthesized. The molecular structures of HASPO **4c**, **$Pd(OAc)_2$(3a)**, **$PdBr_2$(3b)** and **$Pd(OAc)_2$(3c)** and **$[Cu(NO_3)(3d)^+][NO_3^-]$** were determined by single-crystal X-ray diffraction method. Catalysis of *in-situ* Suzuki-Miyaura cross-coupling reactions for aryl bromides and phenylboronic acid using diamine **3a** as ancillary ligand showed that the optimized reaction condition at 60 °C is the combination of 2 mmol% **3a**/3.0 mmol KOH/1.0 mL 1,4-dioxane /1 mmol% $Pd(OAc)_2$. Moreover, moderate reactivity was observed when using aryl chlorides as substrates (supporting information). When diamine **3d** was employed in Heck reaction, good tolerance of functional groups of aryl bromides were observed while using 4-bromoanisole and styrene as substrates. The optimized condition for Heck reaction at 100 °C is 3 mmol% **3d**/3.0 mmol CsF/1.0 mL toluene/3 mmol% $Pd(OAc)_2$. In general, cyclohexane-1,2- diamine derivatives exhibited better catalytic properties than those of benzene-1,2-diamines.

Keywords: 1,2-diamines; Secondary phosphine oxides; Suzuki reactions; Heck reactions.

INTRODUCTION

Palladium-catalyzed cross-coupling reactions such as Suzuki-Miyaura and Heck reactions provide chemists with readily accessible toolkits to make carbon-carbon bond under mild conditions. The central part of cross-coupling methodology lies in the linking of an electropositive carbon moiety with an electronegative carbon or heteroatom fragment (e.g. aryl halide with arylboronic acid for Suzuki-Miyaura reaction). The first literature addressing Suzuki-Miyaura and Heck catalytic cross-coupling reactions can be traced back to 1979[1,2] and 1971[3]-1972,[4] respectively. Among all the methods of C-C bond formation, Suzuki-Miyaura cross-coupling reaction is regarded as one of the most frequently used tool.[5-7] For Heck reaction, the construction of new C-C single bond between organic halide/triflate and olefin can be accomplished even at room temperature.[8-10]

The progresses of Suzuki-Miyaura and Heck reactions heavily rely on the development of ancillary ligands.[11] Trialkyl or aryl phosphines have long been the ligands of choice due to their readily tunable electronic and steric effects through alternating the electron-withdrawing/donating substituents and the steric property ushered by the three substituents.[12-14] In addition to phosphines, 1,2-diaminoethane derivatives represent a series of well-known bidentate ligands, which are inexpensive, easily accessible, environmentally benign and substituent-tunable (Figure 1). Applications of 1,2-diaminoethane-coordinated copper complexes to catalyze coupling reactions between aryl halides and amines were reported with good efficiencies by Buchwald *et al.*[15-19]



$R^1,R^2,R^3,R^4 = H, Me, Et, Bu, {}^iPr$

Fig. 1. Acyclic and cyclic 1,2-diaminoethane derivatives.

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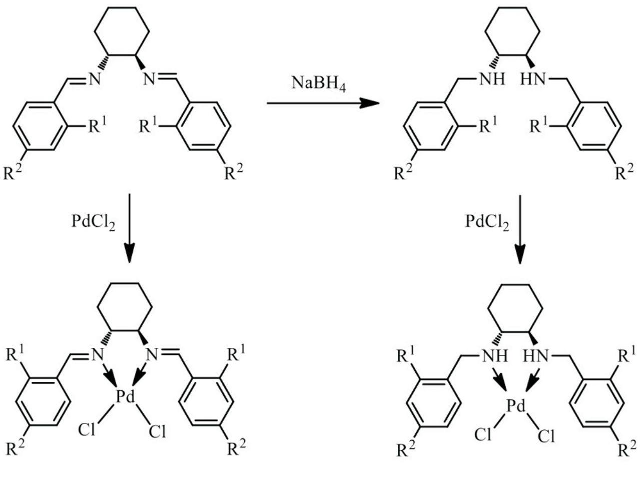
In Suzuki-Miyaura or Heck cross-coupling reactions, the use of diamine[20-25] or diimine[26-29] as ancillary ligands have been reported. In most cases, elevated temperature is required to achieve high catalytic yield. For Suzuki-Miyaura cross-coupling to be efficiently carried out at room temperature, electron-donating groups should be functionalized on 1,4-diazabutadiene.[29] Recently, palladium complexes chelated by cyclic 1,2-diaminoethane and 1,2-diiminoethane derivatives with benzyl substituents on nitrogen atoms were employed as pre-catalysts in palladium-catalyzed Suzuki-Miyaura cross-coupling reactions with fair efficiencies by Franzén et al. (Scheme 1).[22,30] It was found that the catalytic performance of diamines are generally better than that of diimines. Nevertheless, it remains plenty of room for improvement in this system since harsh condition, high reaction temperature and long reaction hours (i.e. 120 °C and 24 hrs), is typically required.

Scheme 1 Cyclic 1,2-diaminoethane and 1,2-diiminoethane derivatives chelated palladium complexes

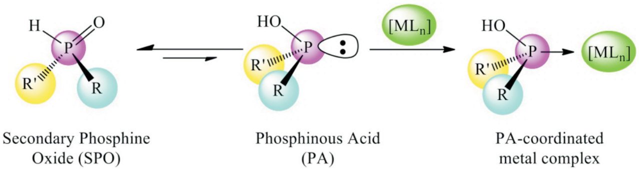


R^1, R^2 = H, OH, NO_2, OMe, CF_3, F.

Utilizing the molecular backbone of diamine[31,32] or diimine,[33-36] the synthetic protocols of heteroatom-substituted N-P-N type secondary phosphine oxides (HASPO) or *saturated* diaminochlorophosphane/*unsaturated* diaminochlorophospholene (HASPO precursor) have been established. A series of N-P-N/O-P-O type HASPO were shown in Figure 2.[37] By combining *tert*-butyl substituted N-P-N type SPO with $Pd(dba)_2$ as the catalytic system, good performances were observed in Suzuki-Miyaura reaction as well as in amination reaction even with less reactive aryl chloride.[31] Furthermore, Ackermann et al. firstly applied saturated O-P-O type HASPO to Kumada-Corriu reaction for inactivated aryl heteroaryl tosylates.[38] Asymmetric HASPO has also been synthesized and applied to asymmetric catalytic reactions.[39]

Penta-valent secondary phosphine oxide (R'R"PH (=O), SPO) is the tautomer of tri-valent phosphinous acid (R'R"POH, PA).[40] The latter can be used as a coordinating ligand via its lone-pair electrons. SPO-to-PA tautomerization is a chemical equilibrium normally favorable to the SPO form.[41] It can be balanced to PA tautomer in the presence of transition-metal fragment (Scheme 2).[42] SPO behaves as pre-ligand in a catalytic reaction,[39] and one merit of employing it lies in its air- and moisture-stability.[32,37,43-48] Li et al. firstly showed that air-stable SPO ($R_2P(O)H$: R = -*t*Bu) is an efficient pre-ligand for C-C, C-N and C-S cross-coupling bond formation for inactivated aryl chlorides, aryl bromides, olefins, amines, and thiols, given that elevated temperature is normally required.[47-49]

Scheme 2 The tautomerization of phosphinous acid and its coordinated metal complex



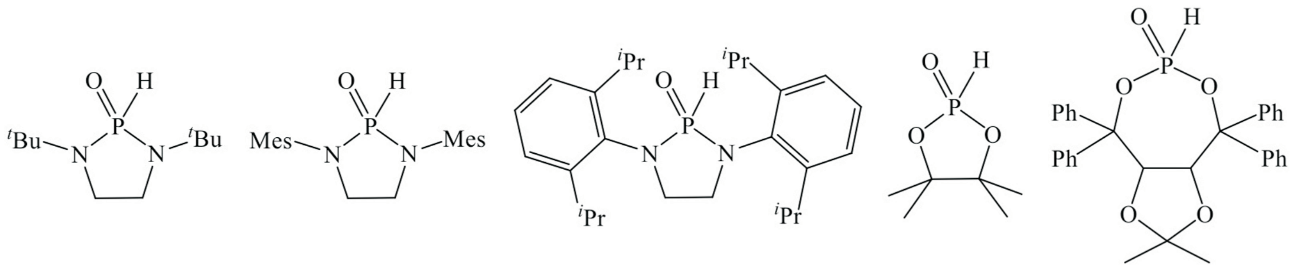
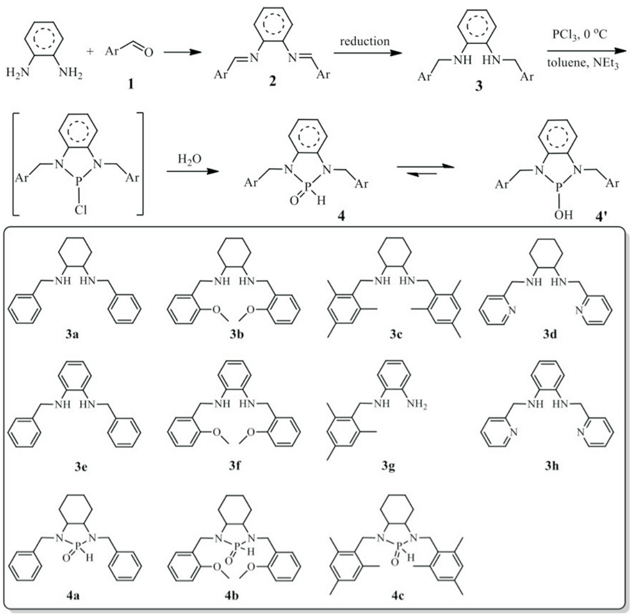


Fig. 2. Selected heteroatom-substituted secondary phosphine oxides (HASPO) from the literature.[31,37,38]

In this study, we explored the use of diamines as precursors to develop a series of saturated HASPO preligands. The capacities of saturated/unsaturated cyclic diamines and the given HASPOs as ligands for Suzuki-Miyaura and Heck reactions were subsequently investigated. Attempts to synthesize saturated HAPA-coordinated palladium complexes were made but the diamine-coordinated complexes were obtained. Therefore, the coordination chemistry of these diamine ligands toward palladium and copper sources was further investigated. Finally, the optimized reaction conditions for *in-situ* Suzuki-Miyaura and Heck cross-coupling catalytic reactions were screened for diamine ligands.

Scheme 3 Preparation of cyclic diamines (**3a-3h**) and heteroatom substituted secondary phosphine oxides (HASPO **4a-4c**). See Ref. 30 for the detail of the preparations of **3a** and **3b**



RESULTS AND DISCUSSION

Preparation of cyclic diamines (3a-3h) and saturated heteroatom-substituted secondary phosphine oxides (HASPO 4a-4c)

Firstly, diimines (**2a-2h**) were prepared in good yields from the reaction of cyclohexane-1,2-diamines or benzene-1,2-diamines with two molar equivalents of the corresponding benzaldehyde or picolinaldehyde (for the synthesis of **3h**) (Scheme 3). The reactions were carried out at refluxed MeOH for 30 minutes. At 25 °C, 2.1 molar equivalents of $NaBH_4$ were added to the solution except in the cases of **3e** and **3f** ($LiAlH_4$ was used, refluxed at THF for 12 hours). Then, the reaction mixture was refluxed for another 15 minutes till the cease of released gas. Subsequently, the mixture was quenched by water and extracted by CH_2Cl_2. Purified diamines (**3a-3f**) were collected after column chromatography. Note here, in **3g** only one amino group was functionalized presumably due to severer steric hindrance between the two bulky substituents inherent to the structural rigidity of planar benzene-1,2-diamine. Further reactions of **3a-3c** with PCl_3 in toluene and the presence of NEt_3 at 0 °C for 3 hours presumably led to the formation of precursors, 2-chloro-1,3,2-diazaphospholene.

The targeted saturated heteroatom-substituted secondary phosphine oxides (HASPO **4a-4c**) were obtained after the hydrolysis of the corresponding **3a-3c** and thereafter workup (Scheme 3). Nevertheless, our attempts to synthesize unsaturated HASPO **4e** from benzene-1,2-diamine **3e** were not successful due to its highly unstable nature. It decomposed within 15 minutes at ambient temperature after workup. Hence, no further attempts for the synthesis of HASPO from the benzene-1,2-diamines **3f-3h** were pursued. In addition to the structural rigidity of benzene-1,2-diamine, the high chemical instability of (benzene-1,2-diamine)-based unsaturated HASPO with respect to the metastability of (cyclohexane-1,2-diamine)-based saturated HASPO will be addressed in more details.

The structure of **4c** was determined by X-ray diffraction method and was depicted in Figure 3. The bond length of P(1)-O(1) is 1.605(4) Å, a typical double bond. The atoms, P(1), N(1), C(1), C(6), N(2), in the five-membered ring are not co-planar. Rather, the shape is more like a cyclopentane. Lone-pair electrons on the two nitrogen atoms are pointing to the opposite directions with respect to the five-membered ring. In the crystal structure of **4c**, two substituents on nitrogen atoms have the potential to create severe steric hindrance when phosphinous acid HAPA **4c**' coordinates to transition metal fragments.

Several attempts to prepare saturated HAPA-coordinated palladium complex were unsuccessful, and the followed X-ray structural determination of these reaction products were resolved as diamine-coordinated complexes. Initially, monitored closely by ^{31}P NMR, the reaction of HASPO 4b with $PdBr_2$ in THF at 60 °C was carried out for 12 hours (Scheme 4). The disappearance of characteristic $J_{P\text{-}H}$ might indicate the conversion of HASPO **4b** to its corresponding HAPA **4b'**, and then to **4b'**-coordinated palla-

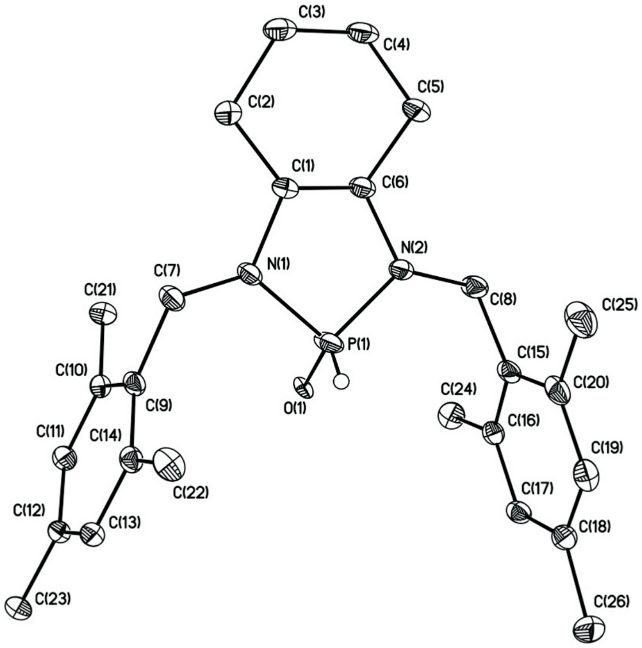
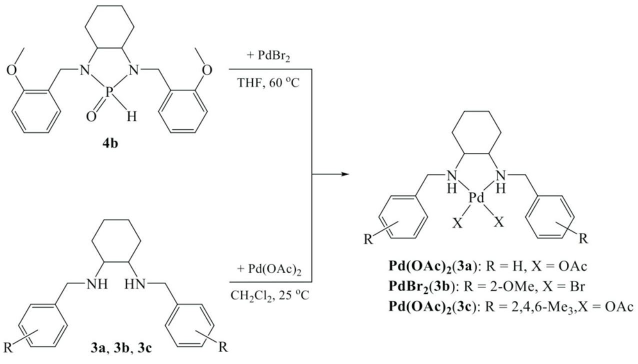


Fig. 3. Molecular structure of HASPO **4c**. Some hydrogen atoms are omitted for clarity.

dium complex. Nevertheless, an unexpected **3b**-coordinated palladium complex (**$PdBr_2$(3b)**) was obtained while trying to grow crystals of product in THF solution. This could be originated from the unstable nature of **4b'** caused by the existence of trace amount of water during the reaction or crystal-growing process. ORTEP diagram of **$PdBr_2$(3b)** is depicted in Figure 4b. It seems that the *endocyclic* P-N or *exocyclic* P-O bond in unsaturated HAPA were fragile. Similar reactions of **4a** and **4c** with $PdBr_2$ gave only the uncharacterized reaction mixtures together with the decomposed HASPO moieties.[50] When $Pd(OAc)_2$, $Pd(COD)Cl_2$ or $Pd(dba)_3$ were employed as the palladium sources in the related reactions with **4a**, **4b** or **4c**, similar uncharacterized reaction mixtures were obtained. Moreover, the same structure of diamine-chelated palladium complex could be obtained directly from the reaction of the corresponding diamine **3b** with $PdBr_2$ (Scheme 4). For the formation of diamine **3a-** and **3c-** coordinated $Pd(OAc)_2$ complexes, it is evidenced by the crystal structures of both **$Pd(OAc)_2$(3a)** and **$Pd(OAc)_2$(3c)** (Scheme 4).

The crystal structures of **$Pd(OAc)_2$(3a)**, **$PdBr_2$(3b)** and **$Pd(OAc)_2$(3c)** reveal that they are all diamine chelated palladium complexes. The bond lengths of Pd-N are in the range of 2.025~2.081 Å. The bond angles of N(1)-Pd(1)-N(2) are 84.48(11)°, 85.0(2)° and 84.12(7)° for **$Pd(OAc)_2$(3a)**, **$PdBr_2$(3b)** and **$Pd(OAc)_2$(3c)**, respectively. In Cambridge Structure Database (CSD),[51,52] only twelve diamine-coordinated palladium complexes were found within the searching constraints of Pd(diamine), in which diamine represents cyclohexane-1,2-diamine with an extended alkyl group attached to each nitrogen sites on the Pd-containing five-membered ring.[53] In addition to diamine ligand, other ancillary ligands coordinated to palladium center of the twelve hits are required to fulfill the 16-electron count of square planar d^8-Pd(II) center. Among them, three complexes (CSD Refcode: REWPIT, TUVGIB and VOFSAL) are coordinated by another two chloride ligands, respectively. The Pd-N bond lengths and N-Pd-N bond angles of these three complexes are within 2.045~2.069 Å and 83.46~84.88°, showing consistency with **$Pd(OAc)_2$(3a)**, **$PdBr_2$(3b)** and **$Pd(OAc)_2$(3c)**.

Scheme 4 The formations of diamine-coordinated palladium complexes from different reactions



Interestingly, substituents attached to the two *endocyclic* nitrogen atoms in **$PdBr_2$(3b)** and **$Pd(OAc)_2$(3c)** are in *cis*-relationship; however, they are in *trans*-relationship in **$Pd(OAc)_2$(3a)**. Among those twelve crystal structures, MAPBEM and ZOXFEX (CSD Refcode) are equipped with a tetra-dentate diamine ligand. The remaining ten crystal structures with the PdL_n(diamine) (n = 1 or 2) formula, only one structure (HECFEB) has its two substituents on the two *endocyclic* nitrogen atoms being in *trans*-relationship. Note that *cis*-relationship would bear larger intramolecular steric repulsion. Additionally, **$Pd(OAc)_2$(3a)** and **$Pd(OAc)_2$(3c)** are the first two structures with two acetate as coordinating ligands when compared to those twelve structures. For comparison with Buchwald's work,[15-18] a blue diamine-chelated copper complex **$[Cu(NO_3)(3d)^+][NO_3^-]$** was prepared from the reaction of **3d** with $Cu(NO_3)_2 \cdot 3H_2O$. Its crystal structure was shown in Figure 4d. Close examination of the structure of **$[Cu(NO_3)(3d)^+][NO_3^-]$** has

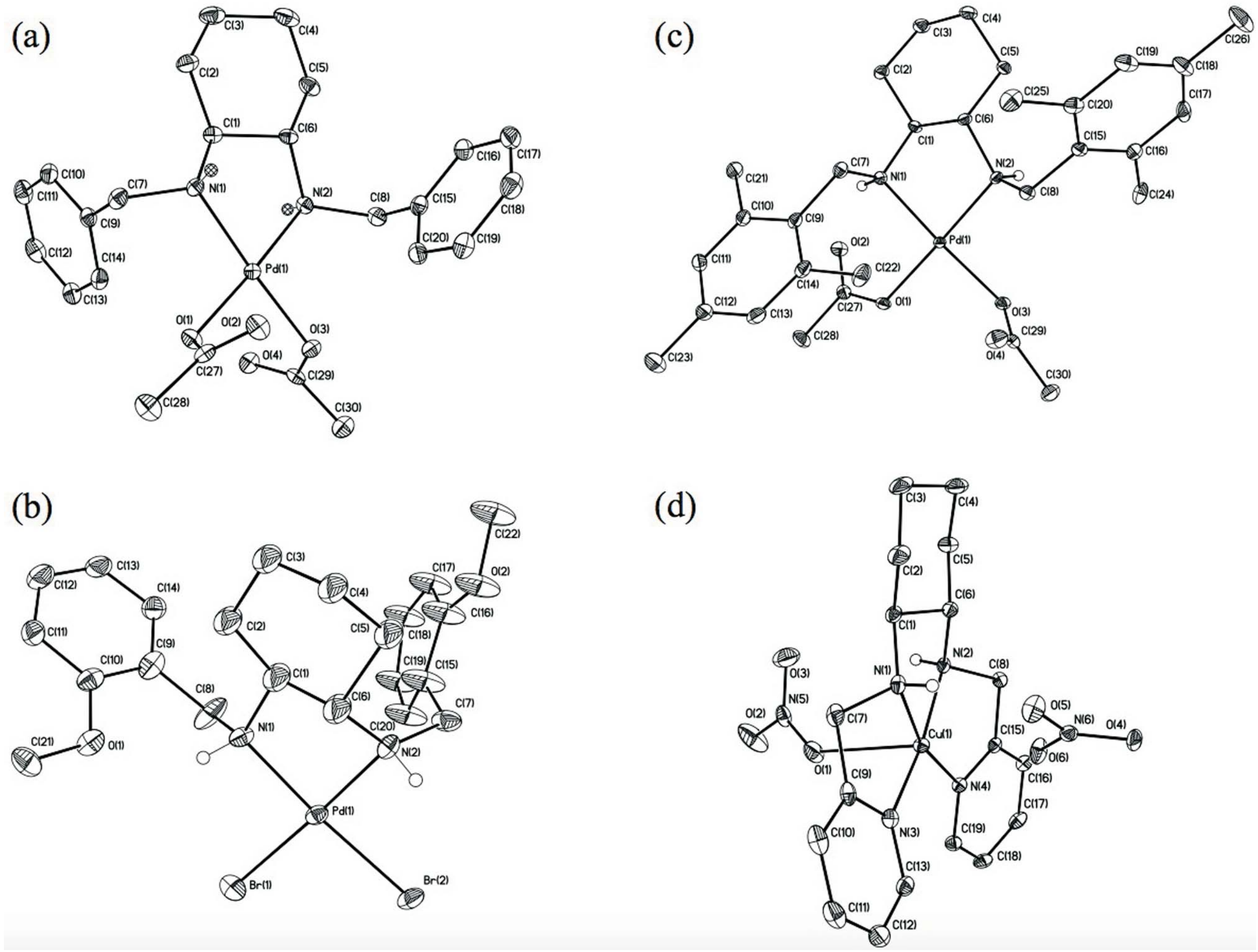


Fig. 4. Molecular structures of (a) **$Pd(OAc)_2$(3a)**, (b) **$PdBr_2$(3b)**, (c) **$Pd(OAc)_2$(3c)** and (d) **$[Cu(NO_3)(3d)^+][NO_3^-]$**. Some hydrogen atoms are omitted for clarity.

revealed that 3d acted as a tetra-dentate ligand. Two types of NO_3^- are coexistence in a molecule: one acts as ligand and the other as counterion. The bond lengths of Cu(1)-N range from 1.985~2.013 Å. The bond distance of Cu(1)-O(1) is 2.3887(12) Å. It is 2.472 Å for Cu(1)···O(6). The bond angles are 81.63(6)°, 85.80(5)° and 82.75(5)° for N(3)-Cu(1)-N(1), N(1)-Cu(1)-N(2), and N(2)-Cu(1)-N(4), respectively.

Instability of unsaturated HASPO 4e and metastability of saturated HASPO 4a-4c

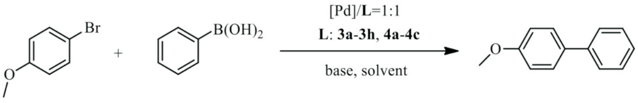
Saturated HASPO **4a-4c** are metastable compounds and will undergo decomposition slowly in ambient temperature, while *unsaturated* HASPO **4e** decomposed rather quickly in 15 minutes after synthesized. HASPO **4a** and **4c** are white solids, and **4b** is yellow liquid. Being preserved in nitrogen-filled vials at 4 °C for 10 months, about 20% decomposition of **4a** and **4c** were observed by their respective ^{31}P NMR spectra, while nearly 40% **4b** was disintegrated to unspecified species. Obviously, **4a-4c** are thermodynamically metastable.

In addition, ^{31}P NMR spectrum of HASPO **4a** showed up to 50% decomposition when dissolved in THF and heated at 60 °C for 2 hours (the integration of peak at 20.8 ppm became smaller and two new peaks at 4.3 and -6.4 ppm appeared). In the same reaction conditions, quantitative decomposition of **4b** was observed by ^{31}P NMR spectrum (peak at 22.3 ppm disappeared while two new peaks showed at 5.2 and -6.8 ppm). As to **4c**, 10% of thermal degradation was recorded (peak at 19.4 ppm turned weaker in intensity and new emerging peak showed at -6.60 ppm). According to ^{1}H NMR spectra of **4a-4c** collected after heated for 2 hours, their respective diamine peaks were observed. Since **4a-4b** have been obtained and characterized, we believe that the failure to obtain the HAPA **4a’-4b’** coordinated palladium complexes mainly lies in the metastability of HAPA **4a'-4c'**. In summary, the ambient and thermal stability is decreased in the order of HASPO/HAPA **4c** > **4a** > **4b**.

Palladium-catalyzed Suzuki-Miyaura reactions using diamines 3a-3h and HASPO 4a-4c as ligands

Palladium-catalyzed Suzuki-Miyaura cross-coupling reactions of aryl halides and phenylboronic acid were carried out by employing these newly-made diamines **3a-3h** and HASPO **4a-4c** auxiliary ligands (Scheme 5). As revealed, cyclohexane ring functionalized on the 1,2-diamine ligands reinforces the chelating ability in providing flexibility of the bidentate ligands. Several factors that affect the efficiency of the reactions, including the palladium sources, ligand-to-metal ratio, bases, temperature, reaction time, solvent and concentration etc., had been screened to search for the optimized condition for the reaction.

Scheme 5 Suzuki-Miyaura cross-coupling reactions of arylbromides and phenylboronic acid catalyzed by the combination of palladium salt and ligand



Firstly, *in-situ* Suzuki-Miyaura cross-coupling reactions were carried out to examine the catalytic efficiencies of these newly made ligands. The general procedure for the Suzuki-Miyaura cross-coupling reactions under investigation is described below. A 20 mL Schlenk tube was placed with 1.0 mmol of aryl halides, 1.5 mmol of phenylboronic acid, 1.0 mol% of palladium salt and 1.0 mol% of ligand, 1.0 mL of solvent and 3.0 mmol of base. The mixture was stirred at designated temperature and time depending on the reactions executed. The conversion rate is decided from the integration of ^{1}H NMR peak of product against standard; while the isolated yield was determined after purified by column chromatography.

As shown in Table 1, the conversions are almost quantitatively in 3.0 hours for using **3a**, **3b**, **3c**, HASPO **4a** as ligands from the preliminary screening (entries 1, 2, 3, 9). Here, **3a** stands out as the best ligand while the reaction time is reduced to 0.5 hour (entry 1). Therefore, **3a** is chosen as the ligand for the optimization of reaction condition thereafter. It is worthy of noting that ligands with cyclohexyl backbone performed more effectively than those with benzene ring backbone in the Suzuki-Miyaura reactions (c.f. entries 1 and 5; Entries 2 and 6). It is believed that the structural flexibility of cyclohexyl backbone in **3a-3c** makes the better chelation of palladium complexes than diamines with benzene backbone, and results in the differences in reactivity. When **3b**/**3c** was employed as ligand in entry 2 and 3, -OCH_3/-CH_3 groups introduced larger steric hindrance; this could hamper the intermolecular interaction between substrate and palladium (entry 1 vs. 2 and 3 in Table 1). In addition, the extremely low catalytic efficiency of diamine **3d** (entry 4) could be ascribed to the formation of stable tetra-coordinated palladium complex.

In entries 9, 10 and 11 in Table 1, HASPO **4a-4c** were used as pre-ligands. It was the HAPA-coordinated palladium that was expected as catalytic active species. However, according to the thermal instability of HASPO **4a-4c** and the result of the reaction of HASPO with various palladium sources discussed in the previous sections, HAPA (HASPO tautomer) could degrade into diamine ligand. Therefore, it could be diamines that play a major role in the Suzuki-Miyaura coupling reaction. It could be evidenced from the catalytic yield within the first half hour is quite low (entries 9, 10 and 11). The possible route for the formation of diamine-Pd active species is HASPO-to-HAPA tautomerization followed by the fast decomposition of HAPA to diamine ligand at 60 °C. Compared to HASPO **4a**, the lower catalytic yield in the cases of HASPO **4b** and **4c** may again correspond to the larger steric hindrance of ligands and longer catalytic induction time. On the contrary, the yield exceeded 99% after three hours for HASPO **4a** (entry 9 in Table 1).

Table 1. Suzuki-Miyaura coupling reactions employing various ligands [a]

Entry	Ligand	Yield (0.5 h) [b]	Yield (3.0 h) [b]
1	**3a**	65	99
2	**3b**	9	99
3	**3c**	50	99
4	**3d**	-	0
5	**3e**	-	53
6	**3f**	-	70
7	**3g**	-	54
8	**3h**	-	13
9	**4a**	13	99
10	**4b**	-	23
11	**4c**	-	55

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), phenyl boronic acid (1.5 mmol), KOH (3.0 mmol), THF (1.0 mL), $Pd(OAc)_2$ (1.0 mol%), ligand (1.0 mol%), Pd:L = 1:1, 60 °C. [b] Determined by ^{1}H NMR.

Among all the influential factors that affect the catalytic efficiency of the cross-coupling reaction, the role played by base probably is the most ambiguous factor.[29,54,55] Thereby, the impact of different bases on the catalytic yields was then investigated with **3a** as ligand, and the results are shown in Table 2. Among all the bases examined, it was found that KOH in THF is the most effective combination (Table 2, entry 1). Unexpectedly, other bases gave poor catalytic yields.

Subsequently, several palladium complexes were screened for Suzuki-Miyaura reaction (diamine **3a** as ligand). The best result was obtained when Pd(OAc)$_2$ was used (entry 1 in Table 3) because the di-valent Pd(OAc)$_2$ is easier to be reduced to Pd(0) in the presence of electron-rich ligand.[56] Unexpectedly, poor performance was observed for a zero-valent palladium source, Pd$_2$(dba)$_3$ (Entry 4 in Table 3). The same reactions were carried out with various copper salts of CuI, CuBr, Cu(OAc)$_2$ and CuI$_2$ in the copper-to-**3a** ratio of 1:1 at 60 °C for 12 hours. Unfortunately, no conversion could be observed for every single case.

Table 2. Suzuki-Miyaura coupling reactions employing various bases [a]

Entry	Ligand	Yield (0.5 h) [b]	Yield (1.0 h) [b]
1	KOH	65	95
2	NaOH	0	2
3	NaO^{t}Bu	0	5
4	K_2CO_3	5	8
5	KO^{t}Bu	0	0
6	Cs_2CO_3	0	3
7	CsF	0	0
8	Na_2CO_3	0	0
9	KF	0	2
10	$K_3PO_4 \cdot nH_2O$	2	2

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), phenyl boronic acid (1.5 mmol), base (3.0 mmol), THF (1.0 mL), Pd(OAc)$_2$ (1.0 mol%), **3a** (1.0 mol%), Pd:L = 1:1, 60 °C. [b] Determined by ^{1}H NMR.

Table 3. Suzuki-Miyaura coupling reactions employing various palladium sources [a]

Entry	Ligand	Yield (0.5 h) [b]	Yield (3.0 h) [b]
1	Pd(OAc)$_2$	65	95
2	Pd(COD)Cl$_2$	50	61
3	PdBr$_2$	13	27
4	Pd$_2$(dba)$_3$	15	22
5	[Pd(Cl)(^{3}-C$_3$H$_5$)]$_2$	12	15
6	PdCl$_2$	1	1

[a] Reaction condition: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), KOH (3.0 mmol), THF (1 mL), palladium source (1.0 mol%), **3a** (1.0 mol%), Pd:L = 1:1, 60 °C. [b] Determined by ^{1}H NMR.

For most cross-coupling reactions, the generation of ionic intermediates are assumed in the catalytic cycle. Thereby, polar solvent is a favourite choice since the solubility of these species is highly related to the overall catalytic performance. As shown in Table 4, the combination of KOH with either toluene, THF or 1,4-dioxane led to excellent results in 1 hour (entries 1-3 in Table 4). As a result, 1,4-dioxane was selected as solvent for searching the optimal reaction conditions. Upon the metal-to-ligand ratio was tuning to 1:2 or 1:3 in the reaction duration of 0.25 hour, the catalytic yield decreased in the later case (c.f. entries 2 and 3 in Table 4). The poor performance of the later case is understandable since excess ligand might retard the formation of unsaturated active palladium species during reaction. Similar catalytic performance of the first two cases is worthy of noting. It is believed that the best combination of Pd(OAc)$_2$/**3a** is still 1:1 because the **3a** acts as a bi-dentate ligand is revealed in the crystal structure. The lower dosage of **3a** is more atom economic. Moreover, the optimized metal-to-ligand ratio is consistent with the conventional observation for a bi-dentate ligand with palladium source.

Zero-valent palladium complex is the active species for the cross-coupling reaction.[57] Besides, the induction time for the reduction of higher valent palladium center is of crucial importance to the overall catalytic performance. As a result, the induction time of the Suzuki-Miyaura reaction was examined by monitoring the 1H NMR conversion yield by using the reaction condition of 1 mol% of **3a**/1 mol% of Pd(OAc)$_2$/3 eq. KOH/1 mL 1,4-dioxane at 60 °C.

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

Entry	Ligand	Yield (0.25 h) [b]	Yield (3.0 h) [b]
1	1,4-dioxane	95	99
2	1,4-dioxane	96^c	-
3	1,4-dioxane	84^d	-
4	Toluene	56	99
5	THF	35	65
6	DMF	8	15
7	MeOH	16	22
8	H_2O	13	21
9	DMSO	0	0

[a] Reaction condition: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), KOH (3.0 mmol), THF (1 mL), palladium source (1.0 mol%), **3a** (1.0 mol%), Pd:L = 1:1, 60 °C. [b] Determined by ^{1}H NMR.

It was found that the conversion yield was 89% in the first 3 minutes and it reached to 99% within 30 minutes (Figure 5). The observation showed that **3a**/Pd(OAc)$_2$ is an efficient catalytic system for Suzuki-Miyaura cross-coupling reactions.

The scope of this Suzuki-Miyaura coupling reaction using various aryl bromides was examined (Table 5). When 1-bromo-2-methylbenzene was used and catalysed by 2 mol% Pd(OAc)$_2$ for 3 hours, moderate catalytic yield of 65% was obtained (entry 1). Worse yield was shown if 2-bromo-1,3,5-trimethylbenzene was chosen as aryl halide (21% in entry 2). Obviously, steric hindrance caused by adjacent methyl groups in 2-bromo-1,3,5-trimethylbenzene is believed to be the cause of low catalytic yield. For electron-rich or deficient aryl bromides shown in entry 3-5, the reactions gave the corresponding products in good yield. Poor yield were observed in the cases having aldehyde, nitro, amino or olefin substituents on the para-position of benzene ring (entry 7, 8 and 9). For substrate with nitrile or hydroxyl substituents, excellent results were obtained (entries 10 and 11). Rather poor performances were observed for heterocyclic aryl halides (entry 12, 13 and 14). The coordination of heteroatom of aryl bromides to the catalytic palladium centre reduces the reactivity of the active species.

Conventionally, aryl chlorides are less reactive than aryl bromides towards Suzuki-Miyaura coupling reaction. It is due to the higher barrier height is estimated for Ar-Cl bond breaking.[57] Nevertheless, the low-cost aryl chloride makes them attractive reaction species. The optimized reaction conditions using **3a** as auxiliary ligand in Suzuki-Miyaura reaction for aryl chlorides were carried out. The performance of **3a** is less efficient in the cases of aryl chlorides than those of aryl bromides (supporting information).

Palladium-catalyzed Heck reactions using diamine 3a-3d as ligands

Having been demonstrated in the previous section, diamine **3a-3d** are more effective ligands than **3e-3h** in the Suzuki-Miyaura reactions. Factors such as ligand type, palladium source, palladium-to-ligand ratio, temperature, base and solvent system strongly influence the catalytic yield of a cross-coupling reaction. Moreover, Heck reaction normally requires more severe reaction condition than that of Suzuki reaction.[58,59] Since high temperature is often required for good catalytic performance, diamine **3a-3d** were employed for Heck reactions at 100 °C with DMF as solvent (Scheme 6). To compare our results with the published work of Hayashi,[60] similar procedure were carried out and described below. A 20 mL Schlenk tube was charged with 1.0 mmol of substituted bromobenzene, 1.2 mmol of styrene, 3.0 mmol of base, 3.0 mol% of palladium

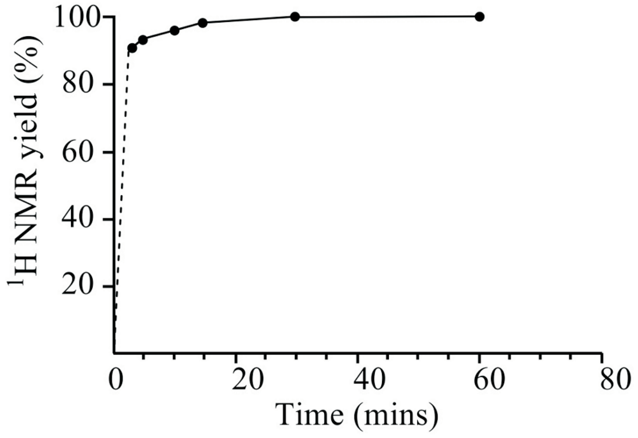
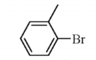
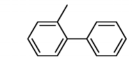
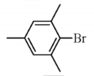
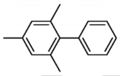
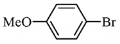
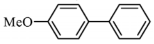
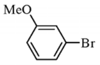
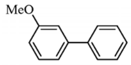
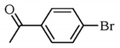
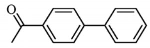
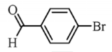
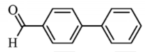
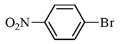
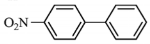
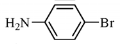
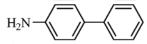
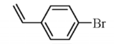
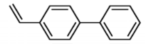
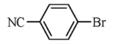
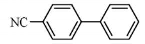
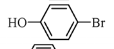
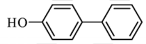
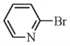
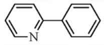
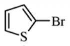
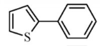
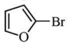
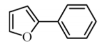


Fig. 5. The conversion rate of Suzuki-Miyaura reaction monitored by ^{1}H NMR.

Table 5. Suzuki coupling reactions employing various aryl halides [a]

Entry	Ligand	Product	Yield (%) [b]
1			65 [c]
2			21 [c]
3			92
4			89
5			94
6			56 [d]
7			25 [d]
8			< 5 [d]
9			0 [d]
10			91 [e]
11			92 [e]
12			< 5 [f]
13			< 5 [f]
14			11 [f]

[a] Reaction conditions: aryl bromide (1.0 mmol), phenylboronic acid (1.5 mmol), KOH (3.0 mmol), 1,4-dioxane (1 mL), Pd(OAc)$_2$ (1.0 mol%), **3a** (1.0 mol%), Pd:L = 1:1, 60 °C, 0.5 h; [b] Isolated yield; [c] Condition: 2 mol% Pd(OAc)$_2$, 3 h; [d] Condition: 3 h; [e] Condition: 30 °C, 3 h; [f] Condition: 5 mol% Pd(OAc)$_2$, 3 h.

salt and 3.0 mol% of **3a-3d** as catalyst precursors. The reaction mixture was stirred at 100 °C and designated reaction time. Work-up process was then followed. Due to steric hindrance, the formation of *trans*-1,2-disubstituted ethylene shall be the major product than its *cis*-counterpart. Meanwhile, the 1,1'-disubstituted ethylene is also expected as a minor side product.

Moderate yields were obtained from preliminary screening for diamine **3a-3d** (Table 6). Interestingly, the performance of **3d** is the best among all four ligands (entry 4 in Table 6). However, **3a** performs poorly in Suzuki-Miyaura reaction (entry 4 in Table 1). Based on our screening tests, **3d** was chosen as the ligand for investigating the optimized reaction condition thereafter. Note that the conformation of **3d** has the capacity to act as a tetra-dentate ligand. At high reaction temperature, the energy is possible high enough to break the pyridyl-Pd bonds and to regenerate active palladium center.

In Heck reaction, base assists the release of hydrogen halide (HX) during the reductive elimination process in order to speed up the overall catalytic cycle. The screening of bases was pursued and results are shown in Table 7. It showed that CsF in DMF was the most effective combination (entry 10 in Table 7). Contrarily, two effective bases in Heck reaction, KOH and NaO^{t}Bu, performed poorly. The results highlight again that base is one of the most unpredictable factors in cross-coupling reactions.

The screening of palladium sources was pursued in this section. The results showed that $Pd(OAc)_2$ was the best choice as in the Suzuki-Miyaura reaction (Table 8). Employing $Pd(OAc)_2$ as the palladium source, minor reduction in yield was observed when the reaction time was reduced to 3 hours in DMF (entry 2 in Table 8). With PdX_2 (X = Cl or Br), greater reduction in yield was observed (entry 4 or 5 in Table 8). Our screening showed that **3d**/DMF/CsF/$Pd(OAc)_2$ is the best combination for Heck reactions performed herein. However, it is still of interests to locate the suitable solvent system for diamine **3d** in the Heck reactions.

Excellent yield (> 99%) was obtained for the reaction carried out at 100 °C for 12 hours using either in 1,4-dioxane or toluene (entry 1 or 2 in Table 9). Moderate yields (75% or 74%) were obtained for reducing the reac-

Table 6. Effect of various ligands in Heck reaction [a]

Entry	Ligand	NMR conv. (%)^b
1	**3a**	41
2	**3b**	43
3	**3c**	58
4	**3d**	68

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), styrene (1.2 mmol), K_2CO_3 (3.0 mmol), DMF (1 mL), $Pd(OAc)_2$ (3.0 mol%), ligand (3.0 mol%), Pd:L = 1:1, 100 °C, 12 h; [b] Determined by ^{1}H NMR.

Table 7. Effect of various bases in Heck reaction [a]

Entry	Ligand	NMR conv. (%)^b
1	NaOH	47
2	KOH	15
3	NaO^{t}Bu	18
4	K_2CO_3	68
5	KO^{t}Bu	28
6	Cs_2CO_3	79
7	Na_2CO_3	36
8	KF	50
9	$K_3PO_4 \cdot nH_2O$	61
10	CsF	82
11	$CsOH \cdot H_2O$	41

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), styrene (1.2 mmol), base (3.0 mmol), DMF (1 mL), $Pd(OAc)_2$ (3.0 mol%), **3d** (3.0 mol%), Pd:L = 1:1, 100 °C, 12 h; [b] Determined by ^{1}H NMR.

Table 8. Effect of various bases in Heck reaction [a]

Entry	Ligand	NMR conv. (%)^b
1	$[Pd(Cl)(\eta^3\text{-}C_3H_5)]_2$	80 (69)
2	$Pd(OAc)_2$	82 (74)
3	$Pd(COD)Cl_2$	75 (52)
4	$PdBr_2$	78 (23)
5	$PdCl_2$	79 (8)
6	Pd_2dba_3	69 (40)

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), styrene (1.2 mmol), CsF (3.0 mmol), DMF (1 mL), palladium salt (3.0 mol%), **3d** (3.0 mol%), Pd:L = 1:1, 100 °C. [b] The conversion was determined by 1H NMR after 12 hours (in parentheses, 3 hours in toluene).

Scheme 6 Heck reaction of 4-bromoanisole and styrene

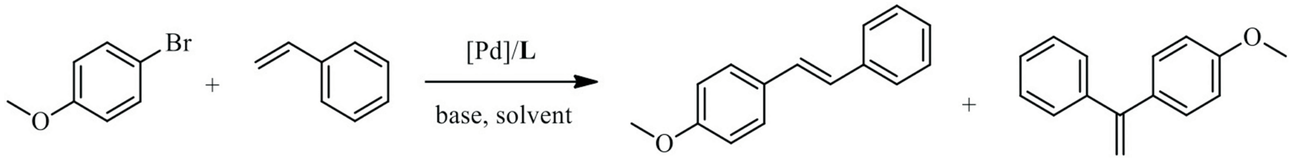
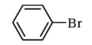
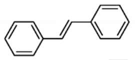
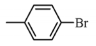
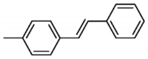
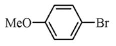
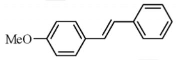
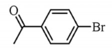
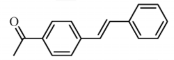
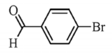
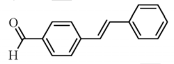
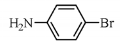
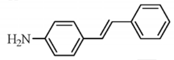
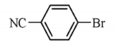
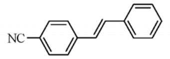
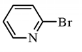
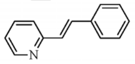


Table 9. Effect of the solvent in Heck reactions [a] NMR conversion yields are in %

Entry	Ligand	NMR conv. [b]	conv. [c]	conv. [d]
1	1,4-dioxane	99	75	31
2	toluene	99	74	45
3	DMF	82	-	-
4	DMSO	25	-	-

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), styrene (1.2 mmol), K_2CO_3 (3.0 mmol), solvent (1 mL), $Pd(OAc)_2$ (3.0 mol%), ligand (3.0 mol%), Pd:L = 1:1, 100 °C, 12 h; [b] Determined by ^{1}H NMR, 100 °C, 12 h; [c] Determined by ^{1}H NMR, 100 °C, 3 h; [d] Determined by ^{1}H NMR, 60 °C, 12 h.

Table 10. Effect of various ligands in Heck reaction [a]

Entry	Ligand	Product	Yield (%) [b]
1			67
2			71
3			80
4			66
5			85
6			85
7			58[c]
8			0

[a] Reaction conditions: arylbromide (1.0 mmol), styrene (1.2 mmol), CsF (3.0 mmol), toluene (1 mL), $Pd(OAc)_2$ (3.0 mol%), **3d** (3.0 mol%), Pd:L = 1:1, 100 °C, 6 h. [b] Isolated yield; [c] Condition: 12 h.

tion time to 3 hours. Similarly, when lowering the temperature to 60 °C for 12 hours, the Heck reactions showed worse NMR conversion yield than reducing the reaction time (c.f. compare the forth and fifth columns in Table 9). It reveals that the reaction temperature is a more important factor than the duration of reaction time. Thereafter, toluene was chosen as the solvent for the optimization of reaction condition. In summary, the optimized reaction condition for Heck reaction in this study is **3d**/CsF/$Pd(OAc)_2$/ toluene.

The scope of this Heck coupling reaction using various aryl bromides was examined using the optimized condition (Table 10). Fair efficiencies were obtained for aryl bromides with either electron-withdrawing or -donating group substituents reacted in 1 mL toluene at 100 °C for 6 hours (entries 1-6 in Table 10). Small amount of side products either from self-coupling of arylbromide or 1,1’-disubstituted ethylene were observed, thus also lessens the conversion rate of the target compound. Moderate performance was observed in the case of 4-bromobenzonitrile although the reaction time was prolonged to 12 hours (entry 7 in Table 10). Rather poor result was obtained for heterocyclic case such as 2-bromopyridine (entry 8 in Table 10).

CONCLUSION

Aiming at developing new HASPO pre-ligands for palladium-catalyzed Suzuki-Miyaura cross-coupling and Heck reactions, we have demonstrated the preparation, characterization and reactivity studies of cyclic 1,2-diamino derivatives and N-P-N type heteroatom-substituted secondary phosphine oxides (HASPO). HASPO can tautomerize to heteroatom-substituted phosphinous acid (HAPA, the genuine ligand for metal-coordination). Crystal structure of HASPO **4c** was well resolved. Efforts toward synthesizing HAPA-coordinated palladium complexes were made as our first step, but the instability of HAPA did not allow us to precede further characterizations. Interestingly, ambient stable diamine-coordinated palladium complexes were successfully obtained from the reaction of HASPO with $PdBr_2$. As a result, the coordinating ability of our diamine ligands toward palladium and copper were investigated herein. Three diamine-coordinated palladium complexes **($Pd(OAc)_2$(3a)**, **$PdBr_2$(3b)**, **$Pd(OAc)_2$(3c))** and one copper complex (**[$Cu(NO_3)$(3d)$^+$][NO_3^-]**) were synthesized and characterized by X-ray diffraction method.

Furthermore, *in-situ* Suzuki-Miyaura and Heck cross-coupling catalytic reactions were carried out for diamine in order to expand the usage of diamine ligands. The functionalized cyclohexyl and benzyl frameworks force the two amino groups residing on the neighboring positions, a plus for chelating a metal center. Preliminary results showed that 1,2-diamino derivatives with cyclohexyl backbone, **3a-3c**, perform better than their benzene counterparts, **3e-3h**, partly due to the electron-donating nature of alkyl substituent. These diamine ligands can be applied to Suzuki-Miyaura reaction at 60 °C to achieve high catalytic yield. Moreover, using HASPO **4a-4c** as ancillary ligands, Suzuki-Miyaura cross-coupling reactions were conducted giving rise to very low catalytic yield within the first half hour. Besides, high temperature is required for catalytic Heck reactions. Moderate catalytic performance employing aryl halides as substrates is provided in the supporting information.

The inefficient catalytic performance can be attributed to the thermal instability of HASPO/HAPA **4a-4c** ligand system evidenced by the NMR specptra. In addition, decomposition of HASPO **4a-4c** was also observed after long-term storage in nitrogen-filled vials at 4 °C. The *exocyclic* P-OH or *endocyclic* P-N single bonds in HAPA is fragile in 60 °C and the compounds decomposed into their corresponding 1,2-diamines.

EXPERIMENTAL

General procedure: 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: 30 m, 0.25 mm, 0.5 μm) with an Agilent® 5972 mass selective detector. Routine ^{1}H NMR spectra were recorded on a Varian-400 spectrometer at 399.760 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 161.8 and 100.5 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.

General procedure for the synthesis of 3a-3d: Into a 100 mL three neck round flask with stir bar was placed (+/-)-trans-1,2-diaminocyclohexane (1.00 g, 8.77 mmol) and 15 mL MeOH. The solution was stirred under refluxed before 2 molar equivalents of benzaldehyde (**1a**) (1.78 mL, 17.54 mmol) was added. The formation of 2a was observable within 30 minutes of refluxing. It was then allowed to cool to 25 °C before 2.1 molar equivalents of $NaBH_4$ (0.70 g, 18.41 mmol) was added. The solution was allowed to reflux further for 15~30 minutes till the ceasing of bubbling. Again, the solution was allowed to cool to 25 °C and then 5 mL of H_2O was added to quench the reaction. Pale yellow solid was extracted by CH_2Cl_2 from separatory funnel. Subsequently, the separation of pure product was performed by column chromatography. The yield of isolated **3a** is 70% (1.80 g, 6.12 mmol).

Similar procedures were applied to the preparations of **3b-3d**. The corresponding starting materials, 2-methoxybenzaldehyde (**1b**) (2.39 g, 17.54 mmol), mesitaldehyde (**1c**) (2.59 g, 17.54 mmol), and 2-pyridinecarboxaldehyde (**1d**) (1.68 mL, 17.54 mmol) were used. Good qualities of **3b** and **3c** could be obtained from participation directly. Recrystallization of **3b-3d** by ethyl acetate and CH_2Cl_2 gave good qualities of products without further separation by column chromatography. The yields of purified **3b** (pale yellow liquid), **3c** (white solid), and **3d** (yellow solid) are 98% (3.04 g, 8.58 mmol), 62% (2.06 g, 5.44 mmol), 90% (2.88 g, 7.89 mmol), respectively.

‡ Spectroscopic data for 3a. ^{1}H NMR($CDCl_3$, /ppm): 7.31 (t, J = 2.8 Hz, 8H, Ar), 7.24 (t, J = 2.8 Hz, 2H, Ar), 3.90 (d, J = 12.8 Hz, 2H, Benzylic), 3.65 (d, J = 13.2 Hz, 2H, Benzylic), 2.26 (d, J = 4.4 Hz, 2H), 2.16 (d, J = 12.0 Hz, 2H), 1.80 (b, 2H), 1.72 (d, J = 9.2 Hz, 2H), 1.23 (t, J = 10.8 Hz, 2H), 1.04 (d, J = 9.6 Hz, 2H); ^{13}C NMR($CDCl_3$, /ppm): 141.0, 128.2, 128.0, 126.6 (Aromatic), 60.8 (Benzylic), 50.8 (CH), 31.5 (CH_2), 25.0 (CH_2). **‡ Spectroscopic data for 3b.** ^{1}H NMR($CDCl_3$, /ppm): 7.28 (d, J = 7.6 Hz, 2H, Ar), 7.21 (t, J = 7.6 Hz, 2H, Ar), 6.90 (t, J = 7.6 Hz, 2H, Ar), 6.82 (d, J = 8.0 Hz, 2H, Ar), 3.92 (d, J = 13.2 Hz, 2H, Benzylic), 3.72 (s, 6H, OMe), 3.64 (d, J = 13.2 Hz, 2H, Benzylic), 2.38 (b, 2H), 2.26 (d, J = 4.8 Hz, 2H), 2.14 (d, J = 12.0 Hz, 2H), 1.71 (d, J = 8.0 Hz, 2H), 1.23 (t, J = 10.8 Hz, 2H), 1.09 (d, J = 9.2 Hz, 2H); ^{13}C NMR($CDCl_3$, /ppm): 157.4, 129.3, 129.1, 127.7, 120.2, 109.9 (Aromatic), 60.8 (Benzylic), 55.0 (OMe), 45.8 (CH), 31.4 (CH_2), 25.0(CH_2). **‡ Spectroscopic data for 3d.** ^{1}H NMR($CDCl_3$, /ppm): 8.51 (d, J = 4.0 Hz, 2H, Ar), 7.61 (t, J = 8.0 Hz, 2H, Ar), 7.38 (d, J = 8.0 Hz, 2H, Ar), 7.12 (d, J = 8.0 Hz, 2H, Ar), 4.02 (d, J = 12.8 Hz, 2H, Benzylic), 3.83 (d, J = 13.2 Hz, 2H, Benzylic), 2.30 (d, J = 4.4 Hz, 2H), 2.23 (b, 2H), 2.13 (d, J = 11.6 Hz, 2H), 1.71 (d, J = 7.2 Hz, 2H), 1.22 (t, J = 8.2 Hz, 2H), 1.08 (t, J = 10.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, /ppm): 160.6, 149.0, 136.4, 122.3, 121.7 (Aromatic), 61.3 (Benzylic), 52.5, 31.5, 25.0.

General procedure for the synthesis of 3e-3f: Into a 100 mL three-neck round flask with stir bar was placed o-phenylenediamine (1.08 g, 10.0 mmol) and 15 mL MeOH. The solution was stirred under refluxed before 2 molar equivalents of benzaldehyde (**1a**) (2.04 mL, 20.0 mmol) was added. The formation of 2e was noticed within 30 minutes of refluxing. It was allowed to cool to 25 °C before 4.0 molar equivalents of $LiAlH_4$ (1.52 g, 40.0 mmol) and 20 mL of THF were added. The solution was allowed to reflux further for another 12 hours. Again, the solution was allowed to cool to 25 °C and then ether acetate and 5 mL of H_2O were added to quench the reaction. More ether acetate was added and yellow liquid was extracted by ether acetate from separatory funnel. Subsequently, the separation of pure product was performed by column chromatography. The yield of isolated **3e** (yellow solid) is 60% (2.72 g, 20.0 mmol). Similar procedures were applied to the preparation of **3f**. The corresponding starting material, 2-methoxybenzaldehyde (**1b**) (2.72 g, 20.0 mmol), was used. The yield of isolated **3f** (yellow solid) is 40% (1.39 g, 3.99 mmol).

‡ **Spectroscopic data for 3e.** ^{1}H NMR(CDCl$_3$, /ppm): 7.40-7.25 (m, 10H, Ar), 6.80-6.70 (m, 4H, Ar), 4.32 (s, 4H, Benzylic), 3.65(b, 2H); ^{13}C NMR(CDCl$_3$, /ppm): 139.4, 137.1, 128.6, 127.8, 127.2, 119.4, 111.9 (Aromatic), 48.7 (Benzylic). ‡ **Spectroscopic data for 3f.** ^{1}H NMR(CDCl$_3$, /ppm): 7.31-7.23 (m, 4H, Ar), 6.93-6.88 (m, 4H, Ar), 6.77-6.71 (m, 4H, Ar), 4.31 (s, 4H, Benzylic), 3.88 (b, 2H), 3.83 (s, 6H, OMe); ^{13}C NMR (CDCl$_3$, /ppm): 157.4, 137.6, 129.1, 128.2, 127.5, 120.5, 119.2, 112.4, 110.2 (Aromatic), 55.2 (Benzylic), 44.1 (OMe).

General procedure for the synthesis of 3g-3h: Similar procedures for the preparation of **3f** are applicable for making **3g** and **3h**. The corresponding 2-pyridinecarboxaldehyde (**1d**) (2.14 g, 20.0 mmol) was firstly used to prepare **2h**. Further reaction with NaBH$_4$ (0.79 g, 21.0 mmol) and workup followed to produce **3h** (yellow solid) in 35% yield (1.02 g, 3.52 mmol). Similar procedures were applied to the preparation of **3g**. The corresponding mesitaldehyde (**1c**) (2.95 mL, 20.0 mmol) was used. Due to severe steric hindrance, only one side of amine is formed. The yield of isolated **3g** (yellow solid) is 68% (1.63 g, 6.79 mmol).

‡ **Spectroscopic data for 3g.** ^{1}H NMR(CDCl$_3$, /ppm): 6.94 (s, 2H, Ar), 6.93 (d, J = 4.0 Hz, 1H, Ar), 6.86 (d, J = 8.0 Hz, 1H, Ar), 6.74 (d, J = 4.0 Hz, 2H, Ar), 4.22 (s, 2H, Benzylic), 3.23 (b, 3H), 2.39 (s, 6H), 2.33 (s, 3H); ^{13}C NMR(CDCl$_3$, /ppm): 138.0, 137.6, 137.2, 134.2, 132.3, 129.0, 120.6, 118.5, 116.1, 111.3, (Aromatic), 42.5 (Benzylic), 20.9 (Mes), 19.4 (Mes). ‡ **Spectroscopic data for 3h.** ^{1}H NMR (CDCl$_3$, /ppm): 8.59 (d, J = 4.2 Hz, 2H, Ar), 7.63 (t, J = 7.6 Hz, 2H, Ar), 7.36 (d, J = 7.6 Hz, 2H, Ar), 7.17 (t, J = 6.0 Hz, 2H, Ar), 6.75 (quin., J = 4.0 Hz, 2H, Ar), 6.66 (quin., J = 4.0 Hz, 2H, Ar), 4.55 (b, 2H), 4.49 (s, 2H, Benzylic); ^{13}C NMR(CDCl$_3$, /ppm): 158.8, 149.2, 136.9, 136.6, 122.0, 121.6, 119.3, 112.1 (Aromatic), 49.8 (Benzylic).

General procedure for the synthesis of 4a-4c: The procedures for the preparation of **4a-4c** were modified from literature.[32] Into a 100 mL round flask with stir bar was placed **3a** (1.17 g, 4.0 mmol). The air was pumped out and backfilled with nitrogen gas before 8 mL of toluene was added. Three molar equivalents of triethylamine (1.66 mL, 12.0 mmol) was injected and then the flask was placed in ice-water bath. Under nitrogen, 5 mL of toluene and 1.5 molar equivalents of phosphorus trichloride (0.35 mL, 6.0 mmol) were added to another 100 mL flask. At 0 °C, the content of the latter flask was transferred to the first one slowly through cannular needle and stirred for 3 hours at that temperature. Certain amount of hexane was added to salt out ionic compounds. Participate was filtrated out and followed by hydrolysis of the filtrated solution with water for 5 minutes. More ether acetate and water were added and the organic phase was collected from separatory funnel. Subsequently, the separation of pure product was performed by column chromatography. The yield of isolated **4a** (white solid) is 58% (0.79 g, 2.32 mmol).

Similar procedures were applied to the preparations of **4b** and **4c** from corresponding **3b** (1.42 g, 4.0 mmol) and **3c** (1.51 g, 4.0 mmol). The yields of purified **4b** (yellow liquid) and **4c** (white solid) are 35% (0.56 g, 1.40 mmol) and 75% (1.27 g, 3.00 mmol), respectively. ‡ **Spectroscopic data for 4a.** ^{1}H NMR(CDCl$_3$, /ppm): 7.52 (d, $J_{\text{P-H}}$ = 604.7 Hz, 1H, P-H), 7.41 (d, J = 10.0 Hz, 2H, Ar), 7.34-7.22 (m, 8H, Ar), 4.40-4.04 (m, 4H, Benzylic), 3.00-2.80 (m, 2H), 1.84-1.66 (m, 4H), 1.26-1.01 (m, 4H); ^{13}C NMR (CDCl$_3$, /ppm): 138.3,138.1, 128.5, 128.4, 128.1, 127.9, 127.3, 127.2 (Aromatic), 63.1, 62.7 (Benzylic), 46.5, 45.9 (CH), 29.3, 28.6 (CH$_2$), 24.1, 24.0 (CH$_2$); ^{31}P NMR(CDCl$_3$, /ppm): 20.8 (d, $J_{\text{P-H}}$ = 605.8 Hz). ‡ **Spectroscopic data for 4b.** ^{1}H NMR (CDCl$_3$, /ppm): 7.39 (d, $J_{\text{P-H}}$ = 614.7 Hz, 1H, P-H), 7.41 (q, J = 7.2 Hz, 2H, Ar), 7.23 (quin. J = 8.4 Hz, 2H, Ar), 6.95-6.82 (m, 4H, Ar), 4.54 (t, J = 15.2 Hz, 1H, Benzylic), 4.35 (q, J = 8.4 Hz, 1H, Benzylic), 4.19 (t., J = 16.8 Hz, 1H, Benzylic), 3.87 (d, J = 13.2 Hz, 1H, Benzylic), 3.83 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.04 (t, J = 11.4 Hz, 1H), 2.79 (t, J = 10.2 Hz, 1H), 2.01 (d, J = 10.4 Hz, 1H), 1.88 (d, J = 11.4 Hz, 1H), 1.70 (t, J = 12.8 Hz, 2H), 1.29-1.14 (m, 3H), 1.07-1.01 (m, 1H); ^{13}C NMR(CDCl$_3$, /ppm): 157.0, 156.9, 129.8, 128.9, 128.4, 128.0, 127.6, 126.2, 120.3, 120.1, 110.1, 110.0 (Aromatic), 64.4, 62.4 (Benzylic), 55.1, 55.0 (OMe), 41.2, 10.1 (CH), 29.4, 28.5 (CH$_2$), 24.3, 24.1 (CH$_2$); ^{31}P NMR (CDCl$_3$, /ppm): 22.3 (d, $J_{\text{P-H}}$ = 615.0 Hz). ‡ **Spectroscopic data for 4c.** ^{1}H NMR (CDCl$_3$, /ppm): 6.57 (d, $J_{\text{P-H}}$ = 609.2 Hz, 1H, P-H), 6.79 (s, 2H, Ar), 6.79 (s, 2H, Ar), 4.17-4.08 (m, 2H, Benzylic), 3.95-3.86 (m, 2H, Benzylic), 3.11 (t, J = 10.4 Hz, 1H), 2.85 (t, J = 9.8 Hz, 1H), 2.36 (s, 6H), 2.33 (s, 6H), 2.22 (s, 3H), 2.21 (s, 3H), 2.01 (d, J = 10.4 Hz, 1H), 2.07 (d, J = 11.2 Hz, 1H), 1.96 (s, 1H), 1.79 (s,1H), 1.35-1.15 (m, 5 H); ^{13}C NMR (CDCl$_3$, /ppm): 137.9, 137.7, 137.5, 137.0, 129.8, 129.4, 129.2, 129.1 (Aromatic), 66.1, 63.7 (Benzylic), 42.8, 41.7 (CH), 29.3, 28.9 (CH$_2$), 24.4, 24.3, (CH$_2$), 20.9, 20.8 (Mes), 20.3, 20.2 (Mes); ^{31}P NMR (CDCl$_3$, /ppm): 19.4 (d, $J_{\text{P-H}}$ = 609.6 Hz). Compound **4c** has been communicated elsewhere.

General procedure for the synthesis of Pd(OAc)$_2$ (3a) and Pd(OAc)$_2$ (3c): Into a 10 mL Schlenk flask was placed **3a** (0.035 g, 0.1 mmol) and Pd(OAc)$_2$ (0.022 g, 0.1 mmol) with 1 mL of CH$_2$Cl$_2$. The solution was stirred at 25 °C for 12 hours. Yellow color and column shape crystals were formed and determined by x-ray diffraction methods as Pd(OAc)$_2$ (**3a**). The same procedures are applicable to the preparation of **3c_Pd** from its corresponding **3c**.

‡ **Spectroscopic data for Pd(OAc)$_2$(3a).** ^{1}H NMR (d$_6$-

DMSO, /ppm): 7.86 (d, J = 7.6 Hz, 2H, Ar), 7.40~7.28 (m, 4H, Ar), 6.92~6.75 (m, 4H, Ar), 6.17(q, J = 10.8 Hz, 1H, N-H), 4.54 (d, J = 11.6 Hz, 1H, N-H) 3.87~3.58 (m, 4H, Benzylic), 2.89~2.80 (m, 1H, cyclohexyl), 2.11~2.00 (m, 3H, cyclohexyl), 1.88 (s, 3H, acetate), 1.84 (s, 3H, acetate), 1.54 (m, 2H, cyclohexyl), 1.23~1.17 (m, 1H, cyclohexyl), 1.06~0.81 (m, 3H, cyclohexyl). ^{13}C NMR ($CDCl_3$, /ppm): 174.9, 172.1, 152.3, 149.1, 137.0, 132.6, 130.1, 128.3, 127.5, 123.8, 123.0, 120.4, 66.0, 62.2, 57.3, 54.9, 49.1, 29.0, 24.6, 24.0, 23.7, 21.3. ‡ **Spectroscopic data for $Pd(OAc)_2$ (3c).** ^{1}H NMR ($CDCl_3$, /ppm): δ = 7.76 (d, J = 10.4 Hz, 1H, N-H), 6.89 (s, 2H, Ar), 6.85 (s, 2H, Ar), 6.19~6.13 (m, 1H, N-H), 4.36~4.30 (m, 1H, Benzylic), 4.12~4.07 (m, 1H, Benzylic), 3.84~3.78 (m, 2H, Benzylic and cyclohexyl), 3.61~3.58 (m, 1H, Benzylic), 2.66~2.57 (m, 1H, cyclohexyl), 2.43 (s, 6H, CH_3), 2.25 (s, 6H, CH_3), 2.23 (s, 6H, CH_3), 2.10~2.07 (m, 1H, cyclohexyl), 1.97~1.92 (m, 1H, cyclohexyl), 1.85~1.78 (m, 1H, cyclohexyl), 1.79 (s, 3H, acetate), 1.67 (d, J = 14.0 Hz, 1H, cyclohexyl), 1.49 (d, J = 13.6 Hz, 1H, cyclohexyl), 1.25 (s, 3H, acetate), 1.23~1.12 (m, 2H, cyclohexyl), 0.87~0.81 (m, 1H, cyclohexyl). ^{13}C NMR ($CDCl_3$, /ppm): 180.6, 180.1, 138.5, 138.2, 137.6, 137.4, 129.8, 129.5, 128.2, 126.7, 67.5, 63.0, 51.6, 43.6, 32.4, 29.8, 24.8, 24.1, 22.9, 22.2, 20.9, 20.8, 20.6.

General procedure for the synthesis of ($[Cu(NO_3)(3d)^+][NO^{3-}]$): Into a 10 mL Schlenk flask was placed **3d** (0.035 g, 0.1 mmol) and $Cu(NO_3)_2{\cdot}3H_2O$ (0.022 g, 0.1 mmol) with 1 mL of CH_2Cl_2. The solution was stirred at 25 °C for 12 hours. Participate was filtrated out and clear blue solution was collected. Blue colored cubic shape crystals were formed gradually from the solution. Its crystal structure was latterly determined by x-ray diffraction methods and assigned as (**$[Cu(NO_3)(3d)^+][NO_3^-]$**). Since it is a paramagnetic species, differentiable NMR spectra were not possible. The major mass pattern of (**$[Cu(NO_3)(3d)^+][NO_3^-]$**) shows the parent peak at m/z = 483 (P^+) and the daughter peak at m/z = 421 ($P\text{-}NO_3^+$) and m/z = 358 ($P\text{-}2NO_3^+$).

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 salt, 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 solution (1.0 M, 5 mL) and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layer was 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.

General procedure for Heck reactions: Schlenk tube was charged with $Pd(OAc)_2$ (0.03 mmol, 6.7 mg), **3a** (0.03 mmol, 8.7 mg) and CsF (3.0 mmol, 0.456 g). This tube was subjected to vacuum for 10 minutes and then toluene (1 mL) was added. To this mixture styrene (1.2 mmol, 0.137 mL) and aryl bromide (1.0 mmol) were added slowly with the help of syringe. The resulting suspension was stirred at certain temperature for designated time. After completion of reaction, the reaction was diluted with EtOAc and filtered through a pad of Celite. The organic layer was then extracted with ethylacetate (10 x 3 mL) and water. The organic layer was collected separately and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude residue. The product was purified by flash chromatography (5% EtOAc/hexane), which yielded the desired trans-stilbene.

X-ray crystallographic studies: Suitable crystals of **$Pd(OAc)_2$ (3a)**, **$PdBr_2$ (3b)**, **$Pd(OAc)_2$ (3c)**, (**$[Cu(NO_3)(3d)^+][NO_3^-]$**) and **4c** 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 (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.[33] 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.[34] Crystallographic data for compounds **$Pd(OAc)_2$(3a)**, **$PdBr_2$(3b)**, **$Pd(OAc)_2$(3c)**, (**$[Cu(NO_3)(3d)^+][NO_3^-]$**) and **4c** are available from

SUPPORTING INFORMATION

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC no. 899551, 899552, 899553, 899554, and 899555 for compound **$Pd(OAc)_2$ (3a)**, **$PdBr_2$ (3b)**, **$Pd(OAc)_2$ (3c)**, (**$[Cu(NO_3)(3d)^+][NO_3^-]$**) and **4c**, respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.

uk). Cross-coupling reactions employing aryl halides as substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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