Pure Appl. Chem., Vol. 79, No. 9, pp. 1481–1489, 2007.
doi:10.1351/pac200779091481

Asymmetric allylic substitution of cycloalkenyl esters in water with an amphiphilic resin-supported chiral palladium complex*

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Abstract: A novel homochiral phosphine ligand, (3*R*,9a*S*)[2-aryl-3-(2-diphenylphosphino)-phenyl]tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one, was designed, prepared, and anchored onto an amphiphilic polystyrene-poly(ethylene glycol) copolymer (PS-PEG) resin. Catalytic asymmetric substitution of a racemic mixture of cycloalkenyl esters with carbon, nitrogen, and oxygen nucleophiles was achieved in water as the single reaction medium under heterogeneous conditions by using the PS-PEG resin-supported palladium-imidazoindole phosphine complex to give optically active substituted cycloalkenes with up to 99 % ee.

Keywords: palladium; asymmetric; aqueous medium; catalysis; polymer support; immobilization.

INTRODUCTION

The development of water-based organic transformations is an area of rapidly growing importance in chemistry [1]. Water is a particularly desirable solvent for new-generation organic chemistry, owing to its safety and harmlessness. On the other hand, the development and use of solid-supported catalysts [2] has been recognized as a most powerful strategy for industrial applications as well as high-throughput organic synthesis. Taking into account the widespread synthetic utility of transition-metal complexes, palladium-phosphine complexes in particular [3], there is good reason to believe that immobilized palladium catalysts exhibiting high catalytic activity in aqueous media offer a viable clean alternative to more traditional methods of accomplishing many organic reactions. We have recently developed palladium and rhodium complexes of amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported phosphine ligands (Fig. 1, compounds **1** and **2**) [4]. The amphiphilic polymeric complexes were found to promote various catalytic transformations smoothly in water under heterogeneous conditions where the advantages of both aqueous- and heterogeneous-switching were combined in one system to achieve a high level of chemical greenness.

Catalytic asymmetric functionalization of carbon frameworks, such as palladium-catalyzed asymmetric π-allylic substitution, constitutes one of the most exciting challenges in modern synthetic chemistry today [5]. Provided that a chiral catalyst immobilized on solid supports [6] exhibits high catalytic activity and enantioselectivity in aqueous media, the catalysis may be considered an almost ideal catalytic organic transformation process. Efficient removal of the chiral metal complexes from the reaction mixture of the catalytic asymmetric process would allow not only the recovery of costly noble metal species and the chiral auxiliary but also the production of chiral compounds uncontaminated by metal species to provide compounds with improved biological utility. The author describes herein the

*Paper based on a presentation at the 12th International Conference on Polymers and Organic Chemistry 2006 (POC'06), 2–7 July 2006, Okazaki, Japan. Other presentations are published in this issue, pp. 1471–1582.

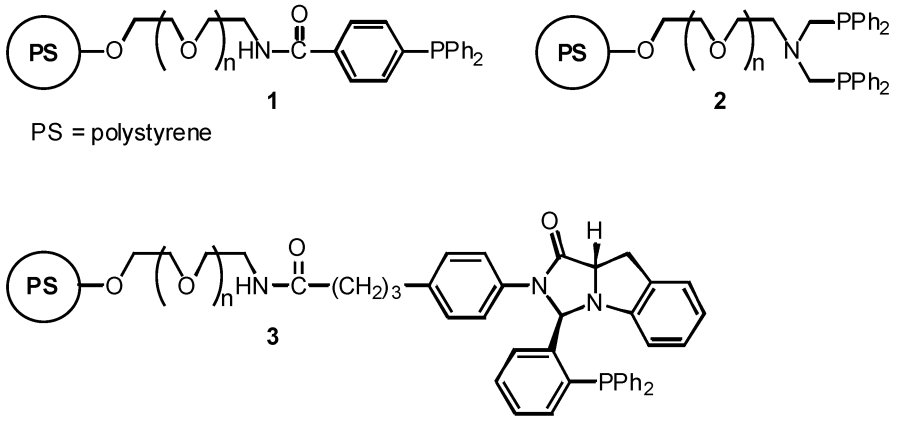


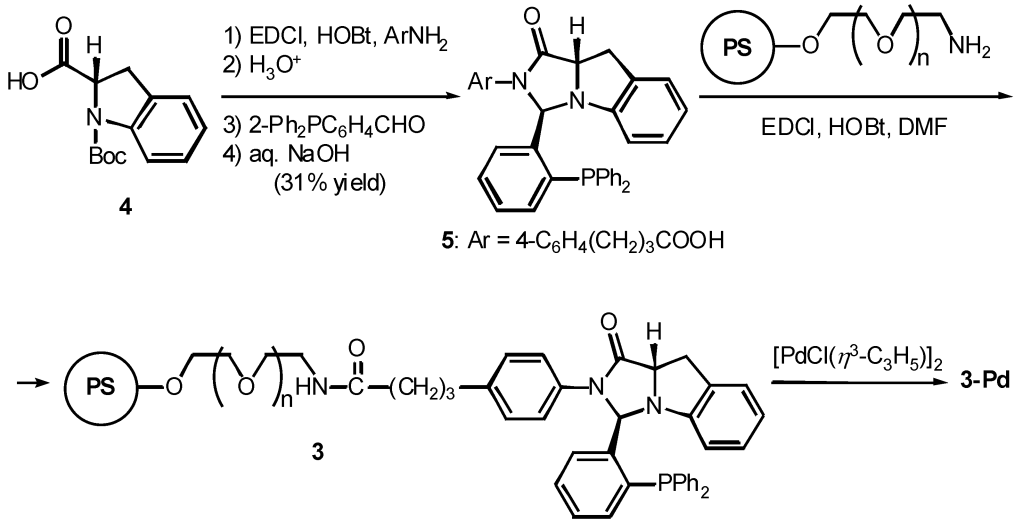
Fig. 1 Representative examples of amphiphilic PS-PEG resin-supported phosphine ligands.

design and preparation of a new homochiral phosphine ligand, (3*R*,9a*S*)[2-aryl-3-(2-diphenylphosphino)phenyl]tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one bound to an amphiphilic PS-PEG resin (Fig. 1, compound **3**) and its use for palladium-catalyzed asymmetric allylic substitution in water, in which enantioselectivity up to 99 % ee was achieved.

RESULTS AND DISCUSSION

Design, preparation, and immobilization of a chiral imidazoindole phosphine-palladium complex

During our studies on the design of new chiral reagents, highly functionalized optically active bicyclic amines having a pyrrolo[1,2-*c*]imidazolone framework were identified as effective chiral agents through a diversity-based approach to new chiral amine catalysts [7]. The results indicated that a novel homochiral ligand having the pyrrolo[1,2-*c*]imidazolone skeleton as a basic chiral unit would be immobilized on the PS-PEG resin to achieve highly enantioselective heterogeneous catalysis in water (Scheme 1). The pyrrolo[1,2-*c*]imidazolone-based phosphine ligand bearing fused benzene ring on the pyrrole group, (3*R*,9a*S*)[2-aryl-3-(2-diphenylphosphino)phenyl]tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one (**5**), was readily prepared from commercially available (*S*)-indoline-2-carboxylic acid (**4**), 4-[(3-methoxycarbonyl)propyl]aniline, and 2-(diphenylphosphino)benzaldehyde by a sequence of reactions shown in Scheme 1. The imidazoindole phosphine **5** was immobilized on PS-PEG-NH_2 resin [8] by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBt) to give the PS-PEG resin-supported chiral ligand (*R*,*S*)-**3** (Scheme 1). Formation of a palladium complex of the polymeric chiral ligand **3** was performed by mixing di(μ-chloro)bis(η^3-allyl)dipalladium(II), $[PdCl(\eta^3\text{-}C_3H_5)]_2$, in toluene at room temperature for 10 min to give the PS-PEG-supported complex **3-Pd** in quantitative yield.

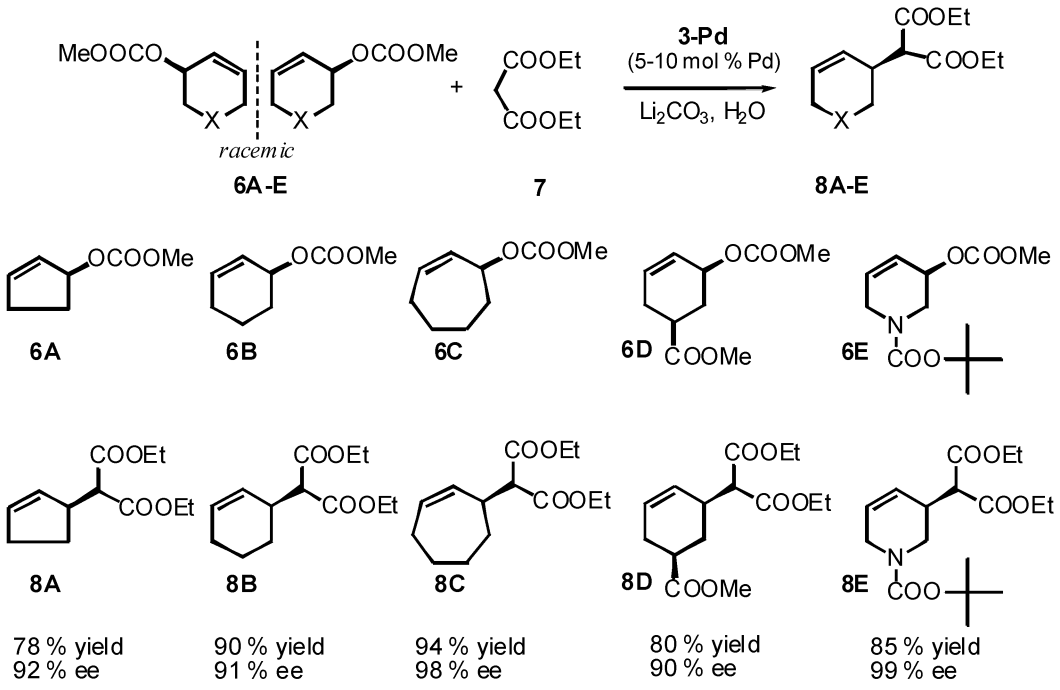


Scheme 1 Preparation of PS-PEG resin-supported imidazoindole phosphine (**3**).

Asymmetric allylic substitution of cycloalkenyl esters in water

Asymmetric allylic alkylation [9]

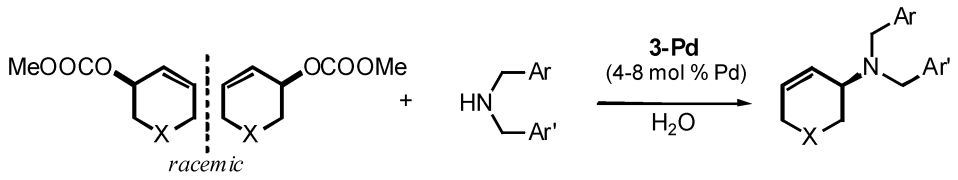
In order to explore the enantiocontrolling potential of the resin-supported complexes in water [10], we elected to study palladium-catalyzed asymmetric allylic substitution of cycloalkenyl substrates, which is still a major challenge even using homogeneous chiral catalysts [11]. We were very pleased to find that high stereoselectivity was achieved in water when the PS-PEG resin-supported catalyst **3-Pd** was used for allylic substitution of the cyclic substrates with dialkyl malonate (Scheme 2). Thus, the reaction of methyl cyclopentenyl carbonate (**6A**) and diethyl malonate (**7**) was carried out in aqueous lithium carbonate in the presence of **3-Pd** to give 78 % isolated yield of the allylic alkylated adduct (*S*)-**8A** with enantiomeric excess of 92 %. The 6-membered substrate **6B** also underwent asymmetric alkylation with **7** to afford the corresponding alkylated adduct **8B** with enantioselectivity of 91 % ee. The best results were obtained for the reactions of cycloheptene ester **6C** and tetrahydropyridyl carbonate **6E** with **7** giving **8C** and **8E** under otherwise similar conditions where the chemical yields and enantiomeric purities were increased to 94 % yield, 98 % ee (*S*) (for **8C**) and 85 % yield, 99 % ee (*S*) (for **8E**). The alkylation of the racemic *cis*-5-carbomethoxy-2-cyclohexenyl methyl carbonate (**6D**) with **7** gave 90 % ee of **8D** in 80 % yield as a single diastereoisomer having the *cis*-configuration, demonstrating that the reaction pathway of allylic substitution in water is essentially the same as that of the homogeneous counterpart in organic solvent. A typical experimental procedure is given for the reaction of **6C** with **7**: A disposable filtration column was charged with polymeric catalyst **3-Pd** (0.27 mmol Pd residue/g; 370 mg, 0.1 mmol Pd), Li_2CO_3 (370 mg, 5.0 mmol), carbonate **6C** (170 mg, 1.0 mmol), diethyl malonate (192 mg, 1.2 mmol), and water (2.5 mL), and the mixture was shaken at 25 °C for 12 h. The resin beads were collected by filtration, rinsed with water, and extracted with $scCO_2$ (30 atom, 40 °C, 20 min) to give 241 mg of (*S*)-**8C**. The enantiomeric excess was determined by gas chromatography (GC) analysis using a chiral stationary-phase capillary column (Cyclodex CB) to be 98 % ee. The absolute configuration was determined by chemical correlation with known dimethyl (*S*)-(cyclohepten-2-yl)malonate.



Scheme 2 Asymmetric alkylation of cycloalkenyl esters.

Asymmetric allylic amination [13]

Amination of the methyl cyclohexenyl carbonate (**6B**) with 5 equiv of dibenzylamine (**9a**) was carried out in water at 25 °C with shaking for 24 h in the presence of 8 mol % of the palladium complex of **3** (**3-Pd**). The reaction mixture was filtered, and the catalyst resin was rinsed with tetrahydrofuran (THF) to extract the desired product. The crude mixture obtained from the extract was chromatographed to give 90 % isolated yield of (*S*)-*N*,*N*-dibenzyl(cyclohexen-2-yl)amine (**10Ba**), whose enantiomeric purity was determined by high-performance liquid chromatography (HPLC) analysis with a chiral stationary-phase column (CHIRALCEL OJ) to be 94 % ee (Scheme 3). The allylic amination with benzyl(4-methoxybenzyl)amine (**9b**) or di(4-methoxybenzyl)amine (**9c**) also proceeded with high stereoselectivity under similar reaction conditions to give 92 % ee of **10Bb** or 90 % ee of **10Bc**, respectively. The *N*-methoxybenzyl groups of **10Bb** and **10Bc** were readily removed by the standard CAN oxidation cleavage to give secondary and primary amines, respectively, opening access to differently *N*-substituted amines. Higher stereoselectivity was observed when cycloheptenyl carbonate (**6C**) was used as the substrate. Thus, amination of **6C** with **9a–c** gave *N*,*N*-dibenzyl(cycloheptenyl)amine (**10Ca**), *N*-benzyl-*N*-4-methoxy benzyl(cyclohepten-2-yl)amine (**10Cb**), and *N*,*N*-di(4-methoxybenzyl)(cyclohepten-2-yl)amine (**10Cc**), whose chemical yields and enantiomeric purities were 91 % yield, 98 % ee (**10Ca**); 82 % yield, 97 % ee (**10Cb**); and 89 % yield, 96 % ee (**10Cc**). It is interesting that, under these conditions, the π-allylic amination does not take place in organic solvent. Thus, the reaction of the cycloheptenyl carbonate **6C** with 5 equiv of **9a** in the presence of 8 mol % palladium of the PS-PEG resin-supported **3-Pd** complex was carried out in dichloromethane or THF, and showed no catalytic activity at 25 °C, whereas the same system in water proceeded smoothly to give 91 % yield of the cycloheptenylamine **10Ca** (Scheme 4). Furthermore, the homogeneous catalytic system using imidazoindole phosphine **11** [13], which lacks PS-PEG supports gave only 6 % of **10Ca** in dichloromethane. In terms of catalytic efficiency, a heterogeneous catalyst generally should be inferior to its homogeneous counterpart. The hydrophobic organic substrates must diffuse into the polystyrene



6B-E **9a-c** (5 equiv) **10Ba-Ec**

a: Ar = Ar' = C_6H_5
b: Ar = C_6H_5, Ar' = $C_6H_4OCH_3$-4
c: Ar = Ar' = $C_6H_4OCH_3$-4

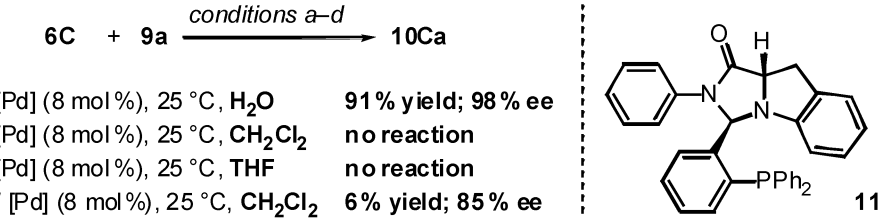
10Ba: 90 yield, 94 % ee
10Bb: 77 yield, 92 % ee
10Bc: 75 yield, 90 % ee

10Ca: 91 yield, 98 % ee
10Cb: 82 yield, 97 % ee
10Cc: 89 yield, 96 % ee

10Da: 61 yield, 90 % ee
10Db: 80 yield, 96 % ee
10Dc: 85 yield, 95 % ee

10Ea: 89 yield, 95 % ee
10Eb: 99 yield, 93 % ee
10Ec: 59 yield, 94 % ee

Scheme 3 Asymmetric amination of cycloalkenyl esters.

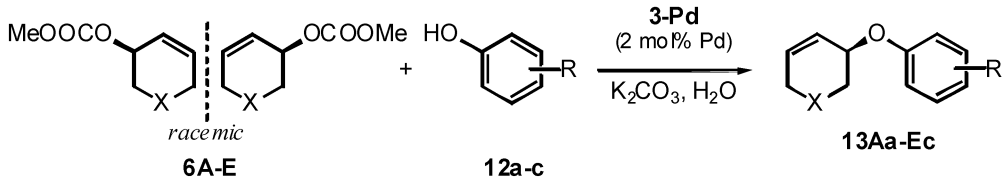


Scheme 4 Asymmetric amination: Aqueous media vs. organic media.

matrix in water to construct a highly concentrated reaction sphere to provide a significant increase in reactivity.

Asymmetric allylic etherification [14]

A vast amount of research has been devoted to the asymmetric π-allylic substitution of acyclic esters (e.g., 1,3-diphenylpropenyl esters) with carbon and nitrogen nucleophiles. However, the well-developed research on catalytic asymmetric substitution of cyclic substrates with oxygen nucleophiles has been limited to isolated reports [15,16]. We next tried the heterogeneous aquacatalytic asymmetric etherification of cycloalkenyl esters with phenolic nucleophiles which was catalyzed by the PS-PEG resin-supported palladium-imidazoindole phosphine complex to give optically active aryl(cycloalkenyl) ethers with up to 94 % ee (Scheme 5). The reaction of methyl cyclohexenylcarbonate (*rac*-**6B**; X = CH_2) and 1.0 equiv of 4-methoxyphenol (**12a**) was carried out in the presence of the PS-PEG resin-supported palladium complex **3-Pd** (2 mol % Pd) and K_2CO_3 (1 mol equiv) in water at 25 °C with shaking for 12 h to give 3-(4-methoxyphenoxy)cyclohexene (**13Ba**). Analytically pure **13Ba** was isolated by silica gel chromatography in 89 % yield and turned out to be the *S*-isomer by measurement of the optical rotation. The enantiomeric purity of **13Ba** was determined by HPLC analysis with a chiral stationary-phase column (Chiralcel AD, 2-propanol/hexane = 1/300) to be 86 % ee. The results obtained for the asymmetric etherification of various cycloalkenylcarbonates **6A–E** with the phenols **12a–c** are shown in Scheme 5. Cyclopentenyl carbonate **6A** also reacted with **12a** under the similar reaction conditions to give cyclopentenyl 4-methoxyphenyl ether **13Aa** with 84 % ee. Cyclohexenyl carbonate **6B** (X = CH_2) underwent the etherification with 4-benzyloxy- and 2-benzyloxyphenol (**12b** and **c**) under similar reaction conditions to give the corresponding cyclohexenyl aryl ethers **13Bb** (92 % yield, 84 % ee) and **13Bc** (80 % yield, 86 % ee). The reaction using the cycloheptenyl carbonate **6C** (X = CH_2CH_2) gave the cycloheptenyl aryl ethers, **13Ca**, **13Cb**, and **13Cc**, in 92 % ee, 89 % ee, and 93 % ee, respectively. The enantioselectivity increased as the steric bulkiness of the substituent X increased. Thus, using the



a: R = OMe-4
b: X = OCH_2Ph-4
c: X = OCH_2Ph-2

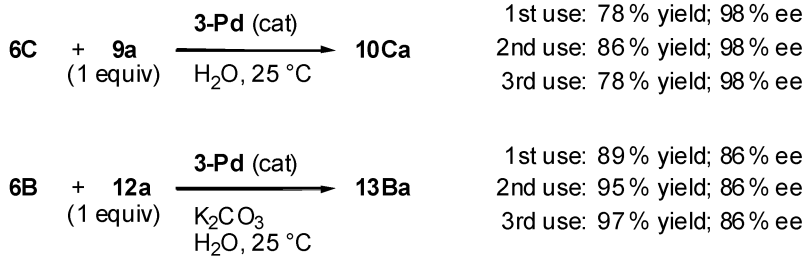
13Aa: 80 yield, 84 % ee
13Ba: 97 yield, 86 % ee
13Bb: 92 yield, 84 % ee
13Bc: 80 yield, 86 % ee
13Ca: 90 yield, 92 % ee
13Cb: 94 yield, 89 % ee
13Cc: 90 yield, 93 % ee
13Da: 93 yield, 93 % ee
13Db: 93 yield, 93 % ee
13Dc: 88 yield, 94 % ee
13Ea: 80 yield, 94 % ee
13Eb: 72 yield, 94 % ee
13Ec: 62 yield, 92 % ee

Scheme 5 Asymmetric etherification of cycloalkenyl esters.

racemic *cis*-5-carbomethoxy-2-cyclohexenyl methyl carbonate (**6D**, X = CHCOOMe), the 4-methoxyphenyl ether **13Da**, the 4-benzyloxyphenyl ether **13Db**, and the 2-benzyloxyphenyl ether **13Dc** were obtained in 93 % ee, 93 % ee, and 94 % ee, respectively, while the reaction of **6B**, which lacks the carbomethoxy substituent at the 5 position, with phenols the **12a–c** resulted in lower enantioselectivity ranging from 84–86 % ee. The exclusive formation of the cycloalkenyl ethers **13D** having the *cis*-configuration from the *cis*-allylic ester **6D** revealed that the π-allylic etherification proceeds via a double-inversion pathway (stereoinversive π-allylpalladium formation and stereoinversive nucleophilic attack with a phenol) in water under the present conditions. The catalytic asymmetric introduction of oxygen functionalities to a piperidine framework also took place with high stereoselectivity. Tetrahydropyridyl carbonate **6E** reacted with the phenols **12a–c** under the similar conditions to afford the phenoxypiperidines **13Ea–c** with 92–94 % enantiomeric excesses.

Recycling experiments

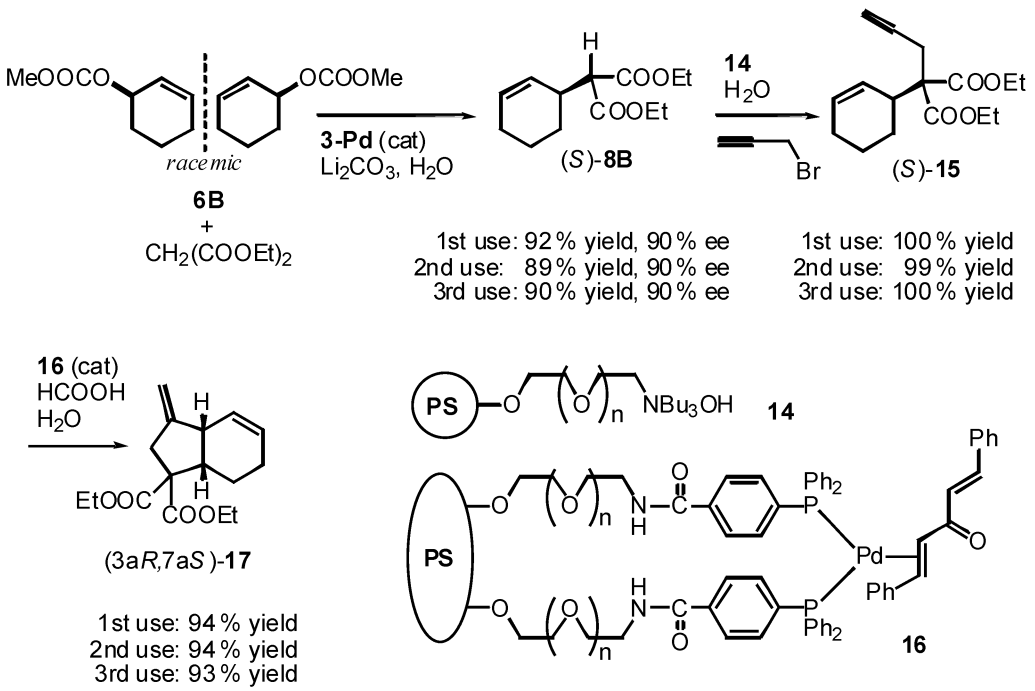
The PS-PEG resin-supported chiral catalyst **3-Pd** exhibited high recyclability for the above-mentioned allylic alkylation amination, and etherification. Representative results on the recycling experiments were given for the amination of the cycloheptenyl ester **6C** and etherification of **6B**. Thus, the allylic amination of **6C** with 1 equiv of dibenzylamine **9a** was carried out under otherwise standard amination conditions (Scheme 3) to give 98 % ee of **10Ca**, the recovered resin catalyst was taken on to a second and third use without any additional charge of palladium, and exhibited no loss of its catalytic activity or stereoselectivity (Scheme 6). For the allylic etherification of cyclohexenyl carbonate **6B**, after the first use of the polymeric chiral palladium catalyst to give 86 % ee of the aryl cyclohexenyl ether **13Ba**, the recovered catalyst beads were also taken on to two subsequent reuses and exhibited stable catalytic activity.



Scheme 6 Recycling experiments.

Asymmetric multistep preparation of a hydrindane framework [17]

The multi-step process approach using polymeric reagents has become an important goal in synthetic organic chemistry [18]. If a multistep asymmetric organic synthesis can be achieved in water under mild conditions with recyclable polymeric catalysts, the synthesis would represent what may be considered an ideal chemical process. The asymmetric synthesis of a hydrindane framework was achieved via a palladium-catalyzed asymmetric π-allylic alkylation, and propargylation of an active methine compound with a polymeric phase-transfer catalyst (PTC) base, and palladium-catalyzed cycloisomerization of 1,6-enynes, where all three steps were performed in water with recyclable polymeric catalysts (Scheme 7). The racemic cyclohexenyl ester *rac*-**6B** reacted with diethyl malonate (**7**) in aqueous Li_2CO_3 in the presence of PS-PEG resin-supported chiral imidazoindole phosphine-palladium complex **3-Pd** to give 90 % ee of **8B** in 90 % yield. The polymeric chiral palladium complex **3-Pd** was reused three times without any loss of stereoselectivity. Propargylation of the cyclohexenylmalonate **8B** with propargyl bromide was performed with PS-PEG ammonium hydroxide **14**, which has been developed as an immobilized PTC base with a view toward use in water to give a quantitative yield of the 1,6-enyne (*S*)-**15** [19]. The polymeric ammonium reagent was recovered as its bromide salt, which was reactivated by washing with aqueous KOH and reused. The enyne (*S*)-**15** underwent cycloisomerization with the amphiphilic polymeric palladium **16** to afford 90 % ee of the hydrindane (3a*R*,7a*S*)-**17** in 94 % yield.



Scheme 7 Heterogeneous aquacatalytic asymmetric synthesis of hydrindane.

CONCLUSION

In summary, we have designed and prepared an amphiphilic PS-PEG resin-supported chiral palladium complex where palladium species was immobilized by coordination of a novel homochiral phosphine ligand, (3*R*,9a*S*)[2-aryl-3-(2-diphenylphosphino)phenyl]tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one, covalently anchored on the PS-PEG resin. Catalytic asymmetric substitution of a racemic mixture of cycloalkenyl esters with carbon, nitrogen, and oxygen nucleophiles was achieved in water as the single reaction medium under heterogeneous conditions by using the PS-PEG resin-supported palladium-

imidazoindole phosphine complex which was prepared by mixing the polymeric chiral ligand and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ to give optically active substituted cycloalkenes with up to 99 % ee. The catalyst was readily recovered by simple filtration and was reused without any loss of activity and stereoselectivity. To the best of our knowledge, this is the first successful work on immobilized recyclable asymmetric catalysis in water.

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