Polymer-Supported Chiral Phosphinooxazolidine Ligands for Pd-catalyzed Asymmetic Allylic Substitution

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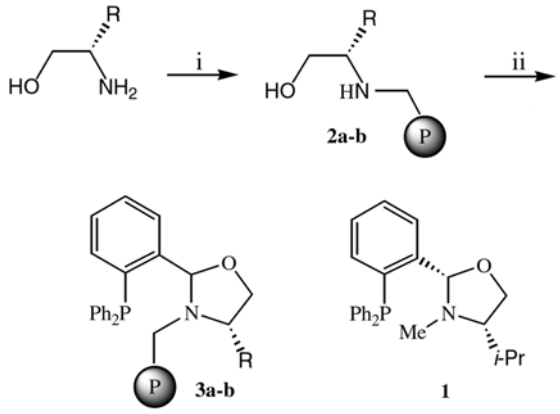
Pd-catalyzed asymmetric allylic substitution is an attractive method for the enantioselective carbon-carbon bond formation in organic synthesis.[1] Much efforts have been made to search for efficient chiral ligands in the reaction.[2] Previously we showed the use of chiral phosphinooxazolidine ligand **1** in the allylic substitution.[3] The phosphinooxazolidine-Pd catalysts induced an efficient reaction with high ee's. The successful development of homogeneous catalysts has been often followed by attempts to attach them onto an insoluble polymeric support. The advantages of immobilized chiral catalysts are well-documented in literatures.[4] In the case of expensive materials, their regeneration is attractive from an economical viewpoint. Our interest in the area led us to prepare polymer-supported phosphinooxazolidine **3** which may have unique advantages over the homogeneous counterpart. Herein, we describe the use of polymer-supported phosphinooxazolidine ligands for the Pd-catalyzed allylic substitution.

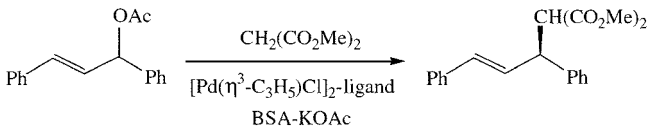


a: R = *i*-Pr, **b**: R = Ph

i) Merrifield resin, toluene, K_2CO_3, reflux
ii) 2-(diphenylphosphino)benzaldehyde, benzene, reflux

The linkage of chiral phosphinooxazolidine moiety to Merrifield resin was conveniently achieved in two steps from optically pure (*S*)-valinol or (*S*)-2-phenylglycinol. According to the established method, polymer-supported valinol **2a** was obtained by chemical modification of 1% crosslinked Merrifield resin (1.0 mmol Cl^-/g, 100-200 mesh) with (*S*)-valinol.[5] The polymer **2a** was next converted to polymer-supported phosphinooxazolidine **3a** by treatment with a 1.5-fold excess of 2-(diphenylphosphino)benzaldehyde in refluxing benzene for 24 h. The immobilized ligand had a loading 0.72 mmol of ligand/gram of polymer. The polymer **3b** (0.70 mmol/g) was also prepared from (*S*)-2-phenylglycinol in the same procedure as for **3a**. The conversion of **2** to **3** seemed to be nearly quantitative from weight gain and elemental analysis. During the formation of oxazolidine, a new stereogenic center at C2 of the ring is formed. It is well-known that condensation of chiral *N*-alkylaminoalcohol with aldehyde leads diastereoselectively to the formation of the *cis*-oxazolidine.[6] A similar discussion is applicable to the reaction of **2** with 2-(diphenylphosphino)benzaldehyde. Thus we consider that the polymers **3** with *cis*-oxazolidine moiety are preferentially produced. In addition to this, phosphinooxazolidine **1** was obtained as a 10 : 1 diasteromeric mixture and the diasteromeric mixture gave 98% ee in the Pd-catalyzed allylic alkylation.[3a] It reveals that the absolute configuration of the C2 has only a minor impact on the ee of the product. The catalytic behavior of the polymers **3** was tested in the Pd-catalyzed allylic substitution. Reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate/*N*,*O*-bis(tri-

Table 1. Allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate by *in situ* Pd-**3** catalyst[a]



Entry	Ligand	Solvent	Temp. (°C)	Time (h)	Conv.[b] (%)	%ee[c]
1	**3a**	THF	0	12	77	90
2	**3a**	THF	RT	2	99	90
3[d]	**3a**	THF	RT	4	90	86
4[e]	**3a**	THF	RT	5	92	88
5	**3a**	CH_2Cl_2	0	1	98	80
6	**3a**	CH_2Cl_2	RT	1	99	86
7[e]	**3a**	CH_2Cl_2	RT	1	95	85
8	**3b**	THF	RT	4	96	65
9	**3b**	CH_2Cl_2	RT	3	97	60

[a]Reactions were carried out with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), ligand **3** (10 mol%), BSA (3 equiv.), KOAc (10 mol%) and dimethyl malonate (3 equiv.) unless otherwise noted. [b]Measured as %-conversion into the product by GC. [c]Determined by HPLC with a chiralcel OD-H column. Absolute configuration was assigned by the sign of the optical rotation and the elution order from a chiral column. [d]LiOAc was used as an additive. [e]Recycled polymer-supported ligand **3a** was used.

methylsilyl)acetamide (BSA) combined with a small amount of potassium acetate was carried out in the presence of a palladium catalyst generated in situ from polymer ligands **3** and π-allylpalladium chloride dimer. The reaction conditions and results are summarized in Table 1. The initial trial of alkylation with 10 mol% of **3a** took place in good enantioselectivity of 90% with relatively high reactivity (entry 1). The immobilized catalyst gave lower enantioselectivity than the homogeneous counterpart **1**. This is probably because the chiral environment and freedom of the catalytic sites may be partially restricted by the steric hinderance of the polymer matrix. The effect of temperature was detectable but not very significant on asymmetric induction. In addition, CH_2Cl_2 as solvent gave lower enantioselectivity than THF (entries 5-7). The polymer was easily separated by centrifugation and removal of the solution phase after reaction. The recycled polymer was found to be also effective in the next run (entries 4 and 7). Polymer ligand **3b** having a phenyl group on the oxazolidine ring provided lower % ee than **3a** having an isopropyl group (entries 8 and 9).

A representative procedure for allylic substitution: In a Schlenk tube polymer ligand **3a** (70 mg, 10 mol% based on phosphinooxazolidine) and allylpalladium chloride dimer (4.8 mg, 0.013 mmol, 2.5 mol%) were dissolved in THF (1.1 mL) and the mixture was stirred at room temperature for 20 min. To this solution were successively added 1,3-diphenyl-2-propenyl acetate (130 mg, 0.52 mmol) in THF (1.2 mL), dimethyl malonate (206 mg, 1.56 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (317 mg, 1.56 mmol) and KOAc (3.5 mg, 0.05 mmol). The mixture was stirred at a given temperature. After the reaction was complete, the immobilized catalyst was separated by centrifugation and used directly for the next run. The solution phase was diluted with ether (10 mL), washed with cold saturated aqueous ammonium chloride solution (5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15% EtOAc/hexane). The enantiomeric excess was determined by HPLC analysis (chiralcel OD-H column; flow rate, 0.5 mL/min; hexane : isopropanol = 99 : 1, t*r* = 23.4 min, t*s* = 25.0 min). Absolute configuration was assigned by the sign of the optical rotation[2a] and the known elution order from a chiral column.

To summarize, we have successfully applied polymer modification method to the preparation of polymer-supported chiral phosphinooxazolidines **3**. In particular, the polymer **3a** was effectively served as chiral ligands for enantioselective allylic alkylation and reused without any significant loss in catalytic activity and enantioselectivity. Further studies are in progress to introduce different chiral ligands on polymeric supports.

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