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Palladium-Catalyzed Asymmetric Allylic Substitution in Aqueous Media Using Amphiphilic Resin-Supported MOP Ligands

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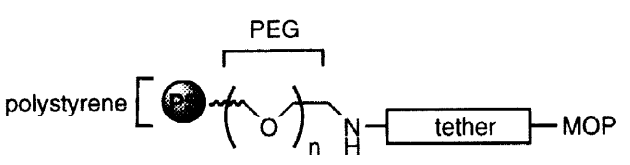
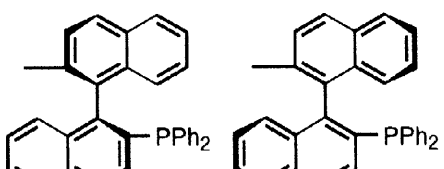
Abstract: A series of amphiphilic resin-supported MOP ligands PEP-MOP were prepared on a polyethylene glycol-polystyrene graft copolymer. Palladium complexes of PEP-MOP were found to be effective as catalysts for the asymmetric substitution of 1,3-diphenyl-2-propenyl acetate with 3-methyl-2,4-pentanedione in aqueous K_2CO_3 to give 1,3-diphenyl-4-acetyl-4-methyl-1-hexen-5-one of up to 81% ee.

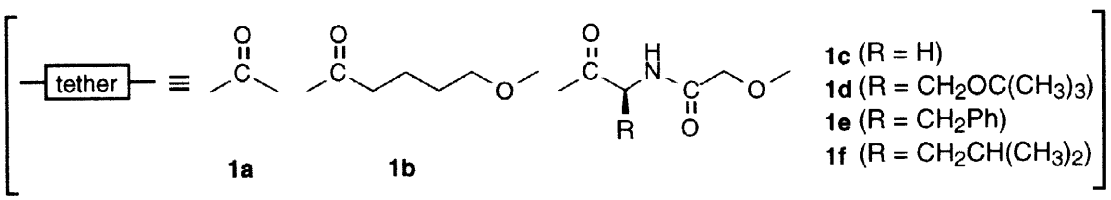
The use of water as a reaction media for transition metal-catalyzed reactions is of great value to organic synthesis for both practical and safety reasons.[1,2] Development of solid-supported catalysts, in particular chiral catalysts, is an important goal in the field of catalytic organic synthesis in order to achieve economically viable and environmentally sound catalytic processes.[3] Providing that a chiral catalyst immobilized on solid-supports exhibits high catalytic activity and enantioselectivity in aqueous media, the catalysis would represent an almost ideal catalytic organic transformation process. We have previously reported design and preparation of amphiphilic palladium-phosphine complexes bound to PEG-PS resin which exhibit high catalytic activity in allylic substitution reactions of allyl acetates with various nucleophiles in aqueous media under mild reaction conditions.[4] On the other hand, we have continued our efforts to develop new chiral phosphine ligands and found that 2-diarylphosphino-1,1'-binaphthyls MOP[5] are very effective for several types of palladium-catalyzed asymmetric reactions[6] including organic transformations by way of π-allylpalladium intermediates.[7] We report here preparation of MOP ligands bound to amphiphilic resin and their use as solid-supported chiral ligands for palladium-catalyzed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate in aqueous media.[8]



PEP-MOP (**PEG-PS** resin–MOP) (**1**)



(*R*)-MOP (*S*)-MOP



1a **1b**

1c (R = H)
1d (R = $CH_2OC(CH_3)_3$)
1e (R = CH_2Ph)
1f (R = $CH_2CH(CH_3)_2$)

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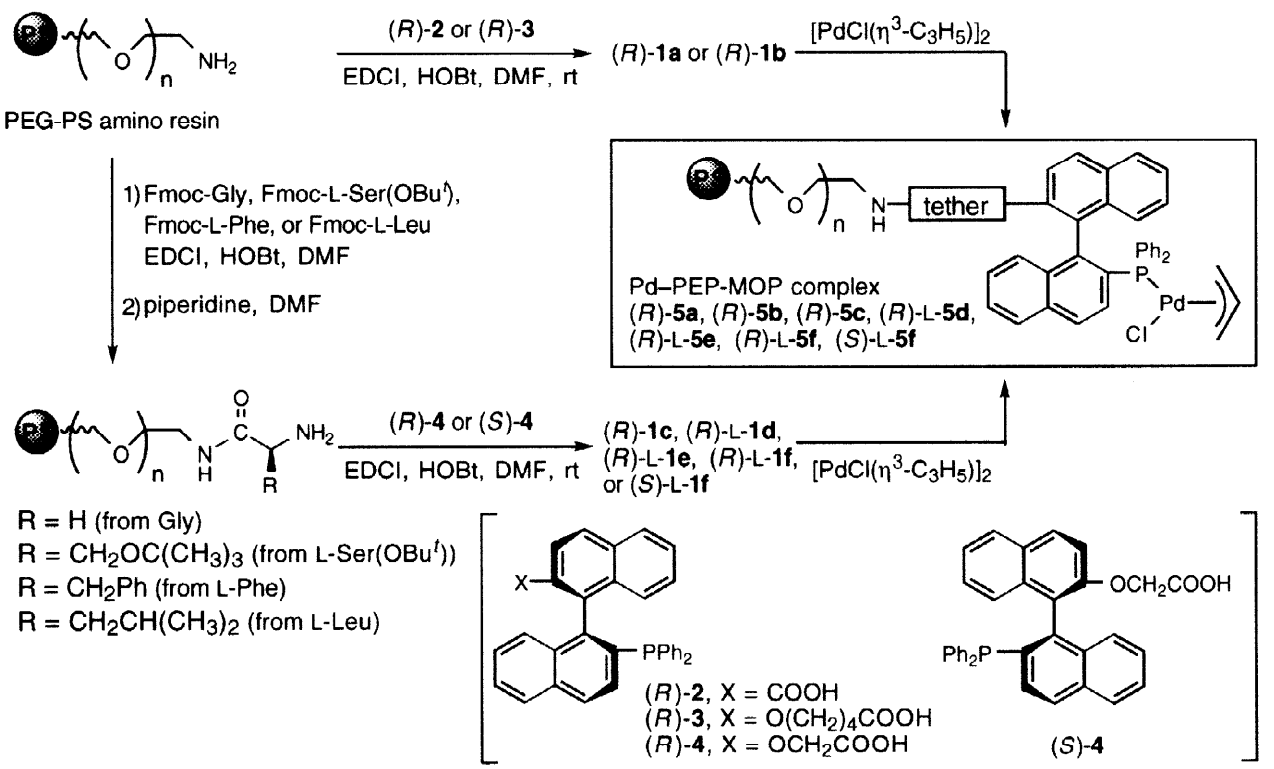
Amphiphilic resin-supported MOP ligands PEP-MOP (PEG-PS resin-supported MOP) **1a** and **1b** were readily prepared on a polyethylene glycol-polystyrene graft copolymer having amino group (PEG-PS amino resin) from (*R*)-2-diphenylphosphino-1,1'-binaphthyl-2'-carboxylic acid ((*R*)-**2**)[5b] and (*R*)-5-(2-diphenylphosphino-1,1'-binaphthyl-2'-oxy)pentanoic acid ((*R*)-**3**),[9] respectively, in a similar manner to the reported procedure.[4] Thus, a mixture of PEG-PS amino resin, 2 equiv of (*R*)-**2** or (*R*)-**3**, EDCI[10] (3 equiv), and HOBt[10] (4 equiv) was agitated in DMF at ambient temperature on a wrist-action shaker until a negative Kaiser test indicating the completion of the reaction to form (*R*)-PEP-MOP (*R*)-**1a** or (*R*)-**1b**, quantitatively. According to the same procedure, the PEP-MOP ligands containing α-amino acid unit in their tether regions, *e.g.* (*R*)-**1c**, (*R*)-L-**1d**, (*R*)-L-**1e**, (*R*)-L-**1f**, and (*S*)-L-**1f**, were prepared from resin-bound amino acids[11] and (*R*)- or (*S*)-2-(2-diphenylphosphino-1,1'-binaphthyl-2'-oxy)acetic acid ((*R*)- or (*S*)-**4**).[9,12] Treatment of PEP-MOP **1** with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in dichloromethane at ambient temperature for 10 min gave corresponding resin-supported palladium-phosphine complexes **5a-f** (Scheme 1).[13]

Scheme 1



Asymmetric catalysis in water was realized in the palladium-catalyzed allylic substitution by use of the amphiphilic resin-supported chiral palladium-phosphine complexes **5** prepared above. Thus, asymmetric substitution of 1,3-diphenyl-2-propenyl acetate (**6**) with 3-methyl-2,4-pentanedione (**7**) 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 **5** to give optically active 1,3-diphenyl-4-acetyl-4-methyl-1-hexen-5-one (**8**) (Scheme 2).[14] The substituted product **8** was isolated by silica gel column chromatography and the enantiomeric excess was determined by HPLC analysis using chiral stationary column (Chiralcel OD-H, eluent: n-hexane/2-propanol =

98/2). The absolute configuration of **8** was determined 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.[15] It was found that the catalytic activity and the enantioselectivity of palladium-PEP-MOP complexes are affected by their tether unit. Thus, the allylic substitution with palladium complex (*R*)-**5b** which has 5-oxypentanoyl tether gave 55% ee of (*R*)-**8** in 56% yield, while (*R*)-**5a** gave <5% yield of (*R*)-**8** with much lower enantioselectivity (14% ee) (Table 1, entries 1 and 2). The use of a palladium complex (*R*)-**5c**, in which MOP moiety is located seven atoms away from the PEG region as is in (*R*)-**5b**, showed almost the same catalytic activity as (*R*)-**5b** to give 58% yield of **8**, and the enantioselectivity was increased to 74% ee (*R*) under the same reaction conditions (entry 3). The palladium-PEP-MOP complexes (*R*)-L-**5d**, (*R*)-L-**5e**, and (*R*)-L-**5f**, which contain L-Ser(OBu^t), L-Phe, and L-Leu groups in their tether regions, were found to be effective chiral catalysts for the present allylic substitution (entries 4, 5, and 6). They gave (*R*)-**8** of 81% ee. Effect of inorganic bases on the enantioselectivity and/or catalytic activity has been examined using this catalyst system. Of lithium, sodium, potassium, and cesium carbonates, potassium carbonate gave the best result (entries 6–9). Lithium carbonate gave lower chemical yield (45%) of **8**, though the enantioselectivity was 84% ee. Comparing a pair of diastereomeric palladium–PEP-MOP complexes (*R*)-L-**5f** and (*S*)-L-**5f**, both of which contain the L-Leu group in their tether regions, the catalytic activity of (*R*)-L-**5f** is higher than that of (*S*)-L-**5f** and the stereochemical outcome is determined mainly by the configuration of MOP moiety (entries 6 and 10).

Scheme 2

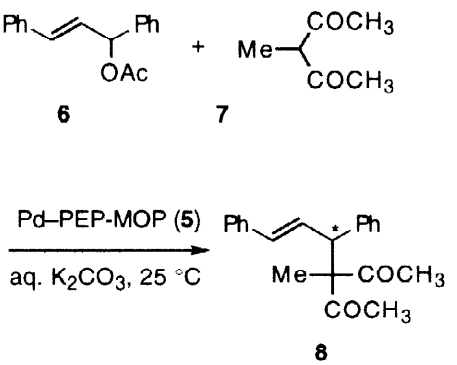


Table 1. Asymmetric Substitution of **6** with **7** in Aqueous Potassium Carbonate Catalyzed by Palladium-PEP-MOP Complexes[a]

entry	catalyst	base	yield (%)[b] of **8**	% ee[c] (abs. config.)
1	(*R*)-**5a**	K_2CO_3	<5	14 (*R*)
2	(*R*)-**5b**	K_2CO_3	56	55 (*R*)
3	(*R*)-**5c**	K_2CO_3	58	74 (*R*)
4	(*R*)-L-**5d**	K_2CO_3	68	81 (*R*)[d]
5	(*R*)-L-**5e**	K_2CO_3	75	81 (*R*)
6	(*R*)-L-**5f**	K_2CO_3	75	81 (*R*)
7	(*R*)-L-**5f**	Li_2CO_3	45	84 (*R*)
8	(*R*)-L-**5f**	Na_2CO_3	58	77 (*R*)
9	(*R*)-L-**5f**	Cs_2CO_3	62	77 (*R*)
10	(*S*)-L-**5f**	K_2CO_3	49	78 (*S*)

[a] The reaction was carried out in aqueous potassium carbonate in the presence of 2 mol % palladium of a Pd-PEP-MOP complex **5** at 25 °C for 12 h with agitation on a wrist action shaker. The ratio of **6** (mol)/**7** (mol)/base (mol)/H_2O (L) = 1.0/1.5/4.5/3.0. [b] Isolated yield by silica gel column chromatography. [c] Determined by HPLC analysis with chiral stationary phase column (Chiralcel OD-H, eluent: hexane/isopropanol = 98/2). [d] $[\alpha]_D^{24}$ –22 (*c* 1.7, ethanol).

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9 (*R*)-**3**: ^{1}H NMR δ ($CDCl_3$) 1.09-1.33 (m, 4H), 1.87 (t, *J* = 7.3 Hz, 2H), 3.70-3.81 (m, 2H), 6.91-7.97 (m, 22H); ^{31}P NMR δ ($CDCl_3$) −14.6 (s); $[\alpha]_D^{26}$ +50 (*c* 2.0 chloroform). (*R*)-**4**: ^{1}H NMR δ ($CDCl_3$) 4.26 (d, *J* = 16.3 Hz, 1H), 4.45 (d, *J* = 16.3 Hz, 1H), 6.79-7.99 (m, 22H); ^{31}P NMR δ ($CDCl_3$) −13.2 (s); $[\alpha]_D^{26}$ +31 (*c* 2.0 chloroform).

10. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. HOBt = 1-hydroxybenzotriazole.

11 The resin-bound amino acids were prepared by standard Fmoc procedure. For a recent review, see: Bunin, B. A. "*Combinatorial Index*" Academic Press, London, 1998, and references cited therein.

12 A library of PEP-MOP ligands containing various chiral α-amino acids in their tether regions was prepared and used for optimization of the enantioselectivity and the catalytic activity, where (*R*)-L-**1d-f** turned out to be the best ligands in the present allylic substitution.

13 Ananlysis of **5** for contents of palladium and phosphorus by ICP-atomic emmision spectroscopy showed the ratio of Pd/P = 1/1.

14 The allylic alkylation of **6** with the sodium salt of **7** in THF in the presence of palladium-(*R*)-MeO-MOP (ref. 5a) complex (2 mol %) gave <5% yield of (*R*)-**8** (57% ee) at 25 °C for 12 h.

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