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Catalytic Asymmetric Allylic Alkylation in Water with a Recyclable Amphiphilic Resin-Supported *P,N*-Chelating Palladium Complex

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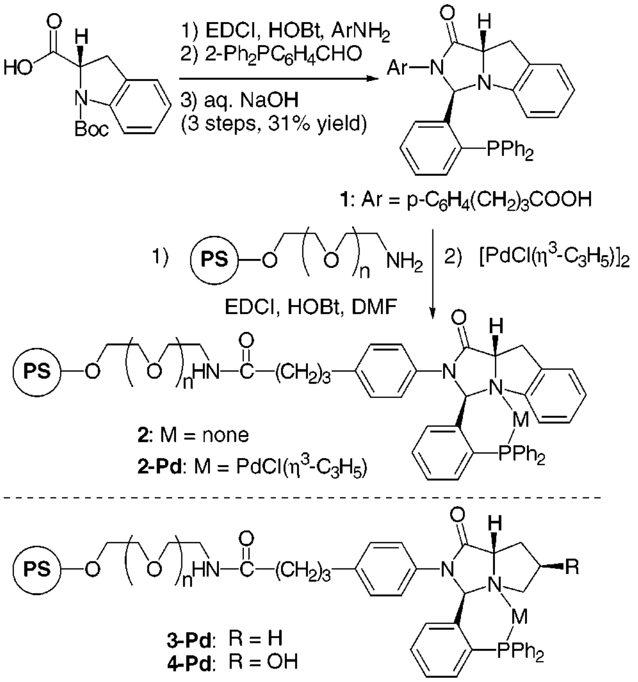
Highly enantioselective reactions in water with recyclable immobilized chiral catalysts are an important goal in synthetic organic chemistry.[1,2] We recently reported that several palladium-catalyzed reactions,[3] including π-allylic substitution,[3a,d] carbonylation,[3c] the Heck reaction,[3c] and Suzuki−Miyaura cross-coupling,[3b] took place in water[4] by use of palladium−phosphine complexes bound to an amphiphilic polystyrene−poly(ethylene glycol) graft copolymer (PS-PEG) resin.[5] These encouraging results prompted us to design new chiral complexes supported on the amphiphilic PS-PEG resin, which would exhibit catalytic activity as well as enantioselectivity in water in several types of transition metal-catalyzed asymmetric organic transformations.[6] We describe herein the design and preparation of a new *P,N*-chelate chiral ligand bound to PS-PEG resin and its use for palladium-catalyzed asymmetric allylic substitution in water, in which enantioselectivity up to 99/1 was achieved.

During our studies on the design of new chiral reagents,[7] 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.[8] The results indicated that a novel *P,N*-chelate chiral ligand having the pyrrolo[1,2-*c*]imidazolone skeleton as a basic chiral unit would be readily immobilized on the PS-PEG resin to achieve highly enantioselective heterogeneous catalysis in water (Scheme 1). (3*R*,9a*S*)-(2-Aryl-3-(2-diphenylphosphino)phenyl)-tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one (**1**), which was readily prepared from (*S*)-indoline-2-carboxylic acid, 4-{3-(methoxycarbonyl)propyl}aniline, and 2-(diphenylphosphino)benzaldehyde by a sequence of reactions shown in Scheme 1, was immobilized on PS-PEG-NH_2 resin[9] to give the PS-PEG resin-supported chiral *P,N*-chelate ligand (*R*,*S*)-**2** (Scheme 1).[10] 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 **2-Pd** in quantitative yield. Following the same procedure, PS-PEG resin-supported complexes **3-Pd** and **4-Pd** were also prepared.

Scheme 1



To explore the enantiocontrolling potential of the resin-supported complexes in water,[11] we elected to study palladium-catalyzed asymmetric allylic substitution of cyclic substrates, which is still a major challenge even with homogeneous chiral catalysts.[12] We were very pleased to find that high stereoselectivity was achieved in water when the PS-PEG resin-supported catalyst **2-Pd** was used for allylic substitution of the cyclic substrates with dialkyl malonate (Scheme 2). Thus, the reaction of methyl cyclopentenyl carbonate (**5**) and dimethyl malonate (**8a**) was catalyzed by **2-Pd** in aqueous lithium carbonate at 40 °C to give 68% isolated yield of the allylic alkylated adduct (*S*)-**9a** with enantiomeric excess of 92% (Table 1, entry 1).[13] The reactions with diethyl malonate (**8b**) in place of **8a** afforded approximately

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[2] (2) For a review, see: De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A., Eds. *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: Weinheim, 2000.

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[4] (4) For a review, see: Herrmann W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524.

[5] (5) Recently, palladium-catalyzed reactions in water with polymer-supported palladium−phosphine complexes have been reported, see: Bergbreiter, D. E.; Liu, Y.-S. *Tetrahedron Lett.* **1997**, *38*, 7843.

[6] (6) As a preliminary result, we have reported PS-PEG supported MOP ligands which achieved asymmetric π-allylic substitution of 1,3-diphenylpropenyl acetate in water with up to 84% ee: Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8303.

[7] (7) (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. (b) Hayashi, T.; Iwamura, H.; Naito, M.; Matsumoto, Y.; Uozumi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 775. (c) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063.

[8] (8) (a) Uozumi, Y.; Mizutani, K.; Nagai, S.-I. *Tetrahedron Lett.* **2001**, *42*, 407. (b) Uozumi, Y.; Yasoshima, K.; Miyachi, T.; Nagai, S.-I. *Tetrahedron Lett.* **2001**, *42*, 411.

[9] (9) (a) Rapp, W. In *Combinatorial Peptide and Nonpeptide Libraries*; Jung, G., Ed.; VCH, Weilheim, 1996; p 425. (b) Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678. (c) Gooding, O. W.; Baudert, S.; Deegan, T. L.; Heisler, K.; Labadie, J. W.; Newcomb, W. S.; Porco, J. A., Jr.; Eikeren, P. *J. Comb. Chem.* **1999**, *1*, 113.

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[11] (11) For recent examples of nonasymmetric palladium-catalyzed allylic substitutions in water, see: (a) Safi, M.; Sinou, D. *Tetrahedron Lett.* **1991**, *32*, 2025. (b) Genêt, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715. (c) Blart, E.; Genêt, J. P.; Safi, M.; Savignac, M.; Sinou, D. *Tetrahedron* **1994**, *50*, 505. (d) Sigismondi, S.; Sinou, D. *J. Mol. Catal. A: Chem.* **1997**, *38*, 3557. (e) Kobayashi, S.; Lam, W. W.-L.; Manabe, K. *Tetrahedron Lett.* **2000**, *41*, 6115.

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10.1021/ja005866j CCC: $20.00

Scheme 2

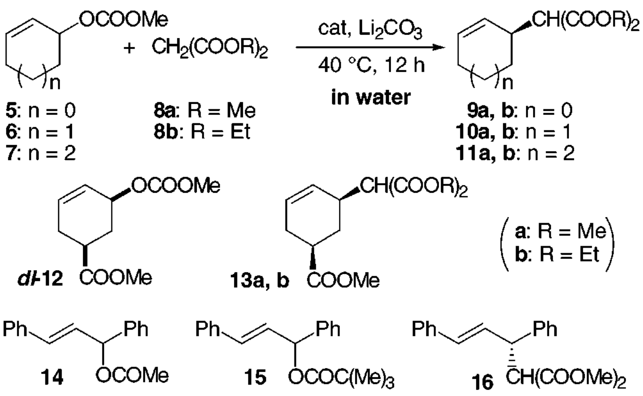

Table 1. Catalytic Asymmetric Alkylation of Allylic Esters in Water by Use of PS-PEG Resin-Supported Pd Complexes[a]

entry	allylic ester	nucleo-phile	catalyst	product	yield (%)[b]	% ee[c] (config)[d]
1	**5**	**8a**	**2-Pd**	**9a**	68	92 (*S*)
2	**5**	**8b**	**2-Pd**	**9b**	67	92 (*S*)
3	**6**	**8a**	**2-Pd**	**10a**	71	89 (*S*)
4	**6**	**8b**	**2-Pd**	**10b**	78	89 (*S*)
5[e]	**6**	**8b**	**2-Pd**	**10b**	60	91 (*S*)
6	**7**	**8a**	**2-Pd**	**11a**	84	97 (*S*)
7	**7**	**8b**	**2-Pd**	**11b**	94	98 (*S*)
8	**12**	**8a**	**2-Pd**	**13a**	71	90 (*S*)
9	**12**	**8b**	**2-Pd**	**13b**	80	90 (*S*)
10	**12**	**8b**	**3-Pd**	**13b**	55	23 (*S*)
11	**12**	**8b**	**4-Pd**	**13b**	44	32 (*S*)
12[f]	**12**	**8b**	**2-Pd**	**13b**	35	87 (*S*)
13[e]	**14**	**8a**	**2-Pd**	**16**	86	91 (*S*)
14[e,g]	**15**	**8a**	**2-Pd**	**16**	50[h]	94 (*S*)

[a] All reactions were carried out at 40 °C for 12 h in 0.9 M aqueous Li_2CO_3 under N_2 unless otherwise noted. The ratio of cyclic substrate (mol)/nucleophile (mol)/catalyst (Pd equiv)/H_2O (L) = 1.0/3.0/0.3/5.0. [b] Isolated yield. [c] For **9a**,**b**: determined by NMR shift experiment with use of Eu(hfc)$_3$. For **10**−**13**: determined by GC analysis with use of a chiral stationary phase capillary column (Cyclodex CB).For **16a**,**b**: determined by HPLC analysis with use of a chiral stationary phase column (Dicel OD-H; hexane/i-PrOH = 98/2). [d] See Supporting Information. [e] Carried out at 25 °C. [f] Carried out in dichloromethane. [g] 5 mol % Pd of **2-Pd** complex was used. [h] 35% of **15** was recovered.

the same results (67% yield, 92% ee (*S*)) (entry 2). The six-membered substrate **6** also underwent asymmetric alkylation with **8a** and **8b** to afford the corresponding alkylated adducts **10a** and **10b** with enantioselectivity of 89% ee (entries 3 and 4). The best results were obtained for the reactions of cycloheptene ester **7** with **8a** and **8b** giving **11a** and **11b** under otherwise similar conditions where the chemical yields and enantiomeric purities were increased to 84% yield, 97% ee (*S*) (for **11a**) and 94% yield, 98% ee (*S*) (for **11b**) (entries 6 and 7).

The alkylation of the racemic *cis*-5-carbomethoxy-2-cyclohexenyl methyl carbonate (**12**) with **8b** gave 90% ee of **13b** 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.[14] Other PS-PEG supported catalysts, **3-Pd** and **4-Pd**, were examined for the allylic substitution of **12** with **8b**. The catalysts **3-Pd** and **4-Pd**, which lack the fused aromatic moiety on their pyrroloimidazolone ring system, gave **13b** with much lower selectivity (23% ee in 55% yield, and 32% ee in 44% yield, respectively) (entries 10 and 11).

It is noteworthy that the immobilized complex **2-Pd** is less catalytically active in an organic solvent. Thus, the alkylation of **12** with **8b** in dichloromethane in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and lithium acetate gave 35% yield of the adduct **13b** with 87% ee, whereas the reaction proceeded smoothly in aqueous lithium carbonate (entries 9 and 12). In the aqueous media, the organic substrates (e.g., **12** and **8**) must diffuse into the hydrophobic PS matrix to form the highly concentrated reaction sphere that should react with ionic species (e.g., aqueous alkaline) through the interfacial PEG region[15] exhibiting higher reactivity than those in an organic solvent.

The PS-PEG supported catalyst **2-Pd** was effective for the asymmetric allylic alkylation of both cyclic and acyclic substrates in water.[12a,e] The reactions of 1,3-diphenylpropenyl acetate (**14**) and pivalate (**15**) were catalyzed by **2-Pd** under the same reaction conditions to give **16** of 91% ee and 94% ee, respectively.[16]

The recycle experiments were examined for the asymmetric substitution of **6** with **8b** catalyzed by **2-Pd**. After the first run giving 91% ee of the adduct **10b** (Table 1, entry 5), the reaction mixture was filtered and the catalyst-resin was rinsed twice with THF.[17] The recovered resin-supported catalyst **2-Pd** was successively subjected to a second and a third series of the reactions to give **10b** of 90% ee in 70% yield (second run) and of 90% ee in 65% yield (third run).

In summary, we have developed an immobilized palladium complex of a *P*,*N*-chelate chiral ligand on an amphiphilic PS-PEG resin, which catalyzed the asymmetric π-allylic substitution of both cyclic and acyclic substrates in water with enantioselectivity of up to 98% ee. The catalyst was 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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Supporting Information Available: Characterization data and experimental procedures for compounds **1**, **2**, **2-Pd**, **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **13a**, and **13b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The remaining starting material was not detected on ^1H NMR and GC analyses of the crude mixture.

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(16) Quite recently, asymmetric π-allylic substitutions in water have been reported, in which the allylic substrate was limited to 1,3-diphenylpropenyl acetate. (a) Hashizume, T.; Yonehara, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2000**, *65*, 5197. (b) Rabeyrin, C.; Nguefack, C.; Sinou, D. *Tetrahedron Lett.* **2000**, *41*, 7461.

(17) ^{31}P NMR (MAS NMR, 162 MHz, chloroform-*d*) of the recovered resin catalyst; 24 ppm (singlet). It has been reported that a PS-PEG resin-supported palladium-phosphine complex was stable during 30 continuous runs (see, ref 3c).