Paper in Celebration for the 2010 Nobel Prize in Chemistry

doi:10.1246/cl.2011.934

C–N and C–S Bond Forming Cross Coupling in Water with Amphiphilic Resin-supported Palladium Complexes

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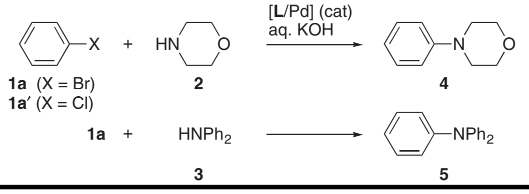
(Received April 18, 2011; CL-110324; E-mail: uo@ims.ac.jp)

Catalytic C–N and C–S bond forming reactions of haloarenes with secondary amines and benzenethiols were achieved in water under heterogeneous conditions by the use of immobilized palladium complexes coordinated with the amphiphilic polystyrene–poly(ethylene glycol) resin-supported di(*tert*-butyl)phosphane ligand to afford aryl(dialkyl)amines and diaryl sulfides in high yield.

Organic reactions in water have recently received much attention because water is a readily available, safe, and environmentally benign solvent.[1–3] On the other hand, clean organic synthesis by use of solid-supported reagents has been recognized as an effective methodology to prevent contamination of the reagent residue in the products by simple manipulations.[2,3] We have developed amphiphilic polystyrene–poly(ethylene glycol) (PS–PEG) resin-supported palladium–phosphane complexes, which catalyze various palladium-mediated reactions, including cross-coupling reactions, smoothly in water under heterogeneous conditions to meet the requirements of green, safe, and clean organic synthesis.[4] Thus, for example, various C–C bond forming cross-couplings, e.g., the Suzuki–Miyaura cross-coupling,[4a,4b,4e,4f] the Mizoroki–Heck reaction,[4c] and the Sonogashira[4d,4g] reaction, have been achieved in water using palladium complexes immobilized by coordination with a phosphane ligand anchored on an amphiphilic PS–PEG resin. As part of our effort to demonstrate the wide utility of this catalyst system, we decided to examine the Buchwald–Hartwig type C–N and C–S bond forming reactions.[5] While, we have previously reported the Buchwald–Hartwig amination of aryl halides with diarylamines in water to form triarylamines,[6] the aqueous-switching of C–N coupling with alkylamines and C–S coupling reactions still remains a major challenge. We report herein our results demonstrating that coupling reactions of various aryl halides with amines and thiols proceed in water in the presence of a palladium complex of a PS–PEG resin-supported *tert*-butylphosphane ligand.

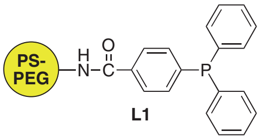
We have examined several amphiphilic PS–PEG resin-supported phosphane ligands for the amination reaction of bromobenzene (**1a**) (Table 1). Thus, the C–N bond forming coupling reaction of **1a** with morpholine (**2**) was carried out in refluxing aqueous KOH solution in the presence of a PS–PEG resin-supported 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. 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)phosphane resin **L3** is the best catalyst for the amination reaction of **1a** and **2** in water.

Table 1. Amination of halobenzene in water[a]

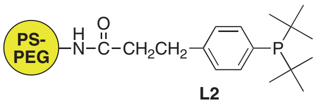


Entry	L	P/Pd	Product	Yield/%[b]
1	**L1**	1/1	**4**	10
2	**L2**	1/1	**4**	22
3	**L3**	1/1	**4**	74
4[c]	**L3**	1/1	**4**	64
5	**L3**	2/1	**4**	86
6	**L1**	1/1	**5**	<1
7	**L2**	1/1	**5**	<1
8	**L3**	1/1	**5**	82
9[c]	**L3**	1/1	**5**	81
10	**L3**	2/1	**5**	92
11[d]	**L3**	2/1	**5**	95
12	**L4**	1/1	**5**	41

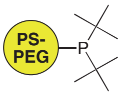
[a] All reactions were carried out with PhBr (**1a**) in 20 M aqueous KOH solution under reflux in the presence of 5 mol % 1/2[PdCl(η^3-C_3H_5)]$_2$ and a polymeric ligand (**L**) for 17–24 h, unless otherwise noted. The ratio of **1** (mol)/**2** or **3** (mol)/H_2O (L) = 1.0/1.5/2.0. [b] Isolated yields. [c] PhCl (**1a′**) was used. [d] Recycled polymeric palladium complex (**L3**/Pd; 5th reuse) was used.



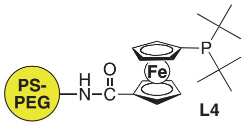
L1



L2

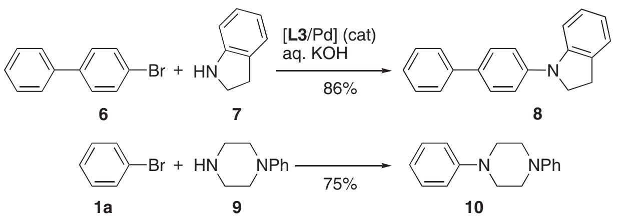


L3



L4

Thus, the palladium complex immobilized by coordination with an alkyl[di(*tert*-butyl)]phosphane group which was anchored on an amphiphilic PS–PEG resin catalyzed the reaction of **1a** and **2** in an aqueous KOH solution to give 74% isolated yield of *N*-phenylmorpholine (**4**) (Entry 3). Lower catalytic activity was observed in water with the PS–PEG resin-supported triarylphosphane **L1** and aryl[di(*tert*-butyl)]phosphane ligand **L2** (Entries 1 and 2). It is noteworthy that the polymeric 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(η^3-C_3H_5)]$_2$ in a ratio of P/Pd = 2/1 where the target compound **4** was obtained in 86% yield (Entry 5). A



Scheme 1. C–N coupling with nitrogen heterocycles.

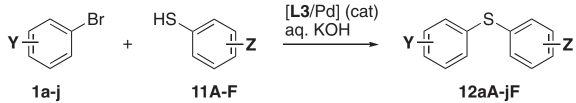
similar trend was also observed in the reaction of **1a** with diphenylamine (**3**) (Entries 6–12).[6] The amination with diphenylamine hardly proceeded with a palladium complex of polymeric arylphosphanes (Entries 6 and 7). Ferrocenyl[di(*tert*-butyl)]phosphane **L4** gave a moderate yield of triphenylamine (**5**) under similar conditions (Entry 12). A palladium complex of sterically demanding alkylphosphane **L3** promoted the amination of bromobenzene (**1a**) as well as chlorobenzene (**1a′**) in refluxing aqueous KOH solution to give triphenylamine (**5**) in 82 and 81% yield, respectively (Entries 8 and 9). A polymeric palladium complex prepared from **L3** (P/Pd = 2/1) provided **5** in 92–95% yield through 5 reuses of the catalyst beads (Entries 10 and 11). 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).

With the efficient aqueous heterogeneous catalytic system for the C–N bond forming coupling in hand, we next examined the C–S bond forming catalysis with the catalytic system (Table 2). Thus, bromobenzene (**1a**) reacted with 2-methylbenzenethiol (**11A**) in refluxing aqueous KOH solution in the presence of 5 mol % Pd of the polymeric palladium complex **L3**/Pd for 24 h to give 74% isolated yield of 2-methylphenyl phenyl sulfide (**12aA**) (Entry 1).[7] Benzenethiol bearing 3-methyl (**11B**), 2-methoxy (**11C**), 3-methoxy (**11D**), 4-methoxy (**11E**), and 4-*tert*-butyl (**11F**) reacted with **1a** under similar 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. Thus, 2-, 3-, and 4-(trifluoromethyl)bromobenzenes **1b**–**1d** reacted with 4-(*tert*-butyl)benzenethiol (**11F**) under similar conditions to give 4-(*tert*-butyl)phenyl *n*-trifluoromethylphenyl sulfides (*n* = 2 (**12bF**), 3 (**12cF**), and 4 (**12dF**)), 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 **12eF**–**12jF** in 57–96% yield (Entries 10–15).

In conclusion, we have developed a novel C–N and C–S bond forming catalytic protocol with an amphiphilic polymeric palladium complex of sterically demanding alkylphosphane 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.

We acknowledge the JSPS (Grant-in-Aid for Scientific Research on Innovative Area No. 2105) and the NEDO GSC project for partial financial support of this work.

Table 2. C–S Coupling of bromoarenes in water[a]



Entry	1	11	Y	Z	Product	Yield/%[b]
1	**1a**	**11A**	H	2-CH_3	**12aA**	74
2	**1a**	**11B**	H	3-CH_3	**12aB**	71
3	**1a**	**11C**	H	2-CH_3O	**12aC**	71
4	**1a**	**11D**	H	3-CH_3O	**12aD**	68
5	**1a**	**11E**	H	4-CH_3O	**12aE**	93
6	**1a**	**11F**	H	4-*t*-Bu	**12aF**	91
7	**1b**	**11F**	2-CF_3	4-*t*-Bu	**12bF**	84
8	**1c**	**11F**	3-CF_3	4-*t*-Bu	**12cF**	75
9	**1d**	**11F**	4-CF_3	4-*t*-Bu	**12dF**	78
10	**1e**	**11F**	2-CH_3	4-*t*-Bu	**12eF**	96
11	**1f**	**11F**	3-CH_3	4-*t*-Bu	**12fF**	82
12	**1g**	**11F**	4-CH_3	4-*t*-Bu	**12gF**	86
13	**1h**	**11F**	2-CH_3O	4-*t*-Bu	**12hF**	57
14	**1i**	**11F**	3-CH_3O	4-*t*-Bu	**12iF**	72
15	**1j**	**11F**	4-CH_3O	4-*t*-Bu	**12jF**	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 a polymeric ligand (**L**) for 24 h, unless otherwise noted. The ratio of **1** (mol)/**11** (mol)/H_2O (L) = 1.5/1.0/2.0. [b] Isolated yields.

This paper is in celebration of the 2010 Nobel Prize awarded to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi.

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7 *General procedure*: A mixture of catalyst (**L3**–Pd complex (P/Pd = 2/1), 0.015 mmol of Pd), aryl halides (0.45 mmol) and arylthiols (0.30 mmol) in 20 M KOH aqueous solution (0.6 mL) under a nitrogen atmosphere was shaken for 24 h under reflux conditions. After being cooled, the mixture 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.