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A Combinatorial Approach to Heterogeneous Asymmetric Aquacatalysis with Amphiphilic Polymer-Supported Chiral Phosphine-Palladium Complexes

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Abstract: A library of amphiphlic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported chiral phosphine ligands was prepared by the split method using porous miniature reactors. A polymeric (*R*)-2-(diphenylphosphino)binaphthyl (MOP) ligand anchored onto the PS-PEG resin by an (*S*)-alanine tether unit was identified through the library-based screening to be an effective chiral ligand for the asymmetric palladium-catalyzed π-allylic substitution under heterogeneous aqueous conditions.

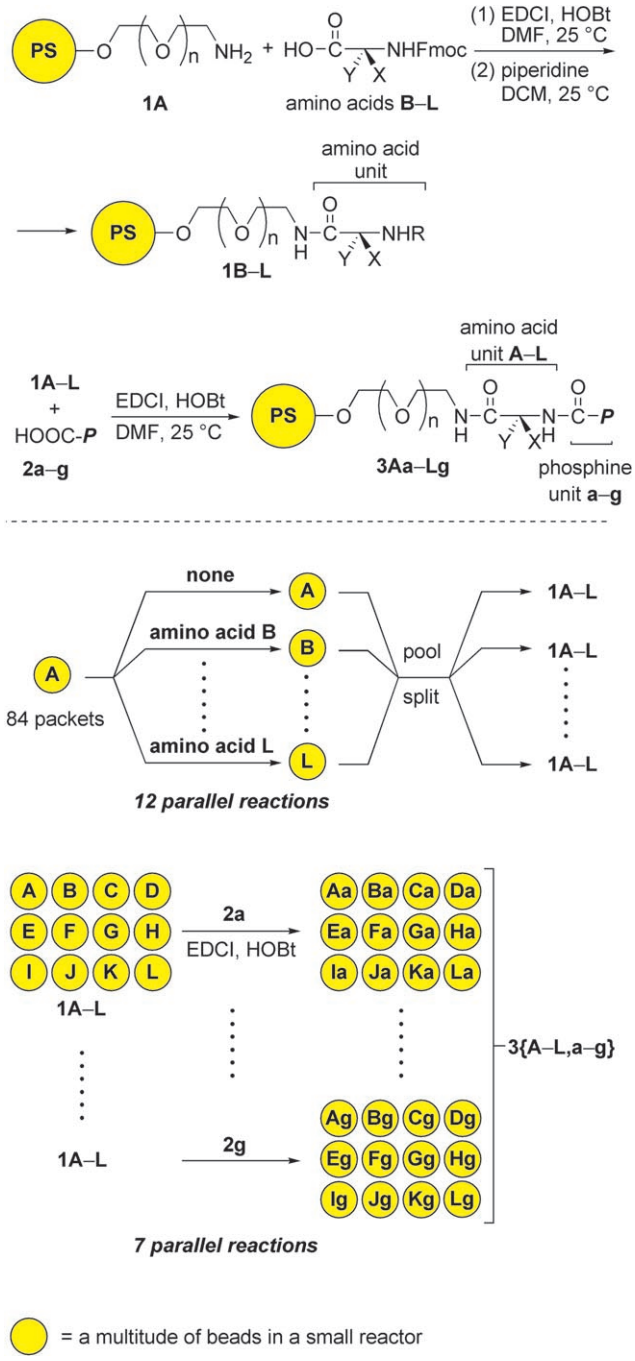
Keywords: allylic substitution; aqueous media; asymmetric catalysis; combinatorial chemistry; palladium; polymer-supported catalyst

Introduction

The development of water-based organic transformations is rapidly becoming an area of importance in chemistry.[1] Water is one of the most suitable solvents for organic chemistry of the next generation owing to its safety and harmlessness. In addition, the development and use of solid-supported catalysts[2,3] has been recognized as one of the most powerful strategies for industrial applications as well as for high-throughput organic synthesis. Taking into account the widespread synthetic utilities of transition metal complexes, palladium-phosphine complexes in particular, there is good reason to believe that immobilized complex catalysts exhibiting high catalytic activity in aqueous media will offer a viable and clean alternative to more traditional methods for accomplishing many organic reactions. We have recently developed palladium and rhodium complexes of amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported phosphine ligands which promote various catalytic transformations smoothly in water under heterogeneous conditions.[4] On the other hand, asymmetric reactions catalyzed by transition metal complexes containing optically active phosphine ligands have attracted significant interest for their synthetic utility. One of the most exciting and challenging subjects in research on catalytic asymmetric synthesis is the development of a chiral ligand which will realize high enantioselectivity in a given reaction. Provided that a chiral transition metal complex immobilized by coordination with a ligand anchored on solid-supports exhibits high catalytic activity and enantioselectivity in aqueous media, the catalysis would represent an almost ideal catalytic organic transformation process.[5] Solid-phase organic synthesis (SPOS) has been recognized as a powerful method to construct a combinatorial chemical library. With a view to obtaining enantioselective complex catalysts, we are particularly interested in a diversity-based SPOS approach[6] to chiral phosphine ligands possessing enantiocontrolling abilities as well as aquacatalytic activity. Herein we report the simple construction of a PS-PEG supported library of chiral monophosphine ligands and its use in the screening of immobilized chiral palladium catalysts for the asymmetric π-allylic alkylation in water in which a PS-PEG supported MOP-based ligand was identified as an enantioselective catalyst.[7]

Results and Discussion

A library of chiral phosphine ligands was prepared on amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin beads from achiral and chiral amino acids **1** and phosphines **2**, including axially chiral MOP ligand derivatives **2d–g**, by the parallel or the split-pool method, the outline of which is illustrated in Scheme 1 and Figure 1. Thus, 7 each of porous polypropylene miniature reactors[8] of PS-PEG resin-supported amino acids **1A–L** (12 members including a dummy **A**; total 84 packets) were prepared by the standard Fmoc method[9] where each reactor contained a unique radiofrequency tag chip[10] to give 84



Scheme 1. A split-and-pool approach to an 84-membered library of PS-PEG resin-supported chiral phosphine ligands.

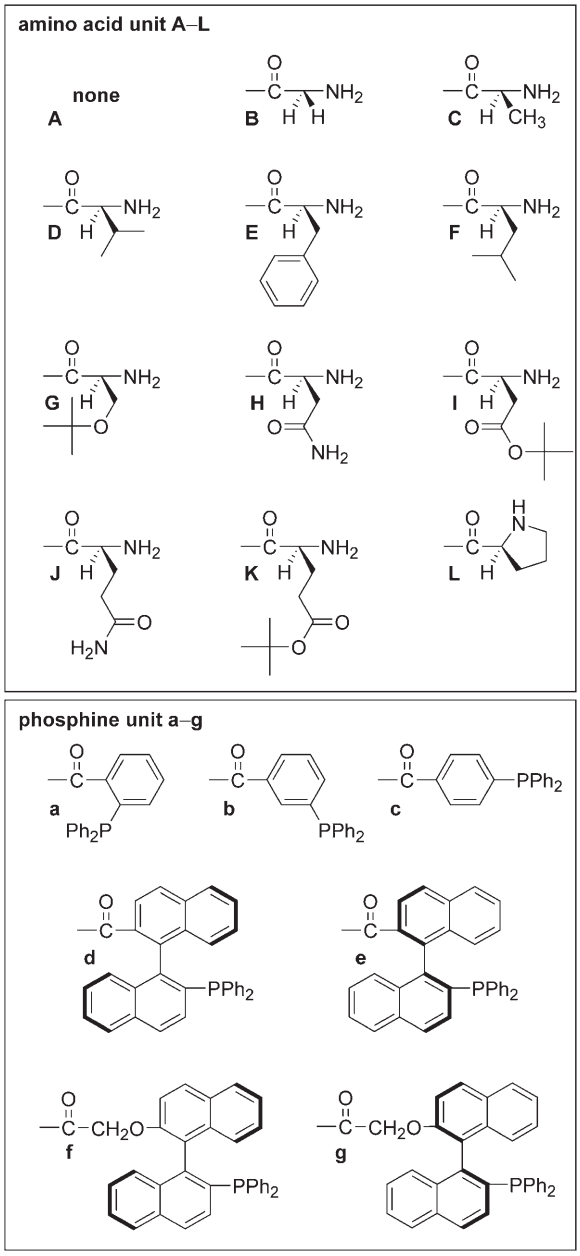
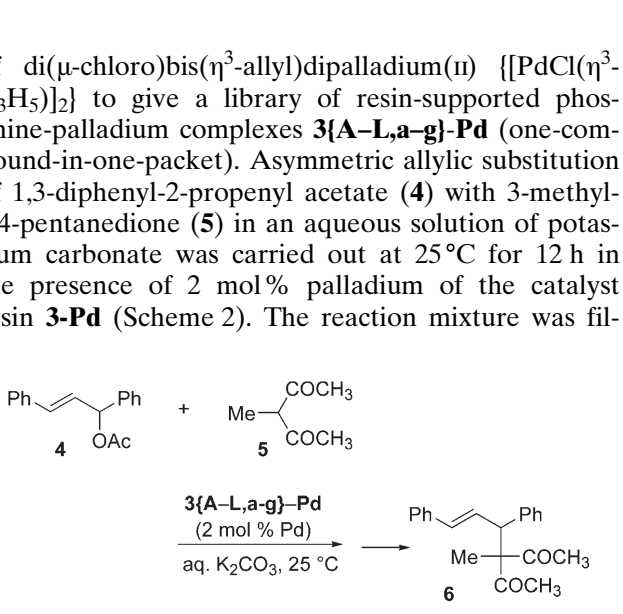


Figure 1. Structures of the amino acid units (**A–L**) and phosphine units (**a–g**).

packets of amino acid beads. The 12 resin-supported amino acids, thus prepared and stored in the miniature reactors, were pooled and divided to 7 sets of 12 resin-supported amino acids **1A–L**. The sets of **1A–L** were combinatorially treated with 7 phosphinecarboxylic acids **2a–g**, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), and 1-hydroxybenzotriazole (HOBt), in DMF, at 25 °C and the resulting 7 kinds of sets were combined to afford an 84-membered library of PS-PEG resin-supported ligands **3{A–L,a–g}**, where all 84 members of phosphine ligands were obtained as discrete products, and only one copy of each one-compound-in-one-packet was prepared.

With a library of amphiphilic PS-PEG resin-supported chiral phosphine ligands, the enantiocontrolling ability as well as catalytic potency of the polymeric ligands were examined in water for the palladium-catalyzed π-allylic alkylation of 1,3-diphenylpropenyl acetate (**4**) with 3-methyl-2,4-pentanedione (**5**). Thus, the 84 packets of phosphines prepared above were pooled together into a single flask and complexed with palladium by treatment with a toluene solution

of di(μ-chloro)bis(η^3-allyl)dipalladium(II) {[PdCl(η^3-C_3H_5)]$_2$} to give a library of resin-supported phosphine-palladium complexes **3{A–L,a–g}-Pd** (one-compound-in-one-packet). Asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate (**4**) with 3-methyl-2,4-pentanedione (**5**) in an aqueous solution of potassium carbonate was carried out at 25 °C for 12 h in the presence of 2 mol% palladium of the catalyst resin **3-Pd** (Scheme 2). The reaction mixture was filtered and the resin-in-packet was extracted with chloroform or ether to give 1,3-diphenyl-4-acetyl-4-methyl-1-hexen-5-one (**6**). The chemical yield and the enantiomeric purity of the product **6** were determined by GC-MS and HPLC (Chiralcel OD-H, eluent: *n*-hexane/2-propanol = 98/2) analyses, respectively. Eighty-four parallel reactions were examined with each library member. Figure 2 and Figure 3 (see also Tables 1 and 2 in the Experimental Section) show the chemical yields and the enantiomeric excesses of **6** obtained by the π-allylic substitution reaction with the library of **3-Pd**. As can be seen from Figure 2,



Scheme 2. Catalytic asymmetric allylic alkylation.

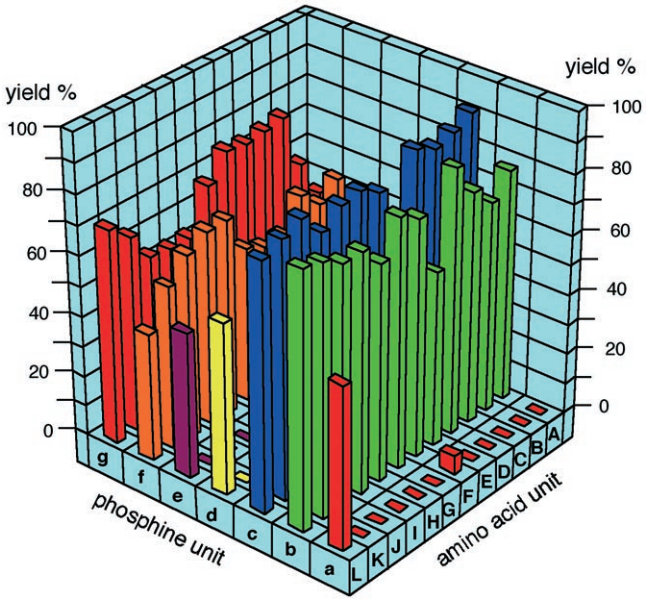


Figure 2. Results of the π-allylic alkylation of **4** with **5**: Chemical yield (%) of **6.**

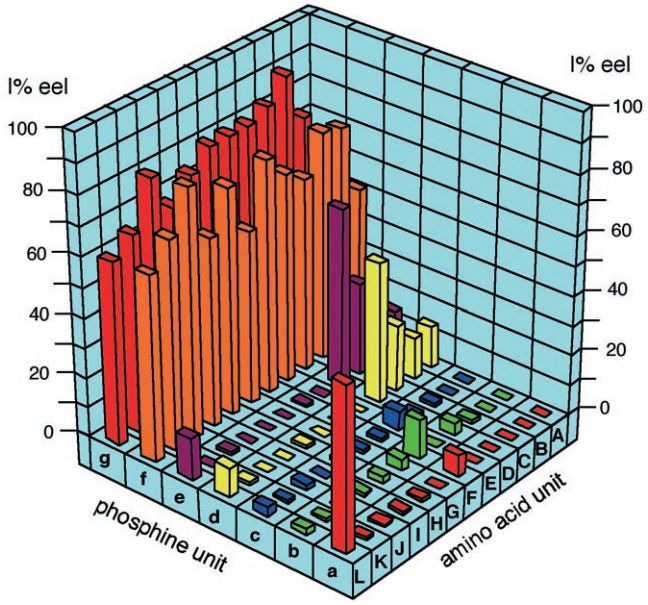


Figure 3. Results of the π-allylic alkylation of **4** with **5**: Enantiomeric purity (% *ee*) of **6.**

with PS-PEG the allylic substitution hardly proceeded with resin-supported *ortho*-tethered triarylphosphines **3{A–K,a}**. A polymeric palladium complex **3La–Pd**, a combination of proline (**1L**) and *o*-diphenylphosphinobenzoic acid (**2a**), catalyzed the reaction in water, although the chemical yield and the enantioselectivity were both moderate [54% yield, 55% *ee* (*R*)].[11] The aquacatalytic allylic substitution was well-promoted with palladium complexes of *meta*- and *para*-anchored triarylphosphines, **3{A–L,b}** and **3{A–L,c}**, whereas the enantiomeric purity of the alkylated product **6** was extremely low (0–13% *ee*). A series of MOP ligands connected *via* a 2′-carbamide group[12] (**3{A–L,d}** and **3{A–L,e}**) showed low catalytic activity. Moderate activity and enantioselectivity were observed when valine or proline was used as the tether unit. Thus, the resin-supported ligands **3Dd**, **3De**, **3Ld**, and **3Le** gave the alkylated product **6** with 47%, 60%, 10%, and 14% *ee*, respectively.

A combination of an amino acid and a 2′-oxyacetyl-MOP unit (**2f** or **g**) was found to provide high enantioselectivity for the π-allylic alkylation. Thus, the π-allylic alkylation was carried out in aqueous solution of potassium carbonate with the palladium complexes of **3{A–L,f}** and **3{A–L,g}**, which were prepared with (*S*)- and (*R*)-C(O)CH$_2$O-MOP (**2f** and **g**) and PS-PEG resin-supported (*S*)-amino acid tether groups **1A–L**. The enantiomeric excess of the product **6** were ranged from 61% *ee* to 90% *ee* (*S*). The palladium complex **3Ag-Pd**, which lacks an amino acid unit, gave lower stereoselectivity to afford 51% *ee* of **6** in a moderate yield. The diastereomeric combination **3{A–K,f}** prepared from (*S*)-C(O)CH$_2$O-MOP (**2f**)

and polymeric amino acids **1** gave the alkylated product **6** with 58–83% *ee* (*R*), where the absolute stereochemistry of **6** was determined by the configuration of the binaphthyl skeleton. The highest enantioselectivity was obtained with a palladium complex of PS-PEG resin-supported phosphine **3Cg** which was prepared from (*S*)-alanine and (*R*)-C(O)CH_2O-MOP (**2g**). Thus, the allylic ester **4** reacted with 1,3-diketone **5** in aqueous potassium carbonate at 25 °C in the presence of 2 mol% palladium of the polymeric palladium complex **3Cg-Pd** to afford a 77% yield of **6** with 90% *ee* (*S*). It is noteworthy that the hydrophobicity may play a key role to control the activity of the catalyst **3**. Thus, when a series of **3{B–L,g}** ligands bearing the (*R*)-MOP unit was used, the chemical yield of **6** in a given reaction time increased as the cLogP value[13] of the amino acid tether group increased (Figure 4). The diastereomeric **3{B–L,f}** ligands bearing the (*S*)-MOP unit exhibited a reverse trend to decrease the chemical yield of **6**.

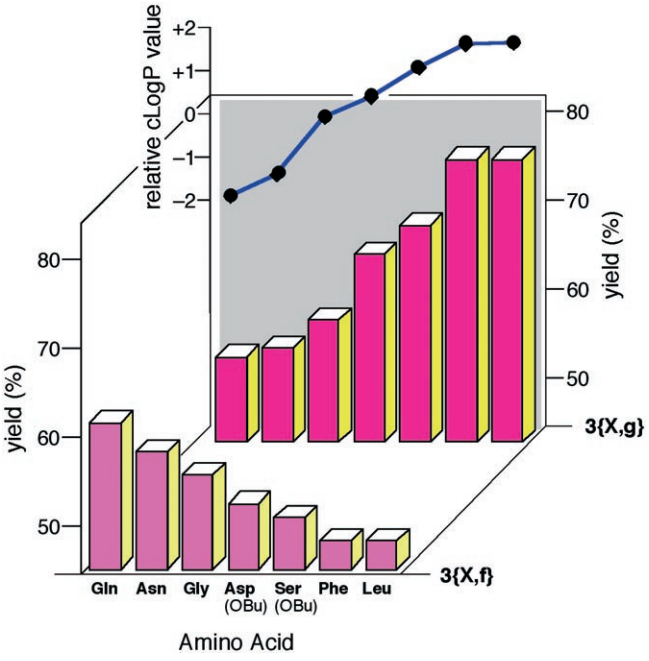
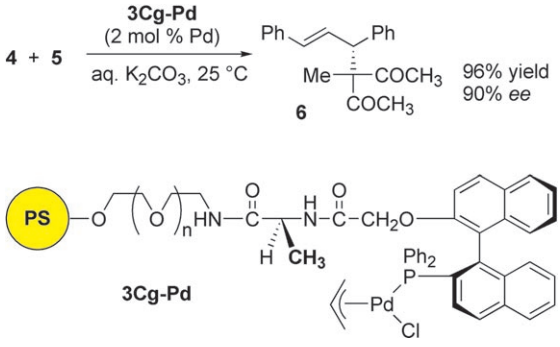


Figure 4. Relationship between catalytic activity and hydrophobicity of palladium complexes of polymeric **3{X,f–g}**.

In order to confirm the asymmetric aquacatalytic efficiency of **3Cg-Pd**, which was identified through the above-mentioned combinatorial approach, we have re-synthesized the polymeric complex **3Cg-Pd**. PS-PEG resin-supported (*S*)-alanine was condensed with (*R*)-C(O)CH_2O-MOP (**2g**) using EDCI and HOBt in DMF to give PS-PEG-[(*S*)-alanine]-[(*R*)-C(O)CH_2O-MOP] (**3Cg**). A negative Kaiser test[14] indicated that the condensation was completed to form polymer-supported triarylphosphine **3Cg** quantitatively. Formation of a palladium-phosphine complex on the resin was performed by mixing [PdCl(η^3-C_3H_5)]$_2$ and **3Cg** (Pd/P = 1.5/1) in toluene at ambient temperature for 20 min to form a polymeric palladium complex **3Cg-Pd**. The progress of the complexation reaction was conveniently monitored by gel phase $^{31}P\{^1H\}$ MAS-NMR spectroscopy.[15] After the reaction being completed, a narrow singlet at $\delta = -10.1$ ppm observed for starting phosphine **3Cg** disappeared and was replaced by a new resonance at $\delta = +26.1$ ppm. Aquacatalytic activity as well as enantiocontrolling ability of re-synthesized **3Cg-Pd** was examined for the π-allylic substitution of 1,3-diphenylpropenyl acetate (**4**) with 3-methyl-2,4-pentanedione (**5**). Thus, a mixture of allylic ester **4** (0.5 mmol), 1,3-diketone **5** (1.7 equivs.), and potassium carbonate (4.0 equivs.) in 2 mL of water was shaken in the presence of 2 mol% of the solid-supported complex **3Cg-Pd** (50 mg, 0.01 mmol Pd) at 25 °C for 12 h (Scheme 3). The reaction mixture was filtered and the resin was rinsed with chloroform. The combined filtrates were concentrated and the residue was chromatographed on silica gel (eluent: hexane/EtOA*c* = 10/1) to give a 96% yield of 1,3-diphenyl-4-acetyl-4-methyl-1-hexen-5-one (**6**). The enantiomeric excess of the resulting **6** was determined by HPLC analysis to be 90% *ee* using a chiral stationary phase column (Chiralcel OD-H, eluent: *n*-hexane/2-propanol = 98/2). The absolute configuration of **6** was determined to be (*S*) by comparison of its retention time of the HPLC analysis with an authentic sample prepared from (*R*)-1,3-diphenyl-4-acetyl-1-hexen-5-one. The results obtained with re-synthesized **3Cg** are consistent with those observed in the combinatorial screening using a library **3{A–L,a–g}**.



Scheme 3. Catalytic asymmetric allylic alkylation with the re-synthesized **3Cg-Pd**.

Conclusions

In conclusion, an amphiphilic resin-supported chiral ligand, PS-PEG-[(*S*)-alanine]-[(*R*)-C(O)CH_2O-MOP] (**3Cg**) was identified as an immobilized stereoselective

phosphine ligand through the diversity-based approach. The palladium complex of the ligand **3Cg-Pd** catalyzed the π-allylic alkylation of 1,3-diphenylpropenyl acetate in water to give 90% *ee* of the alkylated product **6** in 96% yield. These results demonstrate that a combinatorial approach should be effective to develop a catalyst bearing desired catalytic functions.

Experimental Section

All manipulations were carried out under a nitrogen atmosphere unless otherwise noted. Nitrogen gas was dried by passage through P_2O_5. NMR spectra were recorded on a JEOL JNM-AL400 spectrometer (400 MHz for ^1H, 162 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR. The ^{31}P NMR data are reported relative to external 85% H_3PO_4. NMR spectra were recorded in $CDCl_3$ at 25 °C. Optical rotations were measured on a JASCO P-1020 polarimeter. Commercially available reagents were used without any purification. TentaGel S NH_2 (Rapp Polymere; $\Phi = 90$ mm, loading $= 0.2$ mmol g)$^{-1}$ was used as a PS-PEG resin support. PS-PEG resin-supported amino acids **1A–L** were prepared by the standard Fmoc method (refs.[7,9]). MOP derivatives **2d–g** were prepared by reported procedure (refs.[7,12]). Porous polypropylene miniature reactors were purchased from IRORI, La Jolla, CA (http://www.irori.com/).

Preparation of a Library, 3{A–L,a–g}-Pd

A typical procedure is given for the preparation of **3{A–L,g}-Pd**. Twelve kinds of PS-PEG resin-supported amino acids (**1A–L**, including a dummy), each of which was prepared individually and stored in a porous polypropylene miniature reactor (cylindrical device with porous mesh side wall), were pooled together in one single flask, where each reactor was charged with 50 mg of resin-supported amino acid **1** (loading value: 0.2 mmol g^{-1}) and a radiofrequency tag chip (ref.[10]). A mixture of **1A–L** (in distinct miniature reactors), **2g** (123 mg, 0.240 mmol), EDCI·HCl (92 mg, 0.48 mmol), and HOBt (97 mg, 0.72 mmol) was stirred in DMF (36 mL; 3.0 mL/Kan) at 25 °C for 4 h. The reaction mixture was filtered and the beads in miniature reactors were washed with DMF (40 mL, 5 times) and dichloromethane (40 mL, 5 times), and a selected member was subjected to the Kaiser test. The resin was dried under reduced pressure to give **3{A–L,g}** as a one-compound-in-one-packet library. **3Cg**: $^{31}P\{^1H\}$ NMR (gel-phase): $\delta = -10.1$ (s).

Similar manipulations with 7 phosphine units **2a–g** were carried out individually to afford seven series of a 12-membered library of resin-supported phosphines. All reaction packets were pooled together into a single reaction flask, 100 mL of a toluene solution of di(μ-chloro)bis(η^3-allyl)dipalladium(II) (366 mg, 1.0 mmol) were charged into the flask at 25 °C. The mixture was stirred at 25 °C for 20 min. After filtration, the resin was washed with dichloromethane (100 mL, 5 times) and dried under reduced pressure to give an 84-membered library of **3{A–L,a–g}-Pd** in a one-compound-in-one-packet manner. **3Cg-Pd**: $^{31}P\{^1H\}$ NMR (gel-phase): $\delta = 26.1$ (s). An analysis of **3Cg-Pd** for contents of palladium and phosphorus by ICP-atomic emission spectroscopy showed the ratio of Pd/P = 1/1.

Allylic Alkylation of 4 with 5

A typical procedure is given for the reaction with **3Cg-Pd** (Table 1 and Table 2). A mixture of **4** (126 mg, 0.5 mmol), **5** (100 μL, 0.85 mmol), and a packet of **3Cg-Pd** (10 μmol) in 2 mL of aqueous potassium carbonate (1.0 mol/L) solution was shaken on a wrist-action shaker at 25 °C for 12 h. The reaction mixture was filtered and the resin was extracted with chloroform (3 mL, 4 times). The combined extract was chromatographed on silica gel (eluent: *n*-hexane/EtOAc = 10/1) to give **6**; yield: 147 mg (96%). The enantiomeric was dried over Na_2SO_4 and concentrated under reduced pressure. The purity of the residual oil **6** was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, eluent: *n*-hexane/2-propanol = 98/2) to be 90% *ee*; $[\alpha]_D^{24}$: −27 (*c* 2.2, ethanol); ^1H NMR: $\delta = 1.49$ (s, 3H),

Table 1. Results of the π-allylic alkylation of **4** with **5**: chemical yield (%) of **6**.

	2a	2b	2c	2d	2e	2f	2g
1A	0	77	91	5	5	45	45
1B	0	70	88	5	4	58	58
1C	0	77	86	0	2	53	77
1D	0	88	89	25	15	59	76
1E	0	58	54	0	0	49	75
1F	6	79	82	0	0	49	76
1G	0	83	86	0	0	52	68
1H	0	72	85	0	0	65	54
1I	0	79	80	0	0	65	54
1J	0	79	88	0	0	61	55
1K	0	83	85	0	0	54	65
1L	54	85	82	57	48	42	71

Table 2. Results of the π-allylic alkylation of **4** with **5**: Enantiomeric purity (% *ee*) of **6**.[a]

	2a	2b	2c	2d	2e	2f	2g
1A	-	0	0	14 (*R*)	14 (*S*)	51 (*R*)	51 (*S*)
1B	-	0	0	14 (*S*)	12 (*R*)	75 (*R*)	74 (*S*)
1C	-	1	1	-	-	77 (*R*)	90 (*S*)
1D	-	4	1	47 (*S*)	60 (*R*)	65 (*R*)	84 (*S*)
1E	-	0	6	-	-	70 (*R*)	81 (*S*)
1F	7 (*R*)	13 (*S*)	1	-	-	78 (*R*)	81 (*S*)
1G	-	4	1	-	-	58 (*R*)	81 (*S*)
1H	-	2	1	-	-	76 (*R*)	75 (*S*)
1I	-	1	0	-	-	63 (*R*)	68 (*S*)
1J	-	0	2	-	-	83 (*R*)	81 (*S*)
1K	-	1	1	-	-	70 (*R*)	66 (*S*)
1L	55 (*R*)	2	3	10 (*R*)	14 (*R*)	62 (*R*)	61 (*S*)

[a] Absolute configuration in parenthesis.

1.93 (s, 3H), 2.16 (s, 3H), 4.69 (d, $J=8.1$ Hz, 1H), 6.39 (dd, $J=8.1$, 15.6 Hz, 1H), 6.46 (d, $J=15.6$ Hz, 1H), 7.17–7.32 (m, 10H).

Acknowledgements

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References

[1] For reviews on aqueous-switching, see: a) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley-VCH, New York, **1997**; b) P. A. Grieco, *Organic Synthesis in Water*, Kluwer Academic Publishers, Dordrecht, **1997**; c) W. A. Herrmann, C. W. Kohlpaintner, *Angew. Chem. Int. Ed. Engl* **1993**, *32*, 1524; d) U. M. Lindström, *Chem. Rev.* **2002**, *102,* 2751.

[2] For reviews, see: a) B. A. Bunin, *Combinatorial Index*, Academic Press, London, **1998**; b) D. C. Bailey, S. H. Langer, *Chem. Rev.* **1981**, *81*, 109; c) S. J. Shuttleworth, S. M. Allin, P. K. Sharma, *Synthesis* **1997**, 1217; d) S. J. Shuttleworth, S. M. Allin, R. D. Wilson, D. Nasturica, *Synthesis* **2000**, 1035; e) F. Z. Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim **2000**; f) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217; g) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.* **2002**, *102*, 3275; h) Q.-H. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385; i) S. V. Ley, R. N. Baxendale, P. S. Bream, A. G. Jackson, D. A. Leach, M. Longbottom, J. S. Nesi, I. R. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815; j) A. Kirschning, (Ed.), *Immobilized Catalysts, Top. Curr. Chem.* **2004**, Vol. 24.

[3] For a recent review of solid-phase reactions using palladium catalysts, see: a) Y. Uozumi, T. Hayashi, *Solid-Phase Palladium Catalysis for High-throughput Organic Synthesis, in: Handbook of Combinatorial Chemistry*, (Eds.: K. C. Nicolaou, R. Hanko, and W. Hartwig), Wiley-VCH, Weinheim, **2002**, Ch. 19; b) Y. Uozumi, *Top. Curr. Chem.* **2004**, *242*, 77.

[4] For studies on organic transformations with polymer-supported complex catalysts in water, see: a) Y. Uozumi, H. Danjo, T. Hayashi, *Tetrahedron Lett.* **1997**, *38*, 3557 (π-allylic substitution); b) H. Danjo, D. Tanaka, T. Hayashi, Y. Uozumi, *Tetrahedron* **1999**, *55*, 14341 (π-allylic substitution); c) Y. Uozumi, H. Danjo, T. Hayashi, *J. Org. Chem.* **1999**, *64*, 3384 (cross-coupling); d) Y. Uozumi, T. Watanabe, *J. Org. Chem.* **1999**, *64*, 6921 (carbonylation reaction); e) K. Shibatomi, T. Nakahashi, Y. Uozumi, *Synlett* **2000**, 1643; f) Y. Uozumi, Y. Nakai, *Org. Lett.* **2002**, *4*, 2997 (Suzuki–Miyaura coupling); g) Y. Uozumi, T. Kimura, *Synlett* **2002**, 2045 (Heck reaction); h) Y. Uozumi, M. Nakazono, *Adv. Synth. Catal.* **2002**, *344*, 274; i) Y. Uozumi, Y. Kobayashi, *Heterocycles* **2003**, *59*, 71 (Sonogashira reaction); j) Y. Uozumi, M. Kikuchi, *Synlett* **2005**, 1775 (Suzuki–Miyaura coupling).

[5] For examples of chiral processes with polymer-supported catalysts in water, see: a) H. Hocke, Y. Uozumi, *Synlett* **2002**, *12*, 2049; b) H. Hocke, Y. Uozumi, *Tetrahedron* **2003**, *59*, 619; c) H. Hocke, Y. Uozumi, *Tetrahedron* **2004**, *60*, 9297; d) Y. Nakai, Y. Uozumi, *Org. Lett.* **2005**, *7*, 291; e) Y. Uozumi, K. Shibatomi, *J. Am. Chem. Soc.* **2001**, *123*, 2919; f) K. Shibatomi, Y. Uozumi, *Tetrahedron: Asymmetry* **2002**, *13*, 1769; g) Y. Uozumi, H. Tanaka, K. Shibatomi, *Org. Lett.* **2004**, *6*, 281; h) Y. Uozumi, M. Kimura, *Tetrahedron: Asymmetry* **2006**, *17*, 161.

[6] For recent reviews on combinatorial approaches to chiral catalysts: a) B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2494; b) B. Jandeleit, H. W. Turner, T. Uno, J. A. M. van Beek, W. H. Weinberg, *Cattech* **1998**, *2*, 101; c) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, in: *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 1389–1402; d) S. Dahmen, S. Bräse, *Synthesis* **2001**, 1431; e) M. T. Reetz, *Angew. Chem. Int. Ed.* **2001**, *40*, 284; f) M. T. Reetz, *Tetrahedron Lett.* **2002**, *41*, 1335; g) S. R. Gilbertson, in: *Progress in Inorganic Chemistry*, (Ed.: K. Carlin), Wiley, New York, **2001**, Vol. 50; h) J. G. de Vries, A. H. M. de Vries, *Eur. J. Org. Chem.* **2003**, 799; i) C. Gennari, U. Piarulli *Chem. Rev.* **2003**, *103*, 3071.

[7] Preliminary studies on PS-PEG supported MOP-Pd catalysts have been reported, see: Y. Uozumi, H. Danjo, T. Hayashi, *Tetrahedron Lett.* **1998**, *39*, 8303.

[8] R. A. Houghten, *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131.

[9] For example, see ref.[2a], section 4.4.5, p. 117.

[10] a) K. C. Nicolaou, J. N. Pfefferkon, A. J. Roecker, G.-Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939; b) K. C. Nicolaou, J. N. Pfefferkon, S. Barluenga, H. J. Mitchell, A. J. Roecker, G.-Q. Cao, *J. Am. Chem. Soc.* **2000**, *122*, 9954.

[11] In the previous report (ref.[7]), we mis-assigned the absolute configuration of **6**.

[12] a) Y. Uozumi, A. Tanahashi, S.-Y. Lee, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 1945–1948; b) Y. Uozumi, N. Suzuki, A. Ogiwara, T. Hayashi, *Tetrahedron* **1994**, *50*, 4293–4302; c) Y. Uozumi, M. Kawatsura, T. Hayashi, *Org. Syn.* **2002**, *78*, 1.

[13] The logP value which is the logarithm of partition coefficient of a organic compound between *n*-octanol and water, $\log(c_{octanol}/c_{water})$, as well as its computational simulation (cLogP value) is a well established measure of the hydrophilicity of the compound.

[14] E. Kaiser, R. L. Colescott, C. D. Bossinger, P. I. Cook, *Anal. Biochem.* **1970**, *34*, 595.

[15] C. R. Johnson, B. Zhang, *Tetrahedron Lett.* **1995**, *36*, 9253–9256.

