Development of novel amphiphilic polymer-supported palladium complexes and their application to C-X bond-forming cross-coupling reactions in water

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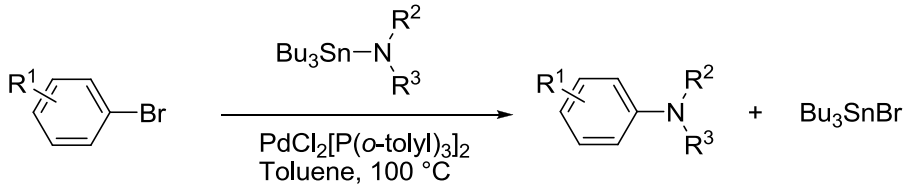
General Introduction

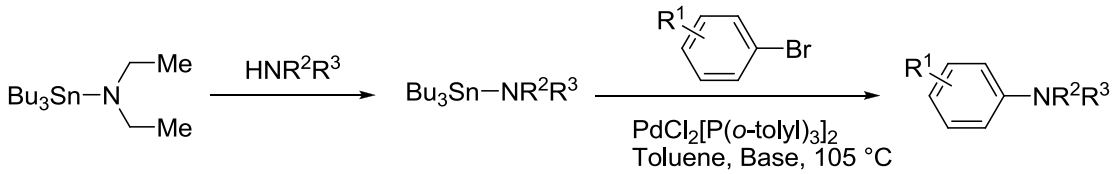
Palladium-catalyzed cross-coupling reactions are indispensable tool in industrial field as well as academic field.[1, 2] The C-N cross-coupling reactions represented by Buchwald-Hartwig reaction are relatively latest in the long history of the palladium-catalyzed cross-coupling reactions.



Scheme 1. Migita's work

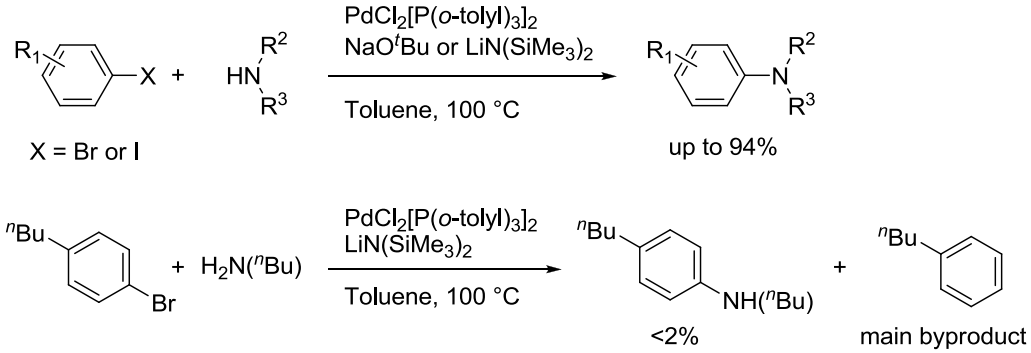
Migita found out the C-N bond-forming cross coupling reaction of aryl bromide and tributyltin diethylamide in the presence of bis(tri-*o*-tolylphosphine)palladium(II) dichloride in 1983 (Scheme 1).[3] This hetero cross-coupling is remarkable, considering its relationship to Stille C-C bond-forming cross coupling reactions, however, the knowledge about the mechanism of this reaction has been limited. Buchwald[4] and Hartwig[5] discovered the mechanism of the palladium-catalyzed C-N bond-forming cross-coupling reactions from the discovery of Migita 10 years later. Buchwald combined the known transamination reaction between amines

and tin amides to provide a convenient method for generating various tin amide reagents *in situ* without isolation of the unstable and water-sensitive tin amides (Scheme 2).[6]



Scheme 2.

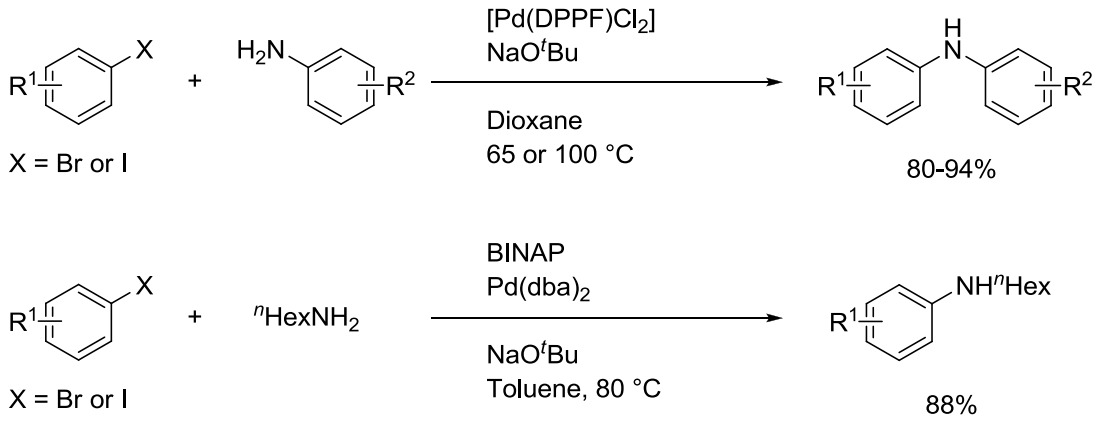
The C-N bond-forming reactions were used harmful and water sensitive tin amides as an amine source in the early stage. Buchwald and Hartwig improved the C-N bond-forming reaction using alkyl amines and strong base such as NaO^{t}Bu or LiN(SiMe$_3$)$_2$ instead of tin amides (Scheme 3).[7]



Scheme 3

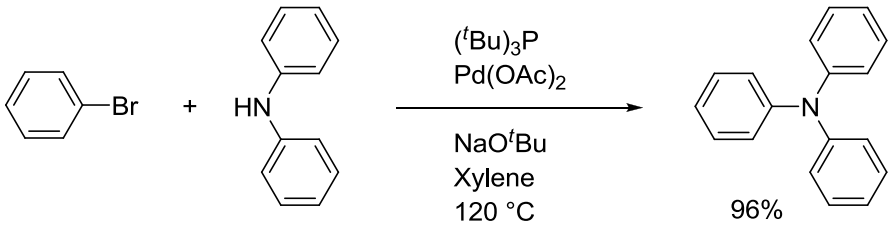
The catalytic system using Pd(dba)$_2$ and (o-Tol)$_3$P had some problems, such as generation of hydrodehalogenated arenes through the β-hydride elimination of primary alkylamido complexes (Scheme 3). In order to

resolve this problem, Buchwald and Hartwig employed bidentate phosphine compounds, such as DPPF [1,1'-bis(diphenylphosphino)ferrocene] and BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] for the reaction of aryl halides and primary alkyl amines containing β-hydrogens (Scheme 4).[8]



Scheme 4

In the same period, Nishiyama and Koie developed the method of synthesizing triarylamines by the using extremely bulky *tert*-butylphosphine and palladium acetate as a catalyst (Scheme 5). [9]



Scheme 5

From this result, it became clear that suitable catalysts for the C-N bond-forming cross-coupling reactions involved an exceptionally hindered and electron-donating ligand. Therefore, some groups have studied various

ligands for the C-N bond-forming cross-coupling reactions with above characters (Figure 1).

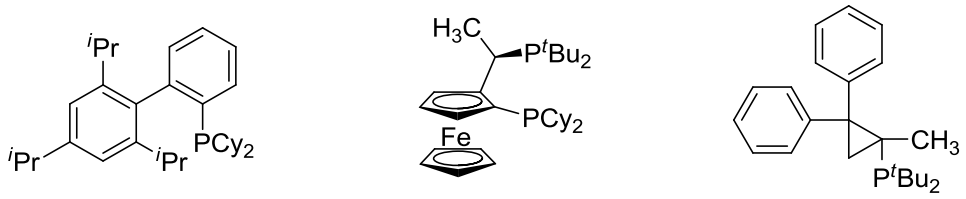


Figure 1

Since Buchwald and Hartwig discovered that the coupling of aryl halides and various amines could be catalyzed by palladium complexes, the catalytic amination of aryl halides, has been called as Buchwald–Hartwig reaction. This reaction has intrigued synthetic chemists and is generally recognized as one of the most powerful methods for preparing a variety of arylamines.[1] However, in spite of increasing concern for the environment and the safety of chemical processes, only scattered interest has been given to the heterogeneous- and aqueous-switching of catalytic amination, which would provide a green alternative to the Buchwald–Hartwig reaction.[10, 11] Arylamines have generated considerable interest owing to their presence as biologically active compounds and material for organic electronics. Efficient removal of the metal complexes from the reaction mixture of the catalytic amination process would allow not only the recovery of costly noble-metal

complexes but also the production of metal-free arylamines to provide clean compounds (Figure 2).

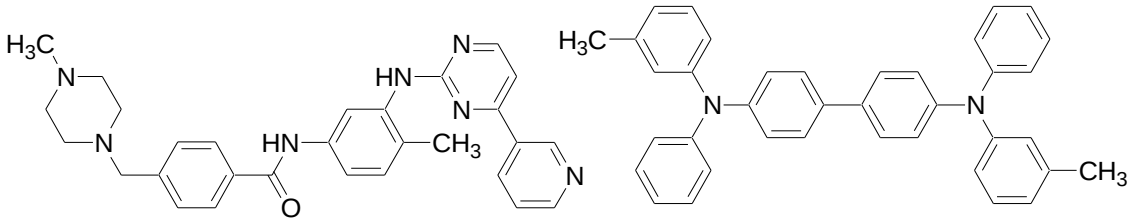
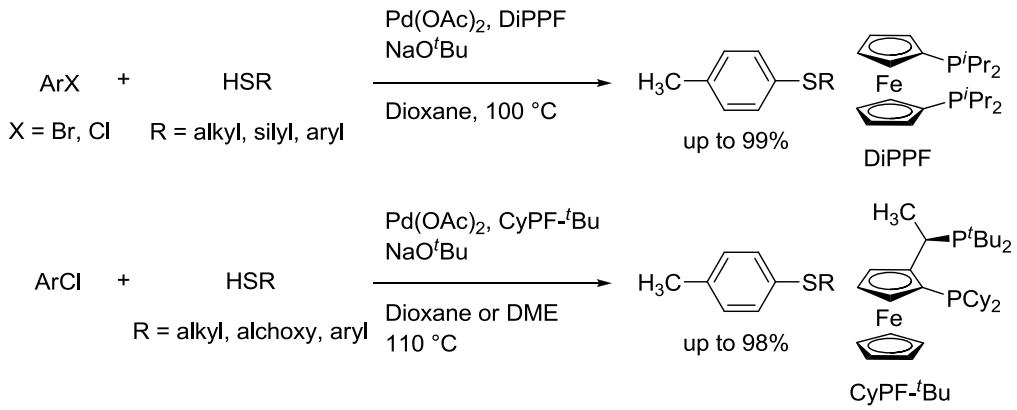


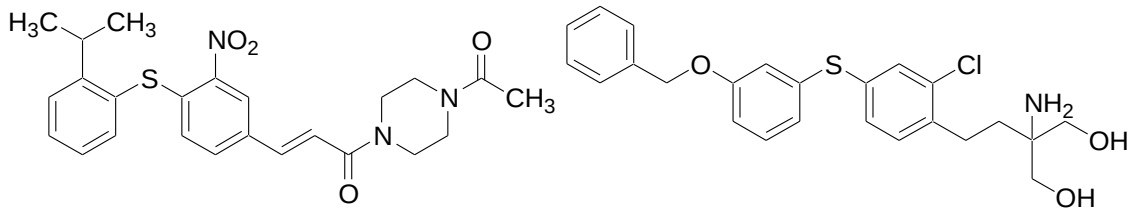
Figure 2

As mentioned above, palladium-catalyzed coupling has become a principal method of forming C-X bonds. However, studies to develop the synthesis of aryl sulfides have been less fruitful.[12] Although palladium thiolates with phosphine ligand, such as DPPE, Ph_3P, form easily and undergo relatively fast reductive elimination with aryl groups, sulfide compounds prevent reductive elimination and deactivate the palladium catalyst owing to their strong coordinate ability.[13]



Scheme 6

Buchwald (Scheme 6)[14] and Hartwig (Scheme 6)[15] achieved the C-S bond-forming coupling with ferrocene-based ligand, which has strong electron-donating ability to palladium, and NaO^{t}Bu in organic solvent to provide corresponding sulfide compounds which often are seems active pharmaceutical ingredient (Figure 3). Active pharmaceutical ingredients required low metal-contamination.



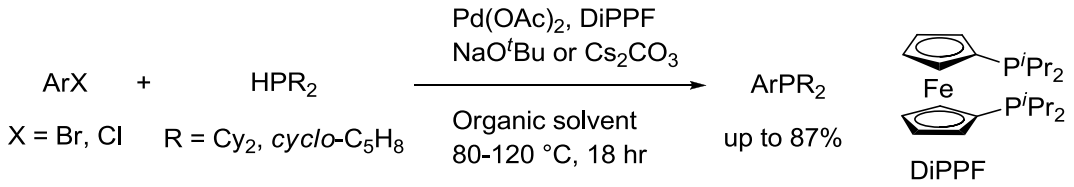
LFA-1/CIAM-1 antagonist (Abbvie)

KRP-203, S1P3 antagonist (Kyorin, Novartis)

Figure 3

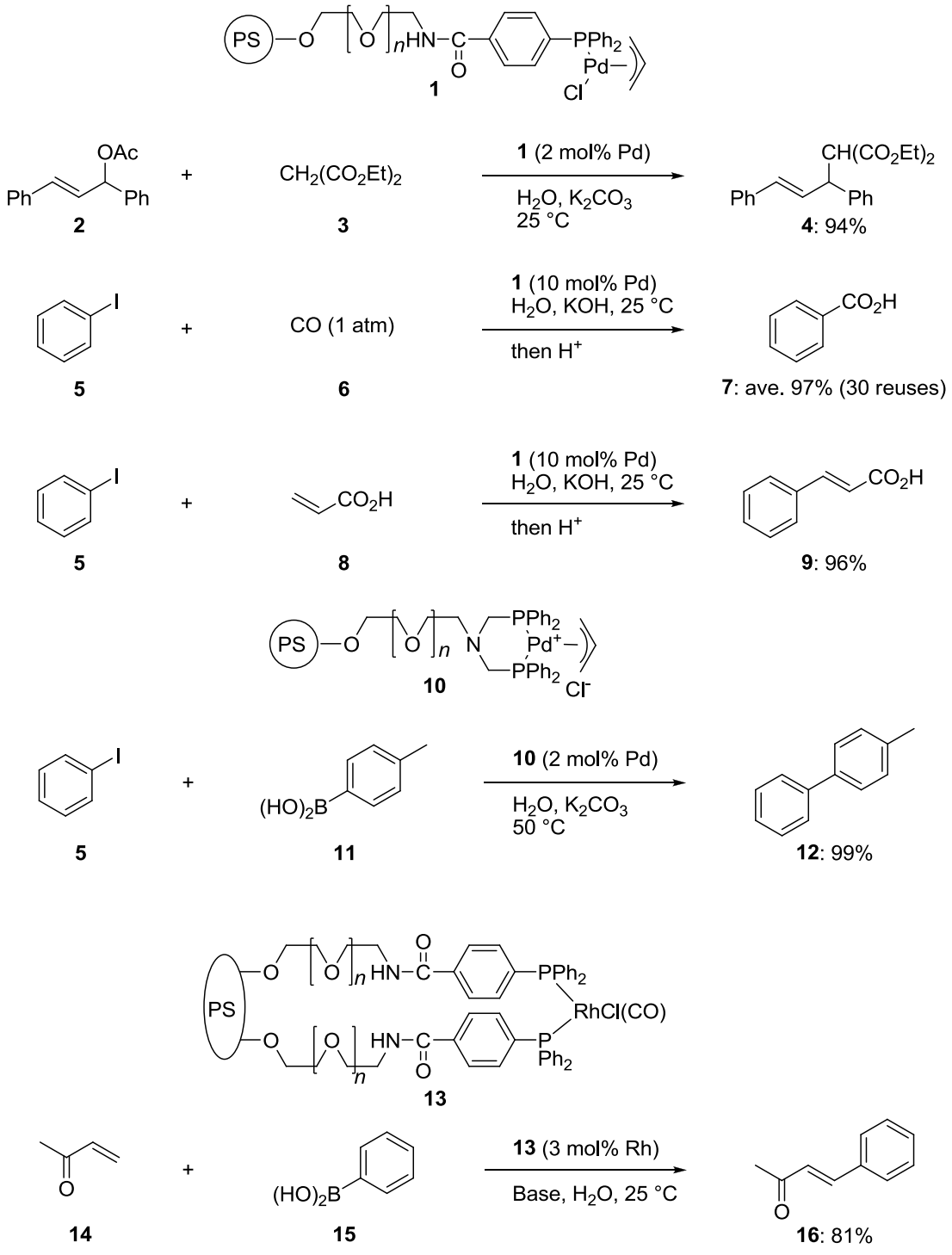
In the case of C-P bond-forming coupling, the resultant phosphine product prevents the desired reaction owing to the strong coordination as well as C-S bond-forming reaction. However, the palladium-catalyzed coupling of various phosphorous-based nucleophiles has previously reported.[16] Tertiary phosphines, which are widely used as ligands for transition metal chemistry, are prepared by the coupling of aryl halides with secondary phosphines in the presence of transition metal catalysts based on palladium[16], nickel[17] or copper[18]. However, common protocols have been

inefficient for the coupling of aryl bromides,[14, 19] and there has been reported of the coupling of electron deficient aryl chloride and with secondary phosphines[14]. In addition, previous reports have been focused on the preparation of triarylphosphines. Thus, developments of C-P bond-forming coupling, especially the reaction of aryl halides and dialkyl phosphine, were limited (Scheme 7).[14]

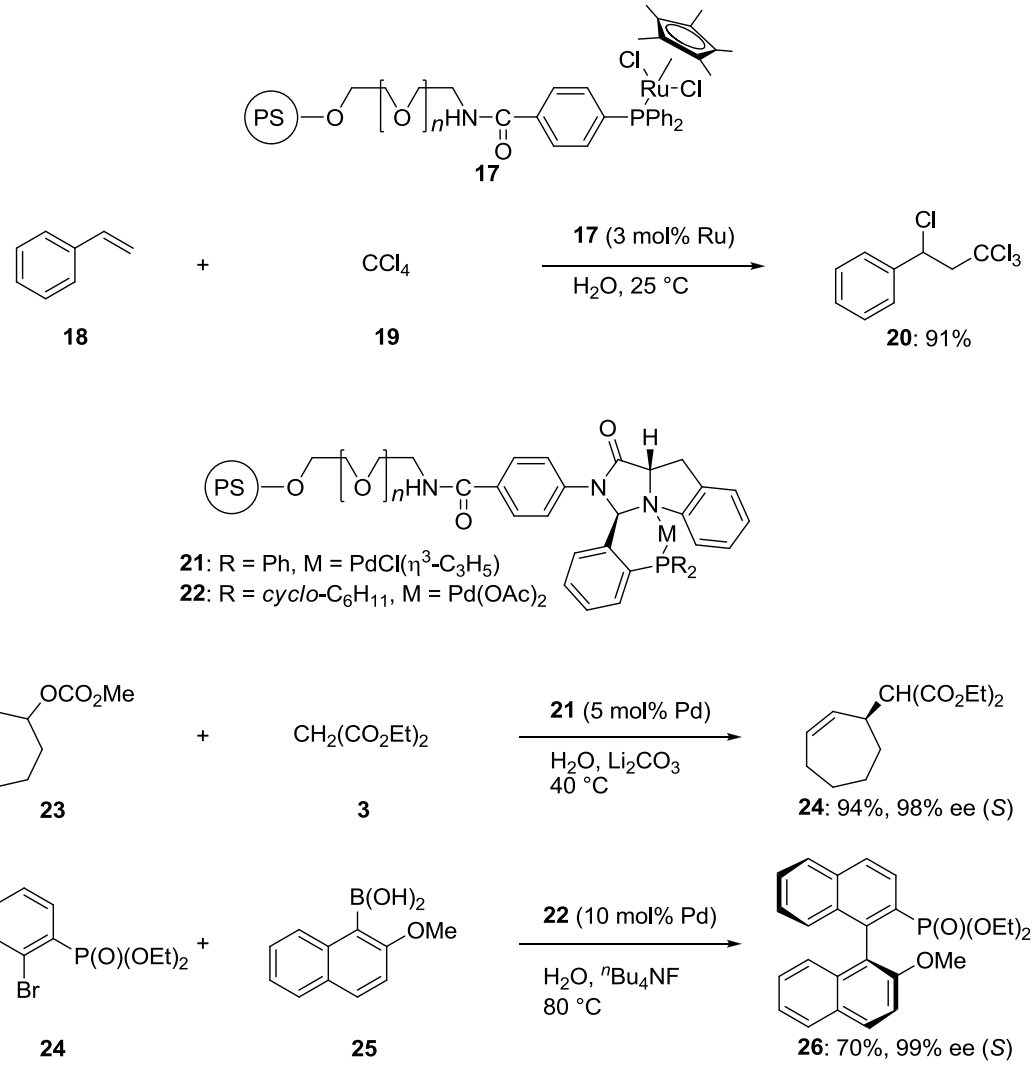


Scheme 7

Our group has recently developed amphiphilic polystyrene–poly(ethylene glycol) (PS-PEG) resin-supported transition metal catalysts[20] which promote various catalytic transformations smoothly in water under heterogeneous conditions, including palladium-catalyzed arylation (Suzuki–Miyaura coupling), alkenylation (Heck reaction), alkynylation (Sonogashira coupling), carbonylation of aryl halides, π-allylic substitution (Tsuji–Trost reaction), cyclization of 1,6-enynes, and addition of Carbon tetrachloride to olefins (Kharasch addition) (Scheme 8, Scheme 9).


PS
O
O
n
HN
C
O
PPh2
Pd
Cl
1
OAc
Ph
Ph
2
+
CH2(CO2Et)2
3
1 (2 mol% Pd)
H2O, K2CO3
25 °C
CH(CO2Et)2
Ph
Ph
4: 94%
I
5
+
CO (1 atm)
6
1 (10 mol% Pd)
H2O, KOH, 25 °C
then H+
CO2H
7: ave. 97% (30 reuses)
I
5
+
CO2H
8
1 (10 mol% Pd)
H2O, KOH, 25 °C
then H+
CO2H
9: 96%
PS
O
O
n
N
PPh2
Pd+
PPh2
Cl-
10
I
5
+
(HO)2B
11
10 (2 mol% Pd)
H2O, K2CO3
50 °C
12: 99%
PS
O
O
n
HN
C
O
PPh2
RhCl(CO)
P
Ph2
13
O
14
+
(HO)2B
15
13 (3 mol% Rh)
Base, H2O, 25 °C
O
16: 81%

Scheme 8



Scheme 9

Many organic reactions are conducted in organic solvents from the viewpoint of solubility of the substrate. The amphiphilic PS-PEG resin-supported transition metal catalysts show interesting characteristics to promote the reaction in the water. The reason for the high activity of these catalysts in water has been clarified as follows. Organic molecules don't dissolve in water; therefore, they are concentrated to polystyrene

matrix which has the highest hydrophobicity in the reaction system. This polymer matrix has transition metal complexes as active center, and the concentrated substrates react quickly to provide desired compounds.(Figure 4) Furthermore, the PS-PEG catalysts have some excellent characters in an environment aspect, for example, easily recovery and recycling, and high level metal uncontamination to products.

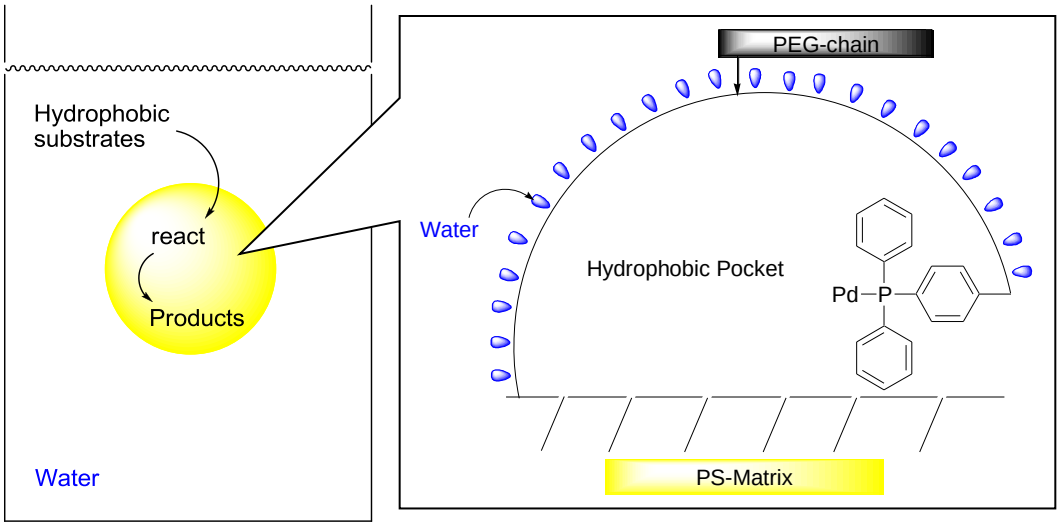


Figure 4. Schematic image of PS-PEG supported Pd complex catalysis in water.

If the C-X bond-forming coupling, including C-N, C-S, and C-P bonds, could be achieved in water with readily recoverable immobilized catalysts, the transformation could be considered an ideal C-X bond-forming coupling process.

From the above, I decided to study the development of novel amphiphilic

polystyrene–poly(ethylene glycol) (PS-PEG) resin-supported transition metal catalysts for various C-X bond-forming coupling. The result of the present study will be described from the next chapter.

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Chapter I: Development of novel amphiphilic polymer-supported phosphine ligands [1]

It has been well-documented that the aromatic amination is efficiently catalyzed by palladium complexes possessing sterically hindered alkylphosphine ligands, for example, RP(*tert*-C_4H_9)$_2$ and RP(*cyclo*-cyclohexyl)$_2$, and a variety of alkylphosphine ligands have been designed and prepared for driving the amination catalysis. The representative examples of the ligands are shown in Figure 1.[2, 3, 4, 5]

The amination is generally carried out in toluene with heating in the presence of a strong alkoxide base, such as NaO^{t}Bu, under homogeneous conditions. Buchwald reported an isolated example of aromatic amination in water in 2003, by use of 2-{di(cyclohexyl)phosphino}-2',4',6'-tri(isopropyl) biphenyl (compound **D,** Figure 1),[5] and pioneering work on the heterogeneous-switching of aromatic amination using an immobilized phosphine–palladium complex (ligand **E**, Figure 1) in 2001.[6, 7, 8]

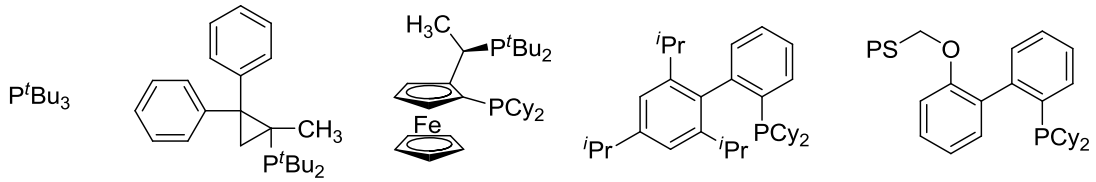
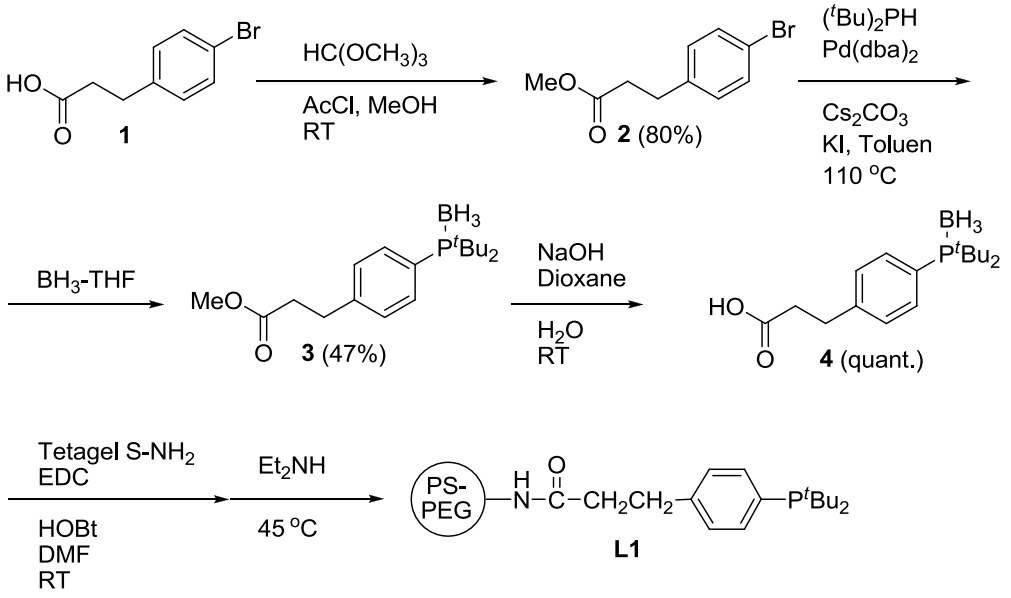


Figure 1. Representative examples of phosphine ligands for the Buchwald-Hartwig amination.

However, to the best of our knowledge, no catalyst system has yet been developed to accomplish the heterogeneous- and aqueous-switching of the amination in one system. As a result, I decided to prepare the palladium complexes co-ordinatively anchored onto the amphiphilic polystyrene–poly(ethylene glycol) copolymer (PS-PEG)[9] resin-supported bulky alkylphosphines as possible water-compatible polymeric ligands, for aromatic amination catalyst.[10, 11]

*Preparation of **L1** (Scheme 1)*: Esterification of compound **1** with trimethyl orthoformate and catalytic hydrogen chloride generated by the reaction of acetyl chloride and MeOH provided the corresponding ester **2** in 80% yield. C-P bond-forming reaction of compound **2** in the presence of Pd catalyst was proceeded, followed by hydrolysis of ester gave phosphine-boran **4** in 47% yield. Condensation reaction of Tentagel S-NH_2 (PS-PEG-NH_2) and compound **4** with 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and

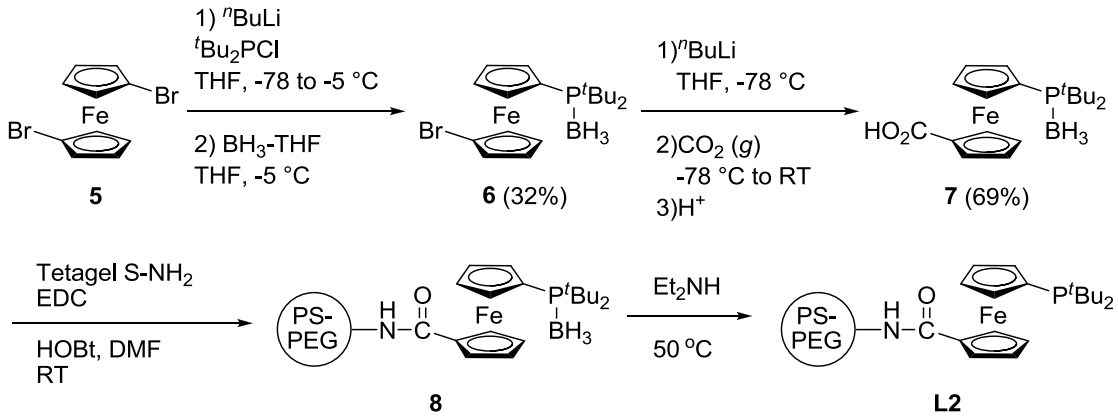
1-Hydroxybenzotriazole (HOBt) in DMF and deprotection with diethylamine gave the corresponding resin-supported phosphine **L1**. The structural studies on the resin-supported phosphine **L1** were performed by gel-phase $^{31}P\{^{1}H\}$ NMR spectroscopy where a narrow singlet at δ = +36.8 ppm was observed to demonstrate the introduction of the di(*tert*-butyl)phosphino group onto the resin.



Scheme 1

Preparing ***L2*** *(Scheme 2)* : Phosphination of monolithiated dibromoferrocene **5** with $^{t}Bu_2PCl$ and the following protection of the resulting phosphine with borane gave compound **6** in 32% yield. The reaction of compound **6** with *n*-butyllithium and the subsequent treatment with carbon dioxide provided the corresponding acid **7** in 69% yield.

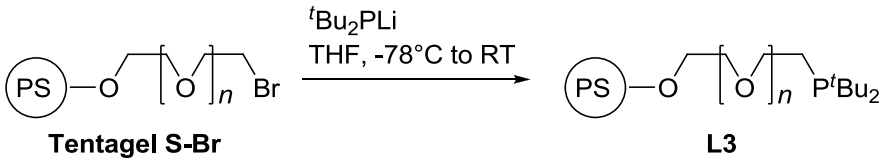
Condensation of Tentagel S-NH_2 with the acid **7** with the same method for the synthesis of **L1** afforded compound **8**. The structural studies on the resin-supported phosphine-boran **8** were performed by gel-phase $^{31}P\{^1H\}$ NMR spectroscopy where a singlet at δ = +43.6 ppm was observed to demonstrate the introduction of the borane protected di(*tert*-butyl)phosphino group onto the resin. Deprotection of phosphine-borane with diethylamine provides **L2**.



Scheme 2

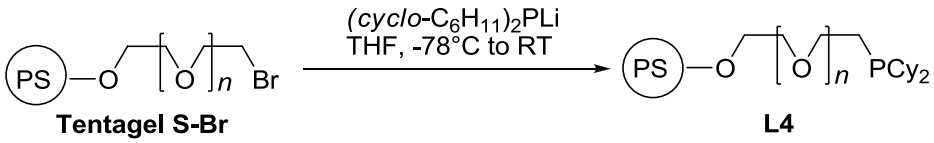
*Preparing **L3** (Scheme 3)*: PS-PEG- $OCH_2CH_2P(tert\text{-}C_4H_9)_2$ (**L3**) was readily prepared via the nucleophilic substitution of PS-PEG-Br[12] with lithium di(*tert*-butyl)phosphide. The structural studies on the resin-supported phosphine **L3** were performed by gel-phase $^{31}P\{^1H\}$ NMR spectroscopy where a narrow singlet at δ = +19.7 ppm was observed to demonstrate the introduction of the di(*tert*-butyl)phosphino group onto the

resin. The ICP-atomic emission spectroscopy (AES) analysis demonstrated the loading value of the phosphine unit to be 0.21 mmol/g.



Scheme 3

*Preparing **L4** (Scheme 4)*: **L4** was prepared by same method of **L3**. The structural studies on the resin-supported phosphine **L4** were performed by gel-phase $^{31}P\{^1H\}$ NMR spectroscopy where a narrow singlet at $\delta = -11.4$ ppm was observed to demonstrate the introduction of the di(*tert*-butyl)phosphino group onto the resin.



Scheme 4

In conclusion, I prepared the amphiphilic PS-PEG resin-supported bulky alkylphosphines, as water-compatible polymeric ligands, for aromatic amination catalysis. In the next chapter, I will describe the Buchwald-Hartwig type amination with these PS-PEG resin-supported phosphine ligands in water.

Experimental section

All manipulations were performed under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. Water was deionized with a Millipore system as a Milli-Q grade and was degassed by the freeze-pump-thaw method prior to use. NMR spectra were recorded on a JEOL JNM-A500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, 202 MHz for ^{31}P) or a JEOL JNM–AL400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 162 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ as an internal standard (δ 77.0). The ^{31}P NMR data are reported relative to external Ph_3P. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or CD_3OD at 25 °C. ICP-AES analyses were performed on Leeman Labs Inc. Profile Plus using palladium standard solution (KANTO CHEMICAL) and phosphine standard solution (KANTO CHEMICAL) as a standard. The ESI mass spectra were recorded on a JEOL JMS-T100LC spectrometer. The GC-MS was measured by an Agilent 6890 GC/5973N MS detector. The FAB mass spectra were recorded on a

JEOL MS700V. The IR spectra were obtained using a JASCO FT/IR-460plus spectrophotometer in ATR mode. PS-PEG amino-resin was purchased from RAPP POLYMERETM (TentaGel®S NH_2, average diameter 0.90 μm, 1% divinylbenzene crosslinked, loading value of bromo residue 0.1-0.3 mmol/g). PS-PEG bromo-resin was purchased from RAPP POLYMERETM (TentaGel®S Br, average diameter 0.90 μm, 1% divinylbenzene crosslinked, loading value of bromo residue 0.2-0.3 mmol/g).

Preparation of polymer supported ligand L1.

To a mixture of 3-(4-bromophenyl)propionic acid (**1**) (3.02 g, 13.2 mmol) and THF (110 mL) was added trimethyl orthformate (18.0 g, 170 mmol) at ambient temperature. The reaction mixture was added Acetyl chloride (1.32 g, 16.9 mmol) in MeOH (18.6 mL) solution at ambient temperature and stirred for 15 hr. The mixture was evaporated in vacuo and added ethyl acetate (50 mL). The organic solution was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentered in vacuo. The residue was purified by flash chromatography to give colorless oil (2.57 g, 80.2 mol% of methyl 3-(4-Bromophenyl)-propionate)

(**2**). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.40 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 3.67 (s, 3H), 2.90 (t, 2H, J = 8 Hz), 2.61 (t, 2H, J = 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 173.0, 139.4, 131.6, 130.1, 120.1, 51.7, 35.4, 30.3.

Under the nitrogen atmosphere, a solution of methyl 3-(4-Bromophenyl)-propionate (**2**) (1.01 g, 4.14 mmol), $^{t}Bu_2PH$ (0.70 g, 4.82 mmol), $Pd(dba)_2$ (127 mg, 0.22 mmol), Cs_2CO_3 (2.03 g, 6.22 mmol), KI (69.2 mg, 0.62 mmol) and toluene (10 mL) was refluxed for 28 h. The reaction mixture was added BH_3-THF (1M solution, 5 mL) at ambient temperature and stirred for 1 h. The mixture was washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give blown oil (625 mg, 47.0 mol% of **3**). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.90 (t, 2H, J = 8 Hz), 7.26-7.27 (m, 2H), 3.68 (s, 3H), 2.99 (t, 2H, J = 8 Hz), 2.66 (t, 2H, J = 8.5 Hz), 1.31 (t, 18H, J = 12.5 Hz), 0.50-1.00 (m,, 3H); ^{31}P NMR (202 MHz, $CDCl_3$, 25 °C) δ +43.1, +42.8; MS (EI(+)): *m/z* 308 $[M-BH_3]^+$.

To a solution **3** (219 mg, 0.68 mmol), 1,4-Dioxane (5 mL), and water (5 mL) was added NaOH (100 mg, 2.40 mmol) and the mixture was stirred for 12 h

at ambient temperature. The reaction mixture was washed with MTBE (10 mL) and added 3M hydrochloric acid (pH = 14 to 1). The mixture was extracted with MTBE (10 mL, 2 times) and the organic layer was washed with brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give **4** in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.91 (t, 2H, J = 8 Hz), 7.28 (d, 2H, J = 7 Hz), 3.00 (t, 2H, J = 7.5 Hz), 2.72 (t, 2H, J = 7.5 Hz), 1.31 (d, 18H, J = 13 Hz), 0.40-1.05 (m, 3H); ^{31}P NMR (202 MHz, $CDCl_3$, 25 °C) δ +43.2, +42.8.

A Merrifield vessel was charged with Tentagel S-NH_2 (1.00 g, 0.123 mmol/g, 0.123 mmol of NH_2), **4** (136 mg, 0.44 mmol), EDCI·H_2O (127 mg, 0.66 mmol), HOBt (119 mg, 0.88 mmol), and DMF (20 mL), and the reaction mixture was shaken on a wrist-action shaker at 25 °C for 4 h. The reaction mixture was filtered and the resin was washed with DMF (20 mL, 5 times) and dichloromethane (20 mL, 8 times). The resin was dried under reduced pressure. The obtained resin and Et_3N (10 mL) was shaken at 45 °C for 13 h. The reaction mixture was filtered and the resin was washed with dichloromethane (10 mL, 2 times). The resin was dried under reduced

pressure to give polymer supported ligand **L1** (1.04 g). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C) δ +36.8.

Preparation of polymer supported ligand L2.

Under the nitrogen atmosphere, to a mixture of 1,1'-dibromoferrocene (2.05 g, 5.95 mmol) and THF (20 mL) was added *n*-Butyllithium (2.77 mol/L in hexane, 2.1mL 5.82 mmol) at -78 °C. The reaction mixture was stirred for 30 min and added $^{t}Bu_2PCl$ (1.19 g, 6.32 mmol). The reaction mixture was warmed to ambient temperature and stirred for 1 h. The reaction mixture was added BH_3-THF complex (1.06 mol/L in THF, 6.3 mL, 6.68 mmol) at -5 °C and stirred at -5 °C for 12 h. The reaction mixture was added MTBE (30 mL) and washed with water (30 mL). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4. The organic layer was concentrated in *vacuo*. The residue was purified by flash chromatography and recrystallized from MTBE and hexane to give **6** (1.11g, 31.7mol%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 4.29-4.53 (m, 8H), 1.29 (d, 18H, J = 13 Hz), 0.40-0.95 (m, 3H); ^{31}P NMR (202 MHz, $CDCl_3$, 25 °C) δ +44.3, +44.0, +43.7, +43.5.

Under the nitrogen atmosphere, to a mixture of **6** (1.00 g, 2.37 mmol) and THF (20 mL) was added *n*-butyllithium (2.77 mol/L in hexane, 0.86 mL, 2.38 mmol) at -78 ˚C and stirred for 30 min. The reaction mixture was added CO_2 (gas) and warmed to ambient temperature. The reaction mixture was stirred for 3.5 h and added MTBE (30 mL) and water (30 mL). The mixture was adjusted to pH=2 with 3N hydrochloric acid and separated. The organic layer was washed with brine (30 mL) and dried over Na_2SO_4. The solution was concentrated in *vacuo*. The residue was purified by flash chromatography to give **7** (633 mg, 68.7 mol%) as orange solid. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ˚C): δ 4.91 (d, 2H, J = 2 Hz), 4.67 (d 2H, J = 2 Hz), 4.58 (s(br), 2H), 4.54 (s(br), 2H), 1.28 (d 18H, J = 13 Hz), 0.70 (m, 3H); ^{31}P NMR (202 MHz, $CDCl_3$, 25 ˚C) δ +43.7; MS (EI(+)): *m/z* 397 $[M+Na]^+$

A Merrifield vessel was charged with Tentagel S-NH_2 (1.00 g, 0.31mol/g, 0.31mol of NH_2), **7** (246 mg, 0.633 mmol), EDCI (131 mg, 0.682 mmol), HOBt (83.7 mg, 0.620 mmol), and DMF (10 mL), and the reaction mixture was shaken on a wrist-action shaker at 25 ˚C for 16 h. The reaction mixture was filtered and the resin was washed with dichloromethane (10 mL, 4 times). The resin was dried under reduced pressure to give **8**. ^{31}P NMR (162 MHz,

$CDCl_3$, 25 °C): δ 43.6. The resulted resin **8** was added Et_3N (10 mL) and shaken at 50 °C for 16 h. The reaction mixture was filtered and the resin was washed with dichloromethane (10 mL, 2 times). The residue was dried in vacuo to give polymer supported ligand **L4** (1.01 g). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): δ 55.9.

Preparation of polymer supported ligand L3.

To a mixture of di-*t*-butylphosphine (10% in hexane, 1.83 g, 1.25 mmol) and THF (10 mL, three freeze pump thaw cycles) was added *n*-butyl lithium (2.69 mol/L in hexane, 0.47 mL, 1.25 mmol) for 1 hour and the mixture was stirred at -78 °C for 1 h under nitrogen atmosphere. The reaction mixture was added to the TentaGel® S Br (2.01g, 0.50 mmol of bromine residue) in THF (20 mL, three freeze pump thaw cycles) at -78 °C under nitrogen atmosphere and stirred for 1 hour. The reaction mixture was warmed up to room temperature slowly and stirred for 1 h at ambient temperature. The mixture was filtered and washed with water (20 mL, 3 times), THF (20 mL, 3 times) and CH_2Cl_2 (20 mL, 3 times). The residue was dried in vacuo for 18 hour to give the polymer supported ligand **L3**. ^{31}P NMR (400 MHz, $CDCl_3$,

25 °C): δ 19.7.

Loading amount of phosphine was analyzed by ICP-AES. Ligand **L3** (19.7 mg) treated with 20% HNO_3 (3 mL) at 90 to 95 °C for 21 h and filtered. The filtrate was filled up with pure water to 50 mL and analyzed by ICP-AES. The loading value of phosphine was 0.21 mmol / g.

Preparation of ligand L4.

Ligand **L4** was prepared by similar procedure for the preparation of **L3**. ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): δ -11.4. The loading value of phosphine was 0.21 mmol / g.

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[1] This chapter are based on following papers, see: a) Y. Hirai, Y. Uozumi, Chem. Commun., 2010, 46, 1103; b) Y. Hirai, Y. Uozumi, Chem. Asian J., 2010, 5 (8), 1788.

[2] Ligand A: a) M. Nishiyama, T. Yamamoto, Y. Koike, Tetrahedron Lett. 1998, 39, 617; b) J. F. Hartwig, M. Kawatsura; S. I. Hauck, K. H. Shaughnessy, L. M. Aleazer-Roman, J. Org. Chem. 1999, 64, 5575; S. I. Hauck, K. H. Shaughnessy, L. M. Aleazer-Roman, J. Org. Chem. 1999, 64, 5575.

[3] Ligand B: K. Suzuki, Y. Hori, T. Kobayashi, Adv. Synth. Catal. 2008, 350, 652.

[4] Ligand C: Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, Angew. Chem. 2005, 117, 1395; Angew. Chem. Int. Ed. 2005, 44, 1371.

[5] Ligand D: a) X. Huang, K. W. Anderson, D. Zim, A. Klapars, S. L. Buchwald, J. Am. Chem. Soc. 2003, 125, 6653; b) K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altma, S. L. Buchwald, Angew. Chem. 2006, 118, 6673; Angew. Chem. Int. Ed. 2006, 45, 6523.

[6] Ligand E: C. A. Parrish, S. L. Buchwald, J. Org. Chem. 2001, 66, 3820.

[7] Kobayashi has also reported the heterogeneous amination catalysis with a polymer-incarcerated Pd with an external alkylphosphine: a) R. Nishio, S. Wessely, M. Sugiura, S. Kobayashi, J. Comb. Chem. 2006, 8, 459; b) T. Inasaki, M. Ueno, S. Miyamoto, S. Kobayashi, Synlett 2007, 3209.

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[9] a) E. Bayer, W. Rapp in Chemistry of Peptides and Proteins, Vol. 3 (Eds.: W.

Voelter, E. Bayer, Y. A. Ovchinikov, V. T. Iwanov), Walter de Gruter, Berlin, 1986, p. 3; b)W. Rapp in Combinatorial Peptide and Nonpeptide Libraries (Ed.: G. Jung), VCH, Weinheim, 1996, p. 425; c) X. Du, R. W. Armstrong, J. Org. Chem. 1997, 62, 5678; d) O. W. Gooding, D. Baudert, T. L. Deegan, K. Heisler, J. W. Labadie, W. S. Newcomb, J. A. Porco Jr. , P. J. Eikeren, J. Comb. Chem. 1999, 1, 113.

[10] Soluble non-crosslinked polymer-supported aryl(dicyclohexyl)- phosphines have been developed for solution-phase aromatic amination under homogeneous conditions; see: A. Leyva, H. Garcia, A. Corma, Tetrahedron 2007, 63, 7097.

[11] PS-PEG resin-supported aryl(dicyclohexyl)phosphine has been reported to promote the Suzuki–Miyaura coupling under heterogeneous conditions; see: a) K. Glegola, E. Framery, K. M. Pietrusiewicz, D. Sinou, Adv. Synth. Catal. 2006, 348, 1728; b) Y. Uozumi, Y. Matsuura, T. Arakawa, Y. M. A. Yamada, Angew. Chem. 2009, 121, 2746; Angew. Chem. Int. Ed. 2009, 48, 2708 (asymmetric cross-coupling).

[12] Tenta Gel S Br (supplier=RAPP Polymer; loading value of Br residue=0.20–0.25 mmol/g; average diameter=90 mm) was used.

Chapter II: Heterogeneous Aromatic Amination of Aryl Halides with Arylamines in Water with PS-PEG Resin-Supported Palladium complexes [1]

The amphiphilic polystyrene–poly(ethylene glycol) copolymer (PS-PEG)[2] resin-supported bulky alkylphosphines were synthesized in the previous chapter (Figure 1).

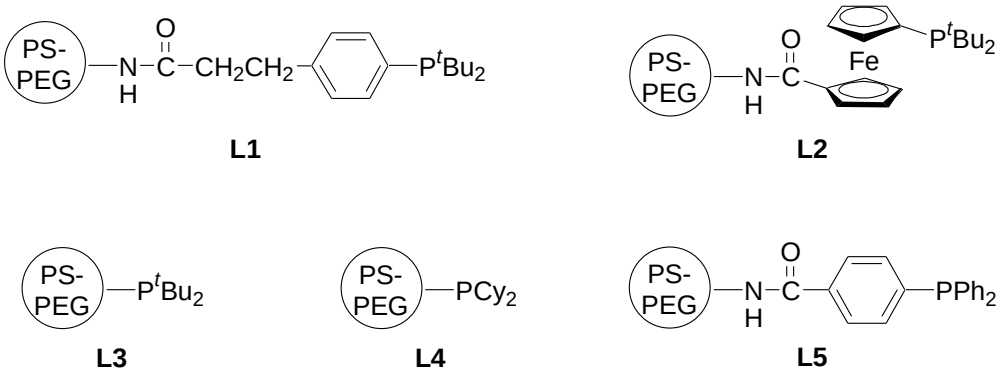
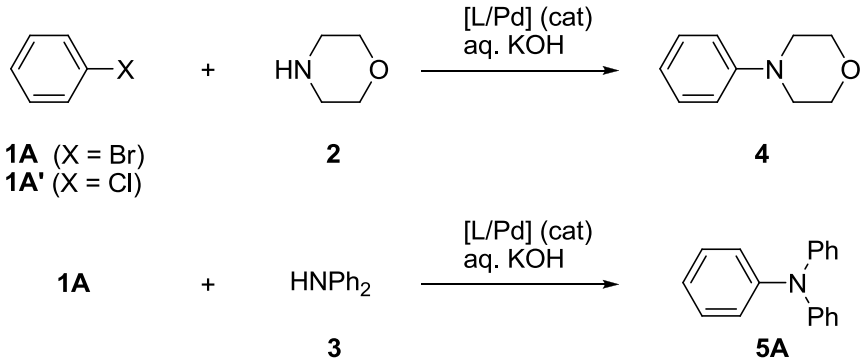


Figure 1

Preliminary screening of condition: I have examined several amphiphilic PS-PEG resin-supported phosphine ligands for the amination reaction of bromobenzene (**1A**) (Table 1). Thus, the C-N bond-forming coupling reaction of **1A** with morpholine (**2**) was carried out in refluxing aqueous KOH solution in the presence of a PS-PEG resin-supported palladium catalyst for 24 h. After being cooled the reaction mixture was filtered, and the catalyst beads were rinsed with EtOAc to extract the organic compounds.

Table 1. Amination of halobenzenes in water[a]



Entry	L	P/Pd	Product	Yield/%[b]
1	**L3**	1/1	**4**	74
2	**L5**	1/1	**4**	10
3	**L1**	1/1	**4**	22
4[c]	**L3**	1/1	**4**	64
5	**L3**	2/1	**4**	86
6	**L5**	1/1	**5A**	<1
7	**L1**	1/1	**5A**	<1
8	**L3**	1/1	**5A**	82
9[c]	**L3**	1/1	**5A**	81
10	**L3**	2/1	**5A**	92
11	**L2**	1/1	**5A**	41
12	**L4**	1/1	**5A**	3
13	**L4**	2/1	**5A**	<2

[a] All reactions were carried out with PhBr (**1A**) in 20M aqueous KOH solution under reflux in the presence of 5mol% 1/2$[PdCl(\eta^3\text{-}C_3H_5)]_2$ and a polymeric ligand (**L**) for 17-24h, unless otherwise noted. The ratio of **1** (mol)/**2** or **3** (mol)/H_2O (L) = 1.0/1.5/2.0. [b] Isolated yields. [c] PhCl (**1A'**) was used.

The combined extract was concentrated and the resulting residue was chromatographed on silica gel to give the *N*-phenylmorpholine (**4**) (Entries 1–5). The results reveal that the palladium-complex bound to the PS-PEG-di(*tert*-butyl)phosphine resin **L3** is the best catalyst for the amination reaction of **1A** and **2** in water. Thus, the palladium complex with L3 catalyzed the reaction of **1A** and **2** in an aqueous KOH solution to give *N*-phenylmorpholine (**4**) in 74% isolated yield (Entry 1). Lower catalytic activity was observed in water with **L5** and **L1** (Entries 2 and 3). It is noteworthy that the polymer supported palladium complex of **L3** also promoted the C-N coupling of chlorobenzene (**1A'**) under similar conditions to give 64% yield of **4** (Entry 4). The best result was obtained with a palladium complex prepared by mixing **L3** and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in a ratio of P/Pd = 2/1 to give compound **4** in 86% yield (Entry 5). A similar trend was also observed in the reaction of **1A** with diphenylamine (**3**) (Entries 6–13). The amination with diphenylamine hardly proceeded with a palladium complex of polymeric arylphosphines (Entries 6 and 7). Ferrocenyl[di(*tert*-butyl)] phosphine **L2** gave a moderate yield of triphenylamine (**5A**) under similar conditions (Entry 11). A palladium complex of sterically demanding

alkylphosphine **L3** promoted the amination of bromobenzene (**1A**) as well as chlorobenzene (**1A'**) in refluxing aqueous KOH solution to give triphenylamine (**5A**) in 82 and 81% yield, respectively (Entries 8 and 9). A polymer supported palladium complex prepared from **L3** (P/Pd = 2/1) provided **5A** in 92% yield (Entry 10). The polymer supported palladium complex generated from the **L4** hardly catalyzed the amination to give only 3% yield of **5A** under similar conditions (entry 12). A polymer supported complex of **L4** (P/Pd=2:1) again showed little catalytic activity for the amination (entry 13). The role of the *P*-substituents (*tert*-butyl vs cyclohexyl) is not clear yet, but it has been reported that [alkyl(^{t}Bu)$_2$P] (Figure 2, **A**, **B**, or **C**) and [aryl(*cyclo*-Hex)$_2$P] (Figure 2, **D** or **E**) can be used as an effective ligands for the Buchwald–Hartwig aromatic amination under the standard homogeneous conditions.

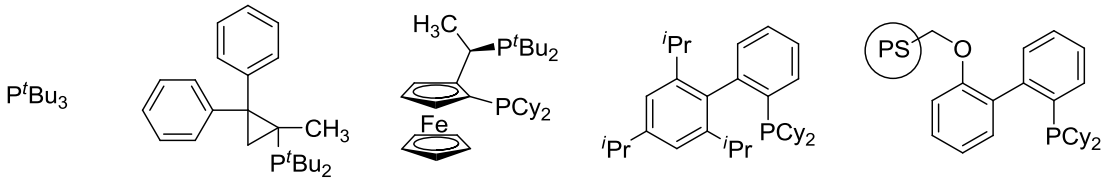
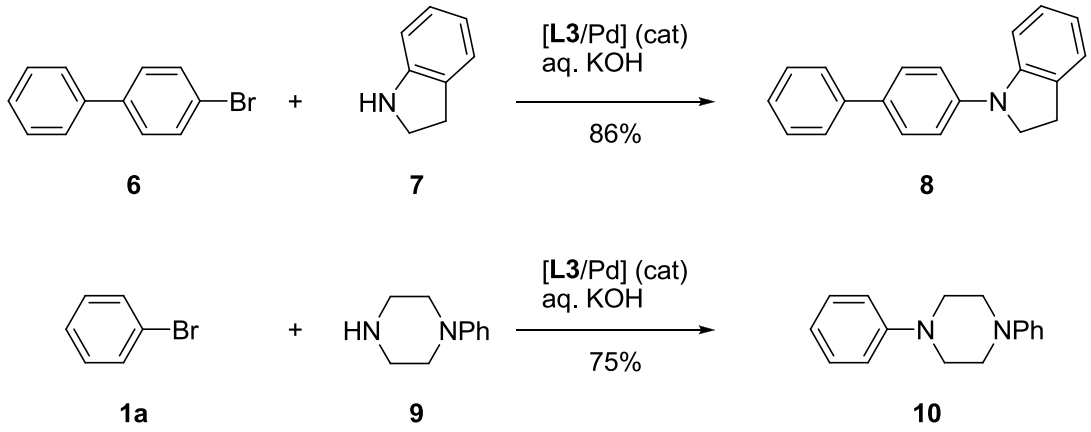


Figure 2. Representative examples of phosphine ligands for the Buchwald-Hartwig amination.

Amination reactions with indoline (**7**) and *N*-phenylpiperazine (**9**) were also examined successfully with **L3** under otherwise the same conditions to

afford *N*-biphenyl-4-ylindoline (**8**) and *N,N'*-diphenylpiperazine (**10**) in 86 and 75% yield, respectively (Scheme 1).



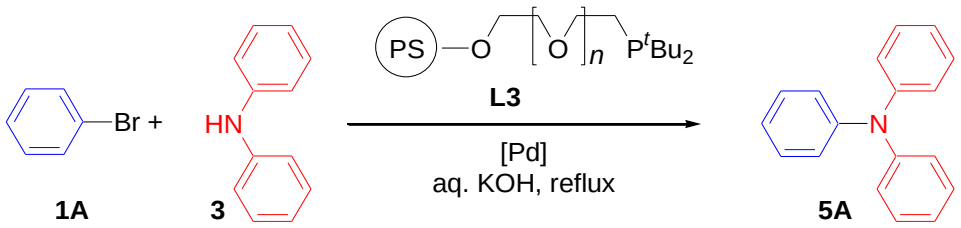
Scheme 1. C-N coupling with nitrogen heterocycles.

Optimization of condition: According to the results for the screening of the ligand and P/Pd ratio, further optimization of reaction conditions was performed with changing Pd precatalyst and P/Pd ratio. Considering the utility of the products as electroactive materials, I decided to study the catalytic aromatic amination with diarylamines affording triarylamines. In contrast to the vast amount of research on aromatic amination with alkylamines, only scant attention has been focused on aromatic amination with diarylamines, which is thus still a major challenge even with homogeneous catalysts.[3] In addition, a clean synthesis of triarylamines with little metal contamination would be a welcome process owing to their

potential optoelectronic properties.[4] The reaction conditions were initially screened for the coupling of bromobenzene (**1A**) with diphenylamine (**3**) to afford triphenylamine (**5A**) with the palladium complexes by mixing the polymer supported phosphine **L3**, and the palladium reagent, $[PdCl(\eta^3\text{-}C_3H_5)]_2$, $[Pd(dba)_2]$, or $[Pd(OAc)_2]$, in an appropriate ratio prior to their catalytic use (Table 2). Thus, the reaction of **1A** with **3** (1.5 equiv to **1A**) was performed with a palladium complex of PS-PEG resin-supported phosphine in aqueous KOH solution under reflux for 24 h. It is also noteworthy that the aromatic amination took place with KOH as a base in water, whereas an alkoxide base (e.g., NaO*t*Bu) is frequently required to promote the reaction under the standard homogeneous conditions in an organic solvent. The hydrophobic organic substrates must diffuse into the hydrophobic polystyrene matrix in water to provide a highly self-concentrated reaction sphere where the coupling reaction releasing KBr into the aqueous phase should be significantly accelerated to reduce the initial molar concentration in the polymer matrix. After being cooled, the mixture was filtered, and the catalyst beads were rinsed with EtOAc to extract the organic products. The extract was concentrated in vacuo to give

crystals of triphenylamine (**5A**) with chemical purity of >95% as was determined by NMR and GC analysis without any chromatographic purification. The recovered polymer beads were recycled for amination under the same conditions without any further purification and additional charge of palladium. Representative results are summarized in Table 1 (entries 8-10), along with the recovered polymeric complexes. When the reaction was carried out in refluxing 20 M aqueous KOH with the polymeric complex prepared from **L3** and di(μ-chloro)bis(η^3-allyl)- dipalladium(II) {[PdCl(η^3-C_3H_5)]$_2$} (P/Pd=1/1), the desired Ph_3N (**5A**) was obtained in 87% yield (Table 2, entry 1) (conversion of **4**=100%, isolated yield of **5A**=87%, purity of **5A**=>95%). The chemical yield of **5A** decreased as the concentration of palladium or base decreased (entries 2 and 3). A palladium complex prepared from [$Pd(OAc)_2$] with L3 exhibited a slightly lower catalytic performance than that prepared from [PdCl(η^3-C_3H_5)]$_2$ (entry 1 vs 4).

Table 2. Screening of the reaction conditions forming Ph3N (5A) via the reaction of PhBr (1A) and Ph2NH (3) in water with polymeric palladium complexes.[a]



entry	Pd source (mol% of Pd)	polymeric phosphine	P/Pd	yield (%)[e]
1	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0)	**L3**	1:1	87
2[b]	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0)	**L3**	1:1	46
3	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (2.5)	**L3**	1:1	51
4	$Pd(OAc)_2$ (5.0)	**L3**	1:1	82
5[c]	$Pd(dba)_2$ (5.0)	**L3**	1:1	96
6	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0)	**L3**	2:1	87
7[d]	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0)	**L3**	2:1	92
8[d]	recycled catalyst beads from entry 1 (3rd reuse)			74
9[d]	recycled catalyst beads from entry 7 (3rd reuse)			90
10[d]	recycled catalyst beads from entry 9 (5th reuse)			91

[a] All reactions were carried out in refluxing aqueous KOH (20M). The ratio of **1A** (mol)/**3** (mol)/H_2O (L)=1.0:1.5:2.0, unless otherwise noted. [b] Aqueous 5 M KOH was used. [c] During the reaction, the polymeric palladium complex decomposed (palladium black precipitated out inside the polymer matrix). [d] The ratio of **1A** (mol)/**3** (mol)/H_2O (L)=1.5:1.0:2.0. [e] Yields of isolated product based on **1A** (entries 1–6) or **3** (entries 7, and 8–10).

While palladium bis(dibenzylideneacetone) [$Pd(dba)_2$] was found to be a good

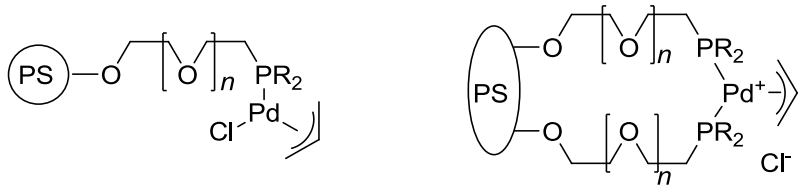
Pd source, affording a high yield of **5A**, as compared to $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the polymeric complex prepared with $[Pd(dba)_2]$ decomposed during the reaction (entry 5). When the amination was examined with the palladium complex prepared by mixing the polymer supported ligand **L3** and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in a ratio of P/Pd=2:1, **5A** was obtained in 87% yield of isolated product (entry 6; yield based on **1A**). When the reaction was carried out with **1A** and **3** in a ratio of 1.5:1.0, i.e., the inverse substrate ratio to that of entry 6, the amination proceeded smoothly as in entry 6, to give **5A** in 92% yield (entry 7; yield based on **3**). Thus, the ratio of the reaction substrates (halide/amine) is optional.

Next, I examined the recyclability of the catalyst beads and found that the stability of the polymer supported catalyst significantly increased with a complexation ratio of P/Pd=2:1 (Table 2, entries 8–10), though the initial catalytic activity was not affected by the complexation ratio of phosphine to palladium (entry 1 vs 6). Thus, the catalyst beads prepared in a P/Pd ratio of 1:1 were recovered from the first run (entry 1) and subjected to several recycling runs through repetition of the standard manipulation (reaction and workup). Catalytic activity decreased as the recycling was repeated,

resulting in a 74% yield of **5A** in the third recycling run. The polymer supported catalyst prepared in a P/Pd ratio of 2:1 was also recovered from the first run (entry 6) and reused to demonstrate its high recyclability. Thus, under similar conditions, the third and fifth reuses showed high catalytic performance affording **5A** in 90% and 91% yield, respectively (entries 8 and 10).[5]

Structural studies on the polymer supported palladium complexes generated by mixing **L3** and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in ratios of 1:1 and 2:1 (P/Pd) were conducted with gel-phase $^{31}P\{^1H\}$ NMR and ICP-AES analyses (Figure 3). Formation of the palladium complexes $[PdCl(\eta^3\text{-}C_3H_5)(phosphine)]$ (P/Pd=1:1) and $[PdCl(\eta^3\text{-}C_3H_5)(phosphine)_2]Cl$ (P/Pd=2:1) was achieved by mixing $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and an appropriate molar equivalent of the phosphine **L3** in dichloromethane at ambient temperature for 60 min. Upon conversion of the polymeric phosphine **L3** to the palladium–phosphine complexes $[PdCl(\eta^3\text{-}C_3H_5)(phosphine)]$ (P/Pd=1:1) and $[Pd(\eta^3\text{-}C_3H_5)(phosphine)_2]Cl$ (P/Pd=2:1), the phosphorus signals shifted downfield to +54.4 ppm and +40.6 ppm, respectively. Thus, the reaction progress with **L3** (P/Pd=1:1) was conveniently monitored by gel-phase

$^{31}P\{^{1}H\}$ NMR spectroscopy of the resin beads dispersed in [D]chloroform. After the complexation was completed, it was noted that a narrow singlet observed at δ = +19.7 ppm of the starting phosphine **L3** disappeared and a new resonance at δ = +54.4 ppm increased. The remarkably low-field shift demonstrates that the phosphino group of **L3** coordinates to palladium forming a π-allylpalladium–phosphine complex on the amphiphilic solid support. Using similar procedures, I prepared a palladium–bis(phosphine) complex by mixing $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 2 molar equivalents of the phosphine **L3** (vs the palladium) where a new narrow singlet resonance at δ=+54.8 ppm had appeared. ICP-AES analysis of the palladium–phosphine complexes **L3**-Pd (P/Pd=1:1) and **L3**-Pd (P/Pd=2:1) showed the ratio of phosphorus, palladium, and chlorine to be 0.9:1.0:1.0 and 1.9:1.0:1.1, demonstrating that their structures are $[PdCl(\eta^3\text{-}C_3H_5)(phosphine)]$ (P/Pd=1:1) and $[PdCl(\eta^3\text{-}C_3H_5)(phosphine)_2]Cl$ (P/Pd=2:1), respectively, as depicted in Figure 3. The high recyclability of the palladium complex, prepared with 2 molar equivalents of the polymeric phosphine **L3** (vs the palladium) (Table 2, entries 8 and 9), can be attributed to the chelating coordination by the two phosphino groups.



L3/Pd (P/Pd = 1/1) (R = ^{t}Bu)

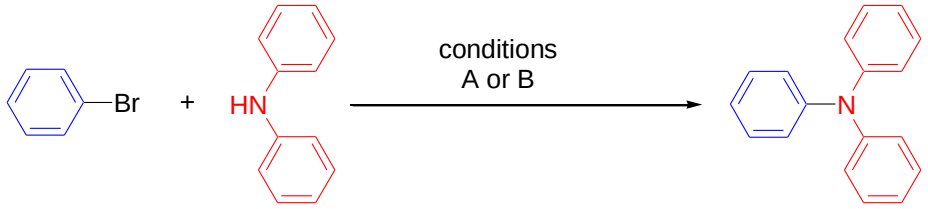
L3/Pd (P/Pd = 2/1) (R = ^{t}Bu)

Figure 3. Proposed structures of the polymeric palladium complexes.

It is also noteworthy that little palladium residue was contaminated in the coupling product **5A** when the procedure in entry 7 of Table 2 was employed. Thus, ICP-AES analysis revealed that the palladium species that leached from the polymeric catalyst to contaminate the 1 st crop crystals of Ph_3N (**5A**; from ethyl acetate-hexane) was lower than the detection limit of ICP-AES analysis. The standard homogeneous amination conditions and usual post treatment (organic-aqueous extraction, filtration, solidification, recrystallization) gave crystals of **5A** infected with 0.071% of palladium (Table 3, conditions B).

Consequently, the catalytic conditions employed in entry 7 of Table 2 were identified as the best system to achieve both heterogeneous- and aqueous-switching of the aromatic amination with high catalytic and recycling performance, which should realize a green and clean preparation of triarylamines with only negligible metal contamination.

Table 3. Comparative studies on the amination product 5A by heterogeneous and homogeneous aromatic amination of 1A with 3.[a]

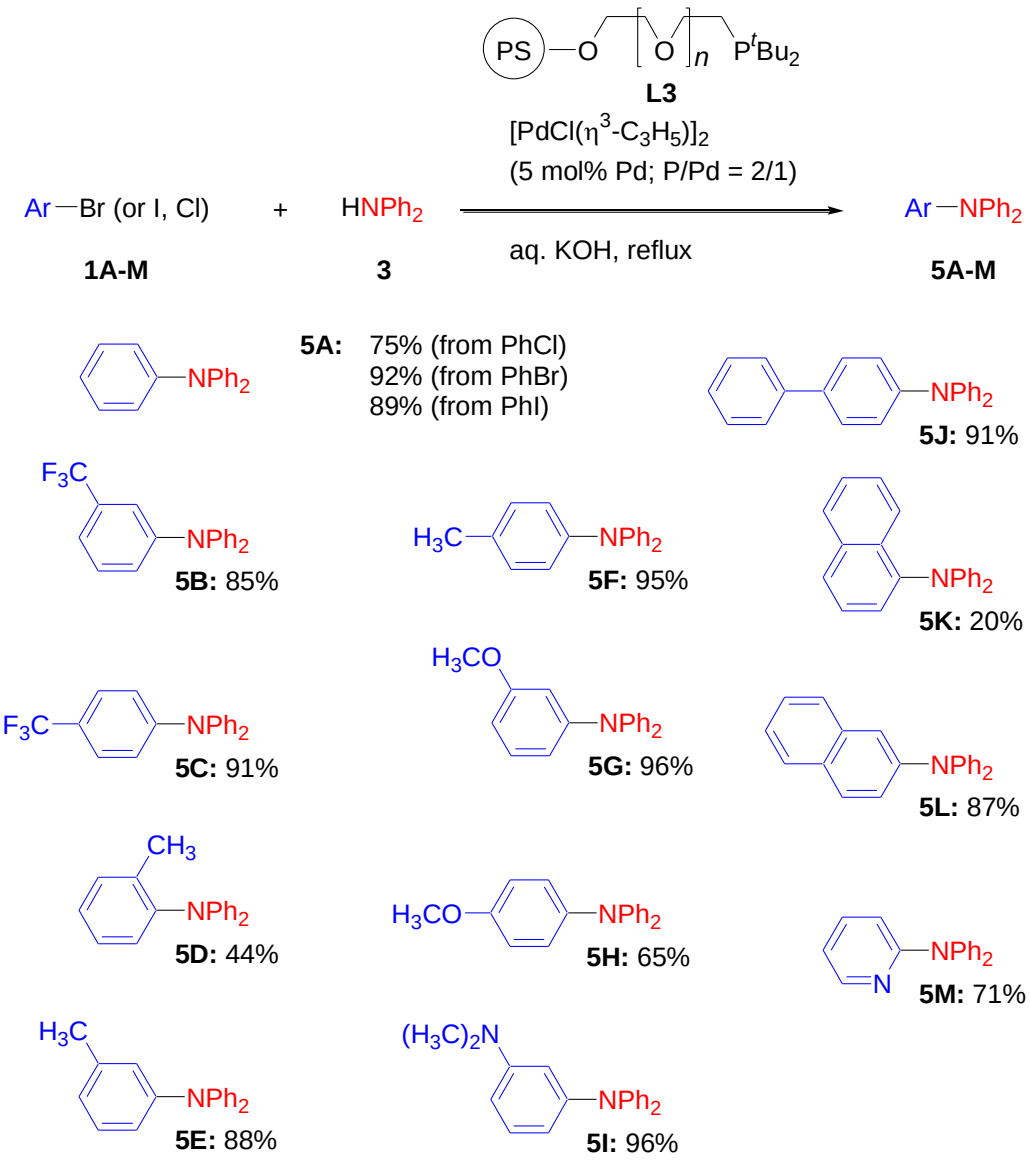


	conditions A[a]	conditions B[b] (homogeneous conditions)
yield (%) of isolated 1st crop crystals[c]	74	73
chemical purity (%)[d]	>99	97
contaminating value (%) of Pd[e]	<0.0015	0.071

[a] Conditions A: According to the conditions employed in Table 2, entry 7. The reaction scale=5.2 mmol (Ph_2NH). [b] Conditions B: The reaction was carried out with [$Pd(dba)_2$] (5 mol% Pd), $^tBu_3P$ (10 mol%), and NaO^tBu (1.1 equiv) in 1,4-dioxane at 100 °C for 3 h (100% conversion). The reaction scale=5.2 mmol (Ph_2NH). The ratio of **1A** (mol)/**3** (mol)/solvent (L)=1.5:1.0:2.0. [c] Recrystallized from EtOAc/hexane. [d] Determined by GC titration with [$(4\text{-}CH_3C_6H_4)_3N$] as an internal standard. [e] Determined by ICP-AES analysis.

Amination of various haloarenes: The heterogeneous aquacatalytic amination in water was examined with a variety of haloarenes under the reaction conditions identified above (see, Table 2, entry 7) and exhibited wide

substrate scope (Scheme 2). Thus, the amination catalysis with phenyl chloride and iodide proceeded in water as smoothly as that with phenyl bromide under the same conditions to afford triphenylamine (**5A**) in 75% and 89% yield, respectively. Electron-withdrawing and electron-donating substituents, such as CF_3, CH_3, OCH_3, $N(CH_3)_2$, and Ph groups, were tolerated under the same conditions to give the corresponding triarylamines **5B**–**5J** in good to excellent yield. The catalytic efficiency of the amination was strongly affected by substituents at the *ortho* position of the bromoarenes. Thus, the amination of *ortho*-tolyl bromide (**1D**) gave 44% yield of **5D**, whereas that of *meta*- and *para*-tolyl bromides (**1E** and **1F**) afforded the corresponding **5E** and **5F** in 88% and 95% yield, respectively. A similar steric effect was also observed with 1- and 2-bromonaphthalene (**1K** and **1L**), where the desired triarylamines **5K** and **5L** were obtained in 20% and 87% yield, respectively. The heteroaromatic halide **1M** also underwent amination in water under similar conditions to give diphenyl(pyridyl)amine **5M** in 71% yield (Scheme 2).



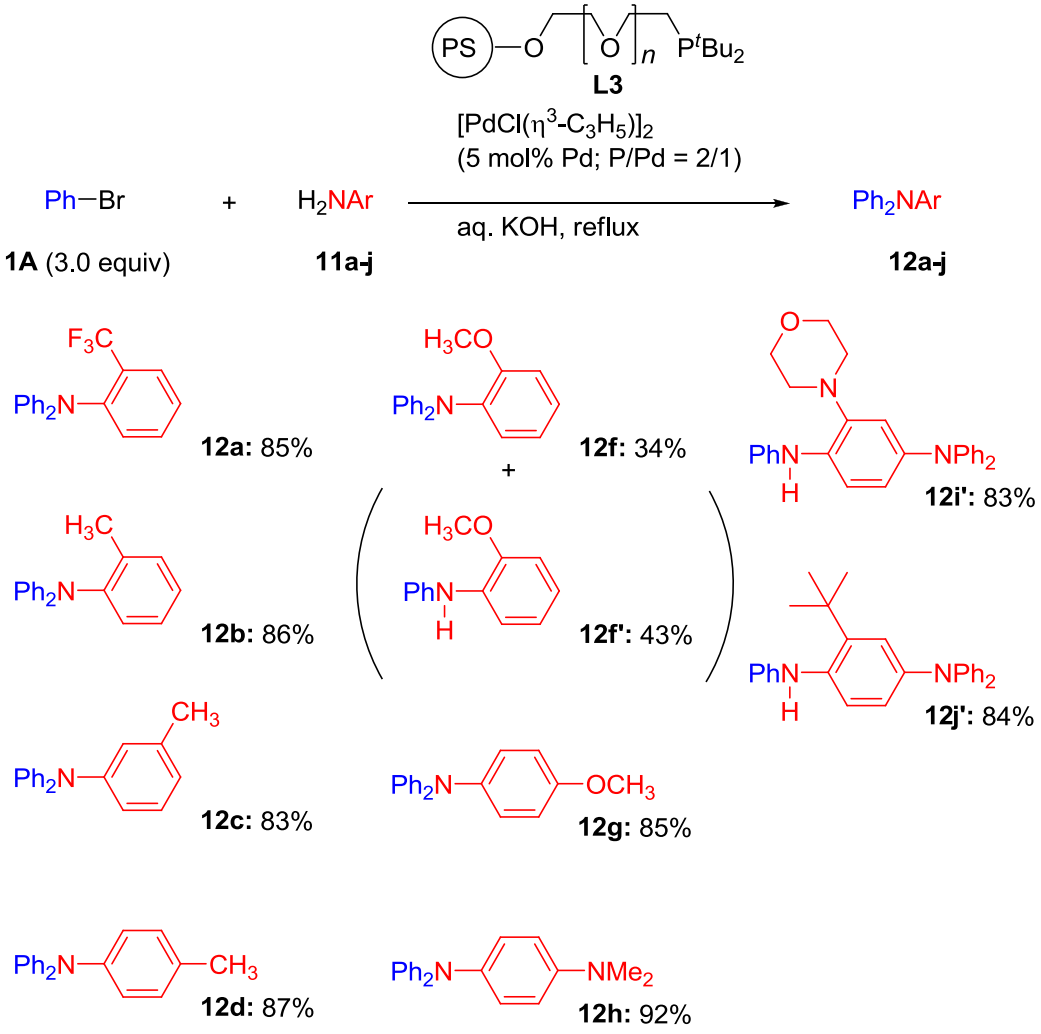
Scheme 2. Amination of various haloarenes.

Double arylation of various anilines: Considering the lack of commercially available diarylamine derivatives (Ar_2NH), the double arylation of primary anilines with haloarenes should offer a practical alternative synthetic route to various triarylamines (Scheme 3). The double arylation was achieved by the catalytic amination with 3 equivalents of bromobenzene with the aniline

11 in water. Thus, when the arylation of anilines bearing 2-trifluoromethyl, 2-methyl, 3-methyl, and 4-methyl substituents (**11a**–**d**) was carried out with the palladium complex with **L3** in water in the presence of KOH, the arylation took place twice successively on the nitrogen of the aniline substrates to give the corresponding triarylamines **12a**, **12b**, **12c**, and **12d** in 85%, 86%, 83%, and 87% yield of isolated product, respectively, where 2.5 mol% molar ratio of palladium toward bromide substituent was enough to promote the double arylation (5 mol% to aniline).

Steric hinderance of the amino groups influenced the efficiency of the double arylation more than electronic factors. Thus, when the double arylation was examined with 2-methoxyaniline (**11f**) under similar conditions, the second *N*-arylation was significantly retarded to give 34% yield of the double-arylated compound **12f** along with 43% of the N-monoarylated compound **12f'**. The double *N*-arylation took place successfully with the electron-rich anilines **11g** and **11h** to afford the N,N-diphenylanilines **12g** and **12h** in 85% and 92% yield, respectively. The reaction of the aniline substrates **11i** and **11j**, bearing the sterically demanding 2-morpholino or 2-*tert*-butyl group with bromobenzene resulted

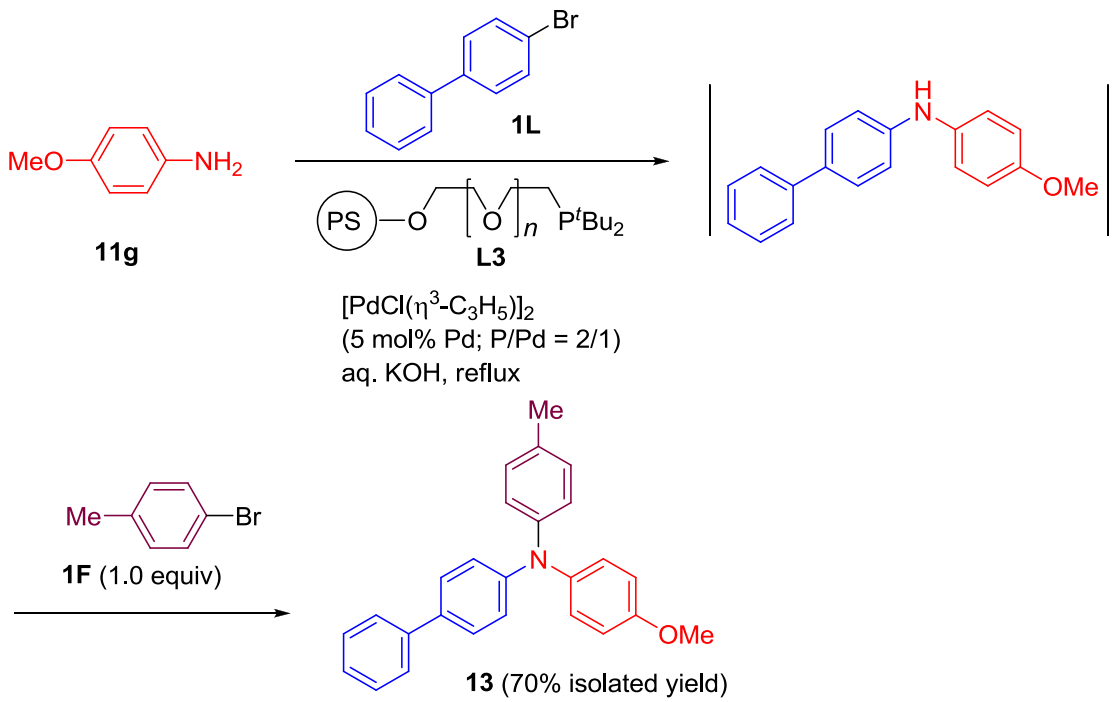
in the formation of the monoarylation products **12i'** and **12j'** in high yield (Scheme 3).



Scheme 3. Double arylation of various anilines.

These observations prompted us to examine the stepwise introduction of different *N*-aryl groups on the nitrogen of anilines. Thus, 4-(dimethylamino)aniline (**11h**) reacted with 1 equiv of 4-bromobiphenyl (**1L**) under the N-arylation conditions in water to give *N*-naphth-2-ylaniline which was subsequently treated with 4-bromotoluene (**1F**, 1 equiv) to give

N-biphen-4-yl-*N*-(4-methoxy)phenyltol-4-ylamine (**13**) in 70% yield (Scheme 4).



Scheme 4. Stepwise *N*-arylation with different aryl groups.

In summary, the Buchwald–Hartwig amination was achieved in water under heterogeneous conditions by use of immobilized palladium complexes, coordinated by amphiphilic polystyrene–poly(ethylene glycol) resin-supported di(*tert*-butyl)phosphino group. I will show an application of the present catalytic system to synthesize some optoelectronic material in the next chapter.

Experimental section

All manipulations were performed under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. Water was deionized with a Millipore system as a Milli-Q grade and was degassed by the freeze-pump-thaw method prior to use. NMR spectra were recorded on a JEOL JNM-A500 spectrometer (500 MHz for ^1H, 125 MHz for ^{13}C, 202 MHz for ^{31}P) or a JEOL JNM–AL400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C, 162 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ as an internal standard (δ 77.0). The ^{31}P NMR data are reported relative to external Ph_3P. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or CD_3OD at 25 °C. ICP-AES analyses were performed on Leeman Labs Inc. Profile Plus using palladium standard solution (KANTO CHEMICAL) and phosphine standard solution (KANTO CHEMICAL) as a standard. The ESI mass spectra were recorded on a JEOL JMS-T100LC spectrometer. The GC-MS was measured by an Agilent 6890 GC/5973N MS detector. The FAB mass spectra were recorded on a

JEOL MS700V. The IR spectra were obtained using a JASCO FT/IR-460plus spectrophotometer in ATR mode. PS-PEG bromo-resin was purchased from RAPP POLYMERETM (TentaGel®S Br, average diameter 0.90 μm, 1% divinylbenzene crosslinked, loading value of bromo residue 0.2-0.3 mmol/g).

Preparation of L1-Pd complex (P/Pd = 1/1): The polymer-supported ligand (L1) (1.00 g, 0.31 mmol of phosphine residue) was mixed with Di-μ-chlorobis[(η-allyl)palladium(II)] (56.7 mg, 0.31 mmol of Pd) in CH_2Cl_2 (10 mL) at ambient temperature and shaken for 1 h under a nitrogen atmosphere. The mixture was filtered and the resulting resin beads were washed with CH_2Cl_2 (10 mL, 3 times), dried in vacuo overnight to provide the L1-Pd complex (1.05 g). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): δ=+62.9.

Preparation of L2-Pd complex (P/Pd = 1/1): Prepared by similar procedure for the preparation of **L1-Pd** complex (P/Pd = 1/1). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): δ +55.9

Preparation of L3-Pd complex (P/Pd=2:1): The polymer-supported ligand (L3) (1.27 g, 0.32 mmol of phosphine residue) was mixed with Di-μ-chlorobis[(η-allyl)palladium(II)] (30.2 mg, 0.17 mmol of Pd) in CH_2Cl_2 (12.7 mL) at ambient temperature and shaken for 1 h under a nitrogen atmosphere. The mixture was filtered and the resulting resin beads were washed with CH_2Cl_2 (12.7 mL, 3 times), dried in vacuo overnight to provide the 1-Pd complex (1.33 g). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): δ=+40.6.

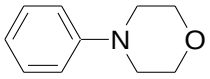
Preparation of L3-Pd complex (P/Pd = 1/1): The mixing of the polymer supported ligand (**L3**) (0.40 g, 0.088 mmol of phosphine residue) with Di-μ-chlorobis[(η-allyl)palladium(II)] (15.6 mg, 0.088 mmol of Pd) in CH_2Cl_2 (12.7 mL) at ambient temperature for 1 hour under nitrogen atmosphere. The mixture was filtered and washed with CH_2Cl_2 (12.7 mL, 3 times). And then the resin was dried in vacuo for over night to provide **L3**-Pd complex (0.42 g). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): δ 54.4. The loading value of phosphine and palladium were 0.21 mmol / g and 0.22 mmol / g, respectively.

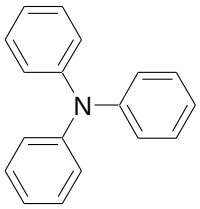
Preparation of L4-Pd complex (P/Pd = 2/1): Prepared by similar procedure

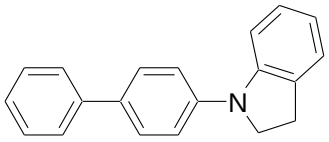
for the preparation of **L3-Pd** complex (P/Pd = 2/1). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): δ +32.0, +29.7, +27.2, +17.8. The loading value of phosphine and palladium were 0.20 mmol / g and 0.10 mmol / g, respectively.

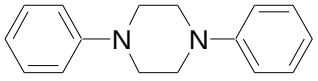
Preparation of L4-Pd complex (P/Pd = 1/1): Prepared by similar procedure for the preparation of **L3-Pd** complex (P/Pd = 1/1). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): δ +29.8. The loading value of phosphine and palladium were 0.20 mmol / g and 0.18 mmol / g, respectively.

General procedure for the amination of haloarenes: To a mixture of catalyst (**L3**-Pd complex (P/Pd = 2/1), 0.015 mmol of Pd), arylhalides (0.45 mmol) and diphenylamine (0.30mmol) in 20 M KOH aqueous solution (0.6 mL) under nitrogen atmosphere was shaken for 24 h under reflux conditions. The mixture was cooled and filtered. The recovered resin beads were extracted with EtOAc (2 mL x 4 times). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography or GPC to give the corresponding triarylamines.

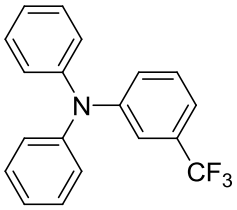
 **N-Phenyl morpholine (4)**: CAS: 92-53-5; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.24-7.19 (m, 2H), 6.86-6.80 (m, 3H), 3.82 (t, 4H, J = 4.5 Hz), 3.12 (t, 4H, J = 4.5 Hz); MS (EI(+)): *m/z* 164 $[M+H]^+$.

 **Triphenylamine (5A)**: CAS: 603-34-9; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.23 (t, J = 7.0 Hz, 6H), 7.08 (d, J = 8.0 Hz, 6H), 6.99 (t, J = 7.0 Hz, 3H); ^{13}C NMR(125 MHz, $CDCl_3$, 25 ^{o}C): δ 147.8, 129.2, 124.1 122.6; MS (EI(+)): *m/z* 245 (M^+).

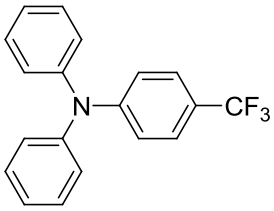
 **1-(Biphenyl-4-yl)indoline (8)**: CAS: 332876-98-9; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.62-7.51 (m, 5H), 7.47-7.43 (m, 2H), 7.35-7.31 (m, 3H), 7.23-7.20 (m, 2H), 7.14-7.10 (m, 1H), 6.79 (dd, 1H, J = 7.2 Hz, 0.8 Hz), 4.02 (t, 2H, J = 8.4 Hz), 3.17 (t, 2H, J = 8.4 Hz); MS (EI(+)) 272 $[M+H]^+$.

 ***N,N'*-Diphenylpiperadine (10)**; CAS: 613-39-8; colorless crystals; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.28 (t, J = 7 Hz, 4H),

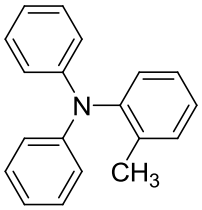
6.97 (d, J = 8.0 Hz, 4H), 6.88 (t, J = 7.5 Hz, 2H), 3.31 (s, 8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 151.2, 129.1, 120.0, 116.3, 49.3; MS (EI(+)): *m/z* 238 (M^+).



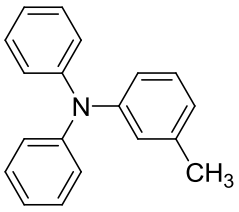
3-Trifluoromethyl-*N,N*-diphenylaniline (5B): CAS:106336-12-3; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.29-7.25 (m, 6H), 7.18 (t, J = 7.5 Hz, 2H), 7.10-7.04 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 148.5, 147.1, 131.6 (q, $J_{C\text{-}F}$ = 31.9 Hz), 129.6, 129.5, 125.7, 124.8, 124.0 (q, $J_{C\text{-}F}$ = 271.4 Hz), 123.8, 119.1 (q, $J_{C\text{-}F}$ = 4.1 Hz), 118.3 (q, $J_{C\text{-}F}$ = 4.1 Hz); MS (EI(+)): *m/z* 313 (M^+).



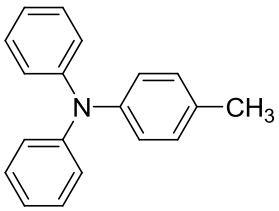
4-Trifluoromethyl-*N,N*-diphenylaniline (5C): CAS: 36809-32-2; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.41 (d, J = 9.2 Hz, 2H), 7.30 (t, J = 7.9 Hz, 4H), 7.13-7.09 (m, 6H), 7.05 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 150.9, 146.8, 129.6, 126.2 (q, $J_{C\text{-}F}$ = 4.1 Hz), 125.5, 124.2, 124.5 (q, $J_{C\text{-}F}$ = 269.4 Hz), 122.8 (q, $J_{C\text{-}F}$ = 33.0 Hz), 121.0; MS (EI(+)): *m/z* 313 (M^+).



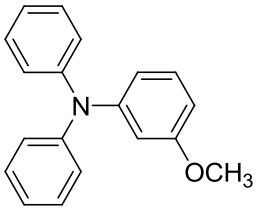
2-(Diphenylamino)toluene (5D (= 12b): CAS: 4316-55-6; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.25-7.11 (m, 8H), 6.97-6.90 (m, 6H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 147.5, 145.4, 136.5, 131.7, 129.7, 129.0, 127.3, 126.0, 121.5, 121.3, 18.6; MS (EI(+)): *m/z* 259 (M^+).



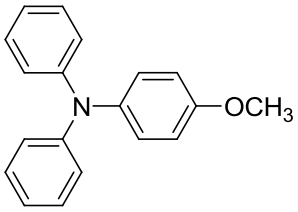
3-(Diphenylamino)toluene (5E (= 12c): CAS:4316-54-5; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.23 (t, *J* = 7.9 Hz, 6H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 4H), 6.99 (t, *J* = 7.3 Hz, 2H), 6.91 (s, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 147.9, 147.8, 139.1, 129.1, 129.0, 125.0, 124.1, 123.7, 122.5, 121.5, 21.4; MS (EI(+)): *m/z* 259 (M^+).



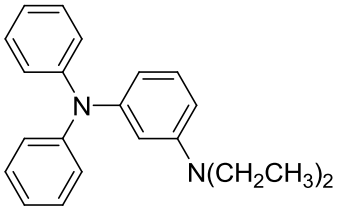
4-(Diphenylamino)toluene (5F (= 12d): CAS: 4316-53-4; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.25-7.20 (m, 4H), 7.08-7.05 (m, 6H), 7.01-6.95 (m, 4H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 148.0, 145.2, 132.7, 129.9, 129.1, 124.9, 123.6, 122.2, 20.8; MS (EI(+)): *m/z* 259 (M^+).



3-Methoxy-*N,N*-diphenylaniline (5G): CAS:20588-62-9; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.24 (t, *J* = 7.9 Hz, 4H), 7.14 (t, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 4H), 7.01 (d, *J* = 7.3 Hz, 2H) , 6.65 (d, *J* = 8.5 Hz, 1H) , 6.62 (s, 1H) , 6.56 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 160.4, 149.1, 147.7, 129.8, 129.2, 124.4, 122.8, 116.4, 109.7, 107.9, 55.2; MS (EI(+)): *m/z* 275 (M^+).

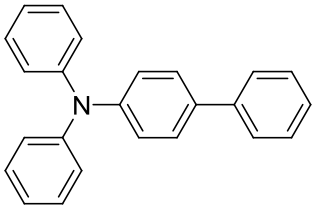


4-Methoxy-*N,N*-diphenylaniline (5H (= 12g): CAS: 4316-51-2; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.21 (t, *J* = 7.3 Hz, 4H), 7.09-7.03 (m, 6H), 6.94 (t, *J* = 7.3 Hz, 2H), 6.84 (dt, *J* = 9.2, 2.4 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 156.1, 148.2, 140.8, 129.0, 127.3, 122.9, 121.8, 114.7, 55.5; MS (EI(+)): *m/z* 275 (M^+).

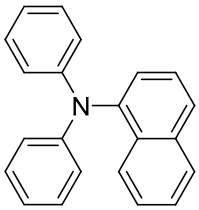


3-(*N,N*-Diethylamino)-*N,N*-diphenylaniline (5I): CAS: 775347-48-3; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.21 (t, *J* = 7.5 Hz, 4H), 7.10 (d, *J* = 7.5 Hz, 4H),

7.08 (t, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 2H), 6.39 (s, 1H), 6.38 (d, J = 8.5 Hz, 1H), 6.35 (d, J = 7.5 Hz, 1H), 3.20 (q, J = 7.5 Hz, 4H), 1.07 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 148.8, 148.7, 148.0, 129.8, 128.9, 123.9, 122.1, 112.3, 108.6, 107.1, 44.4, 12.6; MS (EI(+)): *m/z* 316 (M^+).

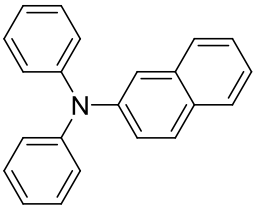


4-Phenyl-*N,N*-bis(diphenyl)aniline (5J); CAS: 4432-94-4; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.57 (d, J = 7.3 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.41 (t, J = 7.3 Hz, 2H), 7.31-7.25 (m, 5H), 7.13 (d, J = 8.5 Hz, 6H) , 7.03 (t, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 147.7, 147.2, 140.6, 135.1, 129.3, 128.7, 127.8, 126.8, 126.6, 124.4, 123.9, 122.9; MS (EI(+)): *m/z* 321 (M^+).

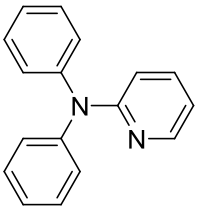


1-(*N,N*-Diphenylamino)naphthalene (5K): CAS: 61231-45-6; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.93 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 8.5 Hz, 4H), 7.02 (d, J = 8.5 Hz, 4H), 6.92 (t, J = 7.5 Hz, 2H); ^{13}C NMR(125 MHz, $CDCl_3$, 25 °C): δ 148.5, 143.6, 135.3, 131.3, 129.1,

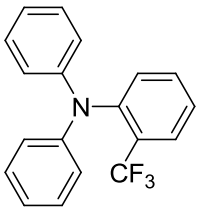
128.4, 127.2, 126.4, 126.35, 126.32, 126.1, 124.3, 121.8, 121.6; MS (EI(+)): *m/z* 295 (M^+).



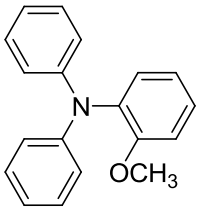
2-(*N,N*-Diphenylamino)naphthalene (5L): CAS: 6940-30-3; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 1.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.29-7.25 (m, 5H), 7.13 (d, *J* = 7.5 Hz, 4H), 7.04 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR(125 MHz, $CDCl_3$, 25 °C): δ 147.8, 145.5, 134.4, 130.0, 129.3, 128.8, 127.5, 126.9, 126.2, 124.45, 124.41, 124.37, 122.9, 120.2; MS (EI(+)): *m/z* 295 (M^+).



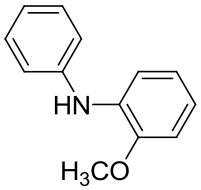
2-*N,N*-diphenylaminopyridine (5M): CAS: 50910-08-2; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.23 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.42 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 4H), 7.17 (d, *J* = 7.5 Hz, 4H), 7.11 (t, *J* = 8.0 Hz, 2H), 6.78-6.74 (m, 2H); ^{13}C NMR(125 MHz, $CDCl_3$, 25 °C): δ 159.0, 148.3, 146.1, 137.2, 129.3, 126.2, 124.4, 116.1, 113.8; MS (EI(+)): *m/z* 246 (M^+).



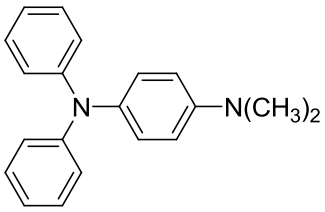
2-trifluoromethyl-N,N-Diphenylaniline (12a): CAS: No Registry; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.29-7.25 (m, 6H), 7.18 (t, J = 7.5 Hz, 2H), 7.10-7.05 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 148.5, 147.1, 131.6 (q, J_{C-F} = 31.9 Hz), 129.6, 129.5, 125.7, 124.8, 124.0 (q, J_{C-F} = 270.5 Hz), 123.8, 119.1 (q, J_{C-F} = 4.1 Hz), 118.3 (q, J_{C-F} = 4.1 Hz); MS (FAB(+)): *m/z* 313 (M^+). HRMS (FAB(+)) calc for $C_{19}H_{14}F_3N$: 313.1078, found: 313.1075, IR (ATR): (cm^{-1}) ν 3064, 3037, 2359, 2342, 1587, 1492, 1337, 1323, 1262, 1164, 1120, 1070, 954, 790, 752, 692.



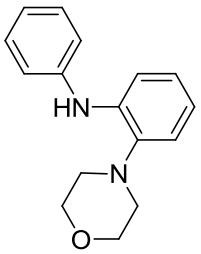
2-(Diphenylamino)anisole (12f): CAS: 20441-01-4; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.22-7.16 (m, 6H), 7.00-6.90 (m, 8H), 3.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 156.1, 147.7, 135.6, 130.2, 128.8, 126.7, 121.6, 121.4, 113.4, 55.9; MS (EI(+)): *m/z* 275 (M^+).



2-(*N*-Phenylamino)anisole (12f'): CAS: 1207-92-7; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.30-7.7.25 (m, 3H), 7.14 (d, *J* = 7.0 Hz, 2H), 6.93 (t, *J* = 7.0 Hz, 1H), 6.88-6.84 (m, 3H), 6.14 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 148.3, 142.7, 133.0, 129.2, 121.1, 120.8, 119.9, 118.6, 114.7, 110.5, 55.6; MS (EI(+)): *m/z* 199 (M^+).

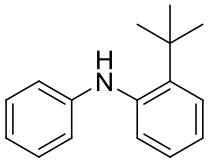


4-(*N*,*N*-Dimethylamino)-*N*,*N*-bis(diphenyl)aniline (12h): CAS: 4316-50-1; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.20 (t, *J* = 7.9 Hz, 4H), 7.05 (d, *J* = 8.5 Hz, 6H), 6.91 (t, *J* = 7.3 Hz, 2H), 6.70 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 148.3, 147.7, 137.1, 128.9, 127.7, 122.4, 121.3, 113.5, 40.9; MS (EI(+)): *m/z* 288 (M^+).

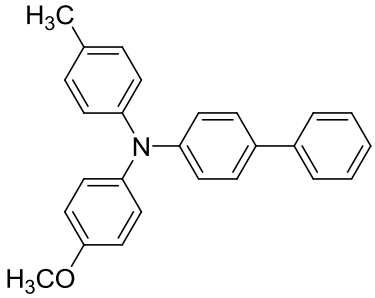


***N*-[2-(phenylamino)phenyl]morpholine (12i'):** CAS: No Registry; colorless oil; ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ 7.19 (t, *J* = 7.5 Hz, 3H), 7.04 (d, *J* = 8.5 Hz, 3H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 2H), 3.75 (t, *J* = 4.5 Hz, 4H), 2.83 (t, *J* = 4.5 Hz, 4H); ^{13}C NMR (125 MHz, CD_3OD, 25 °C): δ 144.7, 143.0, 139.1, 130.2, 125.4,

121.8, 121.6, 120.9, 118.8, 117.4, 68.4, 52.9; MS (EI(+)): *m/z* 254 (M^+). HRMS (EI(+)) calc for $C_{16}H_{18}N_2O_1$: 254.1419, found: 254.1418, IR (ATR): (cm^{-1}) ν 3356, 2848, 1823, 2360, 2341, 1590, 1498, 1223, 1134, 980, 741, 693.



2-*tert*-Butyl-*N*-phenylaniline (12j'): CAS: 168558-34-7; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.22-7.15 (m, 3H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.81 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 145.9, 143.3, 141.2, 129.2, 127.0, 126.9, 125.9, 123.9, 119.2, 115.9, 34.8, 30.6; MS (EI(+)): *m/z* 225 (M^+).



N-biphen-4-yl-N-(4-methoxy)phenyltol-4-ylamine (13): To a mixture of catalyst (**L3**-Pd complex (P/Pd = 2/1), 0.015 mmol of Pd), *para*-anisidine (0.30 mmol) and 4-bromobiphenyl (0.30 mmol) in 20 M KOH aqueous solution (0.6 mL) under nitrogen atmosphere was shaken for 24 h under reflux conditions. The mixture was cooled and added *para*-bromotoluene (0.30 mmol). The reaction mixture was shaken for 24 h under reflux conditions. The mixture was cooled and filtered. The

recovered resin beads were extracted with EtOAc (2 mL x 4 times). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography and GPC to give compound (8) in 70.3% yield. CAS: 134328-08-8; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.54 (d, J = 8.0 Hz, 2H), 7.42-7.37 (m, 4H), 7.27 (t, J = 7.5 Hz, 1H), 7.09-7.00 (m, 8H), 6.83 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 156.0, 147.8, 145.3, 140.8, 140.7, 133.6, 132.2, 129.8, 128.7, 127.5, 127.0, 126.53, 126.49, 124.1, 121.8, 114.7, 55.4, 20.8; MS (EI(+)): *m/z* 365 (M^+).

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[1] This chapter are based on following papers, see: a) Y. Hirai, Y. Uozumi, *Chem. Commun.*, 2010, 46, 1103; b) Y. Hirai, Y. Uozumi, *Chem. Asian J.*, 2010, 5 (8), 1788.

[2] a) E. Bayer, W. Rapp in Chemistry of Peptides and Proteins, Vol. 3 (Eds.: W. Voelter, E. Bayer, Y. A. Ovchinikov, V. T. Iwanov), Walter de Gruter, Berlin, 1986, p. 3; b)W. Rapp in Combinatorial Peptide and Nonpeptide Libraries (Ed.: G. Jung), VCH, Weinheim, 1996, p. 425; c) X. Du, R. W. Armstrong, J.

Org. Chem. 1997, 62, 5678; d) O. W. Gooding, D. Baudert, T. L. Deegan, K. Heisler, J. W. Labadie, W. S. Newcomb, J. A. Porco Jr. , P. J. Eikeren, J. Comb. Chem. 1999, 1, 113.

[3] a) N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, J. Org. Chem. 2002, 67, 5553; b) Q. Shen, T. Ogata, J. F. Hartwig, J. Am. Chem. Soc. 2008, 130, 6586.

[4] a) Y. Shirota, J. Mater. Chem. 2000, 10, 1; b) Y. Shirota, J. Mater. Chem. 2005, 15, 75.

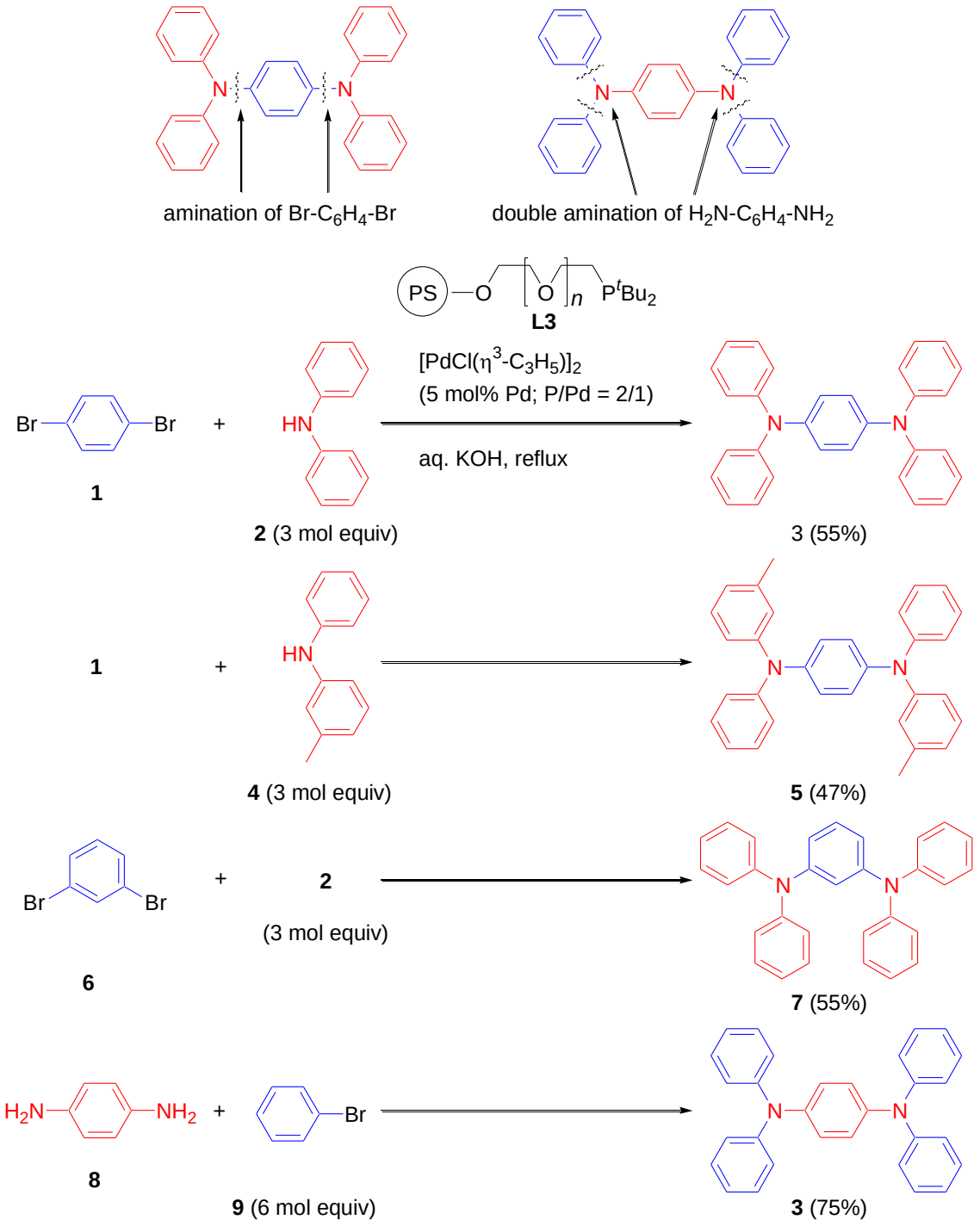
[5] The recycling experiments were carried out with an excess amount of 3A (3A/4=1.5:1.0), where the relatively stable polymeric Pd-(C_6H_5)BrL_n species should be generated in situ with completion of each recycling run to realize high recyclability.

Chapter III: Application of an amphiphilic PS-PEG resin-supported transition metal catalyst to synthesize optoelectronical materials [1]

In the previous chapter II, I showed the development of an environmentally benign and safe heterogeneous catalytic system for palladium-promoted amination of aryl halides in water with a readily recyclable immobilized catalyst to achieve the clean (metal uncontaminated) synthesis of triarylamines. Triarylamines such as optoelectronically active *N,N,N',N'*-tetraphenyl-1,1'-biphenyl-4,4'-diamine (TPD) derivatives are useful compounds in the field of electronic materials. There are two methods of synthesizing TPD derivatives, specifically arylation of phenylenediamines and amination of dihaloarenes. I applied the above-mentioned catalyst to synthesize oligo(triamine)s.

N,N-N'N'-Tetraarylphenylenediamines: Tetraarylphenylenediamines were prepared via double amination of dibromobenzene or the double arylation of phenylenediamine. Double-amination of 1,4-dibromobenzene (**1**) with 3 equiv of diphenylamine (**2**) took place in water in the presence of 5 mol% palladium of the polymeric **L3**-Pd complex (2.5 mol% molar ratio to bromo

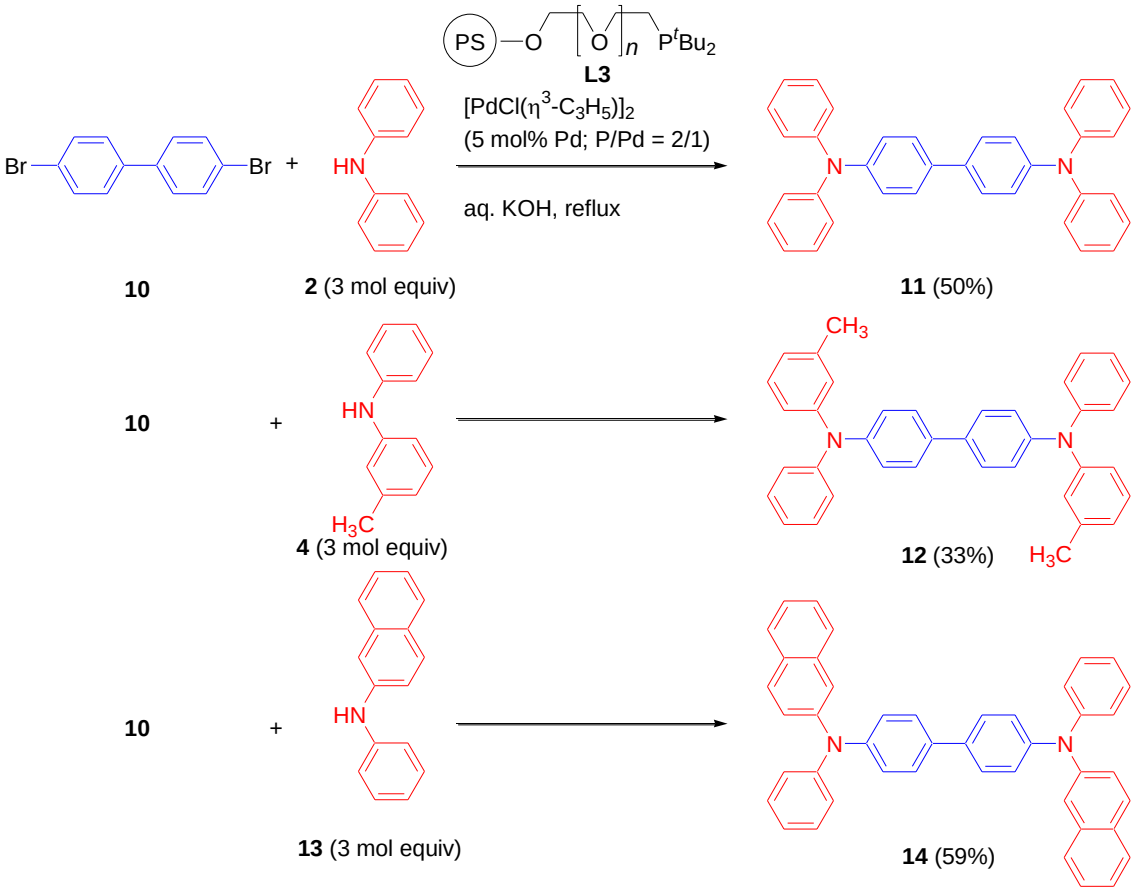
sustituent) to give 55% yield of *N,N,N',N'*-tetraphenyl-*para*-phenylenediamine (**3**).



Scheme 1. Preparation of N,N-N'N'-tetraarylphenylenediamines via diamination.

N-Phenyl-*N*-*m*-tolylamine (**4**) could also be be used for the double-amination of **1** to give **5** in 47% yield. Likewise, 1,3-dibromobenzene (**6**) gave *N,N,N',N'*-Tetraphenyl-*meta*-phenylenediamine **7** in 55% yield under similar aquacatalytic conditions. *N,N,N',N'*-Tetraphenyl-*para*-phenylenediamine (**3**) was also prepared via quadruple arylation of phenylenediamine (**8**) with bromoarenes (**9**). Thus, the *N,N,N'N'*-arylation of **8** was carried out with 6 mol equiv of **9** in water under the arylation conditions to give a 75% yield of *N,N,N',N'*-tetraaryl-*para*-phenylenediamine **3** (Scheme 1).

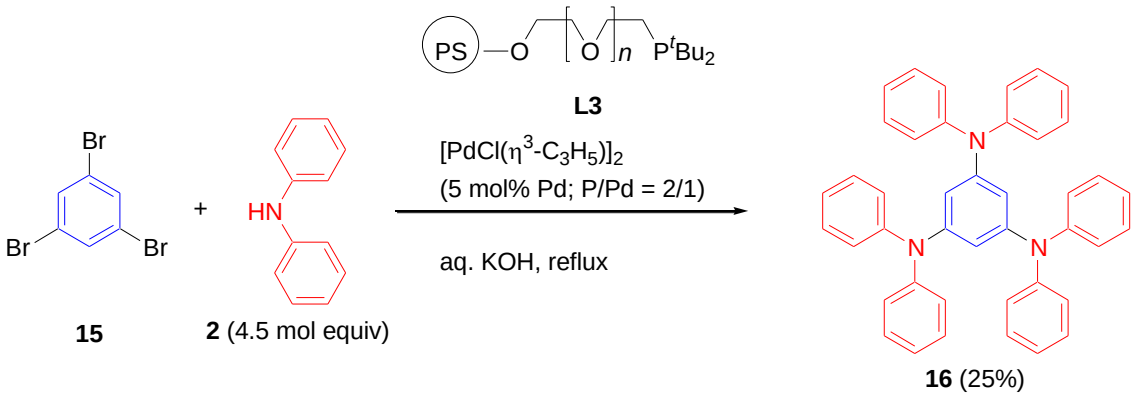
N,N,N',N'-Tetraaryl-1,1'-biphenyl-4,4'-diamines (TPDs): *N,N,N',N'*-Tetra-phenyl-1,1'-biphenyl-4,4'-diamine derivatives (TPDs) are known as optoelectroactive organic materials owing to their hole-transport property.[2] Because of their utility in optoelectronic devices (e.g., EL devices), a costly purification process with sublimation is often required to provide TPDs with a high level of metal-uncontaminated purity. With a clean aromatic amination protocol in hand, I set about demonstrating its applicability for the preparation of TPD derivatives (Scheme 2).[3]



Scheme 2. Preparation of *N,N,N',N'*-tetraaryl-1,1'-biphenyl-4,4'-diamines (TPDs).

The reaction of 4,4'-dibromobiphenyl (**10**) with diphenylamine (**2**) was carried out with 5 mol% palladium of the **L3**-Pd complex (P/Pd=2:1) in aqueous KOH solution under reflux for 24 h. The aromatic amination took place successively at two of the bromo groups of **10** to give a 50% yield of the isolated *N,N,N',N'*-tetraphenyl-1,1'-biphenyl-4,4'-diamine (**11**). Little palladium was observed (lower than the detection limit of ICP-AES analysis) even in the crude product and analytically pure **11** was isolated by simple chromatographic purification or recrystallization. Amination of **10** with

phenyl(*meta*-tolyl) amine (**4**) and naphthylphenylamine (**13**) gave *N,N'*-diphenyl-*N,N'*-di(*meta*-tolyl)-1,1'-biphenyl-4,4'-diamine (**12, TPD**) and *N,N'*-dinaphthyl-*N,N'*-diphenyl-1,1'-biphenyl-4,4'-diamine (**14, β-NPD**) in 33% and 59% yield, respectively. Triple amination of tribromobenzene (**15**) also proceeded under similar conditions, though the chemical yield of the desired triple amination product was moderate. Thus, amination of **15** with 4.5 mol equivalents of **2** was catalyzed by the polymer supported complex **L3**-Pd (5 mol% to **15**, 1.33 mol% to bromo residue) in water under similar conditions to give tris(4-diphenylaminophenyl) amine (**16**), a hole-transport material, in 25% yield (Scheme 3).



Scheme 3. Triple amination forming tris(4-diphenylaminophenyl)amine.

In summry, since little palladium leached from the polymeric catalyst under the water-based reaction conditions, this method provides a green and clean (metal-uncontaminated) protocol for the preparation of triarylamines.

The catalytic system was applied to successive amination of dibromoarenes and *N,N,N'N'*-quadruple arylation of phenylenediamine producing *N,N,N'N'*-tetraarylphenylenediamines. With the heterogeneous catalytic system, electroactive *N,N,N',N'*-tetraaryl-1,1'-biphenyl- 4,4'-diamines (TPDs) were obtained without metal contamination.

Experimental section

All manipulations were performed under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. Water was deionized with a Millipore system as a Milli-Q grade and was degassed by the freeze-pump-thaw method prior to use. NMR spectra were recorded on a JEOL JNM-A500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, 202 MHz for ^{31}P) or a JEOL JNM–AL400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 162 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ as an internal standard (δ 77.0). The ^{31}P NMR data are reported relative to external Ph_3P. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or CD_3OD at 25 °C. ICP-AES analyses were performed on Leeman Labs Inc. Profile Plus using palladium standard solution (KANTO CHEMICAL) and phosphine standard solution (KANTO CHEMICAL) as a standard. The ESI mass spectra were recorded on a JEOL JMS-T100LC spectrometer. The GC-MS was measured by an Agilent 6890 GC/5973N MS detector. The FAB mass spectra were recorded on a

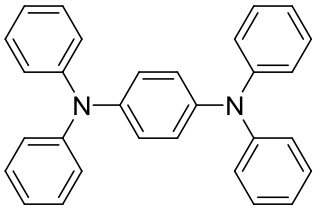
JEOL MS700V. The IR spectra were obtained using a JASCO FT/IR-460plus spectrophotometer in ATR mode. PS-PEG bromo-resin was purchased from RAPP POLYMERETM (TentaGel®S Br, average diameter 0.90 μm, 1% divinylbenzene crosslinked, loading value of bromo residue 0.2-0.3 mmol/g).

General procedure for the double arylation of anilins: To a mixture of catalyst (**L3**-Pd complex (P/Pd = 2/1), 0.015 mmol of Pd), bromobenzene (0.90 mmol) and anilines (0.30 mmol) in 20 M KOH aqueous solution (0.6 mL) under nitrogen atmosphere was shaken for 24 h under reflux conditions. The mixture was cooled and filtered. The recovered resin beads were extracted with EtOAc (2 mL x 4 times). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography or GPC to give the corresponding triarylamines and diarylamines.

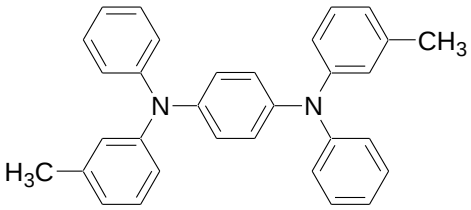
General procedure for the double amination of dihaloarenes: To a mixture of catalyst (**L3**-Pd complex (P/Pd = 2/1), 0.015 mmol of Pd), dihaloarenes

(0.30 mmol) and diarylamines (0.90 mmol) in 20 M KOH aqueous solution (0.6 mL) under nitrogen atmosphere was shaken for 24 to 48 h under reflux conditions. The mixture was cooled and filtered. The recovered resin beads were extracted with EtOAc or CH_2Cl_2 (2 mL x 4 times). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography or GPC to give the corresponding bis(*N*,*N*-diarylamino)arenes.

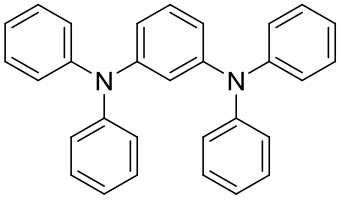
General procedure for the quadruple arylation of diaminoarenes: To a mixture of catalyst (**L3**-Pd complex (P/Pd = 2/1), 0.015 mmol of Pd), diaminoarenes (0.30 mmol) and haloarenes (1.80 mmol) in 20 M KOH aqueous solution (0.6 mL) under nitrogen atmosphere was shaken for 24 h under reflux conditions. The mixture was cooled and filtered. The recovered resin beads were extracted with EtOAc or CH_2Cl_2 (2 mL x 4 times). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography or GPC to give the corresponding bis(*N*,*N*-diarylamino)arenes.



***N,N,N',N'*-Tetraphenyl-*para*-phenylenediamine (3):** CAS: 14118-16-2; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.24 (t, *J* = 8.0 Hz, 8H), 7.10 (d, *J* = 8.0 Hz, 8H), 6.98 (t, *J* = 8.0 Hz, 4H), 6.98(s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 147.8, 142.8, 129.2, 125.4, 123.7, 122.4; MS (EI(+)): *m/z* 412 (M^+).

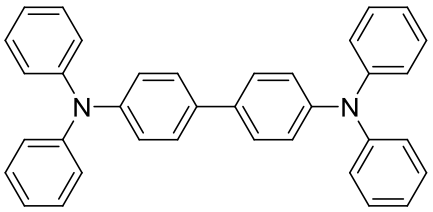


***N,N'*-bis(3-methylphenyl)-*N,N'*-diphenyl-*para*-phenylenediamine (5):** CAS: 80223-39-6; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.23 (t, *J* = 8.0 Hz, 4H), 7.13 (t, *J* = 8.0 Hz, 4H), 7.08 (d, *J* = 8.5 Hz, 4H), 6.98-6.89 (m, 10H), 6.81 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 48.0, 147.8, 142.8, 139.0, 129.1, 129.0, 125.3, 124,6, 123.6, 123.4, 122.2, 121.1, 21.4; MS (EI(+)): *m/z* 440 (M^+).

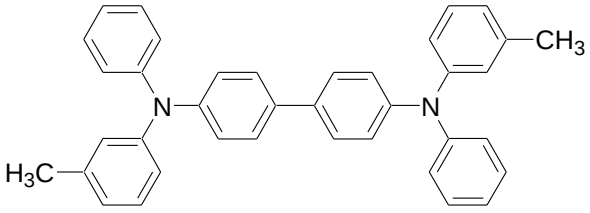


***N,N,N',N'*-Tetraphenyl-*metha*-benzenediamine (7):** CAS: 92899-33-7; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.20 (t, *J* = 8.0 Hz, 8H), 7.06 (d, *J* = 7.5 Hz, 8H), 6.95 (t, *J* = 7.5 Hz, 4H), 6.87 (t, *J* = 2.5 Hz, 1H), 6.65 (dd, *J* = 8.0, 2.5 Hz, 2H);

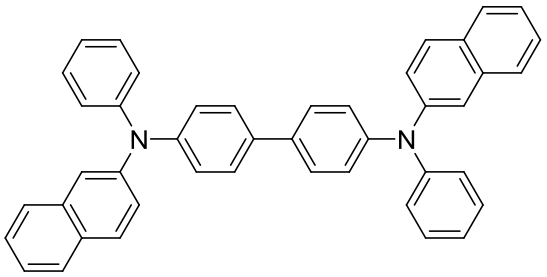
^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 148.5, 147.5, 129.7, 129.1, 124.1, 122.6, 119.7, 118.3; MS (ESI(+)): *m/z* 412 (MH^+).



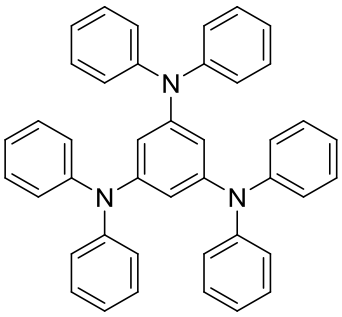
***N,N,N',N'*-Tetraphenyl-1,1'-biphenyl-4,4'-diamine (11):** CAS: 15546-43-7; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.44 (d, *J* = 8.5 Hz, 4H), 7.26 (t, *J* = 7.5 Hz, 8H), 7.13-7.11 (m, 12H), 7.02 (5, *J* = 7.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 147.7, 146.7, 134.7, 129.2, 127.3, 124.3, 124.1, 122.8; MS (ESI(+)): *m/z* 489 (MH^+).



***N,N'*-Diphenyl-*N,N'*-di(*metha*-tolyl)- 1,1'-biphenyl-4,4'-diamine (12):** CAS: 65181-78-4; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.43 (dt, *J* = 8.5, 2.0 Hz, 4H), 7.24 (dd, *J* = 8.5, 7.5 Hz, 4H), 7.16-7.09 (m, 10H), 7.00 (t, *J* = 7.5 Hz, 2H), 6.95 (s, 2H), 6.92 (d, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 147.8, 147.6, 146.8, 139.1, 134.6, 129.2, 129.0, 127.2, 125.1, 124.2, 124.0, 123.8, 122.6, 121.6, 21.4; MS (ESI(+)): *m/z* 517 (MH^+).



N,N'-Dinaphthyl-N,N'-diphenyl-1,1'-biphenyl-4,4'-diamine (14): CAS: 139255-17-7; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 6H), 7.36-7.22 (m, 10H), 7.15-7.13 (m, 8H), 7.02 (t, *J* = 7.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 147.6, 146.7145.3, 134.9, 134.4, 130.1, 129.3, 128.9, 127.5, 127.3, 126.9, 126.3, 124.50, 124.46, 124.44, 124.30, 123.0, 120.4; MS (FAB(+)): *m/z* 588 (M^+).



1,3,5-Tris(*N,N*-diphenylamino)benzene (16): To a mixture of catalyst (**L3**-Pd complex (P/Pd = 2/1), 0.015 mmol of Pd), 1,3,5-tribromobenzene (0.30 mmol) and diarylamines (1.35 mmol) in 20 M KOH aqueous solution (0.6 mL) under nitrogen atmosphere was shaken for 48 h under reflux conditions. The mixture was cooled and filtered. The recovered resin beads were extracted with CH_2Cl_2 (2 mL x 4 times). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated

and the residue was purified by flash chromatography and GPC to give the compound (**22**) in 25% yield. CAS: 126717-23-5; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.15 (t, *J* = 7.5 Hz, 12H), 7.02 (d, *J* = 8.0 Hz, 12H), 6.90 (t, *J* = 7.5 Hz, 6H), 6.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 148.9, 147.2, 129.0, 123.8, 114.5; MS (EI(+)): *m/z* 579 (M^+).

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[1] This chapter are based on following papers, see: a) Y. Hirai, Y. Uozumi, *Chem. Commun.*, 2010, 46, 1103; b) Y. Hirai, Y. Uozumi, *Chem. Asian J.*, 2010, 5 (8), 1788.

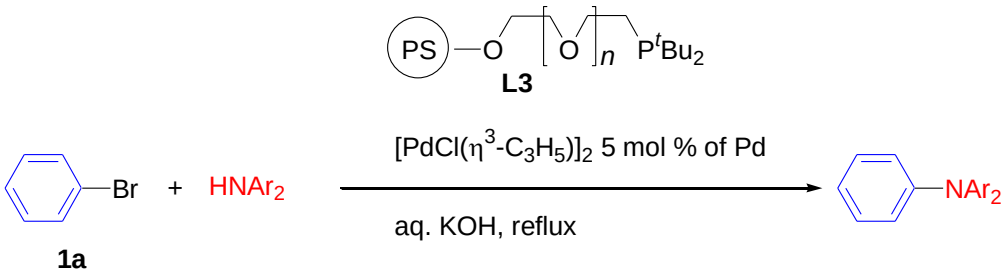
[2] For a recent example, see: R. K. Willardson, E. R. Weber, G. Mueller, Electroluminescence I, Volume 64 (Semiconductors and Semimetals) published by Academic Press

[3] D. S. Surry, S. L. Buchwald, J. Am. Chem. Soc. 2007, 129, 10354.

Chapter IV: C-S Bond-Forming Cross Coupling in Water with an Amphiphilic Resin-supported Palladium Complex [1]

As part of our effort to demonstrate the wide utility of this catalyst system, I decided to examine the Buchwald-Hartwig type C-S bond-forming reactions.[2][3] While, I have previously described the Buchwald-Hartwig amination of aryl halides with diarylamines in water to form triarylamines in the former chapter, the aqueous-switching of C-S coupling reactions still remains a major challenge. I report herein our results demonstrating that coupling reactions of various aryl halides with thiols proceed in water in the presence of a palladium complex of the PS-PEG resin-supported di-*tert*-butylphosphino ligand.

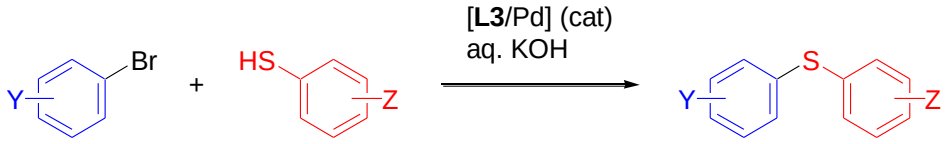
I have examined several amphiphilic PS-PEG resin-supported phosphine ligands for the amination reaction of bromobenzene (**1a**) in the former chapter (Scheme 1).



Scheme 1

All the obtained results for C-S bond-forming reaction with L3/Pd catalyst is summarized in Table 1. Thus, bromobenzene (**1a**) reacted with 2-methylbenzenethiol (**2A**) in refluxing aqueous KOH solution in the presence of 5 mol% palladium complex **L3**/Pd for 24 h to give 74% isolated yield of 2-methylphenyl phenyl sulfide (**3aA**) (Entry 1). Benzenethiols bearing 3-methyl (**2B**), 2-methoxy (**2C**), 3-methoxy (**2D**), 4-methoxy (**2E**), or 4-*tert*-butyl (**2F**) substituent reacted with **1a** under the same conditions to afford the corresponding substituted diphenyl sulfide in 68-93% yield (Entries 2–6). Bromoarenes bearing electron-withdrawing and -donating substituents at the *ortho*-, *meta*-, and *para*-positions are also tolerated as coupling partners.

Table 1. C-S coupling of bromoarenes in water[a]



1a-j **2A-F** **3aA-jF**

Entry	1	2	Y	Z	Product	Yield/%[b]
1	**1a**	**2A**	H	2-CH_3	**3aA**	74
2	**1a**	**2B**	H	3-CH_3	**3aB**	71
3	**1a**	**2C**	H	2-CH_3O	**3aC**	71
4	**1a**	**2D**	H	3-CH_3O	**3aD**	68
5	**1a**	**2E**	H	4-CH_3O	**3aE**	93
6	**1a**	**2F**	H	4-*t*Bu	**3aF**	91
7	**1b**	**2F**	2-CF_3	4-*t*Bu	**3bF**	84
8	**1c**	**2F**	3-CF_3	4-*t*Bu	**3cF**	75
9	**1d**	**2F**	4-CF_3	4-*t*Bu	**3dF**	78
10	**1e**	**2F**	2-CH_3	4-*t*Bu	**3eF**	96
11	**1f**	**2F**	3-CH_3	4-*t*Bu	**3fF**	82
12	**1g**	**2F**	4-CH_3	4-*t*Bu	**3gF**	86
13	**1h**	**2F**	2-CH_3O	4-*t*Bu	**3hF**	57
14	**1i**	**2F**	3-CH_3O	4-*t*Bu	**3iF**	72
15	**1j**	**2F**	4-CH_3O	4-*t*Bu	**3jF**	61

[a] All reactions were carried out with PhBr in 20 M aqueous KOH solution under reflux in the presence of 5 mol% 1/2$[PdCl(\eta^3\text{-}C_3H_5)]_2$ and L3 for 24 h, unless otherwise noted. The ratio of **1** (mol)/**2** (mol)/H_2O (L) = 1.5/1.0/2.0.

[b] Isolated yields.

Thus, 2-, 3-, and 4-(trifluoromethyl)-bromobenzenes **1b-1d** reacted with 4-(*tert*-butyl)benzenethiol (**2F**) under similar conditions to give 4-(*tert*-butyl)phenyl *n*-trifluoromethylphenyl sulfides (n = 2 (**3bF**), 3 (**3cF**),

and 4 (**3dF**)), respectively (Entries 7–9). Bromotoluenes **1e-1g** and bromoanisoles **1h-1j** also underwent the C-S coupling under the same catalytic conditions to afford the corresponding diaryl sulfides **3eF-3jF** in 57-96% yield (Entries 10–15).

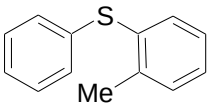
In conclusion, I have developed a novel C-S bond-forming catalytic protocol with an amphiphilic polymer supported palladium complex of sterically demanding alkylphosphine ligand **L3**, which was carried out in water under heterogeneous conditions to realize a high level of chemical greenness. Synthetic application of this protocol is currently under investigation in our laboratory and will be reported in due course.

Experimental section

All manipulations were performed under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. Water was deionized with a Millipore system as a Milli-Q grade and was degassed by the freeze-pump-thaw method prior to use. NMR spectra were recorded on a JEOL JNM-A500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, 202 MHz for ^{31}P) or a JEOL JNM–AL400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 162 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ as an internal standard (δ 77.0). The ^{31}P NMR data are reported relative to external Ph_3P. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or CD_3OD at 25 °C. ICP-AES analyses were performed on Leeman Labs Inc. Profile Plus using palladium standard solution (KANTO CHEMICAL) and phosphine standard solution (KANTO CHEMICAL) as a standard. The ESI mass spectra were recorded on a JEOL JMS-T100LC spectrometer. The GC-MS was measured by an Agilent 6890 GC/5973N MS detector. The FAB mass spectra were recorded on a

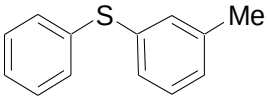
JEOL MS700V. The IR spectra were obtained using a JASCO FT/IR-460plus spectrophotometer in ATR mode. PS-PEG bromo-resin was purchased from RAPP POLYMERETM (TentaGel®S Br, average diameter 0.90 μm, 1% divinylbenzene crosslinked, loading value of bromo residue 0.2-0.3 mmol/g).

General procedure for the thiolation of haloarenes: A mixture of catalyst (**L3**-Pd complex (P/Pd = 2/1), 0.015mmol of Pd), aryl halides (0.45mmol) and arylthiols (0.30mmol) in 20M KOH aqueous solution (0.6mL) under a nitrogen atmosphere was shaken for 24 h under reflux conditions. After being cooled, themixture was filtered, the recovered resin beads were extracted with EtOAc (2 mL, 4 times). The combined extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo, and the resulting residue was chromatographed on silica gel to give the corresponding diaryl sulfides.

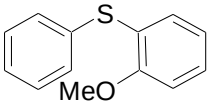


Phenyl-2-tolylsulfide (3aA); CAS: 13963-35-4; pale yellow oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 ^{o}C): δ 7.30-7.13 (m, 9H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 ^{o}C): δ 140.0, 136.2, 133.8, 133.0,

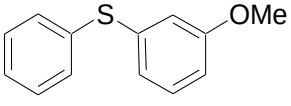
129.7, 129.1, 127.9, 126.7, 126.3, 20.6; MS (EI(+)): *m/z* 200 (M^+).



Phenyl-3-tolylsulfide (3aB); CAS: 13865-48-0; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.23-7.13 (m, 4H), 7.05 (d, *J* = 7.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 139.0, 136.1, 135.2, 131.8, 130.7, 129.1, 129.0, 128.3, 128.0, 126.8, 21.3; MS (EI(+)): *m/z* 200

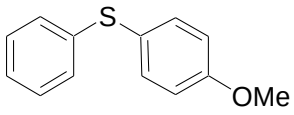


2-Methoxyphenylphenylsulfide (3aC); CAS: 14065-22-6; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.86 (t, *J* = 7.0 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 157.3, 134.5, 131.6, 131.4, 129.1, 128.3, 127.0, 124.0, 121.2, 110.8, 55.8; MS (EI(+)): *m/z* 216 (M^+).

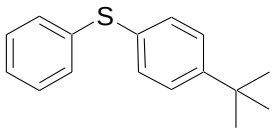


3-Methoxyphenylphenylsulfide (3aD); CAS: 30723-22-6; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.37 (t, *J* = 7.0 Hz, 2H), 7.30 (d, *J* = 7.0 Hz, 2H), 7.26-7.23 (m, 1H),

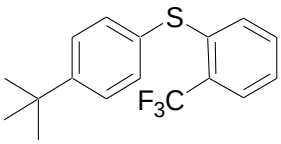
7.20 (t, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.86 (s, 1H), 6.77 (dd, J = 8.0, 2.5 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 160.0, 137.2, 135.2, 131.4, 129.9, 129.2, 127.2, 122.9, 115.9, 112.8, 55.2; MS (EI(+)): *m/z* 216 (M^+).



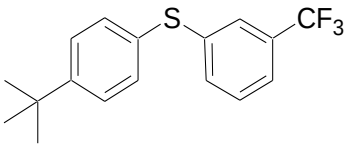
4-Methoxyphenylphenylsulfide (3aE); CAS: 5633-57-8; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.41 (d, J = 9.5 Hz, 2H), 7.22 (t, J = 7.5 Hz, 2H), 7.16 (d, J = 6.5 Hz, 2H), 7.12 (t, J = 7 Hz, 1H), 6.88 (d, J = 10.5 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 159.8, 138.6, 135.3, 128.9, 128.2, 125.7, 124.3, 114.9, 55.3; MS (EI(+)): *m/z* 216 (M^+).



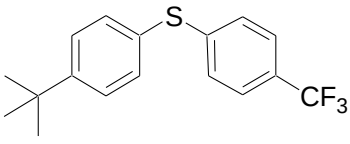
4-tert-Butylphenylsulfide (3aF); CAS: 85609-03-6; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.35-7.18 (m, 9H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 150.6, 136.6, 131.6, 131.5, 130.3, 129.0, 126.6, 126.3, 34.6, 31.2; MS (EI(+)): *m/z* 242 (M^+).



4-tert-Butylphenyl-2-trifluoromethylphenylsulfide (3bF); CAS: No Registry; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 ^{o}C): δ 7.65 (d, J = 8.0 Hz, 1H), 7.40-7.7.36 (m, 4H), 7.32 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 ^{o}C): δ 151.9, 137.7, 133.4, 131.9, 131.4, 129.5, 128.8 (q, J_{C-F} = 29.9 Hz), 126.7, 126.6 (q, J_{C-F} = 5.1 Hz), 125.7, 123.9 (q, J_{C-F} = 272.4 Hz), 34.7, 31.2; MS (EI(+)): *m/z* 310 (M^+), HRMS (FAB(+)) calc for $C_{17}H_{17}F_3S$: 310.1003, found: 310.1008,

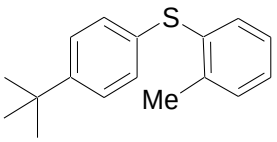


4-tert-Butylphenyl-3-trifluoromethyphenylsulfide (3cF); CAS: 643017-26-9; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 ^{o}C): δ 7.50 (s, 1H), 7.41-7.32 (m, 7H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 ^{o}C): δ 151.8, 139.2, 132.7, 132.1, 131.4 (q, J_{C-F} = 31.9 Hz), 129.5, 129.3, 126.7, 125.6 (q, J_{C-F} = 4.1 Hz), 123.8 (q, J_{C-F} = 271.5 Hz), 122.8 (q, J_{C-F} = 4.1 Hz), 34.7, 31.2; MS (EI(+)): *m/z* 310 (M^+).

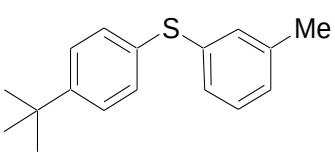


4-tert-Butylphenyl-4-trifluoromethyphenylsulfide

(3dF); CAS: No Registry; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 ^{o}C): δ 7.45 (d, J = 8.5 Hz, 2H), 7.42 (s, 4H), 7.23 (d, J = 8.0 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 ^{o}C): δ 152.3, 143.6, 133.7, 128.4, 127.6 (q, $J_{C\text{-}F}$ = 29.9 Hz), 127.6, 126.8, 125.7 (q, $J_{C\text{-}F}$ = 4.1 Hz), 124.1 (q, $J_{C\text{-}F}$ = 269.4 Hz), 34.7, 31.2; MS (EI(+)): *m/z* 310 (M^+), HRMS (FAB(+)) calc for $C_{19}H_{14}F_3N$: 310.1003, found: 310.0999.

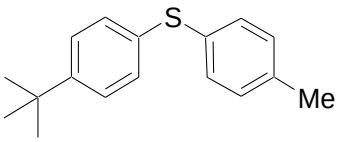


4-tert-Butylphenyl-2-methylphenylsulfide (3eF); CAS: 19711-56-9; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 ^{o}C): δ 7.30 (d, J = 8.5 Hz, 2H), 7.22-7.14 (m, 5H), 7.10 (t, J = 7.0 Hz, 1H), 2.38 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 ^{o}C): δ 149.9, 139.1, 134.8, 131.9, 131.8, 130.4, 130.3, 127.3, 126.6, 126.2, 34.5, 31.3, 20.5; MS (EI(+)): *m/z* 256 (M^+).

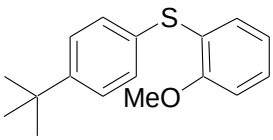


4-tert-Butylphenyl-3-methylphenylsulfide (3fF); CAS: 643017-26-9; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 ^{o}C): δ 7.32 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.17-7.14 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 2.89 (s, 3H), 1.30 (s,

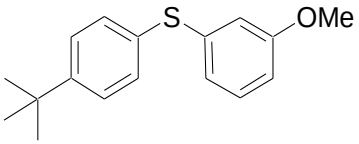
9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 150.3,138.9, 136.0, 132.0, 131.2, 131.1, 128.9, 127.7, 127.6, 126.2, 34.5, 31.3, 21.3; MS (EI(+)): *m/z* 256 (M^+).



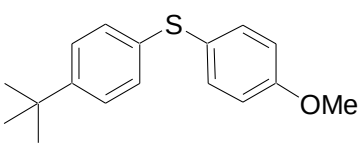
4-tert-Butylphenyl-4-methylphenylsulfide (3gF); CAS: 875713-05-6; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 149.9, 137.1, 133.0, 132.1, 131.6, 130.2, 129.9, 126.1, 34.5, 31.2, 21.1; MS (EI(+)): *m/z* 256 (M^+).



4-tert-Butylphenyl-2-methoxyphenylsulfide (3hF); CAS: No Registry; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.35 (dd, *J* = 10.5, 8.5 Hz, 4H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 156.6, 150.8, 132.4, 130.1, 129.9, 127.5, 126.3, 125.4, 121.2, 110.6, 55.8, 34.6, 31.2; MS (EI(+)): *m/z* 272 (M^+), HRMS (FAB(+)) calc for $C_{19}H_{14}F_3N$: 272.1235, found: 272.1248, IR (ATR): (cm^{-1}) ν 2960, 1577, 1475, 1432, 1394, 1271, 1066, 1024, 829, 681.



4-tert-Butylphenyl-3-methoxyphenylsulfide (3iF); CAS: 643017-25-8; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.33 (s, 4H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.73 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.73 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 160.0, 150.8, 138.1, 131.8, 131.1, 129,8, 126.3, 122.2, 115.3, 112.2, 55.2, 34.6, 31.2; MS (EI(+)): *m/z* 272 (M^+).



4-tert-Butylphenyl-4-methoxyphenylsulfide (3jF); CAS: 114606-26-7; colorless oil; ^{1}H NMR (500 MHz, $CDCL_3$, 25 °C): δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCL_3$, 25 °C): δ 159.5, 149.1, 134.8, 134.6, 128.5, 126.0, 125.1, 114.8, 55.3, 34.4, 31.2; MS (EI(+)): *m/z* 272 (M^+).

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[1] This chapter are based on following paper, see: Y. Hirai, Y. Uozumi, Chem. Lett., 2011, 40, 934.

[2] For recent reviews, see: a) J. E. R. Sadig, M. C. Willis, Synthesis 2011, 1. b)

J. F. Hartwig, Acc. Chem. Res. 2008, 41, 1534.

[3] M. A. Fernández-Rodráguez, J. F. Hartwig, J. Org, Chem., 2009, 74, 1663

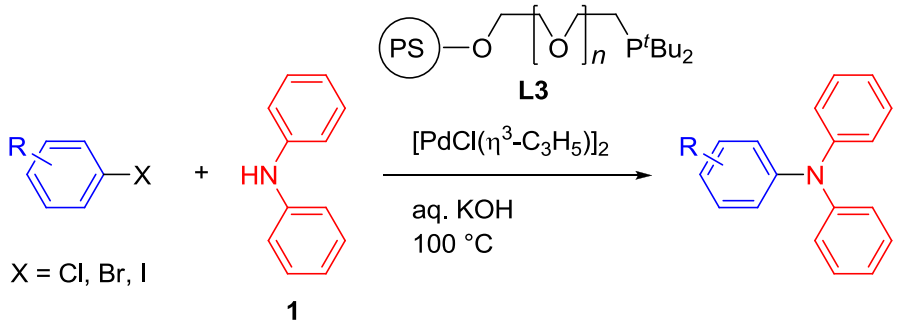
Chapter V: C-P Coupling Reaction by using an Amphiphilic Resin-supported Palladium Complex [1]

Organic reaction in water have recently received much attention because water is a readily available, safe, and environmentally friendly solvent.[2, 3, 4] On the other hand, clean organic synthesis by use of solid-supported catalyst has been recognized as an effective methodology to prevent contamination of the catalyst residue in products by simple manipulation.[3, 4]

As we all known, phosphine compounds are important for organic synthesis and have been synthesized by various methods. The synthetic study of triarylphosphines in particular is performed energetically and many examples using catalytic reaction are reported. [5, 6, 7, 8] However there are only one report of catalytic synthesis of dialkylphosphine and aryl halide which was reported by Buchwald group (Scheme 1).[9] Because the products of C-P coupling reaction between dialkylphosphines and aryl halides are dialkylarylphosphines, they have strong coordination ability to palladium. Therefore the products poison palladium catalyst and prevent catalytic C-P bond formation.

Scheme 1. Buchwald's work

On the other hand, we have developed amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported transition metal catalysts[10] which promoted various catalytic transformations smoothly in water under heterogeneous conditions, including palladium-catalyzed arylation (Suzuki-Miyaura coupling), alkenylation (Heck reaction), alkynylation (Sonogashira coupling), carbonylation of aryl halides, π-allylic substitution (Tsuji-Trost reaction), cyclization of 1,6-enynes, Kharasch addition. In addition, I achieved the Buchwald-Hartwig reaction in water under the heterogeneous conditions by use of immobilized palladium complex, coordinated with amphiphilic polystyrene-poly(ethylene glycol) resin-supported bulky alkyl di(*tert*-butyl)phosphine ligand **L3**. In particular, the ligand **L3** is superior in the synthesis of triarylamines which are useful for electron material (Scheme 2). [11]

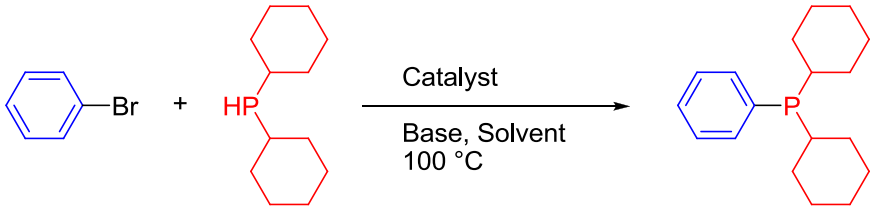


Scheme 2

Here I report the achievement of Pd-catalyzed dicyclohexyl phosphination of aryl halides in the presence of the ligand **L3** in water.

At first, I applied above conditions for C-N bond-forming reaction to C-P bond-forming reaction. Dicyclohexylphosphine (**3**) reacted with bromobenzene (**2a**) in the presence of **L3** and di(μ-chloro)bis(η³-allyl)dipalladium(II) ([PdCl(η³-C_3H_5)]$_2$) (P/Pd = 1:1) in refluxing 20 M aqueous KOH to provide desired Dicyclohexylphenyl-phosphine in 90% yield (Table 1, entry 1). When **L3** and [PdCl(η³-C_3H_5)]$_2$ (P/Pd = 2:1) was used, the reaction proceeded smoothly to give **4A** in 88% yield (Table 1, entry 2). Instead of water and KOH, the use of toluene as a solvent and lithium *tert*-butoxide as a base were not effective (Table 1, entry 3).

Table 1. Dicyclohexylphosphination of bromobenzene



2A 0.55 mmol | **3** 0.50 mmol | **4A**

Entry	Catalyst	P/Pd	Base	Solvent	Time	Yield (%)[j]
1[a]	**L3**/$[PdCl(\eta^3\text{-}C_3H_5)]_2$	1:1	KOH	H_2O	10 h	90%
2[b]	**L3**/$[PdCl(\eta^3\text{-}C_3H_5)]_2$	2:1	KOH	H_2O	2 h	88%
3[c]	**L3**/$[PdCl(\eta^3\text{-}C_3H_5)]_2$	1:1	LiO^tBu	Toluene	23 h	55 (conv.)[k]
4[d]	CuI		Cs_2CO_3	Toluene	10 h	Trace
5[e]	CuI/$(MeNHCH_2)_2$		Cs_2CO_3	Toluene	10 h	Trace
6[f]	$NiCl_2$/dppe		DABCO	DMF	10 h	36%
7[g]	recycled catalyst beads from entry 1 (2nd reuse)				33 h	90%
8[g]	recycled catalyst beads from entry 7 (3rd reuse)				11h	Trace
9[h]	recycled catalyst beads from entry 2 (3rd reuse)				12 h	94%
10[i]	recycled catalyst beads from entry 9 (5th reuse)				33 h	95%

[a] Reaction conditions: **L3** (0.025 mmol of P residue), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.025 mmol), 20 M KOH_{aq} (0.5 mL), 100 °C, under N_2. [b] Reaction conditions: **L3** (0.05 mmol of P residue), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.025 mmol), 20 M KOH_{aq} (0.5 mL), 100 °C, under N_2. [c] Reaction conditions: **L3** (0.025 mmol of P residue), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.025 mmol), LiO^tBu (0.5 mL), 100 °C, under N_2. [d] CuI (0.05 mmol), Cs_2CO_3 (0.75 mmol), Toluene (1 mL), 100 °C, under N_2. [e] CuI (0.05 mmol), N,N'-Dimethyethylenediamine (0.10 mmol), Cs_2CO_3 (1.00 mmol), Toluene (1 mL), 100 °C, under N_2. [f] $NiCl_2$/dppe (0.025 mmol), DABCO (1.00 mmol), Toluene (1 mL), under N_2. [g] **2A** (0.65 mmol). [h] **2A** (0.95 mmol). [i] **2A** (1.00 mmol). [j] Isolated yield. [k] determained by GC.

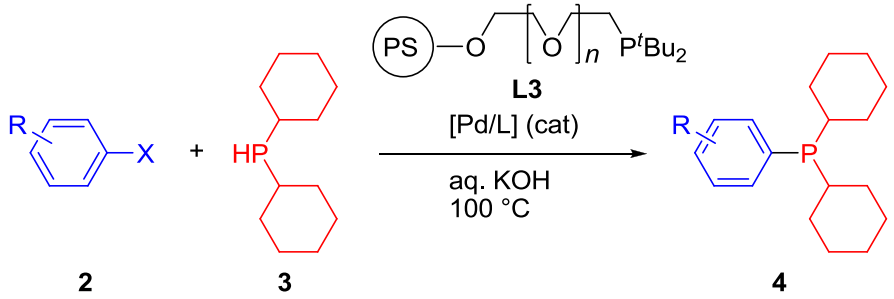
The result indicated that the product, dicyclohexylphenylphosphines, did not

promote this C-P bond formation. The phosphination of iodobenzene in the presence of CuI was reported,[7] but this condition was not effective for phosphination of bromobenzene (Table 1, entry 4, 5). $NiCl_2$ with diphenylphosphinoethane catalyzed the reaction of **3** and **2A** to give **4A** in 36% yield (Table 1 entry 6).[8]

Next, I examined the recyclability of the catalyst beads. **L3** and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (P/Pd = 1:1) could not reuse 3 times (Table 1, entry1, 7, 8). **L3** and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (P/Pd = 2:1) were able to reuse not less than 4^{th} reuse, but catalytic activity was slightly decrease (Table 1, entry 2, 9, 10).

The heterogeneous catalytic phosphination was examined in water a variety of haloarenes under similar reaction conditions and exhibited wide substrate scope (Table 2). Electron-withdrawing and electron-donating aromatic substituents, such as CF_3, CH_3, and OCH_3 groups, were tolerated under the same conditions to give the corresponding dicyclohexylaryl-phosphines (**4A-4K**) in good to excellent yield. 2-Bromobiphenyl (**2K**) reacted with **3** to provide a popular Cyclohexyl-Johnphos (**4K**) in 81% yield.

Table 2. Dicyclohexylphosphination of bromoarenes [a]



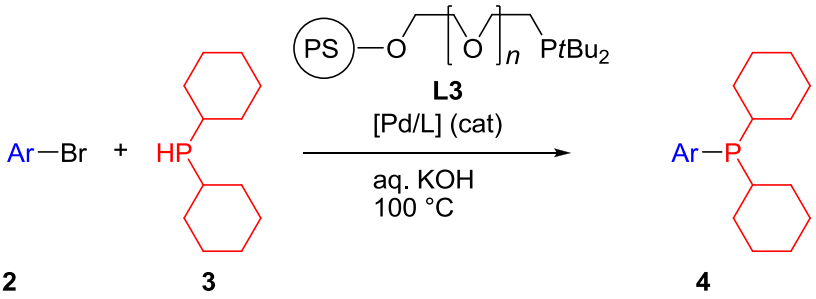
2 **3** **4**

Entry	**2**	R	X	Products	Yield (%)[b]
1	**2A**	H	Br	**4A**	88
2[c]	**2B**	2-CF_3-	Br	**4B**	81
3	**2C**	3-CF_3-	Br	**4C**	80
4	**2D-Br**	4-CF_3-	Br	**4D**	78
5[c]	**2D-Cl**	4-CF_3-	Cl	**4D**	66
6	**2E**	2-CH_3-	Br	**4E**	85
7	**2F**	3-CH_3-	Br	**4F**	83
8	**2G**	4-CH_3-	Br	**4G**	91
9	**2H**	2-CH_3O-	Br	**4H**	86
10	**2I**	3-CH_3O-	Br	**4I**	85
11	**2J**	4-CH_3O-	Br	**4J**	77
12	**2K**	2-Ph	Br	**4K**	81

[a] Reaction conditions: **2** (0.55 mmol), **3** (0.50 mmol), **L3** (0.05 mmol of P residue), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.025 mmol), 20 M KOH_{aq} (0.5 mL), 100 °C, under N_2, reaction time is up to 24 h. [b] Isolated yield. [c] **L3** (0.025 mmol of P residue).

In addition, the coupling reaction of **3** with electron deficient aryl chloride could be carried out in 66% yield (Entry 5). There has been no report of the coupling with aryl chloride in water under heterogeneous conditions.[9]

Table 3. Dicyclohexylphosphination of bromoheteroarenes [a]

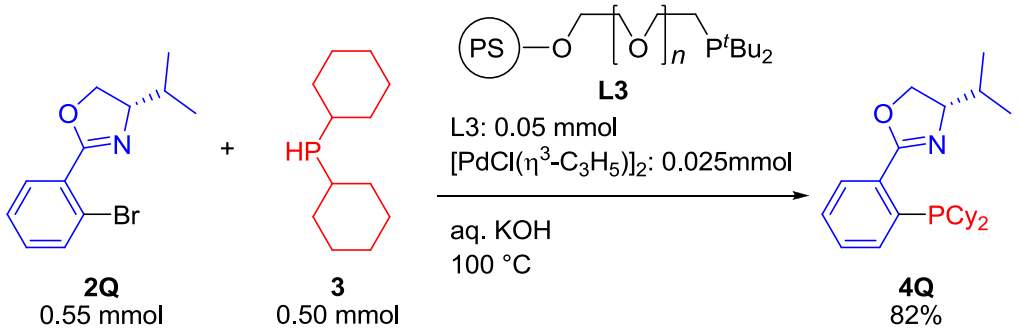


2 **3** **4**

Entry	**2**	Products	Yield (%)[b]
1	**2L** (2-bromopyridine)	**4L**	88
2	**2M** (3-bromopyridine)	**4M**	80
3	**2N** (4-bromopyridine)	**4N**	75
4 [c]	**2O** (2-bromothiophene)	**4O**	73
5	**2P** (3-bromothiophene)	**4P**	88

[a] Reaction conditions: **2** (0.55 mmol), **3** (0.50 mmol), **1** (0.05 mmol of P residue), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.025 mmol), 20 M KOH (0.5 mL), 100 °C, under N_2. [b] Isolated yield. [c] **L3** (0.025 mmol of P residue), **2P** (0.65 mmol)

Heteroarenes, such as bromopyridine and bromothiophene, underwent phosphination under the same conditions to provide corresponding heteroaryldicyclohexylphosphines in 73-88% yield (Table 3). Our methods could be applied to phosphination of **2Q** as an aryl halide to give a bidentate phosphine-oxazoline ligand **4Q**, being useful for asymmetric reactions, in 82% yield (Scheme 3).[12]



2Q
0.55 mmol

3
0.50 mmol

4Q
82%

Scheme 3. C-P coupling of optically active oxazoline derivartive

As showed above, our catalyst promoted the C-P bond formation without being prevented by products. Previously our group reported that coordination ability of electron rich tricyclohexylphosphine to palladium is larger 580 times than dicyclohexylphenylphosphine.[13] Therefore electron rich trialkylphsphine ligand of our catalyst coordinated palladium prior to products. In addition, **L3** and [PdCl(η^3-C$_3$H$_5$)]$_2$ (P/Pd = 1/1) is able to be coordinated by products. On the other hand, **L3** and [PdCl(η^3-C$_3$H$_5$)]$_2$ (P/Pd = 2/1) form chelating complex, therefore the catalyst preformed activity for C-P bond formation.

In conclusion, I have developed a novel C-P bond-forming catalytic protocol with amphiphilic polymer supported palladium complex of trialkylphosphine ligand **L3**, which was carried out in water under heterogeneous conditions to realize a high level of chemical greenness. Synthetic application of this protocol is currently under investigation in our laboratory and will be

reported in due course.

Experimental section

All manipulations were performed under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. Water was deionized with a Millipore system as a Milli-Q grade and was degassed by the freeze-pump-thaw method prior to use. NMR spectra were recorded on a JEOL JNM-A500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, 202 MHz for ^{31}P) or a JEOL JNM–AL400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 162 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ as an internal standard (δ 77.0). The ^{31}P NMR data are reported relative to external Ph_3P. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ at 25 °C. The ESI mass spectra were recorded on a JEOL JMS-T100LC spectrometer. The IR spectra were obtained using a JASCO FT/IR-460plus spectrophotometer in ATR mode. PS-PEG bromo-resin was purchased from RAPP POLYMERETM (TentaGel®S Br, average diameter 0.90 μm, 1% divinylbenzene crosslinked, loading value of bromo residue 0.2-0.4 mmol/g).

General procedure for the amination of haloarenes: To a mixture of **L1** (0.05

mmol of P), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.025 mmol), arylhalides (0.55 mmol) and dicyclohexylphosphine (0.50mmol) in 20 M KOH aqueous solution (0.5 mL) under nitrogen atmosphere was shaken for few hour under reflux conditions. The mixture was cooled and filtered. The filtrated was extracted with Toluene (2 mL). The recovered resin beads were extracted with Toluene (2 mL x 4 times). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography to give the corresponding aryldicyclohexylphosphine.

Dicyclohexylphenylphosphine (4A): CAS: 6476-37-5; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.37-7.42 (m, 2H), 7.25-7.27 (m, 3H), 1.51-1.86 (m, 12H), 0.88-1.29 (m, 10H); MS (ESI(+)): *m/z* 274 (M^+).

Dicyclohexyl(2-trifluoromethylphenyl)phosphine (4B): CAS: No Registry; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.71-7.73 (m, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 1.89-1.94 (m, 4H), 1.76-1.79 (m, 2H), 1.64-1.65 (m, 4H), 1.03-1.40 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 136.8 (dq, $J_{C\text{-}F}$ = 28, $J_{C\text{-}P}$ = 24 Hz), 136.5 (d, $J_{C\text{-}P}$ = 34 Hz), 134.4 (d, $J_{C\text{-}P}$ = 3.0 Hz), 130.6, 128.6, 126.0 (quin, $J_{C\text{-}F,\ C\text{-}P}$ = 6 Hz), 124.2 (q, $J_{C\text{-}F}$ = 274 Hz), 35.5 (d, $J_{C\text{-}P}$ = 14.4 Hz), 30.7 (d, $J_{C\text{-}P}$ = 19 Hz),

29.4 (d, J_{C-P} = 9 Hz), 27.1 (d J_{C-P} = 5 Hz), 27.0, 26.3; ^{31}P NMR (200 MHz, $CDCl_3$, 25 ^{o}C): δ -7.5 (q, J_{P-F} = 54 Hz); MS (ESI(+)): *m/z* 342 (M^+). HRMS (ESI(+)) calc for $C_9H_{26}F_3P$: 342.1724, found: 342.1714, IR (ATR): (cm^{-1}) ν 2923, 2850, 1447, 1308, 1255, 1162, 1132, 1112, 1035, 850, 769, 738, 694, 647, 597.

Dicyclohexyl(3-trifluoromethylphenyl)phosphine (4C): CAS: No Registry; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.71 (d, *J* = 6.5 Hz, 1H), 7.64 (t, *J* = 6.5 Hz, 1H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 1.85-1.96 (m, 4H), 1.77-1.80 (m, 2H), 1.64-1.70 (m, 4H), 1.56-1.59 (m, 2H), 1.32 (tq, *J* = 13.0, 3.5 Hz, 2H), 1.23 (tq, *J* = 13.0, 3.5 Hz, 2H), 1.05-1.62 (m, 4H), 0.92-1.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 137.7 (d, J_{C-p} = 185 Hz), 136.5 (d, J_{C-p} = 21 Hz), 131.2 (dq, J_{C-P} = 22 Hz, J_{C-F} = 4 Hz), 130.1 (dq, J_{C-P} = 7 Hz, J_{C-F} = 32 Hz), 128.0 (d, J_{C-P} = 6 Hz), 125.5 (q, J_{C-F} = 4 Hz), 124.2 (q J_{C-F} = 272 Hz), 32.4 (d, J_{C-P} = 12 Hz), 29.9 (d, J_{C-P} = 16 Hz), 28.7 (d, J_{C-P} = 7 Hz), 27.1 (d J_{C-P} = 12 Hz), 26.9 (d, J_{C-P} = 7 Hz), 26.3; ^{31}P NMR (200 MHz, $CDCl_3$, 25 ^{o}C): δ -2.7; MS (ESI(+)): *m/z* 342 (M^+). HRMS (ESI(+)) calc for $C_9H_{26}F_3P$: 342.1724, found: 342.1715, IR (ATR): (cm^{-1}) ν 2924, 2850, 1448, 1414, 1322, 1268, 1164, 1123, 1068, 1000, 888, 850, 798, 701, 651, 558.

Dicyclohexyl(4-trifluoromethylphenyl)phosphine (4D): CAS: No Registry; colorless solid; mp 53-55 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.55-7.60 (m, 4H), 1.57-1.95 (m, 12H), 0.92-1.37 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 140.0 (d, J_{C-P} = 21 Hz), 134.8 (d, J_{C-F} = 20 Hz), 130.7 (q, J_{C-F} = 32 Hz), 124.4 (m), 124.2 (q, J_{C-F} = 270 Hz), 32.4 (d, J_{C-P} = 12 Hz), 29.9 (d, J_{C-P} = 16 Hz), 28.8 (d, J_{C-P} = 7 Hz), 27.2 (d, J_{C-P} = 12 Hz), 26.9 (d, J_{C-P} = 7 Hz), 26.3; ^{31}P NMR (200 MHz, $CDCl_3$, 25 ^{o}C): δ 2.2; MS (ESI(+)): *m/z* 342 (M^+). HRMS (ESI(+)) calc for $C_9H_{26}F_3P$: 342.1724, found: 342.1726, IR (ATR): (cm^{-1}) ν 2929, 2852, 1446, 1393, 1016, 885, 851, 693, 601.

Dicyclohexyl(*o*-tolyl)phosphine (4E): CAS: 173593-25-4; yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.37 (d, *J* = 7.5 Hz, 1H), 7.13-7.23 (m, 3H), 2.55 (s, 3H), 1.54-1.93 (m, 12H), 0.97-1.34 (m, 10H); MS (ESI(+)): *m/z* 288 (M^+).

Dicyclohexyl(*m*-tolyl)phosphine (4F): CAS: No Registry; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 7.06-7.21 (m, 4H), 2.28 (s, 3H), 1.51-1.86 (m, 12H), 0.86-1.29 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ^{o}C): δ 137.1, 135.7 (d, J_{C-P} = 22 Hz), 134.3 (d, J_{C-P} = 17 Hz), 131.4 (d, J_{C-P} = 16 Hz), 129.5, 127.5 (d, J_{C-P} = 7 Hz), 32.4 (d, J_{C-P} = 12 Hz), 30.0 (d, J_{C-P} = 16 Hz), 28.8 (d, J_{C-P} = 7 Hz), 27.2 (d, J_{C-P} = 12 Hz), 27.0 (d, J_{C-P}

= 8 Hz), 26.4, 21.5; ^{31}P NMR (160 MHz, $CDCl_3$, 25 ^{o}C): δ 2.7; MS (ESI(+)): *m/z* 288 (M^+). HRMS (ESI(+)) calc for $C_{19}H_{29}P$: 288.2007, found: 288.2011, IR (ATR): (cm^{-1}) ν 2920, 2848, 1591, 1446, 1267, 1177, 1110, 999, 887, 849, 776, 732, 697.

Dicyclohexyl(*p*-tolyl)phosphine (4G): CAS: 19966-99-5; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 7.26-7.29 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 2.26 (s, 3H), 1.48-1.84 (m, 12H), 0.85-1.28 (m, 10H); MS (ESI(+)): *m/z* 288 (M^+).

Dicyclohexyl(2-methoxyphenyl)phosphine (4H): CAS: 226089-00-5; colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 7.29 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.79 (dd, *J* = 8.0, 3.5 Hz, 1H), 1.49-1.95 (m, 12H), 0.89-1.28 (m, 10H); MS (ESI(+)): *m/z* 304 (M^+).

Dicyclohexyl(3-methoxyphenyl)phosphine (4I): CAS: No Registry; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.24 (t, *J* = 8 Hz, 1H), 7.00 (m, 2H), 6.86 (dd, *J* = 8.0, 2.5 Hz, 1H), 3.80 (s, 3H), 1.58-1.87 (m, 12H), 0.85-1.33 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 158.8 (d, J_{C-P} = 9 Hz), 136.2 (d, J_{C-P} = 18 Hz), 128.6 (d, J_{C-P} = 8 Hz), 126.8 (d, J_{C-P} = 18 Hz), 120.4 (d, J_{C-P} = 22 Hz), 113.8, 55.1, 32.5 (d, J_{C-P} = 11 Hz),

30.0 (d, J_{C-P} = 17 Hz), 28.8 (d, J_{C-P} = 7 Hz), 27.2 (d, J_{C-P} = 12 Hz), 26.9 (d, J_{C-P} = 7 Hz), 26.3; ^{31}P NMR (200 MHz, $CDCl_3$, 25 ^{o}C): δ 3.4; MS (ESI(+)): *m/z* 304 (M^+). HRMS (ESI(+)) calc for $C_{19}H_{29}OP$: 304.1956, found: 304.1970, IR (ATR): (cm^{-1}) ν 2920, 2847, 1573, 1446, 1415, 1282, 1244, 1227, 1179, 1045, 999, 885, 849, 776, 693.

Dicyclohexyl(4-methoxyphenyl)phosphine (4J): CAS: 40438-63-9; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 7.29-7.34 (m, 2H), 6.79-6.83 (m, 2H), 3.74 (s, 3H), 1.49-1.82 (m, 12H), 0.79-1.29 (m, 10H); MS (ESI(+)): *m/z* 304 (M^+).

2-(Dicyclohexylphosphine)biphenyl (4K): CAS: 847579-96-8; colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 7.58-7.60 (m, 1H), 7.25-7.38 (m, 8H), 1.55-1.84 (m, 12H), 1.00-1.27 (m, 10H); MS (ESI(+)): *m/z* 350 (M^+).

2-(Dicyclohexylphosphino) pyridine (4L): 4L was easily oxidized by oxygen in the air to provide known oxide, so data was corrected in form of oxide. CAS: No Registry; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 8.72 (d, *J* = 5.0 Hz, 1H), 7.58 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.50 (dd, *J* = 7.0 5.0 Hz, 1H), 7.16-7.19 (m, 1H), 2.12 (tq, *J* = 12.6, 3.0 Hz, 2H), 1.57-1.90 (m, 10H), 0.98-1.37 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25

^{o}C): δ 161.8 (d, J_{C-P} = 12 Hz), 149.9 (d, J_{C-P} = 5 Hz), 134.5 (d, J_{C-P} = 8 Hz), 131.2 (d, J_{C-P} = 34 Hz), 122.4, 32.8 (d, J_{C-P} = 11 Hz), 29.8 (d, J_{C-P} = 15 Hz), 29.3 (d, J_{C-P} = 9 Hz), 27.1 (d, J_{C-P} = 12 Hz), 26.9 (d, J_{C-P} = 8 Hz), 26.4; ^{31}P NMR (200 MHz, $CDCl_3$, 25 ^{o}C): δ 6.1; MS (ESI(+)): *m/z* 275 (M^+). HRMS (ESI(+)) calc for $C_{17}H_{26}NP$: 275.1803, found: 275.1801.

Di(cyclohexyl)-2-pyridylphosphine oxide: CAS: 1415212-05-3, colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 8.74-8.75 (m, 1H), 8.06-8.09 (m, 1H), 7.81 (tq, *J* = 7.6, 1.6 Hz, 1H), 7.35-7.39 (m, 1H), 1.65-2.23 (m, 10H), 1.09-1.56 (m, 12H); MS (ESI(+)): *m/z* 292 ($M+H^+$).

3-(Dicyclohexylphosphino) pyridine (4M): 4M was easily oxidized by oxygen in the air to provide known oxide, so data was corrected in form of oxide. CAS: No Registry; colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 8.58-5.59 (m, 1H), 8.51 (dt, *J* = 4.5, 1.5 Hz, 1H), 7.67-7.71 (m, 1H), 7.21 (dd, *J* = 8.0, 5.0 Hz, 1H), 1.51-1.91 (m, 12H), 0.88-1.29 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 155.0 (d, J_{C-P} = 23 Hz), 149.7, 142.0 (d, J_{C-P} = 17 Hz), 130.6 (d, J_{C-P} = 23 Hz), 122.9 (d, J_{C-P} = 5 Hz), 31.9 (d, J_{C-P} = 11 Hz), 29.8 (d, J_{C-P} = 15 Hz), 28.6 (d, J_{C-P} = 6 Hz), 27.0 (d, J_{C-P} = 12 Hz), 26.8

(d, $J_{C\text{-}P}$ = 8 Hz), 26.2; ^{31}P NMR (200 MHz, $CDCl_3$, 25 ^{o}C): δ -3.9; MS (ESI(+)): *m/z* 275 (M^+). HRMS (ESI(+)) calc for $C_{17}H_{26}NP$: 275.1803, found: 275.1798.

Di(cyclohexyl)-3-pyridylphosphine oxide: CAS: No Registry; colorless solid, mp 159-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 8.75-8.78 (m, 2H), 8.10 (ddt, *J* = 9.6, 7.6, 2.0 Hz, 1H), 7.43-7.47 (m, 1H), 2.02-2.11 (m, 4H), 1.62-1.86 (m, 8H), 1.09-1.37 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 152.0 (d, $J_{C\text{-}P}$ = 2 Hz), 151.2 (d, $J_{C\text{-}P}$ = 11 Hz), 140.1 (d, $J_{C\text{-}P}$ = 6 Hz), 126.2 (d, $J_{C\text{-}P}$ = 81 Hz), 123.5 (d, $J_{C\text{-}P}$ = 8 Hz), 35.1 (d, $J_{C\text{-}P}$ = 68 Hz), 26.2 (d, $J_{C\text{-}P}$ = 10 Hz), 26.1 (d, $J_{C\text{-}P}$ = 9 Hz), 25.7, 25.3 (d, $J_{C\text{-}P}$ = 3 Hz), 24.4 (d, $J_{C\text{-}P}$ = 3 Hz); ^{31}P NMR (160 MHz, $CDCl_3$, 25 ^{o}C): δ 43.5; MS (ESI(+)): *m/z* 291 (M^+). HRMS (ESI(+)) calc for $C_{17}H_{26}NOP$: 291.1752, found: 291.1754, IR (ATR): (cm^{-1}) ν 2929, 2850, 1577, 1167, 852, 760, 714, 620, 570.

4-(Dicyclohexylphosphino) pyridine (4N): 4N was easily oxidized by oxygen in the air to provide known oxide, so data was corrected in form of oxide. CAS: No Registry; colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ 8.50 (dt, *J* = 4.5, 1.5 Hz, 2H), 7.29 (t, *J* = 6.5, 6,0 Hz, 2H), 1.54-.191 (m, 12H), 0.87-1.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ 148.7 (d, $J_{C\text{-}P}$ = 5 Hz), 129.0 (d, $J_{C\text{-}P}$ = 16 Hz), 31.8 (d, $J_{C\text{-}P}$ = 12

Hz), 29.5 (d, J_{C-P} = 15 Hz), 28.7 (d, J_{C-P} = 7 Hz), 27.1 (d, J_{C-P} = 12 Hz), 26.8 (d, J_{C-P} = 7 Hz), 26.2; ^{31}P NMR (200 MHz, $CDCl_3$, 25 ^{o}C): δ -0.5; MS (ESI(+)): *m/z* 275 (M^+). HRMS (ESI(+)) calc for $C_{17}H_{26}NP$: 275.1803, found: 275.1796.

Di(cyclohexyl)-4-pyridylphosphine oxide: CAS: No Registry; colorless solid, mp 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 8.77 (s (*br*), 2H), 7.57 (dd, *J* = 9.6, 5.6 Hz), 2.01-2.07 (m, 4H), 1.58-1.86 (m, 8H), 1.10-1.36 (m, 10H) ; ^{13}C NMR (100 MHz, $CDCl_3$, 25 ^{o}C): δ 149.6 (d, J_{C-P} = 9 Hz), 139.8 (d, J_{C-P} = 78 Hz), 125.6, 34.8 (d, J_{C-P} = 67 Hz), 26.2 (d, J_{C-P} = 10 Hz), 26.1 (d, J_{C-P} = 9 Hz), 25.6 (d, J_{C-P} = 2 Hz), 25.3 (d, J_{C-P} = 3 Hz), 24.4 (d, J_{C-P} = 3 Hz); ^{31}P NMR (160 MHz, $CDCl_3$, 25 ^{o}C): δ 43.9; MS (ESI(+)): *m/z* 291 (M^+). HRMS (ESI(+)) calc for $C_{17}H_{26}NOP$: 291.1752, found: 291.1753, IR (ATR): (cm^{-1}) ν 2920, 2852, 1447, 1409, 1208, 1167, 1124, 897, 856, 818, 758.

Dicyclohexyl(2-thiophenyl)phosphine (4O): CAS: No Registry; yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 7.54 (d, *J* = 4.8 Hz, 1H), 7.26-7.28 (m, 1H), 7.08-7.10 (m, 1H), 1.64-1.90 (m, 12H), 1.04-1.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ^{o}C): δ 136.9 (d, J_{C-P} = 28 Hz), 135.9 (d, J_{C-P} = 38 Hz), 130.6, 127.2 (d, J_{C-P} = 9 Hz), 34.0 (d,

J_{C-P} = 10 Hz), 30.0 (d, J_{C-P} = 16 Hz), 28.9 (d, J_{C-P} = 7 Hz), 27.1 (d, J_{C-P} = 13 Hz), 26.9 (d, J_{C-P} = 8 Hz), 26.3; ; ^{31}P NMR (160 MHz, $CDCl_3$, 25 ^{o}C): -10.1; MS (ESI(+)): *m/z* 280 (M^+). HRMS (ESI(+)) calc for $C_{16}H_{25}PS$: 280.1415, found: 280.1409, IR (ATR): (cm^{-1}) ν 2921, 2848, 2360, 1446, 1408, 1365, 1265, 1215, 1177, 1082, 1000, 983, 887, 849, 742, 579.

Dicyclohexyl(3-thiophenyl)phosphine (4P): CAS: No Registry; yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 7.30-7.46 (m, 2H), 7.11 (dtt, *J* = 15.2, 4.8, 1.6 Hz, 1H), 1.55-1.94 (m, 12H), 0.91-1.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ^{o}C): δ 134.4 (d, J_{C-P} = 21 Hz), 131.8 (d, J_{C-P} = 30 Hz), 131.1 (d, J_{C-P} = 9 Hz), 125.2 (d, J_{C-P} = 4 Hz), 33.0 (d, J_{C-P} = 10 Hz), 30.1 (d, J_{C-P} = 16 Hz), 28.9 (d, J_{C-P} = 7 Hz), 27.1 (d, J_{C-P} = 13 Hz), 26.9 (d, J_{C-P} = 8 Hz), 26.3; ^{31}P NMR (160 MHz, $CDCl_3$, 25 ^{o}C): -11.8; MS (ESI(+)): *m/z* 280 (M^+). HRMS (ESI(+)) calc for $C_{16}H_{25}PS$: 280.1415, found: 280.1422, IR (ATR): (cm^{-1}) ν 2920, 2847, 2359, 2342, 1446, 1340, 1266, 1201, 1177, 1094, 1000, 886, 849, 777, 743, 690, 619.

(*S*)-2-[2-(Dicyclohexylphosphino)phenyl]-4-*i*-propyloxazoline (4Q): CAS: 180260-74-6; colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 7.27-7.66 (m, 4H), 4.37-4.49

(m, 1H), 4.05-4.19 (m, 2H), 1.53-1.98 (m, 13H), 0.89-1.34 (m, 16H); MS (ESI(+)): *m/z* 386 ($M+H^+$).

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Conclusion

Conclusions of each chapter are shown in below.

- Chapter I: I prepared various the palladium complexes co-ordinatively anchored onto the amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) copolymer resin-supported bulky phosphine as possible water-compatible polymeric ligands, for C-X bond-forming coupling.
- Chapter II: I discovered the amphiphilic PS-PEG resin-supported bulky alkyldi(*tert*-butyl)phosphine ligand which was used for Buchwald-Hartwig reaction in water. Aromatic amination of aryl halides with diphenylamine and *N,N*-double arylation of anilines with bromobenzene were found to proceed smoothly in water with broad substrate tolerance to give triarylamines in high yield with high recyclability of the polymeric catalyst beads. Since little palladium leached from the polymeric catalyst under the water-based reaction conditions, this method provides a green and clean (metal-uncontaminated) protocol for the preparation of triarylamines.
- Chapter III: The catalytic system was applied to successive amination

of dibromoarenes and *N,N,N'N'*-quadruple arylation of phenylenediamine producing *N,N,N'N'*-tetraarylphenylenediamines. With the heterogeneous catalytic system, electroactive *N,N,N',N'*-tetraaryl-1,1'-biphenyl- 4,4'-diamines (TPDs) were obtained without metal contamination.

- Chapter IV: C-S bond-forming coupling was accomplished by the catalytic system without suffering from deactivation of catalyst by thiols and sulfides.
- Chapter V: Aromatic phosphination of aryl halides and alkyl phosphine in water were performed with the amphiphilic PS-PEG resin-supported di(*tert*-butyl)phosphine catalyst. The catalytic system is able to prepare the useful phosphine compounds as ligand for example Cyclohexyl JohnPhos and optically active oxazoline substituted phosphine derivertive.

As mentioned above, I achieved the development of novel amphiphilic polymer-supported palladium complexes and their application to C-X bond-forming cross coupling reaction in water. The catalytic system can be used in an optoelectronically material field, a pharmaceutical field and a fine

chemical field with environmental harmony. I believe great potentialities of the amphiphilic polymer-supported palladium complex.

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