Use of Polymer-Supported Terpyridine Palladium Complex for Suzuki–Miyaura Cross-Coupling Reaction in Water and the Synthesis of 2,6-Disubstituted Pyrimidines

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In this study, a polymer-supported terpyridine–palladium complex was prepared and found to promote the Suzuki–Miyaura cross-coupling reaction in water. The terpyridine ligand was prepared from 4-methoxycarbonylbenzaldehyde, 2-acetylpyridine according to the reported procedures. The terpyridine ligand was immobilized onto a PS–PEG resin, and the complexation of the PS–PEG terpyridine ligand with Pd(II) gave the PS–PEG terpyridine–Pd(II) complex. The polymeric catalyst showed high catalytic activity and high reusability for this cross-coupling reaction. This catalyst was also applied to the synthesis of 2,6-disubstituted pyrimidines in water.

Key words: cross coupling, terpyridine, pyrimidine, palladium

1. INTRODUCTION

We have previously developed an amphiphilic polystyrene-poly(ethylene glycol) (PS–PEG) resin-supported terpyridine copper catalyst through the formation of a covalent bond to the amino group instead of an ionic bond to the amino group with resin, which promotes the Huisgen [3+2] cycloaddition reaction smoothly in water under heterogeneous and aerobic conditions without leaching of Cu into water [1-2]. Our continuing interest in the catalytic utility of polymeric catalyst 2 instead of the previously chosen preparation catalyst 1 led us to examine the cross-coupling reaction in water and the synthesis of 2,6-disubstituted pyrimidine derivatives in water using the polymeric catalyst 2 [3]. Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions are one of the most well-known examples of carbon–carbon bond-forming reactions in modern organic synthesis of symmetrical and unsymmetrical biaryl compounds [4], which are the key components in many natural products as well as in the field of engineering materials, such as conducting polymers, molecular wires, and liquid crystals [5]. On the other hand, carbon–nitrogen bond-forming reactions, the so-called Buchwald–Hartwig-type reactions [6-7], are also important cross-coupling reactions in synthetic organic chemistry. For example, 4,6-disubstituted pyrimidines having carbon–nitrogen bonds allowed the efficient identification of potent and highly selective inhibitors of both enzymatic and cellular EGFR kinase activity [8]. Most of these catalytic systems for cross-coupling reactions, which combine palladium salts with various ligands such as phosphines and N-heterocyclic carbenes under homogeneous conditions, are highly efficient only in organic solvents or in a mixture of water and organic solvent.

If these cross-coupling reactions took place in water with recyclable palladium catalysts under aerobic conditions, where neither aqueous-organic solvent wastes nor metal-contaminated wastes were produced, this would meet green chemical requirements. We report herein the Suzuki–Miyaura cross-coupling reactions of various aryl halides in water with a palladium complex of an amphiphilic PS–PEG resin-bound terpyridine ligand and the synthesis of 2,6-disubstituted pyrimidine using the same catalyst (Scheme 1).

Scheme 1. Preparation of PS–PEG terpyridine–Pd(II) complex and its application to the cross-coupling reaction
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and a HITACHI R1900 spectrometer (90 MHz for 1H and 22 MHz for 13C). 1H and 13C NMR spectra were recorded in CDCl3 or dimethyl sulfoxide-d6 (DMSO-d6) at 25 °C. Chemical shifts of 13C NMR were given relative to CDCl3 and DMSO-d6 as an internal standard (δ77.0 ppm and 39.7 ppm). Mass spectral data were measured on a JEOL JMS-T100GCV MS detector (GC-MS) and a JEOL JMS-T100LP MS detector (LC-MS); “bp” denotes the base peak. GC analysis was performed on a Shimadzu GC-2014 GC, and IR analysis was performed on a JASCO FTIR-410 spectrometer. ICP-AES spectral data were measured on a Shimadzu ICP-E-9000 spectrometer. Elemental analysis was performed on a J-Science, JM10, elemental analyzer.

2.2 Materials

The PS-PEG-supported terpyridine ligand was prepared from PS-PEG amino resin (Tenta Gel S NH2, average diameter 90 μm, 1% divinylbenzene cross-linked, loading of amino residue 0.31 mmol/g; purchased from RAPP POLYMERE) and terpyridine ligand 1 according to the reported procedures [9-10].

2.3 Synthesis of 2a

Twenty eight percent of NH4OH solution (0.2 mL) and NaOH (80 mg, 2.0 mmol) dissolved in a minimum amount of water were added to a solution of 4-methoxybenzylaldehyde (164 mg, 1.0 mmol) and 2-acetlypyridine (242 mg, 2.0 mmol) in EtOH (4.1 mL). After the addition of NaOH, the solution turned yellow and then red after 1 h. The solution was stirred vigorously at room temperature in a flask exposed to air for 17 h, after which a yellow suspension was obtained. Then, water (50 mL) was added and the solution was neutralized with concentrated HCl to yield a light yellow precipitate and a red solution. The precipitate was collected by filtration and washed with water. For further purification, the precipitate was refluxed for 1 h in EtOH (10 mL) before 77.6 mg (22% yield) of 2a was collected by filtration. 1H NMR (DMSO-d6): δ 13.2 (br s, 1H), 8.79-8.76 (m, 4H), 8.69 (d, J = 7.9 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H), 8.05 (td, J = 7.6, 1.8 Hz, 4H), 7.56-7.53 (m, 2H); 13C NMR (DMSO-d6); δ 166.6, 155.8 (2C), 154.9 (2C), 149.0 (2C), 148.4, 141.0, 136.9 (2C), 132.4, 129.8 (2C), 126.6 (2C), 124.0 (2C), 120.7 (2C), 117.9 (2C); IR (ATR) (cm−1): ν 3414 (br), 3122, 1684, 1565; HR-ESI-MS: calcd for C22H15N3O2Na (M+Na) 376.1062, found 376.1062. GC analysis was performed on a JASCO FTIR-410 spectrometer. Shimadzu GC-2014 GC, and IR analysis was performed on a JMS-T100LP MS detector (GC-MS) and a JEOL JMS-T100GCv MS detector (GC-MS) and a JEOL JMS-T100MS MS detector (LC-MS); “bp” denotes the base peak. The resulting products were assigned by 1H-NMR, 13C-NMR, MS (EI), and IR analysis. The CAS registry number is shown below. biphosphoryl (5a), 4-methylbiphosphoryl (5b), 4-methoxybiphosphoryl (5c), 4-trifluoromethylbiphosphoryl (5d), 2-methylbiphosphoryl (5e), 3-methylbiphosphoryl (5f), 1-phenylphthalene (5g), 4-fluorobiphosphoryl (5h), 4-chlorobiphosphoryl (5i): CAS registry number: 92-52-4, 644-08-6, 613-37-6, 398-36-7, 643-58-3, 643-93-6, 605-02-7, 324-74-3, 2051-62-9.

2.6 Preparation of Compound 8

The compounds 4,6-dichloropyrimidine 6 (60 mg, 0.40 mmol), aniline 7 (112 mg, 1.2 mmol), and K2CO3 (110 mg, 0.8 mmol) were mixed in H2O in the presence of polymeric catalyst 2 (77 mg, 0.020 mmol). The resulting heterogeneous solution was heated at 40 °C for 8 h and then filtered. The recovered resin beads were rinsed with H2O and extracted three times with EtOAc (6 mL). The EtOAc layer was separated and the aqueous layer was extracted with EtOAc (3 mL). The combined EtOAc extracts were washed with brine (2 mL), dried over MgSO4, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (hexane) to give 60.1 mg (98% yield) of biphosphoryl (5a).

The resulting products were assigned by 1H-NMR, 13C-NMR, MS (EI), and IR analysis. The CAS registry number is shown below. biphosphoryl (5a), 4-methylbiphosphoryl (5b), 4-methoxybiphosphoryl (5c), 4-trifluoromethylbiphosphoryl (5d), 2-methylbiphosphoryl (5e), 3-methylbiphosphoryl (5f), 1-phenylphthalene (5g), 4-fluorobiphosphoryl (5h), 4-chlorobiphosphoryl (5i): CAS registry number: 92-52-4, 644-08-6, 613-37-6, 398-36-7, 643-58-3, 643-93-6, 605-02-7, 324-74-3, 2051-62-9.

2.4 Preparation of PS-PEG resin-supported terpyridine-palladium complex 2

A Merrifield vessel was charged with PS-PEG-NH2 (0.77 g, 0.24 mmol), 2a (127 mg, 0.26 mmol), EDCI (138 mg, 0.72 mmol), HOBt (146 mg, 0.96 mmol), and dimethyl sulfoxide (DMSO) (10 mL). The reaction mixture was shaken on a shaking machine (EYELA CM-1000) at 25 °C for 16 h. The consumption of the primary amino residue of the resin was monitored by the Kaiser negative test. The reaction mixture was filtered and the resin was washed with DMSO and CH2Cl2. The resin was dried under reduced pressure to give the polymer-supported terpyridine 2a (loading value of terpyridine: 0.27 mmol/g, as determined by elemental analysis).

Another Merrifield vessel was charged with resin-supported terpyridine (2a; 444 mg, 0.12 mmol) and 10 mL of toluene. To this suspension, (PhCN)2PdCl2 (72.7 mg, 0.19 mmol) was added, and the mixture was shaken on a shaking machine (CM-1000) at 25 °C for 2 h. After filtration, the resin was washed with toluene and CH2Cl2. The resin thus obtained was dried under reduced pressure to give the polymer-supported palladium complex 2 (loading value of Pd: 0.26 mmol/g), IR (ATR) (cm−1); 2: ν 2868, 1453, 1094.
3. RESULTS AND DISCUSSION

The amphiphilic PS-PEG resin-bound terpyridine ligand was readily prepared from 4-methoxybenzylboronic acid, 2-acetylpyridine, NH₂OH, and PS-PEG-NH₂ resin according to the reported procedures. The coordination of the generated polymeric terpyridine ligand with palladium species took place in toluene in DMSO at room temperature for 16 h, and the complexation of amphiphilic PS-PEG resin-bound terpyridine ligand and Pd(II) took place in toluene. Thus, the immobilization of terpyridine ligand and Pd(II) into the resin was achieved using PS-PEG terpyridine–Pd(II) complex 2 as a brown solid [9-10]. The amphiphilic PS-PEG resin-bound terpyridine ligand was readily prepared from 4-methoxybenzylboronic acid, 2-acetylpyridine, NH₂OH, and PS-PEG-NH₂ resin according to the reported procedures. The coordination of the generated polymeric terpyridine ligand with palladium species took place in toluene in DMSO at room temperature for 16 h, and the complexation of amphiphilic PS-PEG resin-bound terpyridine ligand and Pd(II) took place in toluene. Thus, the immobilization of terpyridine ligand and Pd(II) into the resin was achieved using PS-PEG terpyridine–Pd(II) complex 2 as a brown solid [9-10].

The scope of aryl halides and arylboronic acids for the Suzuki–Miyaura cross-coupling reaction in water was examined using PS-PEG terpyridine–Pd(II) 2 under aerobic conditions. The representative results are summarized in Table 1. PS-PEG resin-supported terpyridine–Pd(II) complex 2 efficiently catalyzed the coupling of iodobenzene (3a) with phenylboronic acid (4a). Thus, the Suzuki–Miyaura cross-coupling reaction of 3a with 4a was carried out with K₂CO₃ (2 mol% Pd) in water to give biphenyl (5a) in 98% yield (run 1). The Suzuki–Miyaura cross-coupling reaction of phenylboronic acid (4a) with iodobenzene derivatives 3b, 3c, and 3d, bearing electron-donating and withdrawing substituents at their para-positions, gave 4-methylbiphenyl (5b), 4-methoxybiphenyl (5c), and 4-trifluoromethylbiphenyl (5d) in 86%, 94%, and 95% yields (runs 2, 3, and 4, respectively). The coupling reaction of meta- and ortho-substituted iodobenzene derivatives 3e, 3f, and 3g, having meta-alkyl and ortho-alkyl groups, with phenylboronic acid (4a) gave 2-methylbiphenyl (5e), 3-methylbiphenyl (5f), and 1-phenylphthalene (5g) in 89%, 94%, and 92% yields (runs 5, 6, and 7, respectively).

In addition, the coupling reactions of bromoarenes 3h, 3i, 3j, and 3k with 4a gave the corresponding biaryls 5a, 5b, 5c, and 5d in 99%, 90%, 88%, and 92% yields (runs 8, 9, 10, and 11, respectively). The reactivity of several boronic acids 4b, 4c, 4d, 4e, 4f, and 4g was also examined under similar conditions to furnish the coupling products 5b, 5e, 5f, 5g, 5h, and 5i in 98%, 96%, 98%, 98%, 95%, and 99% yields (runs 12, 13, 14, 15, 16, and 17, respectively).

Table 1. Suzuki–Miyaura cross-coupling reaction using polymeric catalyst 2 in water

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²All reactions were performed with ArX (3; 0.4 mmol), ArB(OH)₃ (4; 0.8 mmol), and K₂CO₃ (0.8 mmol) using polymeric catalyst 2 in 3.5 mL of H₂O at 100 °C for 6 h under aerobic conditions. ²²Reaction time was 12 h.
The recyclability of PS-PEG terpyridine–Pd(II) 2 was examined for the Suzuki–Miyaura cross-coupling reaction of iodobenzene (3a) with phenylboronic acid (4a). Thus, after the first reaction, which gave 98% of biphenyl (5a), the catalyst was recovered by simple filtration, washed with H2O, dried under vacuum, and reused six times under similar reaction conditions to give 5a in 93%, 98%, 98%, 93%, 93%, and 99% yields, respectively. In particular, the ICP-AES analysis of the aqueous phase revealed barely detectable levels of palladium residue.

For the synthesis of 2,6-disubstituted pyrimidines using polymeric catalyst 2, we also examined the reaction of 4,6-dichloropyrimidine 6 with aniline 7 in the presence of polymeric catalyst 2 in water at 40 °C for 8 h to give 52% yield of 6-chloro-N-phenylpyrimidin-4-amine 8, which was readily converted to EGFR selective inhibitor 10 according to the reported procedures [8].

**Scheme 2. Synthesis of 2,6-disubstituted pyrimidines in water**

![Scheme 2](image)

**REFERENCES**

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