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CATALYTIC ASYMMETRIC SYNTHESIS OF PEPTIDES ON POLYMER SUPPORT

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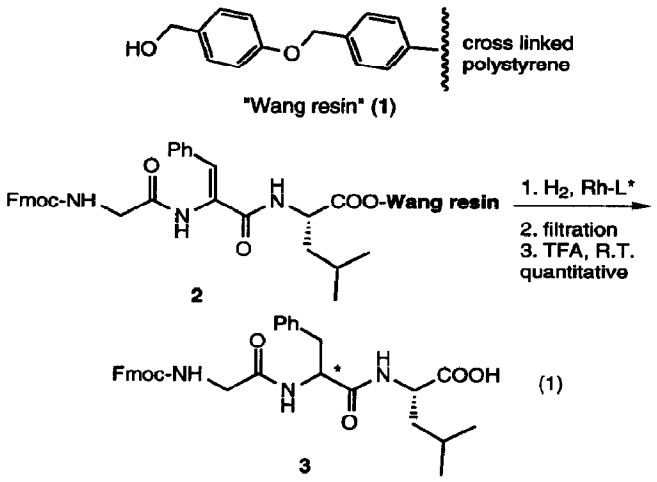
Summary: A novel approach to the synthesis of peptides through the catalytic asymmetric hydrogenation of dehydrotripeptides linked to the Wang resin, using rhodium complexes with chiral diphosphine ligands as the catalysts, is described.

We have been investigating the catalytic asymmetric synthesis on polymer support in which a substrate is anchored on a polymer resin through a linker and a homogeneous catalyst in solution promotes the asymmetric reaction. This is a very unique approach to catalytic asymmetric synthesis using polymer support because efforts in the past concentrated on anchoring chiral homogeneous catalysts on polymer resins in order to solve separation problems associated with usual homogenous catalytic reactions. Although these conventional approaches have scored some success,[1,2] deactivation of the catalyst due to gradual depletion of the metal component is inevitable for these systems since the binding constant of the polymer-anchored ligand such as phosphines to the metal is far from infinite. When a substrate is expensive and a reaction including work-up requires extraction and/or chromatography, it is very beneficial if these separation processes can be avoided.[3,4] Also, recycling or reactivation of chiral catalysts is possible if the catalyst stays in solution. Consideration of these points logically leads to a solution in which (i) the substrate is anchored on a polymer support, (ii) the homogeneous chiral catalyst is used in solution, (iii) separation of the product from the catalyst is performed by simple filtration and washing, and (iv) final isolation is carried out by cleaving the product from the polymer resin, where the separation of the product from the polymer resin is achieved by simple filtration. Based on our experience in peptide syntheses on various polymer supports, we have selected a commercially available "Wang resin" (**1**), a cross-linked polystyrene resin bearing 4-(hydroxymethyl)phenoxymethyl tethers, as the basic polymer support. Substrates bearing carboxylic acid moiety can readily be connected to the Wang resin by simple dehydrative coupling.

We would like to report here our preliminary study on a novel approach to the asymmetric synthesis of a component of an analgesic brain peptide enkephalin using a resin-anchored dehydrotripeptide, Fmoc-Gly-(*Z*)-ΔPhe-Leu-[Wang resin] (**2**),[5] as the substrate for asymmetric hydrogenation catalyzed by rhodium complexes with chiral diphosphine ligands (eq. 1).[6]

Typically, Wang resin – anchored dehydrotripeptide **2** (0.048 mmol) was hydrogenated in the presence of [Rh(diPAMP[7])(NBD)]BF_4 (4.8×10^{-3} mmol) prepared *in situ* (see Supplementary Material) in 5 mL of degassed toluene and 1 mL of isopropanol at 40 °C and 150 psi of hydrogen in a stainless steel autoclave using a Pyrex reaction vessel for 72 h. The resin was transferred to a cartridge, filtered off the catalyst solution, and washed with DMF and methanol to remove by-product(s). Then, the resin was transferred into a 5 mL round-bottom flask, and 5 mL of TFA was added. The suspension was stirred for 2 h at room temperature. The resin was filtered and TFA was removed to give Fmoc-Gly-Phe-Leu-OH (26 mg, 97%). In order to determine the diastereomeric purity, the product was submitted to HPLC analysis using a reversed-phase column, Waters

Resolve C18 (5 μm, 150 mm), and water/acetonitrile containing 0.1% trifluoroacetic acid as the eluant, which indicated that the (*R*,*S*) / (*S*,*S*) ratio of the produced tripeptide was 6.2 / 93.8. Results obtained under different reaction conditions are summarized in Table 1.



As Table 1 shows, the solvents employed exert remarkable effects on the stereoselectivity of the reaction besides the chiral ligands. The reaction temperature also has moderate influence on diastereoselectivity. Best results are obtained when toluene/isopropanol (5/1) is used as the solvent and [Rh(diPAMP)(NBD)]BF_4 (NBD = norbornadiene) (94% *S*,*S*) or [Rh(Ph-CAPP[8])(NBD)]BF_4 (95%, *R*,*S*) as the chiral catalyst at 40°C. After asymmetric hydrogenation and cleavage from the resin, the product, Fmoc-Gly-Phe-Leu-OH (**3**), was obtained in virtually quantitative isolated yield. Therefore, the proposed novel process is proven to be feasible. It is worthy of note that after the asymmetric hydrogenation on the resin, the attachment of additional amino acid residues can readily be continued using Fmoc-based solid phase peptide synthesis.

The high stereoselectivities obtained with [Rh(diPAMP)(NBD)]BF_4 or [Rh(Ph-CAPP)(NBD)]BF_4 in toluene/isopropanol (5/1) are comparable to those obtained for the reactions using Fmoc-Gly-(*Z*)-ΔPhe-Leu-OMe in the corresponding homogeneous reaction systems, and the same absolute configurations are introduced to the produced tripeptides.[9] When rhodium or ruthenium complexes with other chiral phosphine ligands were used for the asymmetric hydrogenation of Fmoc-Gly-(*Z*)-ΔPhe-Leu-OMe in homogeneous systems using ethanol as the solvent at 40°C and 150 psi of hydrogen for 24-48 h, much lower stereoselectivity was realized.[10]

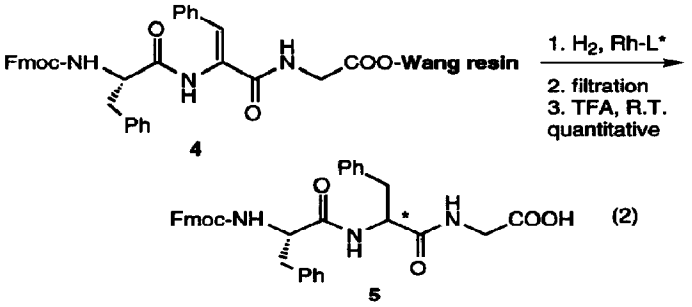
Similar results have been obtained for the reactions using Fmoc-Phe-(*Z*)-ΔPhe-Gly-[Wang resin] (**4**) as the substrate (eq. 2).

Further studies on the applications of this new methodology to different types of asymmetric catalytic reactions as well as to the asymmetric syntheses of peptide mimetics are actively underway.

Table 1. Asymmetric Hydrogenation of Fmoc-Gly-(Z)-ΔPhe-Leu-[Wang resin] (2) with diPAMP-Rh$^+$ and Ph-CAPP-Rh$^+$[a]

Catalyst	Solvent	Temp. (°C)	Time (h)	Conversion (%)	(*R*,*S*)/(*S*,*S*)[b]
[Rh(diPAMP)(NBD)]BF_4	THF	40	72	92	21.3 / 78.7
"	CH_2Cl_2	40	72	87	18.4 / 81.6
"	Toluene/EtOH(4/1)	40	72	98	11.4 / 88.6
"	"	90	72	98	24.2 / 75.8
"	Toluene/^{i}PrOH(5/1)	40	72	100	6.2 / 93.8
"	"	90	72	100	7.1 / 92.9
"	1,4-dioxane	65	96	9	30.9 / 69.1
[Rh(Ph-CAPP)(NBD)]BF_4	THF	40	72	86	43.6 / 56.4
"	Toluene/EtOH(2/1)	65	72	100	62.7 / 37.3
"	Toluene/^{i}PrOH(5/1)	40	72	100	94.9 / 5.1
"	"	65	72	100	93.0 / 7.0
"	"	90	72	100	92.2 / 7.8
"	1,4-dioxane	65	96	46	62.7 / 37.3

[a]All reactions were run with 0.048 mmol of the Wang resin – anchored substrate and 0.0048 mmol of a chiral rhodium catalyst in a solvent (6 mL) under 150 psi of hydrogen in a 25 mL Pyrex reaction vessel in a 300 mL stainless steel autoclave with magnetic stirring. [b]The diastereomer ratios were determined on the basis of HPLC analysis.



diPAMP-Rh: *SS*/*RS* =95/5
Ph-CAPP-Rh: *SS*/*RS* =6/94

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References and Notes

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5. The polymer-linked dehydrotripeptides were readily prepared by reaction of an amino acid attached to the Wang resin with (*Z*)-2-(Fmoc-aminomethyl)-4-benzylidene-5-oxazolone. A typical procedure is as follows. To a solution of ^{t}BOC-Gly-Ser(Ph)-OH (3.07 g, 9.07 mmol) in CH_2Cl_2 (40 mL) was added dropwise 16.5 mL of TFA at 0 °C. The mixture was stirred for about 1 hr and the solvent was removed under reduced pressure. The residue was washed with ether (3 x 30 mL) and the solvent was removed to give TFA·H-Gly-Ser(Ph)-OH (2.74 g, 86%) as a white solid. To a solution of TFA·H-Gly-Ser(Ph)-OH (2.74 g, 7.78 mmol) in CH_3CN (25 mL), water (20 mL), 6.25N NaOH (1.25 mL) and Et_3N (1.08 mL) was added a solution of Fmoc-Su (2.63 g, 7.78 mmol) in CH_3CN (25 mL) at 25 °C. The mixture was stirred for 1 hr and the solvent was removed under reduced pressure. The residue was poured into 20 mL of 1.5N HCl solution and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated to give Fmoc-Gly-Ser(Ph)-OH. A mixture of Fmoc-Gly-Ser(Ph)-OH, NaOAc (0.31 g, 3.78 mmol) and Ac_2O (12.5 mL) was stirred for 1 hr at 0 °C and 12 hr at 25 °C. Then, chilled water (30 mL) was added to the mixture and the precipitated pale yellow crystals of 2-(Fmoc-aminomethyl)-4-benzylidene-5-oxazolone (**6a**) (2.80g, 85%) were collected on a glass filter: One cartridge of Fmoc-Leu-Wang resin (80 mg, 0.048 mmol) was placed in the R^{a}MPS$^{(TM)}$ system. After deprotection of the Fmoc group by the standard procedure (50% piperidine in DMF, 9 min), a solution of the oxazolone **6a** (51 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) and DMF (3 mL) was added to the cartridge. The mixture was rocked for 14 hr, washed with DMF and methanol, tested by Ninhydrin solution to make sure there was no free amino group left, and then dried under vacuum to give **2** in quantitative yield.
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9. The asymmetric hydrogenation of Fmoc-Gly-(*Z*)-ΔPhe-Leu-OMe catalyzed by cationic Rh complexes with Ph-CAPP and diPAMP achieved the best results: [Rh(diPAMP)(NBD)]BF_4, (*R*,*S*)/(*S*,*S*) = 3.8/96.2; [Rh(Ph-CAPP)(NBD)]BF_4, (*R*,*S*)/(*S*,*S*) = 94.0/6.0.
10. [Rh((-)BPPM[11])(NBD)]BF_4, (*R*,*S*)/(*S*,*S*) = 58.6/41.4; [Rh((*S*)-BINAP[12])(NBD)]BF_4, (*R*,*S*)/(*S*,*S*) = 49.4/50.6; [Rh(Degphos)(NBD)]BF_4,[2,13] (*R*,*S*)/(*S*,*S*) = 10.1/89.9; Ru((*S*)-BINAP)$(OAc)_2$,[14] (*R*,*S*)/(*S*,*S*) = 33.2/ 66.8.
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