

Award Accounts

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Heterogeneous Asymmetric Catalysis in Water with Amphiphilic Polymer-Supported Homochiral Palladium Complexes

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Heterogeneous aquacatalytic highly selective organic transformations are what may be considered ideal chemical processes of the next generation, where the advantages of both aqueous- and heterogeneous-switching are combined in one system to meet green sustainable chemical requirements. Heterogeneous aquacatalytic asymmetric reactions were achieved with palladium complexes of homochiral phosphine ligands which were immobilized onto amphiphilic polystyrene–poly(ethylene glycol) (PS–PEG) resin beads via chemical bonding. The catalyst was recovered by simple filtration and was reused without any loss of catalytic activity and stereoselectivity. In particular, a novel chiral P,N-ligand, (3*R*,9a*S*)-2-aryl-3-[2-(diphenylphosphino)phenyl]tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one, was designed and prepared on PS–PEG to realize palladium-catalyzed π-allylic substitution of both cyclic and acyclic substrates with carbon, nitrogen, and oxygen nucleophiles in water with enantioselectivity of up to 99% ee.

Introduction

The development of catalytic asymmetric organic transformations has emerged as one of the most exciting and challenging areas in modern synthetic chemistry. Homogeneous chiral catalysts are widely used for a variety of organic transformations, and transition-metal complexes of homochiral ligands, in particular, have been recognized as very powerful tools in the arsenal of the synthetic organic chemist. The heterogeneous-switching of homogeneous catalytic processes has become a highly useful means for high-throughput synthesis as well as for the industrial production of fine chemicals, where the catalyst residue can be readily removed by simple manipulation before being subjected to the next reaction (reuse and/or recycle).[1,2] Indeed, 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.

However, organic reactions in water recently have begun attracting considerable attention due to water's advantage as a readily available, safe, and environmentally benign solvent.[3,4] Nevertheless, with catalysts designed for use under conventional organic conditions, it is more difficult to achieve high catalytic performance in water than in organic media because of the low water-compatibility of both the catalysts and the organic substrates. So far, several approaches to achieve asymmetric catalysis in water have been reported. The most representative ones are: (1) hydrophilic modification of the chiral catalysts, e.g., sulfonation, quaternary salt formation etc., and (2) the use of amphiphilic additives, e.g., detergent-like additives, phase-transfer catalysts, etc. Although these approaches make water-based catalytic reactions possible, the catalytic species is difficult to recover from the aqueous phase. An asymmetric catalytic protocol performed in water with a solid-supported chiral catalyst under heterogeneous conditions would come close to realizing an ideal asymmetric reaction, where the advantages of both aqueous- and heterogeneous-switching are combined in one system. This article will cover our recent studies on developing catalytic asymmetric processes in water with solid-supported chiral palladium complexes.

Heterogeneous Aquacatalytic Process

Recently, we have achieved a variety of catalytic transformations in water under heterogeneous conditions by use of amphiphilic polystyrene–poly(ethylene glycol) copolymer (PS–PEG) resin-supported catalysts.[5] The amphiphilic property of the PS–PEG resin[6] is essential to promote organic transformations in water where both the hydrophobic reaction matrix (PS) and the hydrophilic PEG region interacting with the water-soluble reactants are combined in one system. Thus, typically, a palladium complex anchored to the PS–PEG resin via coordination to the phosphine ligand group covalently tethered to the resin (Figures 1 and 2) efficiently catalyzed π-allylic substitution, carbonylation, the Heck reaction, the Suzuki–Miyaura coupling, the Sonogashira coupling, cycloisomerization, etc., in water without any organic co-solvents, several representative reactions of which are shown in Scheme 1.

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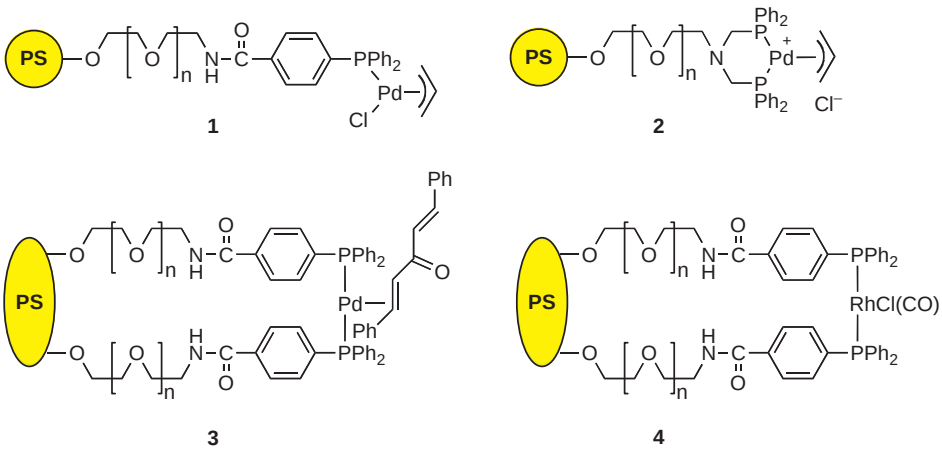
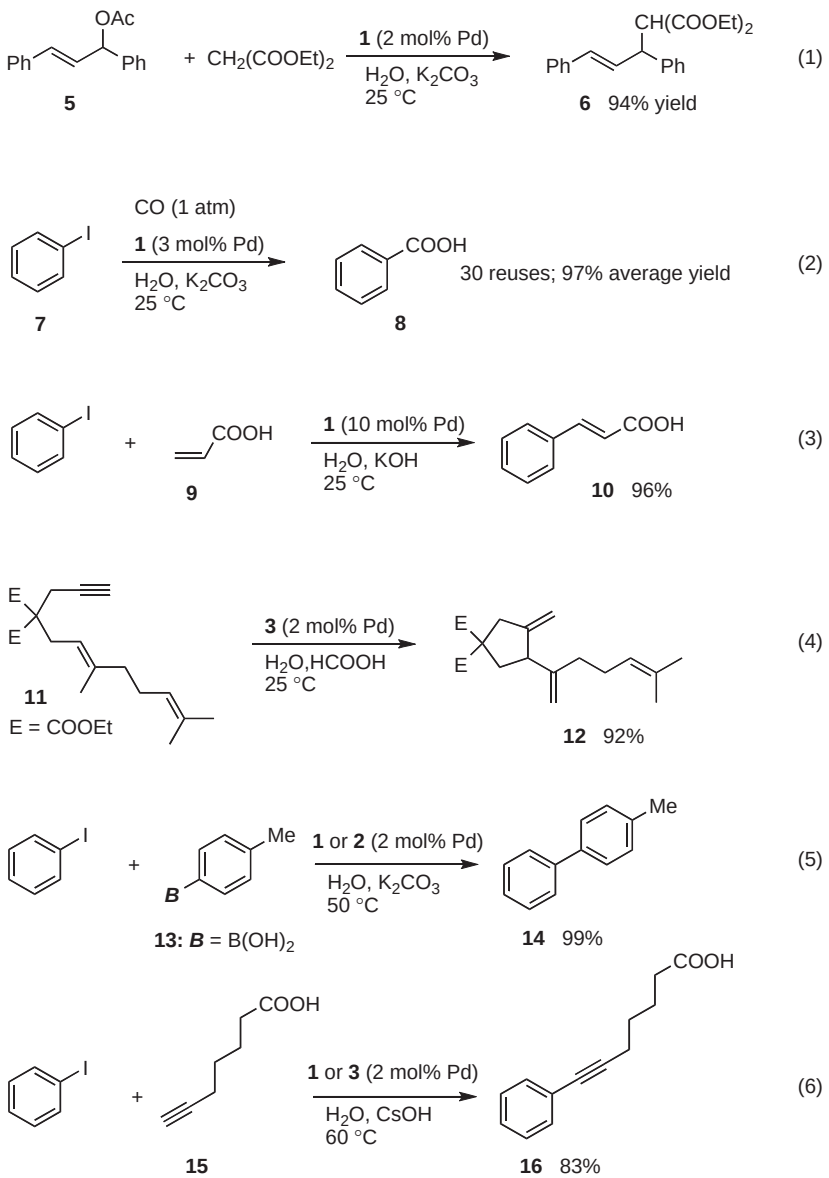


Figure 1. Amphiphilic PS–PEG resin-supported transition metal–phosphine complexes (representative examples).



Scheme 1. Representatives of heterogeneous aquacatalysis with PS–PEG resin-supported palladium catalysts.

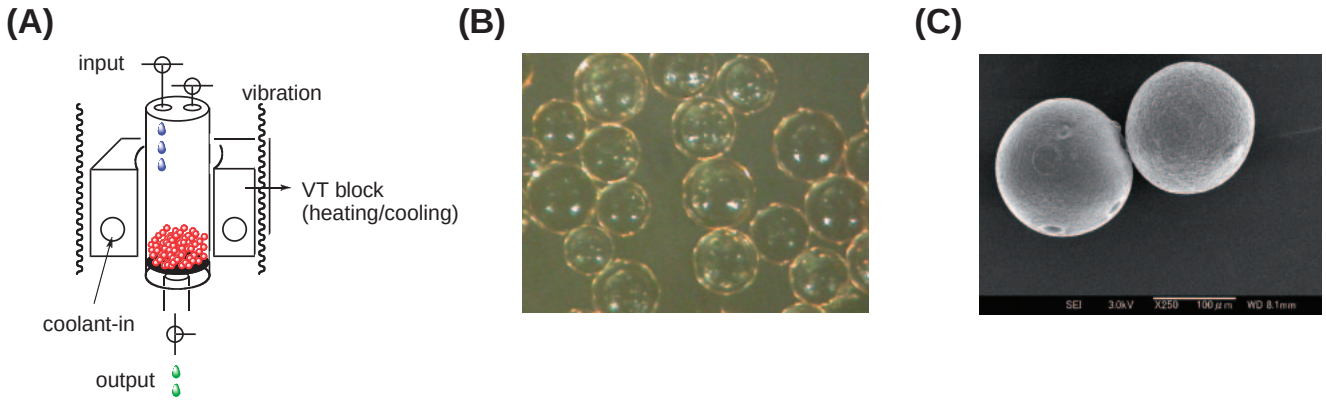


Figure 2. (A) A schematic image of a reaction system, (B) a microscopic photo image of the polymeric catalyst, (C) a SEM image of the polymeric catalyst.

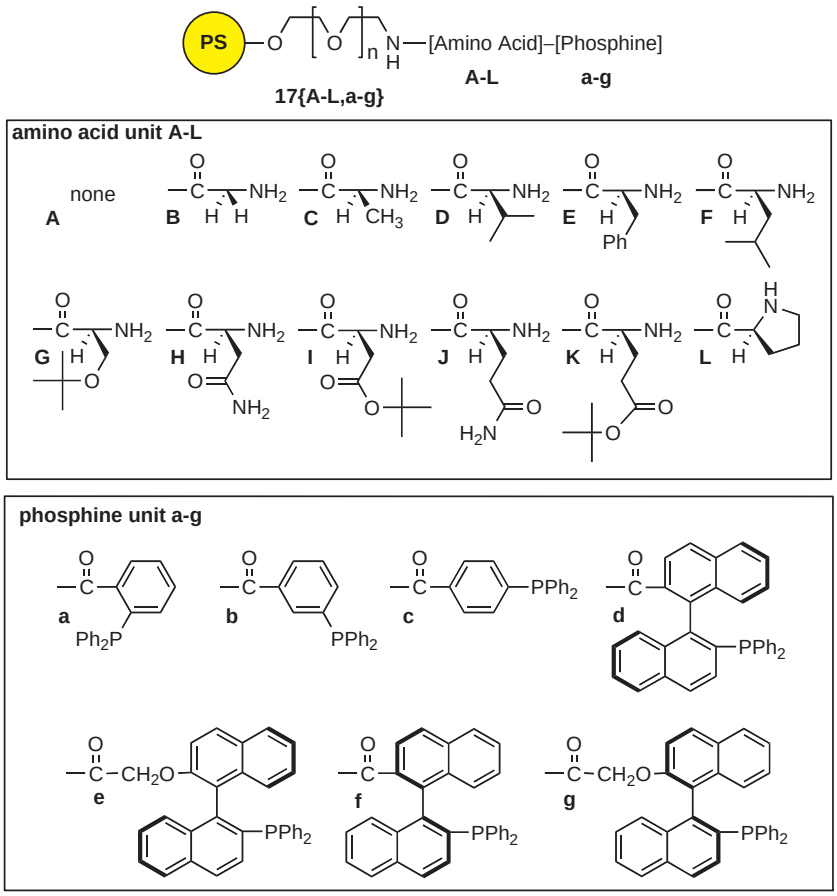
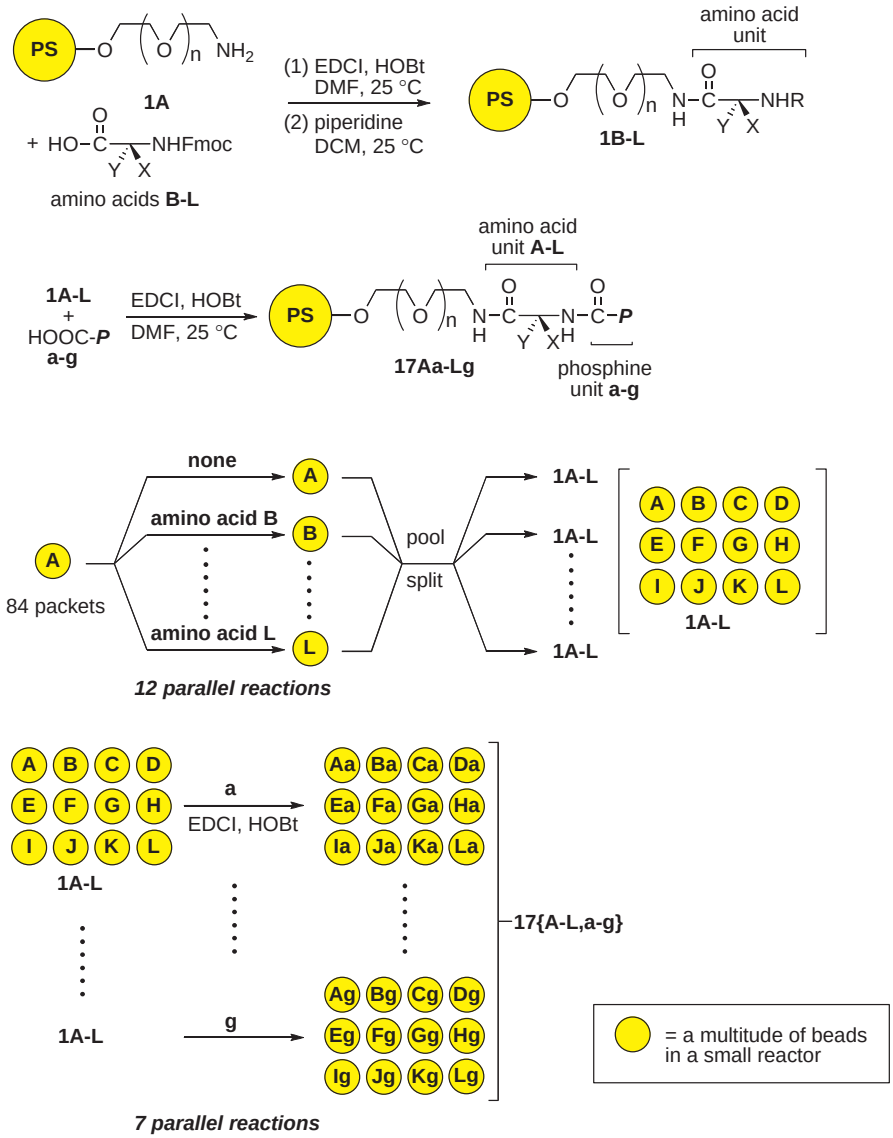


Figure 3. A library of PS–PEG resin-supported chiral phosphine ligands.

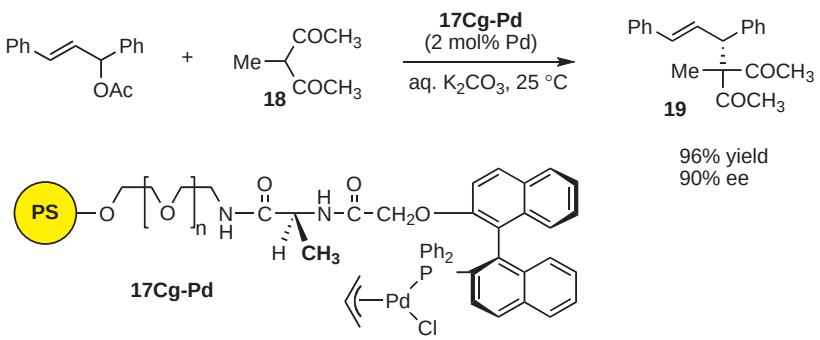
These successful results in developing heterogeneous aquacatalytic processes prompted us to introduce chiral palladium complexes onto the PS–PEG support to realize heterogeneous asymmetric aquacatalyses.

Diversity-Based Approach

Solid-phase organic synthesis (SPOS) has been recognized as a powerful method to construct a combinatorial chemical library.[7] A diversity-based approach was examined to identify a polymeric palladium–phosphine complex exhibiting high stereoselectivity in water.[8] Thus, a library of 84 chiral phosphine ligands **17** was prepared on amphiphilic PS–PEG resin beads from the achiral and chiral amino acids **A**–**L** and phosphines **a**–**g**, including axially chiral MOP ligand derivatives **d**–**g** (Figure 3) via the split-and-pool protocol (Scheme 2). With this library of amphiphilic PS–PEG resin-supported chiral phosphine ligands **17{A–L,a–g}**, the enantiocontrolling ability and catalytic potency of the polymeric ligands were examined in water for palladium-catalyzed π-allylic alkylation of 1,3-diphenylallyl acetate with 3-methyl-2,4-pentanedione (**18**). Through preliminary screening, the highest enantioselectivity was obtained with the palladium complex of PS–PEG resin-



Scheme 2. A combinatorial approach to a PS–PEG-supported chiral ligand library via the split-and-pool protocol.

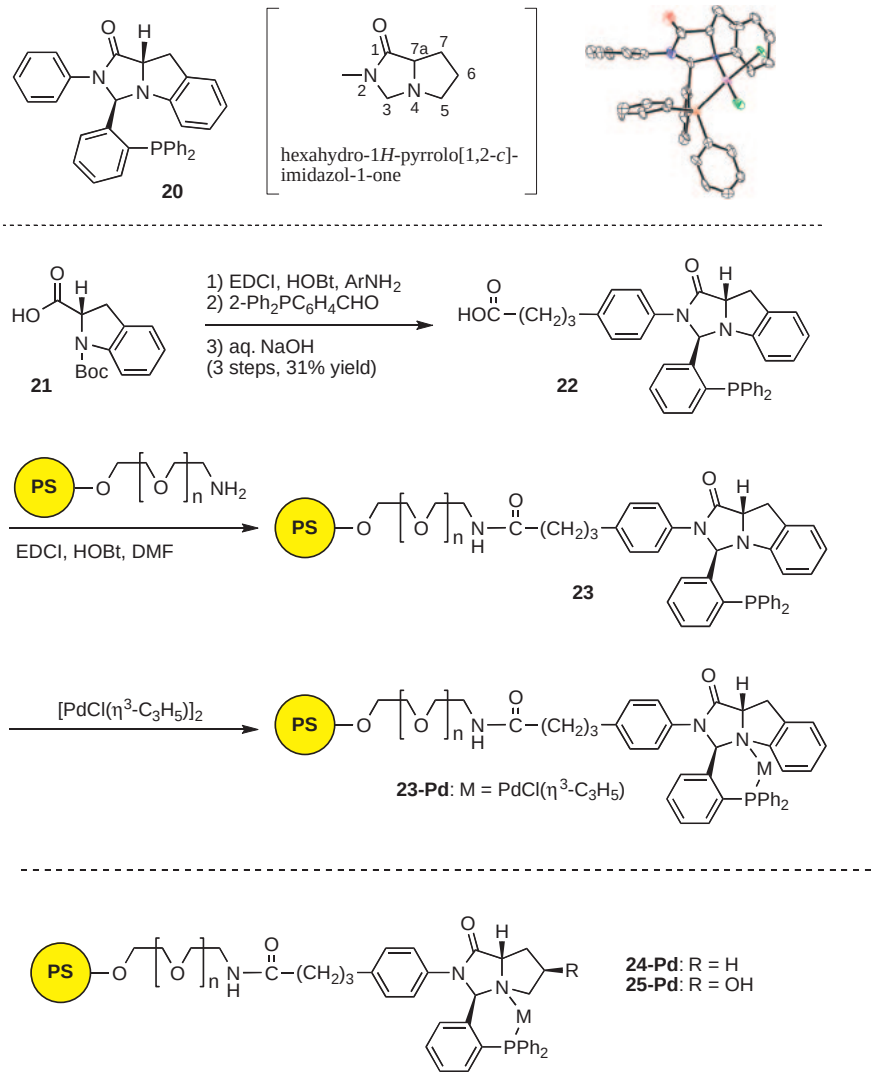


Scheme 3. Asymmetric aquacatalytic allylic substitution with a polymeric chiral palladium–phosphine complex.

supported phosphine **17Cg**, which was prepared from (*S*)-alanine and (*R*)-C(O)CH_2O-MOP (**g**) (Scheme 3). The **17Cg**–Pd was re-synthesized to confirm its asymmetric aquacatalytic efficiency. Thus, the allylic ester, 1,3-diphenylallyl acetate, reacted with the 1,3-diketone **18** in aqueous potassium carbonate at 25 °C in the presence of 2 mol % palladium of polymeric palladium complex **17Cg**–Pd to afford 96% yield of 3-(1,3-diphenylallyl)-3-methyl-2,4-pentadione (**19**) with 90% ee *S*.

Imidazoindole Phosphine

Highly functionalized optically active bicyclic amines having a pyrrolo[1,2-*c*]imidazolone framework were identified as



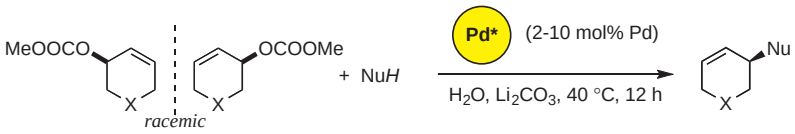
Scheme 4. Preparation of PS–PEG resin-supported chiral palladium complexes.

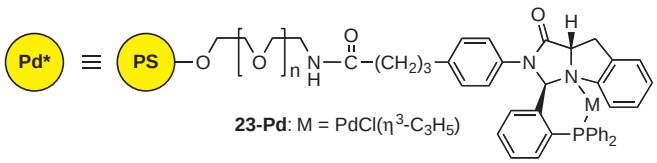
effective chiral agents through a diversity-based approach to new chiral amine catalysts.[9] The results indicated that a novel P,N-chelate chiral ligand having the pyrrolo[1,2-*c*]imidazolone skeleton as a basic chiral unit[10] would be readily immobilized on PS–PEG resin to achieve highly enantioselective heterogeneous catalysis in water (Scheme 4). (3*R*,9a*S*)-2-Aryl-3-[2-(diphenylphosphino)phenyl]tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one **23**, which was readily prepared from (*S*)-indoline-2-carboxylic acid, methyl 4-(4-aminophenyl)butyrate, and 2-(diphenylphosphino)benzaldehyde by a sequence of reactions outlined in Scheme 3, was immobilized on PS–PEG–NH_2 resin to give the PS–PEG resin-supported chiral P,N-chelate ligand (*R*,*S*)-**23**. Formation of a palladium complex of the P,N-chelate ligand was performed by mixing $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in toluene at room temperature for 10 min to give the PS–PEG-supported P,N-chelate complex **23**–Pd in quantitative yield.

Asymmetric Aquacatalytic Allylic Alkylation

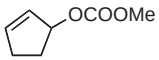
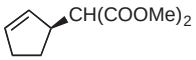
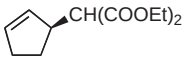
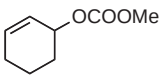
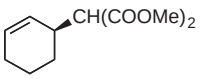
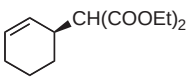
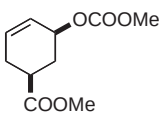
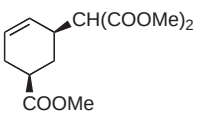
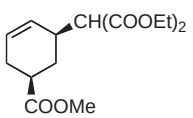
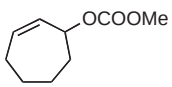
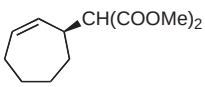
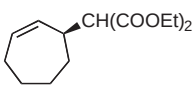
In order to explore the enantiocontrolling potential of the resin-supported complexes in water, we initially elected to study the palladium-catalyzed asymmetric allylic substitution of cyclic substrates, which is still a major challenge even using homogeneous chiral catalysts.[11] It is interesting to note that high stereoselectivity was achieved in water when the PS–PEG resin-supported catalyst **23**–Pd was used for allylic substitution of the cyclic substrates with dialkyl malonate (Table 1).[12] Thus, the reactions of methyl cycloalkenyl carbonates **26**–**30** and dialkyl malonate were carried out in water with 2–10 mol % palladium of the polymeric complex **23**–Pd in the presence of lithium carbonate at 40 °C to give good to excellent yields of the corresponding allylic malonates **33**–**37** with high stereoselectivities of up to 99% ee. The PS–PEG-supported catalyst **23**–Pd was effective for the asymmetric allylic alkylation of both cyclic and acyclic substrates in water. The reactions of 1,3-diphenyl-2-propenyl methyl carbonate (**31**) and *t*-butyl 1,3-diphenyl-2-propenyl carbonate (**32**) were catalyzed by **23**–Pd under the same reaction conditions to give **38** with 91 and 94% ee, respectively (Entries 14 and 15). Alkylation of the racemic methyl *cis*-5-methoxycarbonyloxy-3-cyclohexenecarboxylate (**28**) gave 92% ee of **35b** in 90% yield as a single diastereoisomer having the cis configuration (Entry 9), demonstrating that the reaction pathway of allylic substitution in water is essentially the same as that of the homogeneous counterpart in organic solvent. Other PS–PEG-supported

Table 1. Asymmetric Allylic Alkylation in Water with a Chiral Polymeric Palladium Complex





23-Pd: M = $PdCl(\eta^3\text{-}C_3H_5)$

Entry	Allylic ester	Nu*H*	Product	Yield/%	% ee
1	 **26**	$CH_2(COOMe)_2$	 **33a**	65	92
2		$CH_2(COOEt)_2$	 **33b**	74	92
3	 **27**	$CH_2(COOMe)_2$	 **34a**	88	90
4		$CH_2(COOEt)_2$	 **34b**	90	92
5	(cat; 2nd use)		**34b**	89	90
6	(cat; 3rd use)		**34b**	90	92
7	(cat; 4th use)		**34b**	91	91
8	 **28**	$CH_2(COOMe)_2$	 **35a**	71	90
9		$CH_2(COOEt)_2$	 **35b**	90	92
10	BSA, LiOAc in CH_2Cl_2	$CH_2(COOEt)_2$	**35b**	27	87
11	 **29**		 **36a**	85	97
12		$CH_2(COOEt)_2$	 **36b**	92	98

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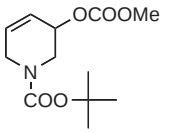
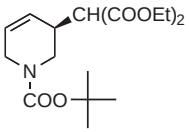
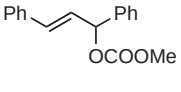
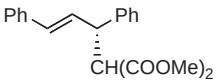
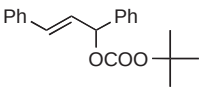
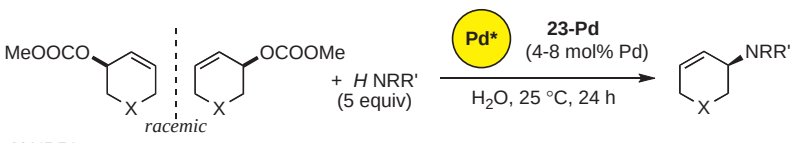
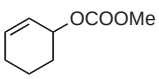
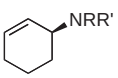
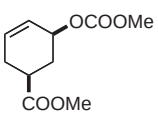
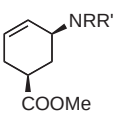
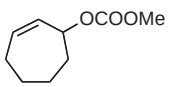
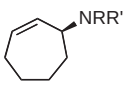
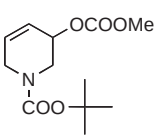
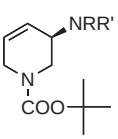
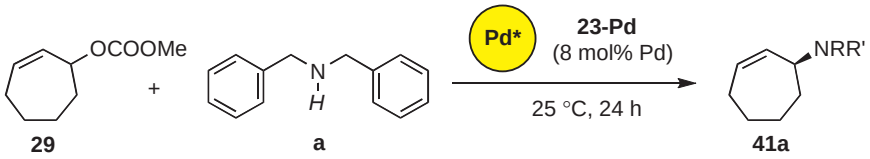
13	 **30**	$CH_2(COOEt)_2$	 **37**	95	99
14	 **31**	$CH_2(COOMe)_2$	 **38**	88	91
15	 **32**	$CH_2(COOMe)_2$	**38**	60	94

Table 2. Asymmetric Allylic Amination in Water with **23**–Pd



Entry	Allylic ester	Amine	Product		Yield/%	% ee
1	 **27**	**a**	 **39**	**39a**	90	94
2		**b**		**39b**	77	92
3		**c**		**39c**	75	90
4		**a**		**40a**	61	90
5		**b**		**40b**	80	96
6	**28**	**c**	**40**	**40c**	85	95
7		**a**		**41a**	91	98
8		**b**		**41b**	82	97
9	**29**	**c**	**41**	**41c**	89	96
10		**a**		**42a**	89	95
11		**b**		**42b**	99	93
12		**c**		**42c**	59	94
	30		**42**			



in H_2O: 91% yield, 98% ee (Table 2, entry 7)
in THF: no reaction
in CH_2Cl_2: no reaction

Scheme 5. Asymmetric amination in various solvents.

catalysts, **24**–Pd and **25**–Pd, which lack the fused aromatic moiety on their pyrroloimidazolone ring system, exhibited much lower selectivity. Interestingly, the immobilized complex **23**–Pd is less catalytically active in an organic solvent. Thus, the alkylation of **28** with diethyl malonate in dichloromethane in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and lithium acetate gave a 27% yield of the adduct **35b** with 87% ee, whereas the reaction proceeded smoothly in aqueous lithium carbonate (Entries 9 and 10). Though it was unclear if the stereoselectivity of the allylic alkylation was affected by the solvent or base used, the significant decrease of the catalytic activity in the organic medium should be attributed to the solvent effect. In the aqueous media, the organic substrates (e.g., **28** and malonate) must diffuse into the hydrophobic PS matrix to form a highly concentrated reaction sphere which should react with the ionic species (e.g., aqueous alkaline) through the interfacial PEG region to afford higher reactivity than that in an organic solvent.

Asymmetric Aquacatalytic Allylic Amination

Amination of the 2-cyclohexenyl methyl carbonate (**27**) with 5 equiv of dibenzylic amines (**a**, **b**, and **c**) was carried out in water at 25 °C with shaking for 24 h in the presence of 4 or 8 mol % of the palladium complex of **23**–Pd.[13] The reaction mixture was filtered and the catalyst resin was rinsed with super critical CO_2 ($scCO_2$) or THF to extract the desired product. The crude mixture obtained from the extract was chromatographed to give the corresponding (*S*)-dialkyl(2-cyclohexenyl)amine **39a**–**39c**, whose enantiomeric purities were determined to be 94, 92, and 90% ee, respectively (Table 2, Entries 1–3). The cyclohexenyl ester **28** bearing a methoxycarbonyl group with the cis configuration also underwent π-allylic substitution with the dibenzylamines **a**–**c** to give the corresponding allylamines **40a**–**40c** having the cis configuration with high enantioselectivity ranging from 90–96% ee (Entries 4–6). Higher stereoselectivity was observed when cycloheptenyl carbonate **29** was used as the substrate (Entries 7–9). Thus, amination of **29** gave dibenzyl(2-cycloheptenyl)amine (**41a**), benzyl(2-cycloheptenyl)(4-methoxybenzyl)amine (**41b**), and (2-cycloheptenyl)bis(4-methoxybenzyl)amine (**41c**), the chemical yields and enantiomeric purities of which were 91% yield, 98% ee (**41a**); 82% yield, 97% ee (**41b**); and 89% yield, 96% ee (**41c**), respectively. The aminopiperidines **42a**–**42c** were also prepared in optically active form from tetrahydropyridyl carbonate **30** under similar conditions (Entries 10–12) with 93–95% enantiomeric excess.

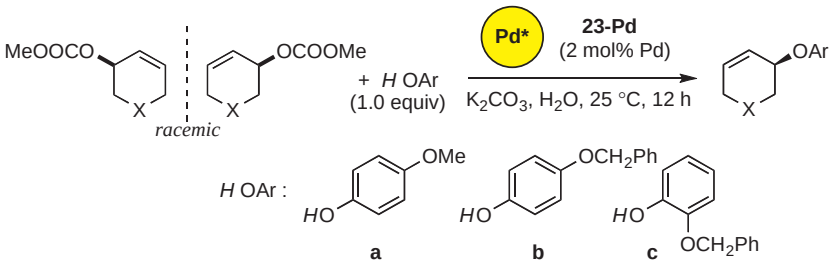
As observed in the aquacatalytic asymmetric alkylation mentioned above, under these conditions, the π-allylic amination does not take place in organic solvents. Thus, the reaction of the cycloheptenyl carbonate **29** with 5 equiv of dibenzylamine in the presence of 8 mol % palladium of the PS–PEG resin-supported **23**–Pd complex was carried out in THF or dichloromethane and showed no catalytic activity at 25 °C, whereas the same system in water proceeded smoothly to give 91% yield of the cycloheptenylamine **41a** (Scheme 5).

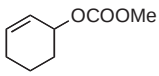
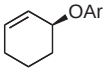
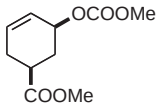
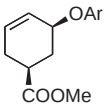
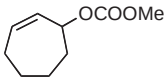
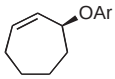
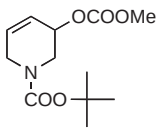
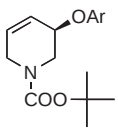
Recycling experiments were examined for the amination of cycloheptenyl ester **29** with 1 equiv of dibenzylamine. After the first use of the polymeric chiral catalyst to give 98% ee of **41a**, the recovered resin catalyst was taken on to a second and third use without any additional charge of palladium, and exhibited no loss of its catalytic activity or stereoselectivity.

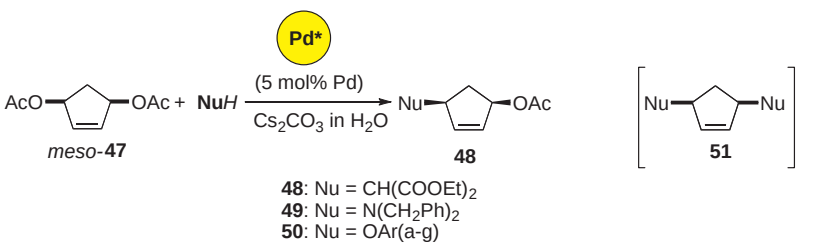
Asymmetric Aquacatalytic Allylic Etherification

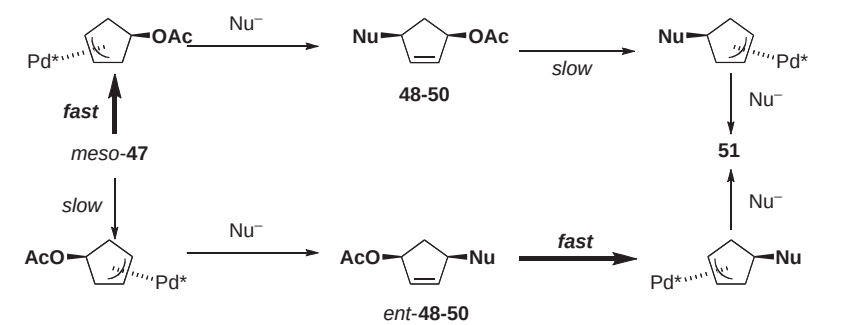
Although a vast amount of research has been devoted to the asymmetric π-allylic substitution of acyclic esters (e.g., 1,3-diphenylallyl esters) with carbon and nitrogen nucleophiles, studies on catalytic asymmetric substitution of cyclic substrates with oxygen nucleophiles have been limited to well-developed albeit isolated reports. We reported that the heterogeneous aquacatalytic asymmetric etherification of cycloalkenyl esters with phenolic nucleophiles, which is catalyzed by the PS–PEG resin-supported palladium–imidazoindolephosphine complex **23**–Pd, gave optically active aryl cycloalkenyl ethers with up to 94% ee (Table 3).[14] Thus, for example, the reaction of 2-cyclohexenyl methyl carbonate (**27**) and 1.0 equiv of 4-methoxyphenol (**a**) was carried out in the presence of 2 mol % palladium of the polymeric complex **23**–Pd and K_2CO_3 (1 mol equiv) in water at 25 °C with shaking for 12 h to give 3-(4-methoxyphenoxy)cyclohexene (**43a**) in 89% yield with 86% ee (S configuration) (Entry 1). The results obtained for the asymmetric etherification of various cycloalkenyl carbonates with the phenols **a**–**c** are summarized in Table 3. With racemic methyl *cis*-5-methoxycarbonyloxy-3-cyclohexenecarboxylate (**28**), the 4-methoxyphenyl ether **44a**, 4-benzyloxyphenyl ether **44b**, and 2-benzyloxyphenyl ether **44c** were obtained in 93% ee (Entry 4), 93% ee (Entry 5), and 94% ee (Entry 6), respectively, while the reaction of **27** with phenols **a**–**c**, which lacks the carbomethoxy substituent at the 5 position, resulted in lower enantioselectivity ranging from 84–86% ee (Entries 1–3). The reaction using cycloheptenyl carbonate **29** gave the aryl cycloheptenyl ethers, **45a**, **45b**, and **45c**, in 92, 89, and 93% ee, respectively (Entries 7–9). The exclusive formation of cycloalkenyl ethers **44** having cis configuration from the *cis*-allylic ester **28** revealed that the π-allylic etherification proceeds via a double-inversion

Table 3. Asymmetric Allylic Etherification in Water with **23**–Pd



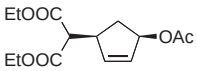
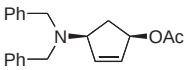
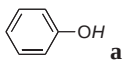
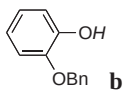
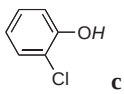
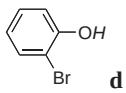
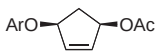
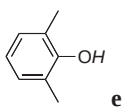
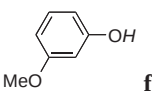
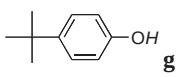
Entry	Allylic ester	*H*OAr	Product		Yield/%	% ee
1		**a**		**43a**	89	86
2		**b**		**43b**	92	84
	27		**43**			
3		**c**		**43c**	80	86
4		**a**		**44a**	93	93
5		**b**		**44b**	93	93
6	**28**	**c**	**44**	**44c**	88	94
7		**a**		**45a**	90	92
8		**b**		**45b**	94	89
9	**29**	**c**	**45**	**45c**	90	93
10		**a**		**46a**	80	94
11		**b**		**46b**	72	94
12		**c**		**46c**	62	92
	30		**46**			





Scheme 6. Enantioselective desymmetrization of *meso*-cycloalkene-1,4-diesters.

Table 4. Asymmetric Desymmetrization of *meso*-Esters

Entry	Nucleophile	Product	Yield/%	% ee
1	$CH_2(COOEt)_2$	 **48**	56 (**51**; 4%)	91
2	$HN(CH_2Ph)_2$	 **49**	62 (**51**; —)	91
3	 **a**	**50a**	64 (**51**; 14%)	99
4	 **b**	**50b**	45 (**51**; —)	97
5	 **c**	**50c**	52 (**51**; 17%)	94
6	 **d**	 **50** **50d**	53 (**51**; 16%)	95
7	 **e**	**50e**	59 (**51**; 4%)	90
8	 **f**	**50f**	43 (**51**; 14%)	96
9	 **g**	**50g**	52 (**51**; 11%)	94

pathway (stereoinversive π-allylpalladium formation and stereoinversive nucleophilic attack with the phenol) in water under the present conditions. The catalytic asymmetric introduction of oxygen functionalities to a piperidine framework also took place with high stereoselectivity. The tetrahydropyridyl carbonate **30** reacted with the phenols **a**–**c** under similar conditions to afford the phenoxytetrahydropyridines **46a**–**46c** with 92–94% enantiomeric excesses (Entries 10–12).

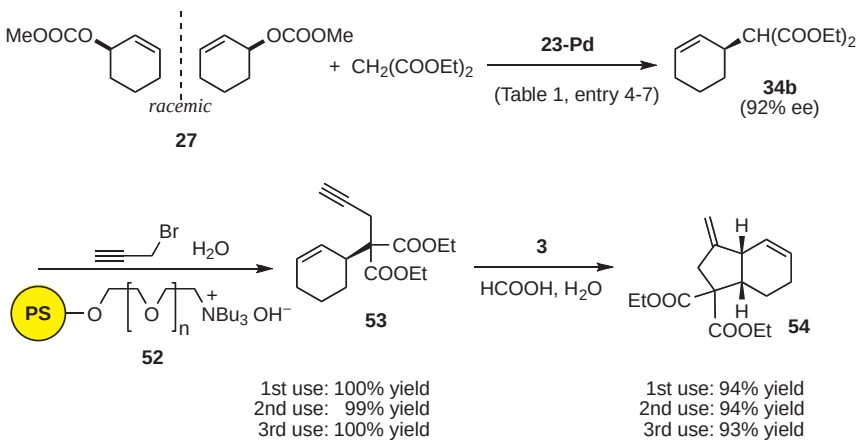
Enantioselective Desymmetrization

Our continuing interest in the utility of the polymeric chiral catalyst under aqueous conditions led us to study its potential in the enantioselective desymmetrization of *meso*-cycloalkene-1,4-diesters where the stereoselectivity should be induced mainly at the π-allylic formation step via the enantio-position selective oxidative addition (Scheme 6 (bottom)).[11,15]

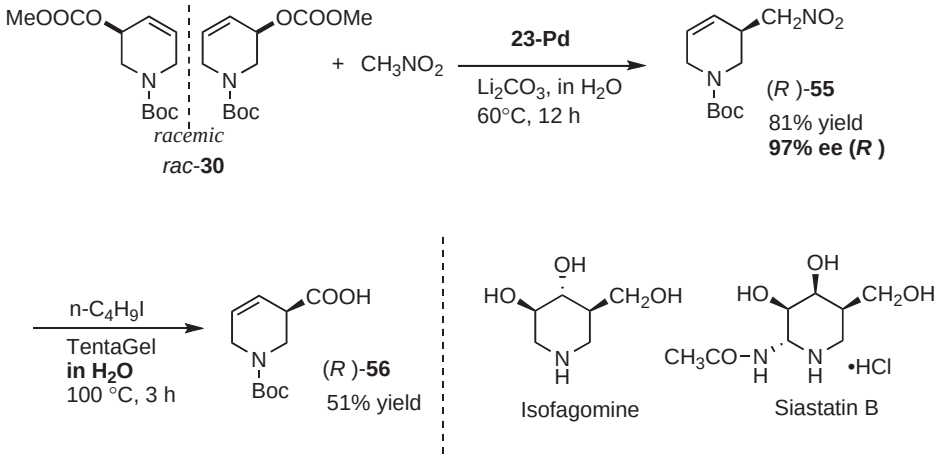
The aquacatalytic asymmetric desymmetrization of the *meso*-cycloalkene-1,4-diesters via π-allylic substitution was examined for alkylation, amination, and, in particular etherification of *cis*-4-acetoxy-2-cyclopentenyl acetate (*meso*-**47**) (Scheme 6). Though quite a few reports on the palladium-catalyzed asymmetric π-allylic hemi-substitution of meso cyclic 1,4-diesters with carbon and nitrogen nucleophiles have appeared so far, research on etherification with oxygen nucleophiles has been limited to isolated reports,[16] and therefore still remains a challenging target. Representative results are shown in Table 4. Thus, for a typical example, the reaction of *cis*-4-acetoxy-2-cyclopentenyl acetate, *meso*-**47**, with phenol as a nucleophile in the presence of the PS–PEG resin-supported chiral complex **23**–Pd under water-based conditions at 0 °C gave 99% ee of **50a** in 64% isolated yield along with 14% of disubstituted product **51**, where the the kinetic resolution at the second etherification forming **51**, preferentially via *ent*-**50**, must contribute to the increase of the enantiomeric excess of the hemi-ether **50a** (Scheme 6).

Synthetic Application

A multi-step asymmetric synthesis of a hydrindane framework was achieved in water via asymmetric allylic alkylation, propargylation, and aquacatalytic cycloisomerization of a 1,6-enyne, where all three steps were performed in water with the recyclable polymeric catalysts.[17] The racemic cyclohexenyl ester **27** reacted with diethyl malonate under the conditions mentioned in Table 1 to give 90–92% ee of **34b**. The polymeric chiral palladium complex **23**–Pd was reused four times without any loss of stereoselectivity (Table 1, Entries 4–7).[18] Propargylation of the cyclohexenylmalonate **34b** with propargyl bromide was performed with PS–PEG ammonium hydroxide **52**,[19] 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*)-**53**. The polymeric ammonium re-



Scheme 7. Asymmetric multistep synthesis of a hydrindane framework in water.



Scheme 8. Asymmetric aquacatalytic allylic nitromethylation.

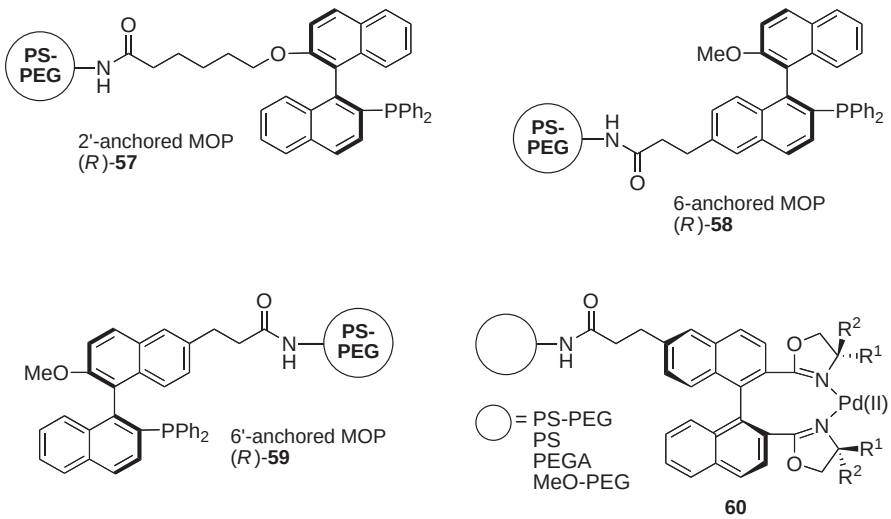


Figure 4. Miscellaneous polymeric chiral ligands.

agent was recovered as its bromide salt, which was reactivated by washing with aqueous KOH and reused. The enyne (*S*)-**53** underwent cycloisomerization (see, Scheme 1, eq 4) with amphiphilic polymeric palladium **3** to afford the hydrindane (3a*R*,7a*S*)-**54** in 94% yield (Scheme 7).

Asymmetric aquacatalytic allylic C1-substitution was also achieved with nitromethane as a C1 nucleophile by using the PS–PEG resin-supported **23**–Pd catalyst in which, under the water-based conditions, nitromethane did not explode even under basic conditions (Scheme 6).[20] To the best of this author's knowledge, research on catalytic asymmetric substitution of cyclic substrates with C1 nucleophiles has been limited to Trost's well-developed report[21] citing the asymmetric π-allylic nitromethylation of cycloalkenyl esters in dichloromethane. Though high enantioselectivities of up to 98% ee were achieved with Trost's chiral bisphosphine ligand, the risk of explosion remains a serious problem.[22] Clearly, while pioneering strides have been made, additional studies on water-based safe protocols are still warranted.

The tetrahydropyridyl ester *rac*-**30** underwent nitromethylation in water with the polymeric chiral catalyst **23**–Pd under similar conditions to give an 81% isolated yield of (*R*)-(nitromethyl)tetrahydropyridine **55** with 97% ee. The resulting (nitromethyl)tetrahydropyridine **55** was readily converted to the tetrahydropyridinecarboxylic acid **56** also in water by modified Carreira conditions,[23] which is a promising synthetic intermediate for Isofagomine and Siastatin B (Scheme 8).[24]

Miscellaneous

Several miscellaneous polymer-supported chiral phosphine ligands and oxazoline ligands are depicted in Figure 4. Binaphthyl monophosphine MOP[25] which was originally developed by this author and Hayashi was anchored on PS–PEG resin at the 2′-, 6-, and 6′-positions of its binaphthyl backbone (compounds **57**, **58**, and **59**).[26] These polymeric ligands realize asymmetric allylic reduction with formic acid under aqueous- and heterogeneous-conditions. A PS–PEG resin-supported chiral oxazoline ligand **60**, boxax,[27] also exhibited aquacatalytic potential as well as stereoselective abilities in catalytic asymmetric Wacker-type cyclization of *o*-allylphenols.[28]

Conclusion

In summary, heterogeneous aquacatalytic asymmetric reactions were achieved with palladium complexes of homochiral phosphine ligands which were immobilized onto amphiphilic polystyrene–poly(ethylene glycol) (PS–PEG) resin beads via chemical bonding. The catalyst was recovered by simple filtration and was reused without any loss of catalytic activity or stereoselectivity. In particular, a novel chiral P,N-ligand, (3*R*,9a*S*)-2-aryl-3-[2-(diphenylphosphino)phenyl]tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one, was designed and prepared on PS–PEG to realize the palladium-catalyzed π-allylic substitution of both cyclic and acyclic substrates with carbon-, nitrogen-, and oxygen-nucleophiles in water with enantioselectivity of up to 99% ee. To the best of the author's knowledge, this is the first successful work on immobilized recyclable asymmetric catalysis in water.

I would like to express to all of my co-workers my deep appreciation for their productive, energetic and hard work in my lab. I also thank Profs. Masakatsu Shibasaki and Tamio Hayashi for their encouragement. These studies were supported by IMS, MEXT, JSPS, JST, and many other foundations which were acknowledged in the original reports.

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