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Asymmetric Allylic Amination in Water Catalyzed by an Amphiphilic Resin-Supported Chiral Palladium Complex

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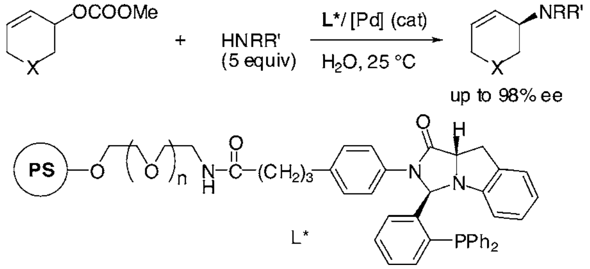
ABSTRACT



Catalytic asymmetric allylic amination of cycloalkenyl carbonates (methyl cyclohexen-2-yl carbonate, methyl cyclohepten-2-yl carbonate, methyl 5-methoxycarbonylcyclohexen-2-yl carbonate, methyl cyclohexenyl carbonate, *tert*-butyl 5-methoxycarbonyloxy-1,2,5,6-tetrahydropyridinedicarboxylate) with dibenzylamines ($(C_6H_5CH_2)_2NH$, $(C_6H_5CH_2)(4\text{-}CH_3OC_6H_4CH_2)NH$, $(4\text{-}CH_3OC_6H_4CH_2)_2NH$) was achieved in water under heterogeneous conditions by use of a palladium complex of (3*R*,9a*S*)-3-[2-(diphenylphosphino)phenyl]-2-phenyltetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one anchored on polystyrene–poly(ethylene glycol) copolymer resin to give the corresponding cycloalkenylamines with high enantiomeric selectivity (90–98% ee).

Aqueous[1] and heterogeneous switching[2] of a given catalytic organic reaction are becoming important research subjects to provide risk-free and environmentally benign processes, as well as efficient methods for product purification and catalyst recycling. Recently, we reported that rhodium- and palladium-phosphine complexes, bound to an amphiphilic polystyrene−poly(ethylene glycol) copolymer (PS−PEG) resin, catalyzed various organic transformations in water under heterogeneous conditions, where the advantages of both aqueous and heterogeneous switching were combined in one system.[3] On the other hand, development of transition-metal-catalyzed asymmetric transformations has emerged as one of the most exciting and challenging subjects in the domain of modern synthetic chemistry.[4] The asymmetric

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(1) For reviews, see: (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley-VCH: New York, 1997. (b) Grieco, P. A. *Organic Synthesis in Water*; Kluwer Academic Publishers: Dordrecht, 1997. (c) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524.

(2) For reviews, see: (a) Bailey, D. C.; Langer, S. H. *Chem. Rev.* **1981**, *81*, 109. (b) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. (c) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035. (d) Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000. (e) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (f) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217. (h) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275.

(3) For studies on polymer-supported palladium catalysts reported by the author's group, see: (a) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 3557 (π-allylic substitution). (b) Danjo, H.; Tanaka, D.; Hayashi, T.; Uozumi, Y. *Tetrahedron* **1999**, *55*, 14341 (π-allylic substitution). (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384 (cross-coupling). (d) Uozumi, Y.; Watanabe, T. *J. Org. Chem.* **1999**, *64*, 6921 (carbonylation reaction). (e) Uozumi, Y.; Nakai, Y. *Org. Lett.* **2002**, *4*, 2997 (Suzuki coupling). (f) Uozumi, Y.; Kimura, T. *Synlett* **2002**, 2045 (Heck reaction). (g) Hocke, H.; Uozumi, Y. *Synlett* **2002**, 2049 (Wacker reaction). (h) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71 (Sonogashira reaction).

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catalytic protocol performed in water under heterogeneous conditions would approach the realization of what may be considered an ideal asymmetric reaction.[5,6] In an earlier study, we found that the asymmetric π-allylic alkylation of cycloalkenyl esters with dialkyl malonates was efficiently catalyzed in water by an immobilized palladium complex coordinated with a novel chiral ligand, (3*R*,9a*S*)-3-[2-(diphenylphosphino)phenyl]-2-phenyltetrahydro-1*H*-imidazo-[1,5-*a*]indole-1-one, bound to an amphiphilic PS−PEG resin (**1**), which was designed and prepared with a view for use in several transition-metal-catalyzed reactions in water, to give optically active cycloalkenyl dialkyl malonates of up to 98% ee.[7] With these results in hand, we were eager to examine the asymmetric π-allylic amination reaction. In contrast to the vast amount of research on the asymmetric π-allylic substitution of acyclic esters (e.g., 1,3-diphenylpropenyl acetate) with malonate nucleophiles, only scattered attention has been focused on cyclic substrates with amine nucleophiles.[8] Here we wish to report the results of our research showing that the palladium-catalyzed asymmetric amination of cycloalkenyl esters forming optically active cyclic allylamines was achieved in water by use of the PS−PEG resin-supported chiral imidazoindole phosphine ligand **1**, with a stereoselectivity of up to 98% ee.

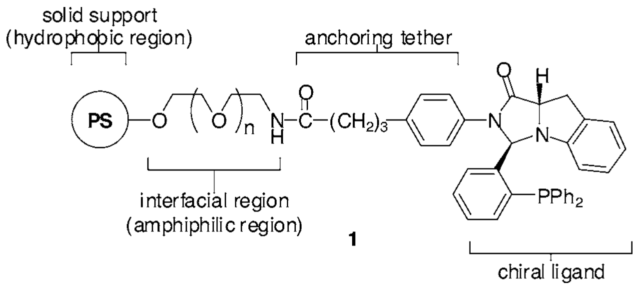
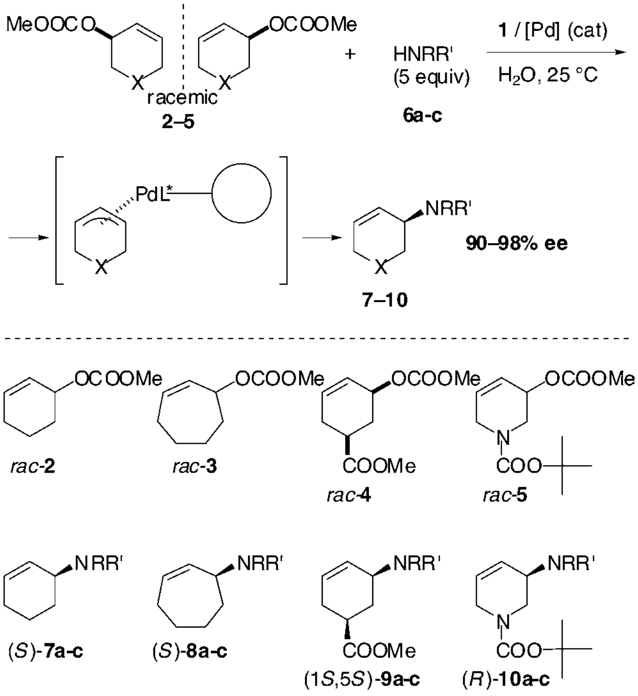


Figure 1. Resin-supported chiral imidazoindole phosphine.

Amination of the methyl cyclohexenyl carbonate (**2**) with 5 equiv of dibenzylamine (**6a**) was carried out in water at 25 °C with shaking for 24 h in the presence of 8 mol % of the palladium complex of **1** (**1**-Pd), which was prepared by mixing **1** and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ just prior to use. The reaction mixture was filtered, and the catalyst resin was rinsed with 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 (**7a**), whose enantiomeric purity was determined by HPLC analysis with a chiral stationary phase column (CHIRALCEL OJ) to be 94% ee (Scheme 1) (Table 1, entry 1). The allylic amination with benzyl(4-methoxybenzyl)amine (**6b**) or di-(4-methoxybenzyl)amine (**6c**) also proceeded with high stereoselectivity under similar reaction conditions to give 92% ee of **7b** or 90% ee of **7c**, respectively (entries 2 and

Scheme 1



a: R = R' = $CH_2C_6H_5$
b: R = $CH_2C_6H_5$, R' = $CH_2C_6H_4OMe$-*p*
c: R = R' = $CH_2C_6H_4OMe$-*p*

Table 1. Asymmetric Amination of Cycloalkenyl Esters in Water Catalyzed by Polymeric Catalyst **1**[a]

entry	allylic ester	amine	product	yield (%)[b]	% ee[c]
1	**2**	**6a**	**7a**	90	94
2	**2**	**6b**	**7b**	77	92
3	**2**	**6c**	**7c**	75	90
4	**3**	**6a**	**8a**	91	98
5	**3**	**6b**	**8b**	82	97
6	**3**	**6c**	**8c**	89	96
7	**4**	**6a**	**9a**	61	90
8	**4**	**6b**	**9b**	80	96
9	**4**	**6c**	**9c**	85	95
10	**5**	**6a**	**10a**	89	95
11	**5**	**6b**	**10b**	99	93
12	**5**	**6c**	**10c**	59	94

[a] All reactions were carried out at 25 °C for 24 h in water under a nitrogen atmosphere. The ratio of cycloalkenyl ester (mol)/amine (mol)/catalyst (Pd equiv)/H_2O (L) = 1.0/5.0/0.08/5.0. [b] Isolated yield. [c] Determined by HPLC analysis with use of a chiral stationary phase column. Absolute configuration of the products was assigned as shown in Scheme 1 (see Supporting Information).

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(4) For a recent review on asymmetric π-allylic substitution, see: (a) Acemoglu, L.; Williams, J. M. J. *Handbook of Organopalladium Chemistry*, p 1945;Negishi, E., Ed.; Wiley, New York, 2002. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(5) For recent reviews on heterogeneous asymmetric catalysis, see: (a) *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, 2000. (b) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385.

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3). The *N*-methoxybenzyl groups of **7b** and **7c** were readily removed by the standard CAN oxidation cleavage to give secondary and primary amines, respectively, opening access to differently *N*-substituted amines (see Supporting Information). Higher stereoselectivity was observed when cycloheptenyl carbonate (**3**) was used as the substrate (entries 4−6). Thus, amination of **3** with **6a**−**c** gave *N*,*N*-dibenzyl(cycloheptenyl)amine (**8a**), *N*-benzyl-*N*-4-methoxy benzyl(cyclohepten-2-yl)amine (**8b**), and *N*,*N*-di(4-methoxybenzyl)-(cyclohepten-2-yl)amine (**8c**), whose chemical yields and enantiomeric purities were 91% yield, 98% ee (**8a**); 82% yield, 97% ee (**8b**); and 89% yield, 96% ee (**8c**).

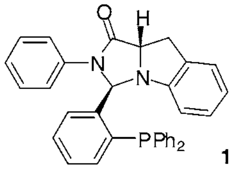
The cyclohexenyl ester **4** bearing a methoxycarbonyl group with the *cis* configuration also underwent π-allylic substitution with the dibenzylamines **6a**−**c** to give the corresponding allylamines **9a**−**c** having the *cis* configuration with high enantioselectivity ranging from 90% to 96% ee (entries 7−9). The aminopiperidines **10a**−**c** were also prepared optically active from the tetrahydropyridyl carbonate **5** under similar conditions (entries 10−12) with 93−95% enantiomeric excess.

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 **3** with 5 equiv of **6a** in the presence of 8 mol % palladium of the PS−PEG resin-supported **1**-Pd complex was carried out in dichloromethane and showed no catalytic activity at 25 °C, whereas the same system in water proceeded smoothly to give 91% yield of the cycloheptenylamine **8a** (Scheme 2). Furthermore, the homogeneous catalytic system using imidazoindolephosphine **11**, which lacks PS−PEG supports, gave only 6% of **8a** 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 matrix in water to construct a highly concentrated reaction sphere to provide a significant increase in reactivity.

Scheme 2

$$\mathbf{3} + \mathbf{6a} \xrightarrow{\textit{conditions a–c}} \mathbf{8a}$$

a: **1** / [Pd] (8 mol%), 25 °C, $\mathbf{H_2O}$ **91% yield; 98% ee**
b: **1** / [Pd] (8 mol%), 25 °C, $\mathbf{CH_2Cl_2}$ **no reaction**
c: **11** / [Pd] (8 mol%), 25 °C, $\mathbf{CH_2Cl_2}$ **6% yield; 85% ee**



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The recycling experiments were examined for the amination of the cycloheptenyl ester **3** with 1 equiv of dibenzylamine **6a**. After the first use of the polymeric chiral catalyst to give 98% ee of **8a**, 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 3).

Scheme 3

$$\mathbf{3} + \underset{\text{(1 equiv)}}{\mathbf{6a}} \xrightarrow[\text{H}_2\text{O, 25 °C}]{\mathbf{1}\text{ / [Pd] (cat)}} \mathbf{8a}$$

1st run: 78% yield; 98% ee
2nd run: 86% yield; 98% ee
3rd run: 78% yield; 98% ee

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Supporting Information Available: Characterization and experimental procedures for compounds **7**−**10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For asymmetric π-allylic substitution of cycloalkenyl esters with high stereoselectivity, see: (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. (b) Knühl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1845. (c) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3047. (d) Gilbertson, S.; Xie, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 2750. (e) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gangne, M. R. *J. Org. Chem.* **1999**, *64*, 2994. (f) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gangne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905. (g) Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4227. (h) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206. (i) Hamada, Y.; Sakaguchi, K.; Hara, O. *Tetrahedron Lett.* **2001**, *42*, 1297. (j) Xiao, L.; Weissensteiner, W.; Mereiter, K.; Widhalm, M. *J. Org. Chem.* **2002**, *67*, 2206. (k) Agarkov, A.; Uffman, E. W.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 2091.