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Recent developments in asymmetric catalysis using synthetic polymers with main chain chirality

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Abstract

Some recent developments in the use of main chain chiral polymer catalysts are summarized. These polymers are different from the traditional polymer catalysts that are prepared by anchoring monomeric chiral catalysts to an achiral polymer backbone. Three classes of synthetic main chain chiral polymers are discussed including: (1) helical polymers represented by polypeptides; (2) polymers with flexible chiral chains such as polyesters and polyamides; and (3) polymers of rigid and sterically regular chiral chains represented by chiral conjugated polybinaphthyls. Some of these polymer catalysts have shown high enantioselectivity in asymmetric organic transformations. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Contents

1. Introduction

Polymeric reagents and catalysts have found broad applications in organic synthesis.[1,2] The primary advantage of these materials is their ease of separation from the reaction mixture which allows very efficient recovery and reuse of the catalysts. When toxic or odorous reagents are attached to polymer supports, handling and processing of these chemicals becomes much safer and simpler. The polymer-supported peptide synthesis developed by Merrifield has been extensively applied in the production of both natural and unnatural peptides.[3] Recently, polymer-based combinatorial chemistry has also

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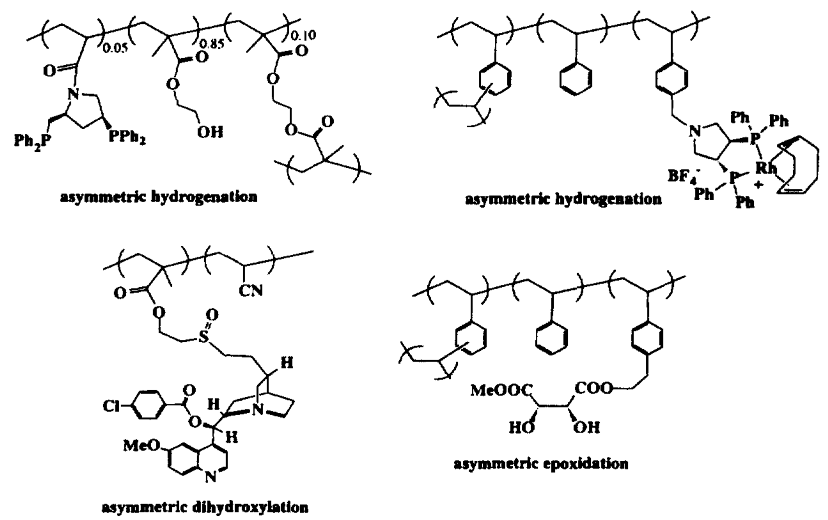
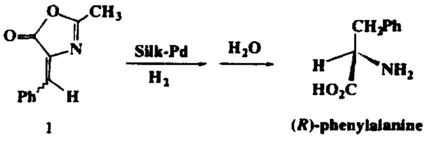


Fig. 1.

become an extremely powerful tool in drug discovery and other applications.[4,5] Optically active catalysts have been anchored to polymer supports to carry out the asymmetric synthesis of organic compounds. Figure 1 shows a few examples of polymer-supported chiral catalysts that have been used in asymmetric hydrogenations, epoxidations and dihydroxylations.[2] All of these catalysts are prepared by attaching the monomeric ligands to achiral and flexible polymer backbones.

Although main chain chiral polymers have also be applied in asymmetric catalysis, their investigations are far more rare. In 1956, Akabori et al. reported the use of silk fibroin supported palladium to catalyze the asymmetric hydrogenation of unsaturated carbon–carbon and carbon–nitrogen bonds.[6] By using this chiral silk-bound Pd catalyst, **1** was hydrogenated to give (*R*)-phenylalanine in 30–70% enantiomeric purity (Scheme 1). Early work on asymmetric hydrogenation, asymmetric hydrolysis and other reactions using main chain chiral polymers have been summarized.[1] This paper will discuss some recent developments in asymmetric catalysis using synthetic polymers of main chain chirality.

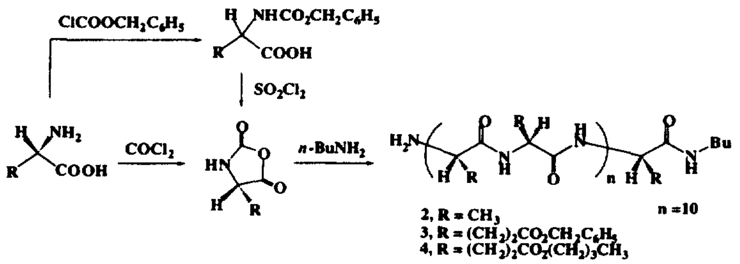


Scheme 1. Asymmetric hydrogenation catalyzed by an inherently chiral polymeric catalyst

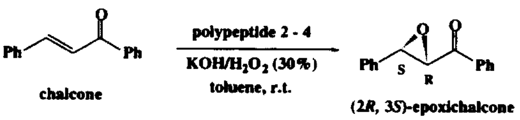
2. Synthetic polypeptide catalysts[7]

Synthetic polypeptides have been used as catalysts to carry out a number of organic reactions such as Michael additions, oxidations, and reductions.[8–10] However, it was not until 1980 that the first highly enantioselective asymmetric reaction using synthetic polypeptides was discovered by Juliá et al.[11] In their study, different polypeptides such as poly[(*S*)-alanine] (**2**), poly[5-benzyl-(*S*)-glutamate] (**3**) and poly[5-butyl-(*S*)-glutamate] (**4**) were synthesized by using the strategy shown in Scheme 2. This strategy involves the preparation of N-carboxyanhydrides from the corresponding chiral amino acids and an *n*-butylamine initiated polymerization. All of these polypeptides contain about 10 amino acid residues. They were used to catalyze the epoxidation of chalcone in toluene in the presence of NaOH/H_2O_2 (30%)

at room temperature (Scheme 3). Among these three polypeptides, **2** was found to be a far better catalyst in terms of both chemical yields and enantioselectivities in this triphasic epoxidation process. When 0.8 equiv. of **2** were used, the epoxy chalcone product was obtained in 85% yield and 86% enantiomeric excess (*ee*) in 24 h. However, recycled **2** gave only 36% yield and 44% *ee*. This is much reduced from the original polymer because the strongly basic conditions degrade the amide bonds in the peptide.



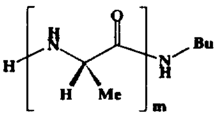
Scheme 2. Synthesis of polypeptides



Scheme 3. Asymmetric epoxidation of chalcone using the polypeptide catalysts

Polypeptide **2** was used to catalyze the epoxidation of a number of chalcone derivatives and the results are summarized in Table 1.[12] All of these reactions were carried out in the polypeptide–water–toluene triphasic system. As shown in Table 1, good enantioselectivity is observed for a few of the chalcone derivatives. However, the enantioselectivity and yield of these reactions are very sensitive to the substituents on the aromatic ring. For example, the epoxidation of alkoxyl substituted chalcones produced the epoxides only in low yields. The epoxidation of cis-α,β-unsaturated ketones such as 2-cyclohexenone showed no enantioselectivity at all.

The enantioselectivity of the epoxidation was found to be dependent on the molecular weight of the polypeptides. When the degree of polymerization of the polypeptides was increased from 10 to 30 (e.g. **2′**, m=30), the enantiomeric purity of the products became the highest. In the presence of **2′**, the epoxidation of chalcone generated the chiral epoxy ketone in 93% *ee*. Replacing toluene with CCl_4 further increased the *ee* to 96%.

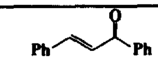
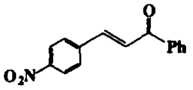
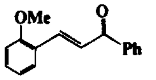
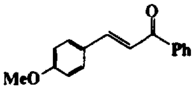
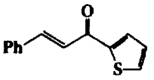
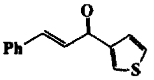
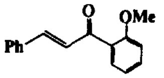
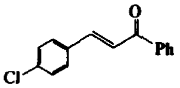
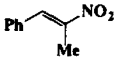
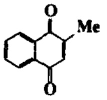
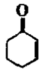


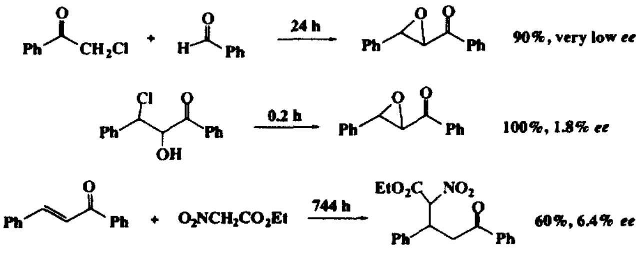
2′, m = 30

Polypeptide **2**, in the presence of NaOH, was also used to catalyze the reactions shown in Scheme 4. For these, only very low *ee*s (1.8–6.4%) were observed.

Additional poly[(*S*)-α-amino acid]s including **5–14** were prepared and tested for the asymmetric epoxidation of chalcone (Fig. 2).[13] The reactions were carried out in a triphasic system containing CCl_4, water and a catalytic amount of the polypeptide in the presence of a large excess of $NaOH/H_2O_2$. Similar to **2** and **2′**, polypeptides **6a**, **6b**, **7** and **13b** produced (2*R*,3*S*)-epoxychalcone in over 80% *ee*. However, other polymers gave less than 40% *ee*. The recycled polypeptides again exhibited diminished enantioselectivity as well as catalytic activity due to the partial hydrolysis of the polymers under the basic reaction condition. When poly[(*R*)-alanine] was used as the catalyst, the resulting epoxychalcone had the same *ee* but the opposite configuration as the one obtained from poly[(*S*)-alanine]. Poly[(*R*,*S*)-alanine]

Table 1
Epoxidation of chalcone derivatives catalyzed by the polypeptide **2**

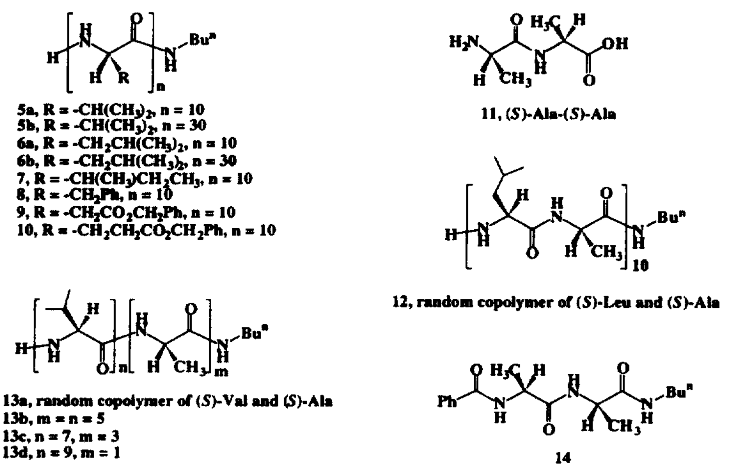
Substrate	Yield	*ee* (%)
	78 - 85	78 - 86
	83	82
	29	–
	53	–
	96	80
	30	70
	54	50
	47	66
	50	7
	100	0
	19	~0



Scheme 4. Attempted reactions using **2** as the catalyst

showed very low catalytic activity and almost no *ee*. Thus, the optically active form of the polypeptide is not only important for the enantioselectivity but also important for the catalytic activity.

No enantioselectivity was observed when the epoxidation of chalcone was carried out in methanol. This suggests that hydrogen bonding might be important in polypeptide-catalyzed asymmetric epoxidation. Both the carbonyl function of chalcone and the oxidant HOO^- can form hydrogen bonds with the polypeptide and these interactions may play a role in the asymmetric oxidation. In support of



5a, R = $-CH(CH_3)_2$, n = 10
5b, R = $-CH(CH_3)_2$, n = 30
6a, R = $-CH_2CH(CH_3)_2$, n = 10
6b, R = $-CH_2CH(CH_3)_2$, n = 30
7, R = $-CH(CH_3)CH_2CH_3$, n = 10
8, R = $-CH_2Ph$, n = 10
9, R = $-CH_2CO_2CH_2Ph$, n = 10
10, R = $-CH_2CH_2CO_2CH_2Ph$, n = 10

11, (*S*)-Ala-(*S*)-Ala

12, random copolymer of (*S*)-Leu and (*S*)-Ala

13a, random copolymer of (*S*)-Val and (*S*)-Ala
13b, m = n = 5
13c, n = 7, m = 3
13d, n = 9, m = 1

14

Fig. 2.

the hydrogen bonding hypothesis, poly[(*S*)-proline], which does not have amide hydrogens, shows no catalytic activity for the epoxidation.[14]

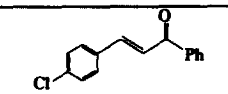
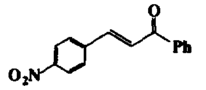
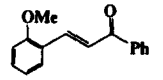
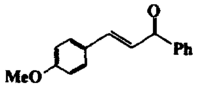
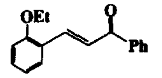
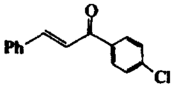
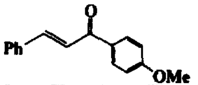
The influence of polypeptide conformation on the stereoselectivity of the epoxidation was also studied. It was found that the polymers with a high content of α-helical conformation, e.g. **2**, **6** and **12**, had the maximum enantioselectivity.[14] The increase in β-structure at the expense of the α-helical conformation, e.g. **13c** and **13d**, leads to significantly reduced stereoselectivity. Short peptides that cannot achieve the α-helical structure, such as **11** and **14**, have almost no enantioselectivity (*ee*=0.7–2%). In general, polypeptides with a degree of polymerization less than 10 give much lower *ee*s. The local structure of the polypeptides is also very important. For example, even though both of the polymers **9** and **10** have an α-helical structure, they show very low *ee*s (3–12%). Polypeptide **9** has a left handed α-helix and **10** has a right handed α-helix, but they give the same levorotatory epoxychalcone. The terminal groups of the polypeptides in general have little effect on the epoxidation.

Colonna and Juliá also found that polypeptides with over 50 amino acid units or polypeptides that are attached to cross-linked polystyrene supports are much easier to filter, thus simplifying catalyst recovery and product isolation.[14] Polystyrene-bound poly[(*S*)-alanine] was prepared by treating (*S*)-alanine derived N-carboxyanhydride with hydroxyl functionalized cross-linked polystyrene. This polymer-supported polypeptide produced epoxychalcone in 84% *ee*.

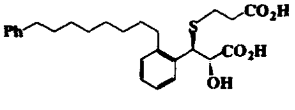
In 1990, Itsuno et al. further investigated the use of polymer-supported poly(amino acid)s for the asymmetric epoxidation of chalcone and its derivatives.[15] Using cross-linked polystyrenes that contain primary amine groups to initiate the polymerization of N-carboxyanhydrides, they obtained a series of poly[(*S*)-alanine] and poly[(*S*)-leucine] catalysts. The highest *ee* (up to 99%) was observed when epoxidation of chalcone was effected by a polymer-supported poly[(*S*)-leucine] of 32 amino acids that had been prepared from a polystyrene made of 32% amine functionalized monomer. These polymer-supported poly(amino acid)s exhibited high *ee*s (76–99%) for chalcone derivatives with different substituents on the phenyl ring. Unlike the unsupported polypeptides, the polymer-supported catalysts were reused multiple times without significant loss of activity. Table 2 lists the asymmetric epoxidation of chalcone derivatives catalyzed by the polymer-supported poly[(*S*)-leucine].

The polypeptide-catalyzed epoxidation of chalcones has been used to prepare natural products such as flavonoids[16–18] and SK&F 104353 (**15**).[19] Compound **15** is a possible drug candidate for the treatment of bronchial asthma and its synthesis is shown in Scheme 5.[19] The asymmetric epoxidation of **16** catalyzed by poly[(*S*)-leucine] gave **17** in 82% yield and 95% *ee*. Unlike what was observed by Juliá

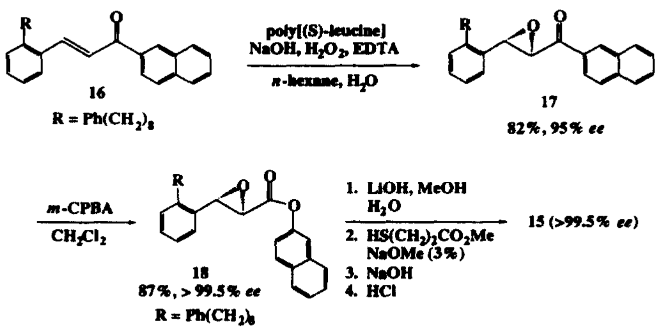
Table 2
Asymmetric epoxidation catalyzed by the polystyrene-supported poly[(*S*)-leucine]

Substrate	Yield	*ee* (%)
	98	99
	89	90
	56	76
	89	90
	56	83
	98	99
	83	87

et al., the recycled poly[(*S*)-leucine] in this reaction showed no change in either catalytic activity or enantioselectivity even after it had been used six times. The epoxide **17** was then oxidized to **18** by *m*-CPBA. After four more steps, including a highly regioselective nucleophilic opening of the epoxide with methyl 3-mercaptopropionate, optically pure **15** was obtained.



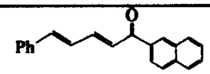
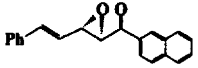
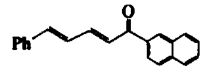
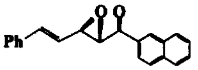
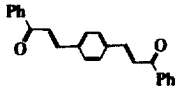
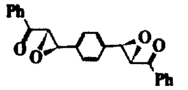
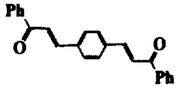
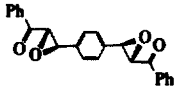
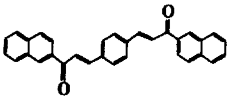
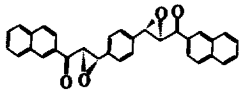
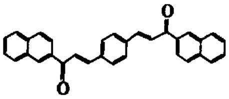
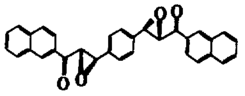
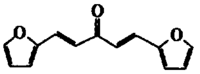
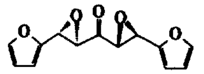
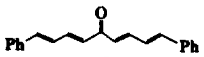
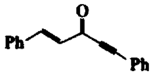
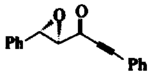
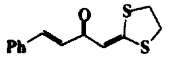
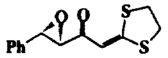
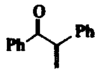
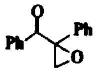
SK&F 104353
15



Scheme 5. Synthesis of the drug candidate **15**

In 1995, Sánchez et al. initiated a program to extend the scope of polypeptide-catalyzed asymmetric epoxidation.[20–22] Tables 3–5 list the results they obtained for the epoxidation of different substrates. The poly[(*S*)-leucine] catalyst always gives the opposite enantiomer of the epoxide product from the poly[(*R*)-leucine] catalyst. Besides hydrogen peroxide, other oxidants such as sodium perborate, sodium percarbonate and *t*-butylhydroperoxide can also be used for the asymmetric epoxidation.

Table 3
Asymmetric epoxidation of ketones containing more than one alkene bond catalyzed by the polypeptides

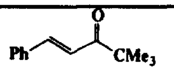
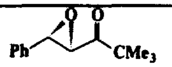
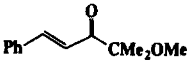
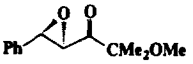
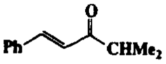
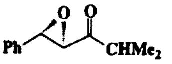
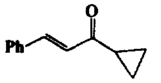
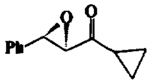
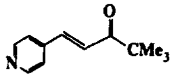
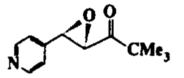
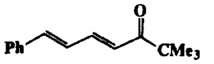
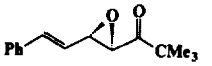
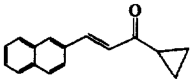
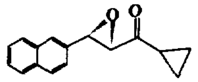
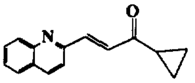
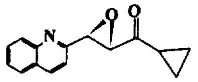
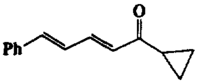
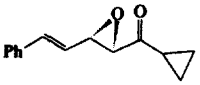
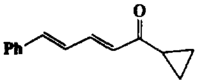
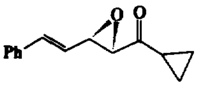
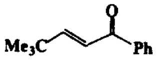
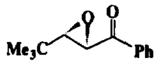
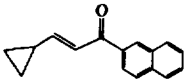
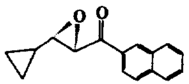
Number	Substrate	Catalyst	Product	Yield (%)	*ee* (%)
19		poly[(*S*)-leucine][a]		78	>96
19		poly[(*R*)-leucine][a]		76	>96
20		poly[(*S*)-leucine][b]		74 de > 88%	>99
20		poly[(*R*)-leucine][b]		91 de > 88%	>99
21		poly[(*S*)-leucine][c]		82 de > 99%	>98
21		poly[(*R*)-leucine][c]		64 de > 99%	>98
22		poly[(*S*)-leucine][b]		60	90
23		poly[(*S*)-leucine][b]		50	80
24		polystyrene-bound poly[(*S*)-leucine][d]		57	90
25		poly[(*S*)-leucine][b]		51	>94
26		polystyrene-bound poly[(*S*)-leucine][d]		78	59

a. NaOH, H_2O_2, H_2O, hexane. b. NaOH, H_2O_2, H_2O, CH_2Cl_2. c. NaOH, $NaBO_3$, H_2O, CH_2Cl_2. d. NaOH, H_2O_2, H_2O, toluene.

Table 3 summarizes the polypeptide-catalyzed epoxidation of ketones **19**–**25** that contain more than one alkene bond. The epoxidation of **26**, a compound with a terminal double bond, is also included. As shown in Table 3, for the dienones such as **19**, the epoxidation occurs specifically at the α,β-positions with excellent enantioselectivity. High diastereoselectivity as well as high enantioselectivity are observed for the double epoxidation of compounds **20**–**23**. For compounds **24** and **25**, the epoxidation of the phenyl substituted double bond occurs preferably over the other unsaturated bonds.

Table 4 shows the epoxidation of α,β-unsaturated ketones with aliphatic substituents. The polypeptide catalysts work very well for the substrates containing *t*-butyl or cyclopropyl substituents such as **27**, **32**, **33**, **36**, **37** and **38**. However, when one of the methyl groups in the *t*-butyl substituent was replaced with a methoxyl group or a hydrogen, e.g. **28** and **29**, the epoxidation proceeded very slowly (84–168 h) to

Table 4
Asymmetric epoxidation of α,β-unsaturated ketones containing aliphatic groups catalyzed by the polypeptides

Number	Substrate	Catalyst	Product	Yield (%)	*ee* (%)
27		poly[(*S*)-leucine]^a		92	89
28		poly[(*S*)-leucine]^a		70	63
29		poly[(*S*)-leucine]^a		60	62
30		poly[(*S*)-leucine]^a		85	77
31		poly[(*S*)-leucine-DAP]^a		70	72
32		poly[(*S*)-leucine]		90	> 97
33		poly[(*S*)-leucine]^a		56	90
34		poly[(*S*)-leucine]^a		94	79
35		poly[(*S*)-leucine]^a		73	74
36		poly[(*S*)-leucine]^b		52	98
37		poly[(*S*)-leucine-DAP]^{a,e}		85	90
38		poly[(*S*)-leucine]^a		73	> 98

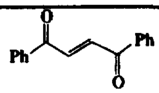
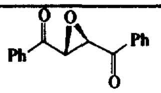
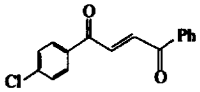
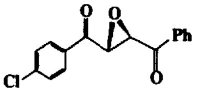
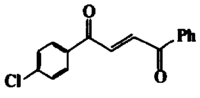
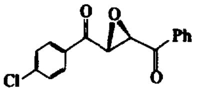
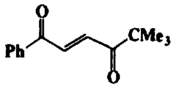
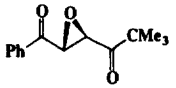
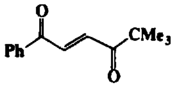
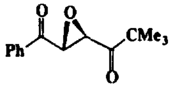
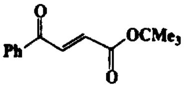
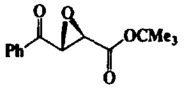
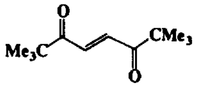
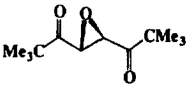
a. NaOH, H_2O_2, H_2O, CH_2Cl_2. b. NaOH, $NaBO_3$, H_2O, CH_2Cl_2. c. NaOH, H_2O_2, H_2O, toluene. d. NaOH, H_2O_2, H_2O, hexane. e. Poly[(*S*)-leucine-DAP] is prepared from (*S*)-leucine N-carboxyanhydride using 1,3-diaminopropane as the initiator.

give much reduced yields and *ee*s. When an isopropyl group was placed at the β-position of the enone, no epoxidation occurred.

Table 5 shows the epoxidation of 1,4-dicarbonyl enones catalyzed by the polypeptides. Good to excellent enantioselectivities are observed for the substrates containing aryl or *t*-butyl substituents.

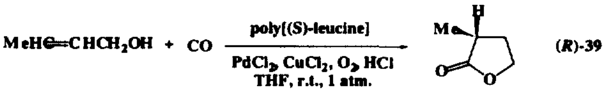
Bentley et al. recently improved upon Juliá's epoxidation reaction.[23] By using urea–hydrogen peroxide complex as the oxidant, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base and the Itsuno's immobilized poly[(*S*)-leucine] as the catalyst, the epoxidation of chalcone was carried out in THF solution. After 0.5 h, the reaction was complete with 100% conversion and >99% *ee*. This process greatly reduced the time required in the original reaction. By using this new catalyst system, the epoxidation of styrylmethyl ketone proceeded with 83% *ee* and 70% yield. This is in contrast to the triphasic polypeptide-catalyzed epoxidation where, when aliphatic substituents other than *t*-butyl or cyclopropyl were introduced to the chalcone substrates, diminished reactivity and enantioselectivity were observed.

Table 5
Asymmetric epoxidation of 1,4-dicarbonyl enones catalyzed by the polypeptides

Substrate	Catalyst	Product	Yield (%)	*ee* (%)
	poly[(*S*)-leucine][a]		76	76
	poly[(*S*)-leucine][b]		60	89
	polystyrene-bound poly[(*S*)-leucine][c]		57	> 98
	poly[(*S*)-leucine][a]		79	82
	polystyrene-bound poly[(*S*)-leucine][c]		75	> 95
	polystyrene-bound poly[(*S*)-leucine][c]		66	> 95
	polystyrene-bound poly[(*S*)-leucine][c]		100	> 95

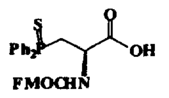
a. NaOH, H_2O_2, H_2O, CH_2Cl_2. b. NaOH, $NaBO_3$, H_2O, CH_2Cl_2. c. NaOH, H_2O_2, H_2O, toluene.

In 1990, Alper et al. found that poly[(*S*)-leucine] could be used as a chiral ligand in a palladium-catalyzed asymmetric allylic alcohol–carbonyl cycloaddition.[24] In the presence of $PdCl_2$, $CuCl_2$, oxygen and poly[(*S*)-leucine] (M~21,7000, DP=192), 2-buten-1-ol reacts with carbon monoxide at room temperature under atmospheric pressure to generate (*R*)-**39** in 61% *ee* and 49% yield (Scheme 6). The amino acid residues in the α-helical polypeptide may serve as bidentate ligands for the Pd centers in this catalytic process. The enantioselectivity of this polypeptide is much better than other chiral ligands such as D-menthol, (*R*)-1,1′-bi-2-naphthol, L-diethyltartrate and (*S*)-2,2′-bis(diphenylphosphine)-1,1′-binaphthyl. When low molecular weight poly[(*R*)-leucine] (M~4000) was used, however, a very low *ee* (8%) was obtained for (*S*)-**39**.



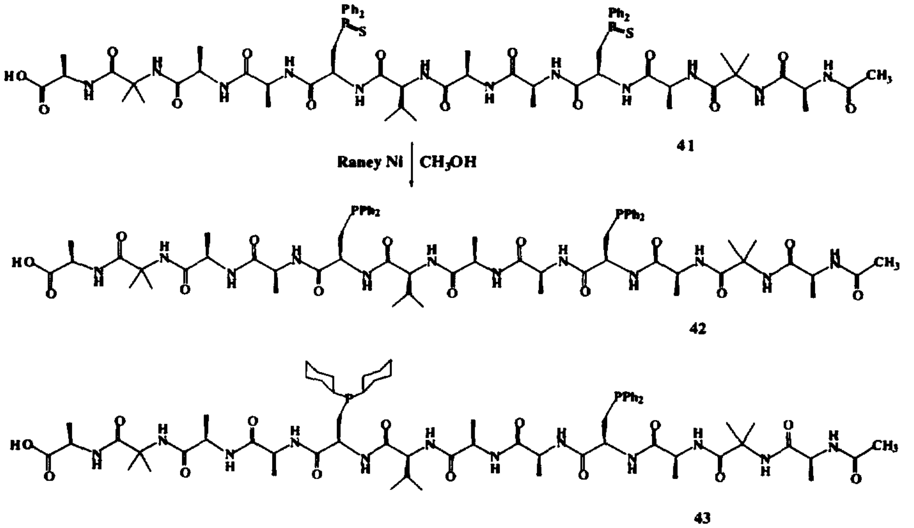
Scheme 6. Asymmetric carbonylation of an allylic alcohol in the presence of poly[(*S*)-leucine]

In 1994, Gilbertson et al. reported the synthesis of phosphine-containing peptides as ligands for transition metals.[25a] From a phosphine sulfide substituted chiral amino acid **40**, a 12-residue peptide **41** that has high α-helical content was obtained via a solid state synthesis (Scheme 7). Treatment of **41** with Raney nickel removed the protecting sulfide functions to give **42**. This peptide was designed in such a way that the two phosphine groups would be on the same side of the α-helical chain of **42** and could act as a chelate ligand to bind one metal center. The reaction of **42** with $RhCl(NBD)^+(ClO_4)^-$ (NBD=norbornadiene) was observed to generate the expected rhodium complex. A peptide **43** that contains two different phosphine ligands was also prepared.[26a] The rhodium complex of **43** was used to catalyze the hydrogenation of methyl 2-acetamidoacrylate (Scheme 8). Although N-acyl alanine methyl ester was obtained in high yield, the ee was very low (8%). A polystyrene bead-bound **43** was also used as the ligand for the rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate. In the presence of this polymer-supported polypeptide catalyst, N-acyl alanine methyl ester was produced in low *ee* (4–9%).[26b]

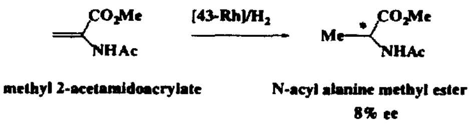


40

FMOC: 9-fluorenylmethyl chloroformate



Scheme 7. Synthesis of phosphine-containing peptides

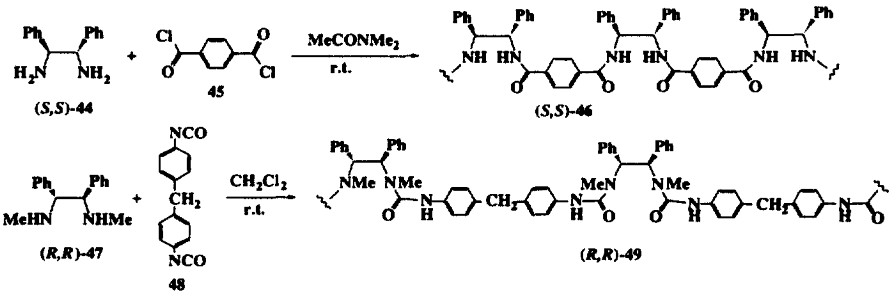


Scheme 8. Hydrogenation catalyzed by the [43-Rh] complex

3. Chiral polymer catalysts containing amide, urea and ester functionality

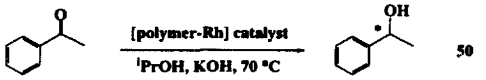
In 1994, Lemaire et al. reported the use of a chiral polyamide and a chiral polyurea for asymmetric reactions.[27] From the condensation polymerization of (*S*,*S*)-**44** with terephthaloyl chloride (**45**), (*S*,*S*)-**46** was obtained (Scheme 9). This polymer is completely insoluble in organic solvents. The condensation of (*R*,*R*)-**47** with bis-(*p*-isocyanatophenyl)methane (**48**) generated (*R*,*R*)-**49**. Unlike (*S*,*S*)-**46**, polymer (*R*,*R*)-**49** can be dissolved in THF and its specific optical rotation is $[\alpha]_D=-314.5$ (c=3.8, THF).

Both of the polymers were used for the catalytic transfer hydrogenation of acetophenone in the presence of $[Rh(C_6H_{10})Cl]_2$ (0.05 equiv., C_6H_{10}=1,5-hexadiene), ^{i}PrOH and KOH (Scheme 10). In this reaction, about 0.1 equiv. of the polymer was used. When the chiral polyamide (*S*,*S*)-**46** was used, the alcohol product (*R*)-**50** was obtained in 28% *ee*. In the presence of the chiral polyurea (*R*,*R*)-**49**, the



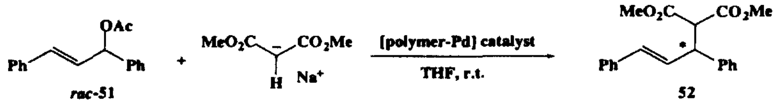
Scheme 9. Synthesis of a chiral polyamide and a chiral polyurea

opposite enantiomeric alcohol (*S*)-**50** was produced in 60% *ee*. Polyurea (*R*,*R*)-**49** showed higher catalytic activity as well as higher enantioselectivity than (*S*,*S*)-**46**. When the monomeric ligand (*S*,*S*)-**47** was used to catalyze the reduction of acetophenone, (*R*)-**50** was obtained in 55% *ee*. Thus, the chiral polyurea (*R*,*R*)-**49** has a slightly increased enantioselectivity over the amine monomer. Compound (*R*,*R*)-**49** also has higher catalytic activity. This polymer was recovered by simple filtration and the twice-recycled polymer exhibited no loss of either catalytic activity or enantioselectivity.



Scheme 10. Asymmetric transfer hydrogenation of acetophenone catalyzed by the chiral polymer catalysts

The use of polymers (*S*,*S*)-**46** and (*R*,*R*)-**49** in an asymmetric nucleophilic allylic substitution was also studied. In the presence of about 0.04 equiv. of bis(dibenzylideneacetonato)palladium and 0.4 equiv. of (*S*,*S*)-**46**, racemic **51** reacted with dimethylmalonate and NaH to give (*R*)-**52** in 80% *ee* and 38% conversion in 2 days (Scheme 11). Under similar conditions, (*R*)-**52** was obtained in 38% *ee* and 72% conversion in the presence of (*R*,*R*)-**49**. The monomer (*S*,*S*)-**47** showed higher catalytic activity and much higher enantioselectivity. It produced (*S*)-**52** with 83% conversion and 95% *ee*.



Scheme 11. Asymmetric allylic nucleophilic substitution catalyzed by the chiral polymer–palladium complexes

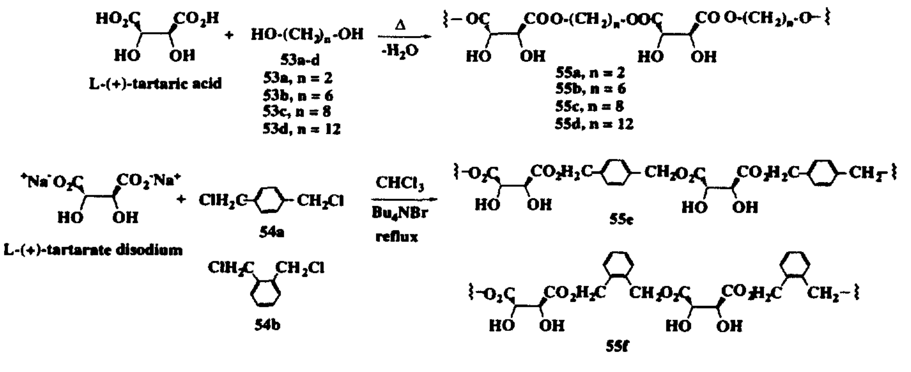
Table 6 summarizes the data of the asymmetric reactions carried out in the presence of the monomer (*S*,*S*)-**47** and the polymers (*S*,*S*)-**46** and (*R*,*R*)-**49**.

In 1997, Canali et al. reported the synthesis of chiral polymers containing tartrate esters in the main chain for the Sharpless epoxidation of allylic alcohols.[28] Polymers **55a–f** were obtained from the polycondensation of L-(+)-tartaric acid or its disodium salt with either the diols **53a–d** or the dichlorides **54a,b** (Scheme 12). All of these polymers are soluble in DMSO. This indicates that cross-linking due to the participation of the secondary hydroxyl groups in the polymerization may not occur. The specific optical rotations of these polymers are in the range of +4 to +25. Polyesters **55a–c** are quite insoluble in methylene chloride but **55d** is soluble in CH_2Cl_2 and THF. The molecular weight of **55d** is M_W=4,200 (PDI=1.7) as measured by GPC in THF relative to polystyrene standards.

The use of the chiral poly(tartaric ester)s **55a–f** in the asymmetric epoxidation of **56** to produce **57** was studied (Scheme 13).[28] Of all of these polymers, **55c** showed the highest enantioselectivity. In the presence of $Ti(O^iPr)_4$ (0.17 equiv.) and *t*-butylhydroperoxide, **55c** (0.2 equiv.) catalyzed the conversion of **56** to **57** in 79% *ee* at −20°C in 7 h. This *ee* is much lower than the monomeric tartrate-based Sharpless epoxidation catalyst which generates **57** in over 98% *ee*. But the enantioselectivity of **55c** is higher than

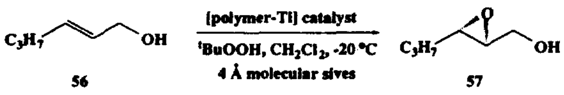
Table 6
The asymmetric reactions in the presence of the monomer (*S*,*S*)-**47** and the polymers (*S*,*S*)-**46** and (*R*,*R*)-**49**

Ligand	Reaction Product	Conversion (%)	Reaction Time (day)	*ee* (%)	Product Configuration
(*S*,*S*)-**47**	**50**	100	3.5	55	R
	52	83	2	95	S
(*S*,*S*)-**46**	**50**	22	7	28	R
	52	38	2	80	R
(*R*,*R*)-**49**	**50**	100	1	60	S
	52	72	2	38	R



Scheme 12. Synthesis of chiral polyesters

the polymeric catalyst made by anchoring a tartrate ester to a polystyrene resin which only produced 50–60% *ee*.[29]



Scheme 13. Asymmetric epoxidation catalyzed by the chiral polyester–Ti(IV) complexes

Under the same conditions, the enantioselectivity increases on going from **55a** to **55b** and **55c**. Although, none of these three polymers is soluble in methylene chloride, **55c** forms a soluble complex with $Ti(O^iPr)_4$. This solubility difference, however, is not the only factor contributing to the different enantioselectivities of these polymers. Polymer **55d** is soluble but shows reduced enantioselectivity compared to **55c**. Therefore, the catalytically active species must not be a simple 1:1 complex of tartrate–Ti(IV) but instead be more complicated. This is consistent with what has been observed in the monomeric tartrate–Ti(IV) catalyst.[30] Polymers **55e** and **55f** were also used for asymmetric epoxidation. Table 7 summarizes the results for the use of the chiral polyesters in the asymmetric epoxidation of **56** to **57**.

Table 7
Asymmetric epoxidation of **56** to **57** in the presence of the chiral polyesters

Ligand	**55a**	**55b**	**55c**	**55d**	**55e**	**55f**
Isolated Yield (%)	50	63	58	61	42	80
ee (%)	8	55	79	64	47	68

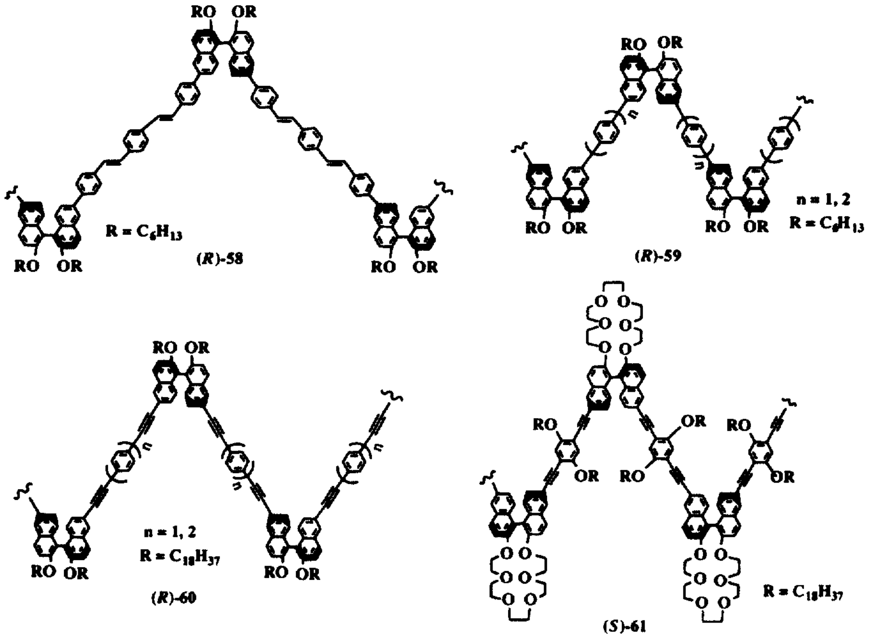
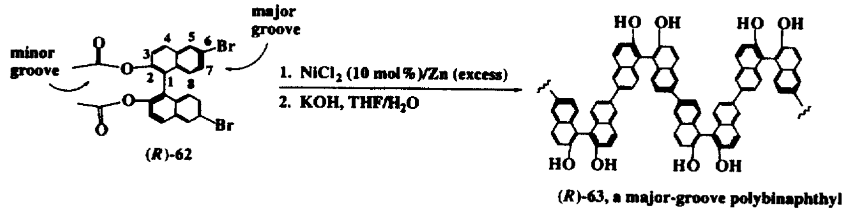


Fig. 3.

4. Chiral polybinaphthyl catalysts

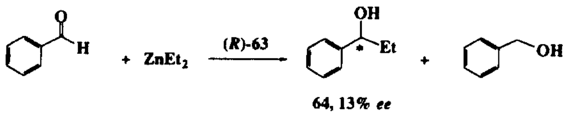
Recently, Pu et al. have used optically active 1,1′-binaphthyls to construct a new class of main chain chiral conjugated polymers.[31–37] For example, the optically active poly(arylenevinylene) (*R*)-**58**,[31a] polyarylenes (*R*)-**59**[31b] and polyaryleneethynylenes (*R*)-**60**[32a] and (*S*)-**61**[32b] were prepared (Fig. 3). These chiral conjugated polymers are potentially useful as novel electrical and optical materials.

The use of the binaphthyl polymers in asymmetric catalysis was also investigated. A binaphthyl monomer (*R*)-**62** was readily prepared from the optically active (*R*)-1,1′-bi-2-naphthol.[38] A rigid and sterically regular chiral polymer (*R*)-**63** was obtained after the polymerization of (*R*)-**62** at the 6,6′-positions in the presence of $NiCl_2/Zn$ followed by hydrolysis (Scheme 14).[39,40] In the helical structure of a 1,1′-binaphthyl molecule, there are major and minor grooves divided by the 1,1′-bond as indicated in Scheme 14 for (*R*)-**62**. Therefore, the polymer obtained from the polymerization at the 6,6′-positions is designated as a 'major-groove' polybinaphthyl and the polymer obtained from the polymerization at the 3,3′-positions is designated as a 'minor-groove' polybinaphthyl. The polymer (*R*)-**63** is a major-groove polybinaphthyl. It is soluble in basic water solutions and DMSO, but it is insoluble in most organic solvents. Its specific optical rotation is $[\alpha]_D = -139.8$ (c=0.5, THF). The polyhydroxyl groups of this polymer allow the introduction of different Lewis acid metal centers to prepare novel polymeric chiral catalysts. In these polymeric complexes, the catalytic sites are expected to be highly organized along the rigid and sterically regular backbone. This is different from most of the polymer-supported catalysts where flexible and sterically irregular polymers are used. The rigidity and stereoregularity of the chiral conjugated binaphthyl polymers makes it possible to systematically adjust the microenvironment of the catalytic sites for the development of enantioselective polymeric catalysts.



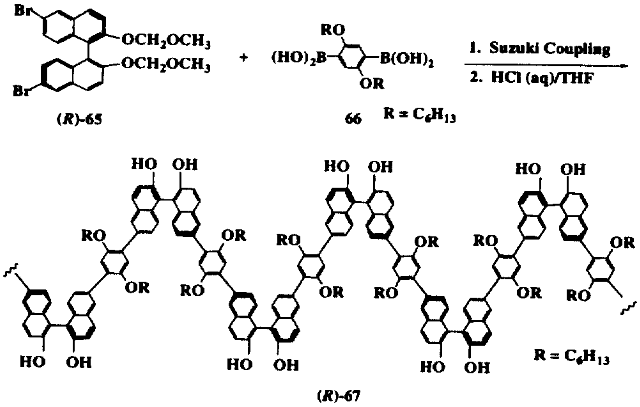
Scheme 14. Synthesis of an optically active major-groove poly(1,1′-bi-2-naphthol) (*R*)-**63**

Polymer (*R*)-**63** was used to catalyze the reaction of benzaldehyde with diethylzinc.[41] At room temperature in methylene chloride solution, the chiral alcohol product **64** and a side product benzylalcohol were obtained in 53:47 ratio (Scheme 15). The *ee* of **64** was 13%.



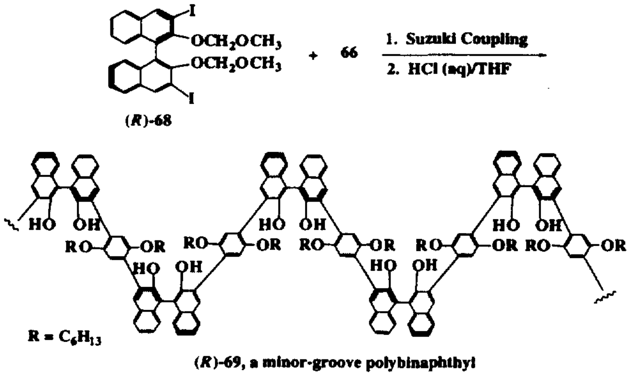
Scheme 15. The reaction of benzaldehyde with diethylzinc catalyzed by (*R*)-**63**

Since the insolubility of (*R*)-**63** may influence its enantioselectivity, a soluble binaphthyl polymer was prepared. Polymer (*R*)-**67** was made from the Suzuki coupling of (*R*)-**65** with **66** followed by hydrolysis (Scheme 16). This polymer is soluble in common organic solvents such as methylene chloride, chloroform and THF due to the flexible hexyloxyl groups in the phenylene spacers. Improved chemical selectivity as well as enantioselectivity were observed when (*R*)-**67** was used to catalyze the reaction of benzaldehyde with diethylzinc. In the presence of (*R*)-**67**, the reaction produced **64** and benzyl alcohol in 71:29 ratio and the *ee* of **64** was 40%.[41]



Scheme 16. Synthesis of a soluble major-groove polybinaphthyl (*R*)-**67**

Both polymers (*R*)-**63** and (*R*)-**67** are the major-groove polymers of (*R*)-1,1′-binaphthyls. To further improve the catalytic properties of the polybinaphthyl catalysts, substituents were introduced to the 3,3′-positions of the binaphthyl units by carrying out the polymerization at the minor groove of a binaphthyl monomer. A minor-groove polymer (*R*)-**69** was obtained from the Suzuki coupling of (*R*)-**68** with **66** followed by hydrolysis (Scheme 17). This polymer was produced in two molecular weights, (*R*)-**69a** [M_W=6,700 (PDI=1.5)] and (*R*)-**69b** [M_W=24,000 (PDI=2.5)], when using either Pd(OAc)$_2$/tris(*o*-tolylphosphine) or Pd(PPh$_3$)$_4$ as the catalyst. Both (*R*)-**69a** and (*R*)-**69b** are soluble in common organic solvents.



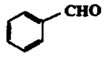
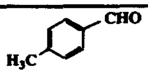
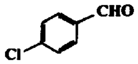
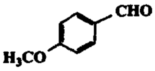
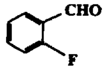
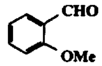
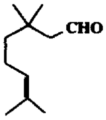
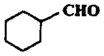
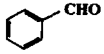
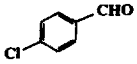
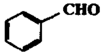
Scheme 17. Synthesis of a minor-groove polybinaphthyl (*R*)-**69**

(*R*)-**69a** induced excellent enantioselectivity in the reaction of benzaldehyde with diethylzinc.[41] In the presence of 5 mol% of (*R*)-**69a**, (*R*)-**64** was produced in 92% *ee* at 0°C in toluene solution. No side product was observed. This polymer was used to catalyze the reaction of different aldehydes with diethylzinc and the results are summarized in Table 8. As shown in the table, high enantioselectivity was observed for the reaction of *para*-substituted benzaldehydes and cinnamaldehyde. But the enantioselectivity for the *ortho*-substituted benzaldehydes was low. The polymer was easily recovered by precipitation with methanol and the recovered polymer showed the same enantioselectivity as the original polymer. The high molecular weight polymer (*R*)-**69b** exhibited the same catalytic property as (*R*)-**69a**. This demonstrates that the polybinaphthyl-catalyzed asymmetric reaction is independent of both the method of the polymer preparation and the molecular weight of the polymer, an excellent property for practical applications. (*S*)-**69** was also synthesized to catalyze the reaction of benzaldehyde with diethylzinc which generated (*S*)-**64** in 93% *ee*.

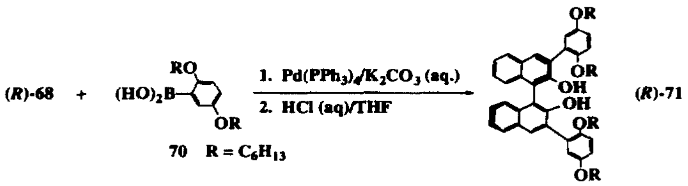
(*R*)-**71** was prepared as the monomeric model compound of (*R*)-**69a** from the Suzuki coupling of (*R*)-**68** with **70** followed by hydrolysis (Scheme 18).[42] (*R*)-**71** was found to be the best enantioselective catalyst yet reported for the reaction of aldehydes with diethylzinc. Table 9 summarizes the results for the use of (*R*)-**71**. As shown in the table, a very broad range of aldehydes, including *para*-, *ortho*- or *meta*-substituted aromatic aldehydes, linear or branched aliphatic aldehydes, and aryl or alkyl substituted α,β-unsaturated aldehydes, can be alkylated in excellent enantioselectivity. Although over a dozen enantioselective catalysts for the reaction of aldehydes with diethylzinc have been reported in the past decade, most of them are either specific for certain types of aldehydes or they require the use of a stoichiometric amount of titanium(IV) complexes.[43–45]

In comparison with the polybinaphthyl catalyst (*R*)-**69**, (*R*)-**71** shows greatly enhanced enantioselectivity especially for *ortho*-substituted benzaldehdyes and aliphatic aldehydes. We attribute this different catalytic property to structural differences between the monomer and the polymer. When (*R*)-**69** was treated with diethylzinc, a polymeric zinc complex like (*R*)-**72** may be produced. (*R*)-**73** is a possible structure of the zinc complex generated from the reaction of (*R*)-**71** with diethylzinc. These zinc complexes are probably the catalytically active species in the reaction of diethylzinc with aldehydes. In (*R*)-**72**, the *p*-dialkoxy phenylene linker acts as a dual ligand to coordinate to the zinc centers for both

Table 8
The asymmetric reaction of aldehydes with diethylzinc in the presence of the polybinaphthol (*R*)-**69**

Catalyst	Aldehyde	Solvent	Isolated Yield (%)	*ee* (%)
(*R*)-**69a**		toluene	89	92
		toluene	91	92[a]
		THF	70	85
		hexane:toluene (2:1)	92	92
		toluene	90	93[a]
		toluene	94	93[a]
		toluene	84	88[a]
		toluene	86	35[a]
		toluene	90	59[a]
		toluene	86	90[a]
		toluene	67	83[a]
	n-$C_8H_{17}CHO$	toluene	89	74
		toluene	70	83[a]
	n-$C_5H_{11}CHO$	toluene	65	74[a]
(*R*)-**69b**		toluene	90	93
		toluene	95	94
(*S*)-**69**		toluene	94	93

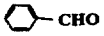
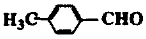
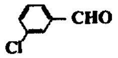
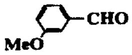
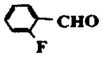
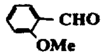
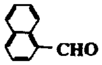
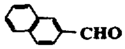
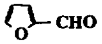
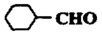
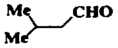
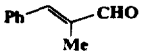
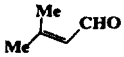
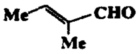
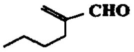
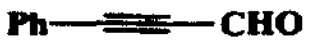
a. The recycled polymer was used.

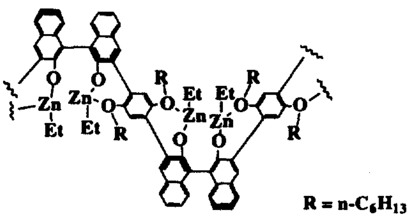


Scheme 18. Synthesis of a monobinaphthyl (*R*)-**71**

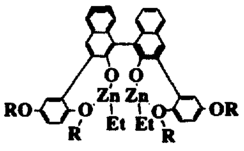
of the adjacent binaphthyl units. This makes the steric and electronic environment of the catalytic sites of the polymer very different from that in the monomer which would lead to the observed differences in stereoselectivity.

Table 9
The reaction of aldehydes with diethylzinc catalyzed by (*R*)-**71**

Aldehyde	Isolated Yield (%)	*ee* (%)
	95	>99
	91	98
	92	97
	96	>99
	97	98
	95	99
	93	94
	90	94
	92	>99
	94	99
	90	91
n-$C_5H_{11}CHO$	89	98
n-$C_6H_{13}CHO$	86	98
n-$C_8H_{17}CHO$	91	98
	90	98
	73	98
	91	92
	86	98
	66	91
	62	93
	64	97
	90	98
	90	93

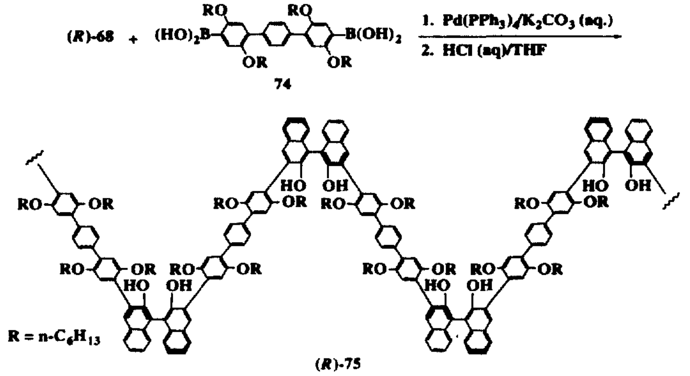


(*R*)-**72**



(*R*)-**73**

In order to improve the enantioselectivity of the polybinaphthyl catalyst, (*R*)-**75** was synthesized by the Suzuki coupling of (*R*)-**68** with **74** followed by hydrolysis (Scheme 19).[46] In (*R*)-**75**, a terphenylene spacer was introduced which makes the catalytic site of this polymer more closely resemble that of the monomer (*R*)-**71**. When (*R*)-**75** was used to catalyze the reaction of aldehydes, it showed excellent enantioselectivity over a very broad range of aldehydes (Table 10). Most of these reactions were carried out in toluene solution at 0°C in the presence of 5 mol% of (*R*)-**75**. After aqueous work-up, addition of excess methanol to the methylene chloride solution of the product mixture precipitated out the polymer. The recovered polymer showed the same enantioselectivity as the original polymer. The results in Table 10 demonstrate that (*R*)-**75** is the best polymeric catalyst yet reported for the enantioselective reaction of aldehydes with diethylzinc.



Scheme 19. Synthesis of (*R*)-**75**

Through systematic design and study of polymers (*R*)-**63**, (*R*)-**67**, (*R*)-**69** and (*R*)-**75**, a highly enantioselective polymeric catalyst system has been obtained. This example demonstrates that the systematic modification of rigid and sterically regular polymers is potentially a very powerful tool in the development of polymeric catalysts for asymmetric synthesis.

5. Summary

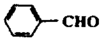
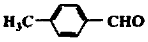
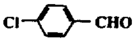
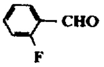
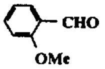
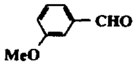
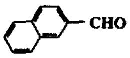
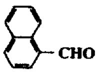
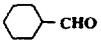
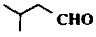
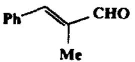
Three classes of synthetic main chain chiral polymers have been applied in asymmetric catalysis, including: (1) helical polymers represented by polypeptides; (2) polymers with flexible chiral chains such as polyesters and polyamides; and (3) polymers of rigid and sterically regular chiral chains represented by chiral conjugated polybinaphthyls.

Synthetic polypeptides such as **2′** have shown high enantioselectivity in asymmetric epoxidation. The helical conformation of these polymers is found to be important for their catalytic activity and stereoselectivity. However, unlike all other polymer-supported catalysts, these polypeptide catalysts do not have ligand-defined catalytic sites and their catalytic processes are much less understood. The phosphine-containing peptides such as **43** represent a new class of poly(amino acid) ligands. These ligands have defined coordination sites for transition metals and their rhodium complexes are found to be active in catalytic hydrogenation. Although high enantioseletivity has not yet been achieved, this peptide-based novel catalyst system certainly is worth pursuing further.

Similar to the traditional polymeric chiral catalysts that are prepared by anchoring monomeric catalysts to flexible polymer chains, the second type of main chain chiral polymers do not have well-defined macromolecular structure. It is therefore difficult to study the structure and reactivity relationship of these polymers.

Because of the rigidity and stereoregularity of polybinaphthyls such as (*R*)-**63**, these materials have a much better defined microenvironment. As shown in the polybinaphthyl-catalyzed enantioselective

Table 10
Asymmetric reaction of aldehydes with diethylzinc catalyzed by polymer (*R*)-**75**

Aldehyde	Isolated Yield (%)	*ee* (%)
	92	98
	90	98[a]
	90	98
	94	98
	89	97
	88	91
	90	93
	93	98
	95	96
	93	98
n-$C_5H_{11}CHO$	71	98
n-$C_7H_{15}CHO$	85	97
n-$C_8H_{17}CHO$	88	97
	81	98
	65	98
	93	92
	92	97

a. Recycled polymer.

reaction of aldehydes with diethylzinc, the structure of these polymers can be *systematically* modified to achieve the desired catalytic activity and stereoselectivity. This strategy may have general applications in the development of enantioselective polymer catalysts.

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