Recent Advances in Asymmetric C–C and C-Heteroatom Bond Forming Reactions using Polymer-Bound Catalysts

Stefan Bräse,[a,*] Frank Lauterwasser,[b] Robert E. Ziegert[b]

[a] Institut für Organische Chemie, Universität Karlsruhe (TH), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
Fax: (+49)-721-608-8581, e-mail: braese@ioc.uka.de
[b] Kekulé-Institut für Organische Chemie und Biochemie der Rheinischen Friedrich-Wilhelms-Universität Bonn, Gerhard-Domagk-Strasse 1, 53121 Bonn, Germany
Fax: (+49)-228-739608

Received: October 3, 2002; Received Revised: April 26, 2003; Accepted: May 8, 2003

Dedicated to Professor Dieter Seebach for his achievements in asymmetric catalysis.

Abstract: The synthesis of enantiomerically pure compounds is one of the major challenges in organic synthesis. In this review, we present the state of the art in asymmetric catalysis using immobilized chiral ligands and complexes for asymmetric C–C and C-heteroatom bond forming reactions. Chiral catalysts based on dendrimers and soluble polymeric supports are considered. In particular, addition reactions to carbon-carbon double bonds, asymmetric 1,2-addition reactions using, e.g., dialkylzinc reagents, metal-catalyzed substitution reactions and cycloaddition reactions are covered. Specific emphasis is placed on enantioselective epoxidation and aldol reactions. A further aspect is the (hetero) Diels–Alder reaction catalyzed by immobilized ligands.

Keywords: asymmetric catalysis; combinatorial catalysis; enantioselectivity; green chemistry; immobilization; metal complexes; polymers; solid-phase synthesis

Abbreviations

Ac: acetyl; acac: acetylacetonate; AD: asymmetric dihydroxylation; AIBN: 2,2′-azobisisobutyronitrile; ALB: AlLi-bis(binaphthoxide); Ar: arene; BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; BINAPHOS: 4-(2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-yloxy)-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]-dinaphthalene; BINOL: 1,1′-bis-2,2′-naphthol; Bn: benzyl; BPPM: 2-diphenylphosphinomethyl-4-diphenylphosphino-1-*t*-butoxycarbonylpyrrolidine; box: bis(oxazoline); Bz: benzoyl; config.: configuration; CM: olefin cross metathesis; conv.: conversion; CPG: controlled-pore glass; Cy: cyclohexyl; de: diastereomeric excess; CHP: cumene hydroperoxide; DET: diethyl tartrate; DHQ: hydroquinine; DHQD: hydroquinidine; DIAB: 3-dimethylamino-7,7-dimethylbicyclo-[2.2.1]heptan-2-ol; DIC: *N*,*N*′-diisopropylcarbodiimide; DIOP: 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphinobutane); DIPEA: diisopropylethylamine; DIPHOL: dibenzophosphole; DIPT: diisopropyl tartrate; DMAP: 4-dimethylaminopyridine; DMF: dimethylformamide; DMSO: dimethyl sulfoxide; dodec: 1-dodecanol; ee: enantiomeric excess;

 DOI: 10.1002/adsc.200202164

equiv.: equivalents; GC: gas chromatography; H_2Por*: 5,10,15,20-tetrakis-[(1*S*,4*R*,5*R*,8*S*)-1,2,3,4,5,6,7,8-octahydro-1,2:5,8-dimethanoanthrance-9-yl]porphyrin; hfc: 3-(hexafluoropropylhydroxymethylene) (+)-camphorate; HKR: hydrolytic kinetic resolution; HPLC: high pressure liquid chromatography; JOSIPHOS: (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine; L-Ala: L-alanine; LDH: layer double hydroxides; MC: microencapsulated; MCPBA: *m*-chloroperbenzoic acid; Mes: mesityl; MOP: (2′-methyl-[1,1′]binaphthalenyl-2-yl)diphenylphosphane; MS: molecular sieve; NCPS: non-cross-linked polystyrene; NMDA: *N*-methyl-D-aspartate; NMO: *N*-methylmorpholine oxide; NpH: neopentane; Nu: nucleophile; p-cym: *p*-cymene; PDMS: polydimethylsiloxane; PEG: polyethylene glycol; PEM: phenoxyethoxymethyl; PHAL: 1,4-phthalazindiyl diether; Phanephos: 13,15-bis(diphenylphos;phanyl)tricyclo[8.2.2.2^{4,7}]hexadeca-1(13),4(16),5,7(15),10(14),11-hexane; PMP: 4-methoxyphenyl; Por: porphyrin; 4-PPNO: 4-phenylpyridine *N*-oxide; *p*TsOH: *para*-toluenesulfonic acid; py: pyridine; RCM: ring closing olefin metathesis; ROM: ring opening olefin metathesis; ROMP: ring opening olefin metathesis polymerization; rt: room temperature; SPOS: solid-phase organic synthesis; TADDOL: α,α,α′,α′-tetraphenyl-1,3-dioxolan-4,5-dimethanol; TBHP: *tert*-butyl hydroperoxide; TBSP: [1-(4-*tert*-butylbenzene-sulfonyl)-pyrrolidin-2-yl]methanediol; Tf: trifluoromethylsulfonyl; TFA: trifluoroacetic acid; TFAA: trifluoroacetic acid anhydride; THF: tetrahydrofuran; TIPS: triisopropylsilyl; TISP: (5*R*,5′*R*)-5,5′-(1,3-phenylene)-bis[1-[2,4,6-tris(1-methylethyl)phenyl]sulfonyl]-L-proline; tmp: tetramethylpiperidine; TMS: trimethylsilyl; Ts: tosyl

Stefan Bräse (center) was born in Kiel, Germany in 1967. He studied at the Universities of Göttingen, Bangor (UK) and Marseille (F) and received his Ph. D. in 1995, after working with Armin de Meijere in Göttingen. After post-doctoral appointments at Uppsala University (Jan E. Bäckvall) and The Scripps Research Institute (K. C. Nicolaou) as a DAAD fellow, he began his independent research career at the RWTH Aachen in 1997. In June 2001, he finished his Habilitation and moved to the University of Bonn as a Professor of Chemistry. Recently, he moved to the University of Karlsruhe as a full Professor. He is recipient of the OrChem prize of the Gesellschaft Deutscher Chemiker (2000) and the Lilly Lecture Award (2001). In 2002, he was a visiting professor at the University of Wisconsin, Madison, USA. His research interests include asymmetric metal-catalyzed processes and combinatorial chemistry towards the synthesis of biologically active compounds.

Robert E. Ziegert (left) was born in Berlin, Germany in 1973. He studied at the University of Dortmund where he received his degree in 2001 in the group of B. Schmidt. Currently, he is a Ph. D. student at the University of Bonn in the group of S. Bräse. His research topics are studies on the asymmetric opening of bicyclic *endo*-peroxides, asymmetric 1,2-addition reaction on solid support and spectroscopic studies on diethylzinc/paracyclophane based *N,O*-ligand complexes.

Frank Lauterwasser (right) was born in Andernach, Germany in 1975. He studied at the Universities of Aachen and York (UK). He received his degree in 2001 in the group of Prof. Dr. D. Enders and is currently a Ph. D. student with S. Bräse at the University of Bonn. His current research interest is focused on the development of new chiral *N,O*-ligands for asymmetric metal-catalyzed processes and their immobilization on solid supports.

1 Introduction

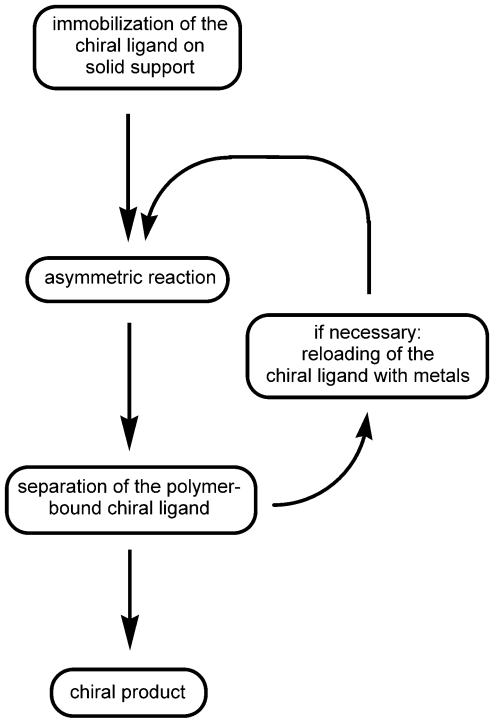
The synthesis of enantiomerically pure compounds is one of the major challenges in organic synthesis. Based on the first ideas in the field of the asymmetric catalysis using transition complexes by Knowles,[1] Kagan[2] and others, organic chemists are now able to conduct various transformations in a stereocontrolled, enantioselective and atom-economic manner using asymmetric transition-metal catalysis. The importance of this field of chemistry was underlined by the granting of the Nobel Price in chemistry in 2001 to Dr. Knowles, Prof. Noyori and Prof. Sharpless for their contributions in enantioselective synthesis.[3]

Since the use of enantiopure compounds as pharmaceuticals and agrochemicals has emerged over the recent years, there is an ongoing interest for the asymmetric synthesis of this kind of compound. For pharmaceuticals, the enantiomeric excess should be over 99% ee and the metal residue under 10 ppm, whereas for agrochemicals 80% enantiomeric purity is generally sufficient. The class of enantiomerically pure compounds is very interesting to industry, in the year 2000 the global sales reached 123 billion US $.[4] However, asymmetric catalysis strongly relies on the access to efficient, selective and readily available catalysts which are based in general on enantiomerically pure ligands and transition metals. Since these are valuable materials, the current trend in asymmetric catalysis focuses on low catalyst loading and/or reuse of the catalyst. Since homogeneous catalysts have been found to be more efficient in asymmetric catalysis than their heterogeneous counterparts, the immobilization of homogeneous catalysts is of great interest.[5] Polymer-bound chiral ligands, which enable the asymmetric synthesis of chiral compounds, have received increasing interest within the last decades. The use of polymer-bound chiral ligands offers the whole advantages of solid phase organic synthesis (SPOS).

The desired product can be isolated and purified by simple filtration in the case of polymer-bound chiral ligands or by precipitation in the case of using soluble polymeric or dendritic chiral ligands. After separation from the reaction mixture, the valuable chiral ligands could easily be recovered and directly be reused for further syntheses (Scheme 1). With these easy purification techniques, in contrast to tedious column chromatographic purification, it is possible to save time, solvents, column material and certainly money. In addition, polymer-bound chiral ligands can be integrated into continuous flow systems.

Many of these advantages support the ideas of green chemistry to protect the environment and save valuable feedstocks.[6]

Since the immobilized ligand systems can be synthesized in principle on solid supports by means of solid phase organic synthesis, combinatorial chemistry/parallel synthesis allows the synthesis and screening of new chiral ligands in a straightforward and fast mode.[7]



Scheme 1. Recycling scheme for a polymer-supported chiral ligand.

However, there are some drawbacks associated with the use of immobilized homogeneous ligands and catalysts. One of the problems of the polymer-bound chiral ligands is the leaching of the central metal. This problem has been found in various applications and can be solved at least in some cases by reloading of the ligand with the central metal to render the polymer-bound chiral catalyst reusable. However, the major problem using immobilization is the decrease of activity and selectivity of the catalyst after its reuse. Nowadays, this problem is more or less solved for various systems. There are examples where the same catalyst can be reused over 20 times without or with only slight loss of activity and selectivity. It is important to note, however, that not every system or catalysis effective in homogeneous solution can directly be transferred to the immobilized case. The key issues to be addressed are solvents, conditions and mostly the support being used.

1.1 Types of Support

Two principle supports have been used for the immobilization of homogeneous catalysts organic (polymeric) and inorganic supports. The inorganic supports are generally inert porous structures with highly specific surface areas. In most cases, amorphous oxides like

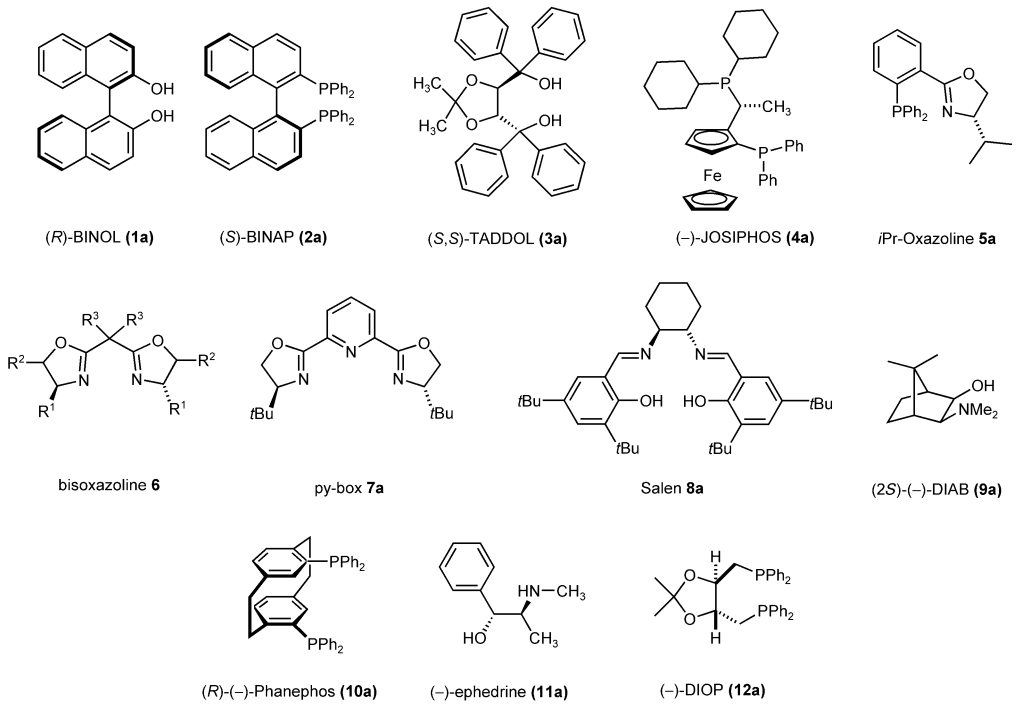


Figure 1. A selection of lead structures for chiral ligands.[21]

silica, alumina, zirconia and zinc oxide are used. There is the opportunity to synthesize a variation in pore size, pore distribution and particle size.[8,9]

Zeolites are also often used supports for the immobilization of chiral catalysts. The zeolites are crystalline materials with well-defined pores and channels in the micropore range.[10,11] An advantage of the silica support is the impossibility to swell in the solvents. This allows conducting the reactions at lower or higher temperatures, higher pressure[12] and the use in continuous flow reactions. Another advantage is the loading of the chiral ligand on the surface of the silica support, which results in high reactivity.

The organic supports used for immobilization are generally soluble or insoluble polymer resins or dendrimers.[13–16] Wandrey, Kragl and Liese et al. have introduced the term "chemzymes" to express the combination of chemical and enzymatic approaches resulting in soluble immobilized catalysts.[17] There are different strategies to separate catalysts and ligands immobilized on soluble polymers. For example, solid/liquid separation, water-soluble polymers,[18] thermally reversible solubility,[19] biphasic systems[20] have been used. To separate soluble immobilized catalysts Wandrey, Kragl and Liese et al. developed ultrafiltration membranes to be applied in a chemzyme membrane reactor (CMR).[17]

The most commonly used organic polymer resin is a divinylbenzene cross-linked polystyrene resin, which is insoluble in the solvents used for catalysis. These kinds of supports are able to swell in some organic solvents increasing their inner surface. Therefore, the catalytic activity is significantly enhanced. The recycling and reuse of insoluble organic polymer resins are easily performed by filtration techniques. Soluble organic polymer and dendritic chiral ligands could be recovered by precipitation. In general, their catalytic activity is higher compared to solid-bound catalysts.

1.2 Types of Chiral Ligands

Most used chiral ligands, which were immobilized, are based on the well-established key ligands as presented in Figure 1.

In particular, BINOL ligands **1**,[22–29] TADDOL ligands **3**,[30–33] bisoxazoline ligands **6**,[34–44] salen ligands **8**[45–51] and others (Figure 1) rank to the most important backbones of chiral catalysts for liquid phase synthesis and have successfully been used as chiral backbones for solid-bound catalysts. These types are well known chiral ligands with numerous variations of substituents, which form complexes with a variety of metals. These systems have been used in a large number of asymmetric reactions, and as a consequence, the development of efficient methods to immobilize these types of chiral ligands will open the way to the preparation of chiral heterogeneous catalysts for those enantioselective reactions.

2 Addition Reactions to Carbon-Carbon Double Bonds

2.1 Epoxidation Reactions

The symmetric and asymmetric epoxidation reactions of alkenes are well known in the synthesis of epoxides and diols on laboratory and industrial scales.[52] The epoxidation is therefore one of the most important oxidation reactions in organic synthesis resulting in a high interest in the immobilization of enantioselective epoxidation catalysts.[53] In 1998, Abbenhuis et al. reported the immobilization of the titanium(IV)-silsesquioxane complex **13** known as an active and durably epoxidation catalyst in solution.[54] Abbenhuis et al. succeeded to immobilize this Ti-complex on MCM-41-molecular sieve by employing the strong adsorption in the MCM-41-channels.

In 1999, Jacobs et al. published the synthesis and first applications of a solid-supported heterogeneous manganese complex **14**,[55] which transfers activated oxygen (X in Figure 2). However, these two solid-supported epoxidation catalysts are not chiral, so that they are not used for asymmetric synthesis.

Around ten years ago, Jacobsen et al. reported chiral manganese salen complexes as superior catalysts for the asymmetric epoxidation of *cis*-substituted alkenes.[56] Since then, chiral salen ligands play a pivotal role in modern oxidation reactions.[45] In 1995 Sivaram, Dhal et al. published the first polymer-bound optically active manganese(III)-salen complex **15** (Figure 3).[46]

The immobilized salen complex **15** (Figure 3) has been used in epoxidation reactions with enantioselectivities on a mediocre level (ee up to 30%).

One year later, Salvadori et al. synthesized a polymer-bound (salen)manganese complex **16** for asymmetric epoxidation reactions.[47] The polymeric catalysts *poly*-**16a – c** were synthesized by radical copolymerization of the monomeric species **16a – c** with styrene and divinylbenzene (ratio 10:75:15) (Figure 4).

In comparison with complexes **15**, an increase in reactivity and selectivity was established using the manganese-salen complexes *poly*-**16a – c**. They were used in epoxidation reactions of several unfunctionalized acyclic and cyclic olefins with MCPBA/NMO as final oxidants. The enantioselectivity of the catalysts is increased in the sequence *poly*-**16a – c**. The selectivities obtained using terminal alkenes like styrene were not as good as when using disubstituted *cis*-olefins. By using cyclic olefins, the enantioselectivities were only slightly lower than with *cis*-β-methylstyrene (ee up to 60%).

In both cases, Sivaram, Dhal et al.[46] and Salvadori et al.,[47] showed that the structural or conformational changes caused by immobilization of the Mn(III)-salen complex may result in the low selectivity. Janssen et al. immobilized a dimeric Mn(III)-salen complex on a

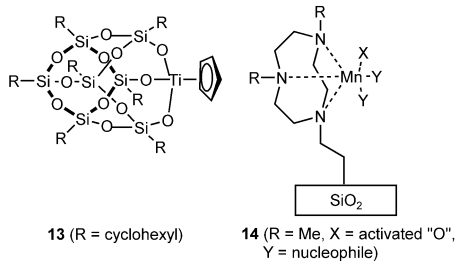


Figure 2. Titanium(IV)-silsesquioxane complex **13** of Abbenhuis et al.[54] and solid-supported complex **14** of Jacobs et al.[55]

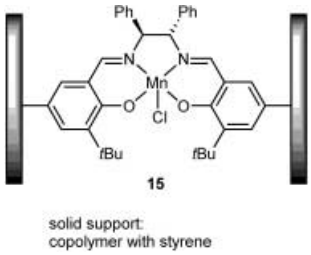


Figure 3. First polymer-supported Jacobsen catalyst **15** of Sivaram, Dhal et al.[46]

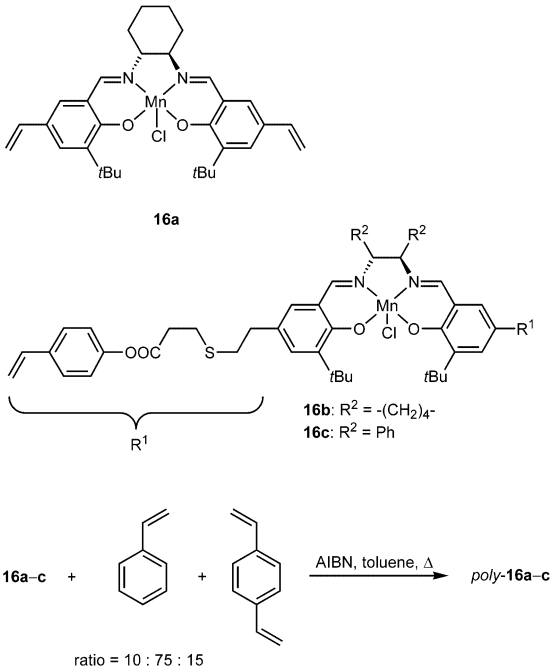
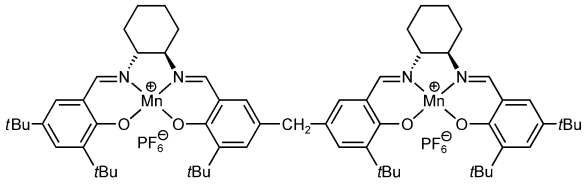


Figure 4. Monomeric and polymeric catalysts **16a – c** and *poly*-**16a – c** prepared by Salvadori et al.[47]

polydimethylsiloxane (PDMS) membrane.[57] The monomer of this Mn(III)-salen complex on a PDMS membrane support was as less active as the polymer-supported catalysts of Sivaram, Dhal et al. and Salvadori et al.[58] The dimeric complex **17** (Figure 5) was included in a PDMS membrane by adding the complex to the synthesis mixture of the membrane. The catalytic



17

Figure 5. Dimeric Mn(III)-salen complex **17** prepared by Janssen et al.[57,58]

activity of the dimer included in the membrane was investigated by a rapid screening reaction with *trans*-β-methylstyrene in a batch reactor with the catalytic membrane cut into 3 – 4 mm pieces. Yields and enantioselectivities were around 20% and 20% ee, respectively.

Since 2000, various immobilized Jacobsen catalysts reaching enantioselectivities of 50% ee and higher were published. A chiral salen complex supported by Mn-exchanged Al-MCM-41 was synthesized by Hutchings et al. and used in epoxidation reactions of (*Z*)-stilbene with yields up to 86% and an enantiomeric excess up to 78% ee.[59]

A polystyrene and polymethacrylate resin-supported Jacobsen catalyst **18** was reported by Sherrington et al.[48] The difference of polymer **18** to comparable systems like resin **15** is the defined structure and morphology of **18**. While Sivaram, Dhal et al. synthesized the catalysts by radical copolymerization. Sherrington et al. generated the catalytic species on the resin. This guaranteed that the reactive center within the complex **18** does not loose activity under the reaction conditions used for the preparation of the resin.

The activity and enantioselectivity of the catalysts **18a – e** (Figure 6) were examined by epoxidation of different aromatic olefins like 1,2-dihydronaphthalene, indene or 1-phenyl-3,4-dihydronaphthalene using standard conditions reported for the soluble Jacobsen catalyst.[60] The enantioselectivities were up to 92% ee (yield up to 90%). Temperature effects, catalyst

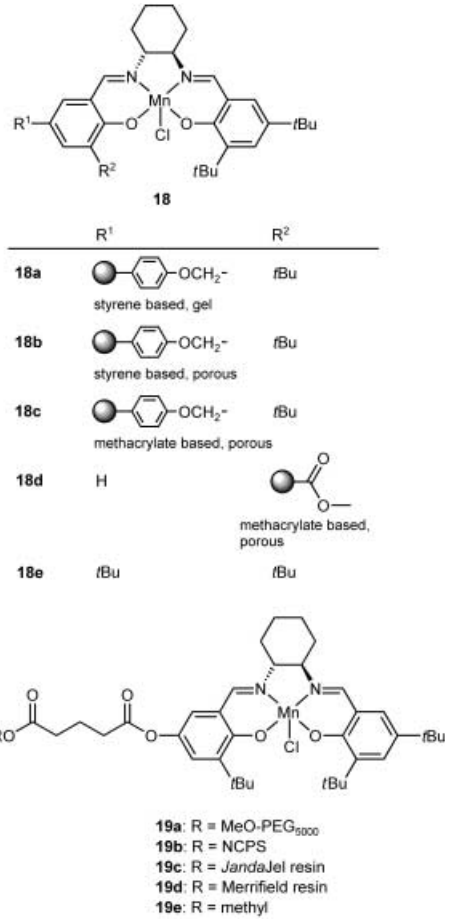


Figure 6. Polystyrene and polymethacrylate based polymer-supported Jacobsen catalysts **18a – e** by Sherrington et al.[48] and **19a – e** by Reger and Janda.[61]

amounts, recycling and stability of the complexes **18a – e** were also examined.[48b]

In 2000, Reger and Janda compared the catalytic activity of both soluble and insoluble polymer-supported Mn-salen complexes in asymmetric epoxidation

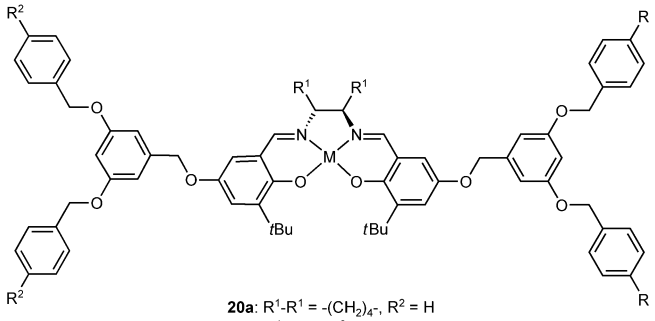
Table 1. Epoxidation reactions catalyzed by different Mn-salen catalysts by Reger and Janda.[61]

	Styrene		*cis*-β-Methylstyrene		Dihydronaphthalene	
Catalyst[a]	ee [%][b]	Yield [%][c]	ee [%][d]	Yield [%][c]	ee [%][b]	Yield [%][c]
18e	57	84	88	82	85	80
19a	52	82	88	79	76	70
19b	51	76	90	79	73	69
19c	51	81	88	77	79	71
19d	35	61	86	75	78	69
19e	52	82	87	80	84	75

[a] Reaction conditions: MCPBA (2 equiv.), NMO (5 equiv.), catalyst (4 mol %), 0 °C.
[b] Enantiomeric excess determined by ^{1}H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$.
[c] Isolated yield.
[d] The enantiomeric excess of the *cis*-epoxide as determined by GC analysis using Chiraldex G-TA chiral column.

reactions.[61] The complex **18e** (Figure 5) and the catalysts shown in Figure 20 and Table 1 were examined for epoxidation reactions of styrene, *cis*-methylstyrene and dihydronaphthalene with MCPBA.

Catalyst loadings of **19c** ranging from 0.70–0.75 mmol/g causing constant enantioselectivies of 51% (styrene) and 88% (methylstyrene) were observed. The recycling of the catalysts gave moderate yields, while the selectivity decreases after the second run.

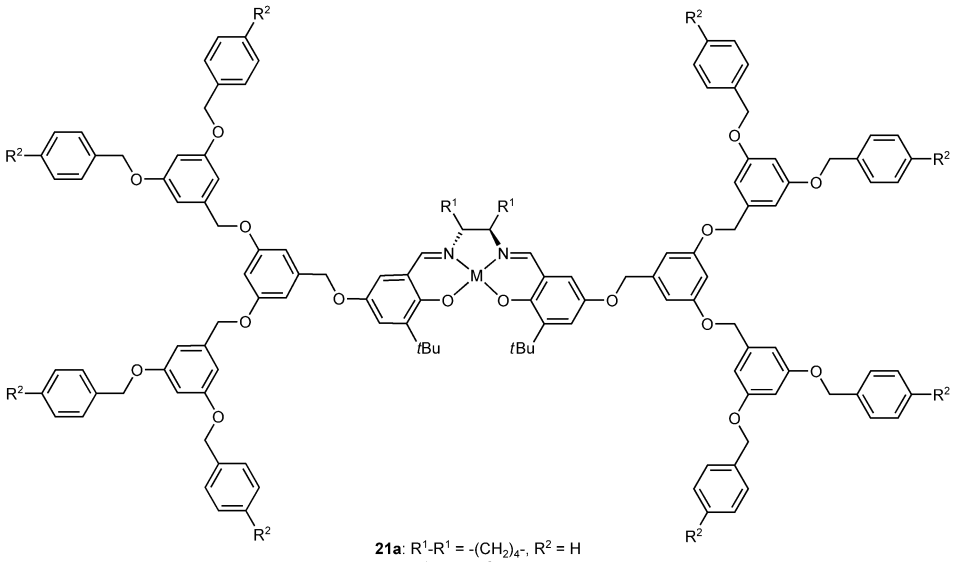


20a: R^1-R^1 = -$(CH_2)_4$-, R^2 = H
20b: R^1 = Ph, R^2 = H
20c: R^1-R^1 = -$(CH_2)_4$-, R^2 = vinyl
20d: R^1 = Ph, R^2 = vinyl

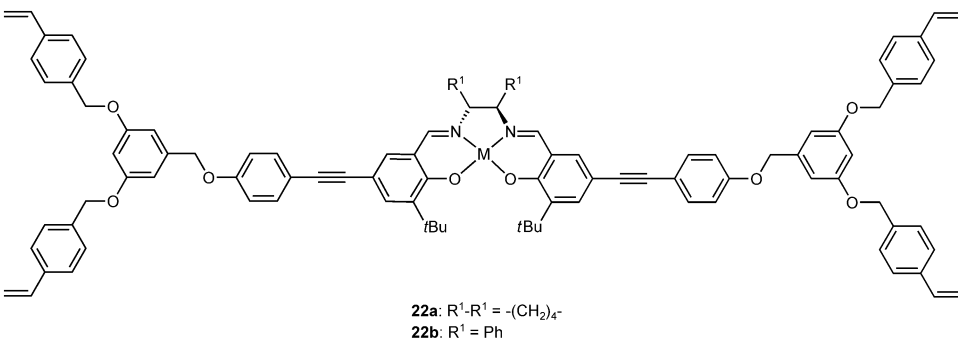
Recently, Seebach et al. prepared dendritic and non-dendritic styryl-substituted Mn- and Cr-salen complexes **20–22** for multiple use in enantioselective epoxidation and also in hetero Diels–Alder reactions (Figure 7).[49]

The enantioselectivities and conversions obtained in the epoxidation of various olefins mediated by the Mn-salen complexes **20–22** are comparable with the results found in homogeneous reactions (conversions up to $>99\%$ and selectivities up to 84% ee). The recycling of the catalysts was also examined. A small decrease of selectivity by using the dendritic catalysts **22** after 10 times of reuse was examined. The selectivities after ten reactions with catalyst **20c** (decrease of selectivity by 10%) and catalyst **20d** (decrease of selectivity by 30%) were moderate.

Very recently, Seebach and Heckel prepared another immobilized salen complex on silica gel by a grafting reaction in the presence of AIBN in chloroform (Scheme 2).[50] The active solid-supported Mn-salen complexes were synthesized by treatment with $Mn(OAc)_2$, oxygen and LiCl. The silica gel-supported salen complex **24a–m** has also being used in enantioselective epoxidation reactions of styrene.[50] The enan-

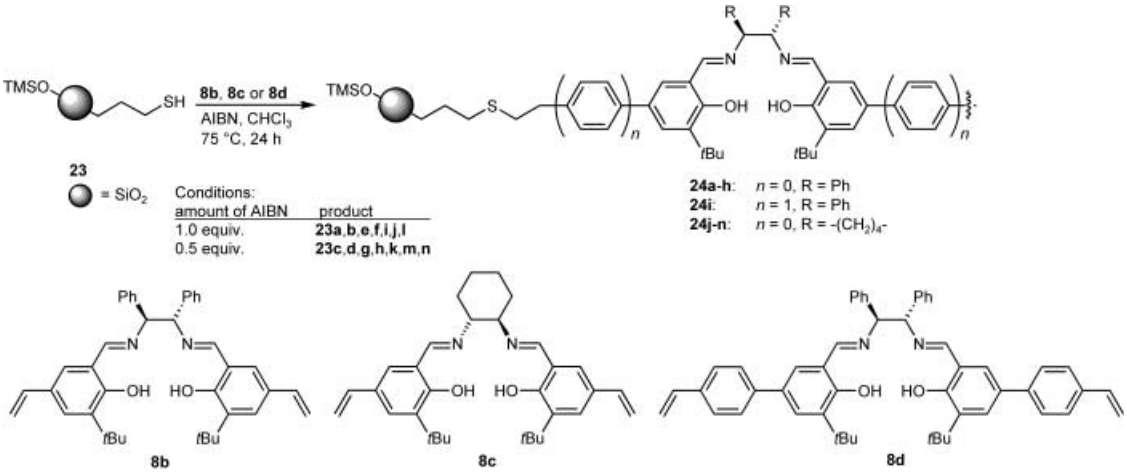


21a: R^1-R^1 = -$(CH_2)_4$-, R^2 = H
21b: R^1 = Ph, R^2 = H
21c: R^1-R^1 = -$(CH_2)_4$-, R^2 = vinyl
21d: R^1 = Ph, R^2 = vinyl



22a: R^1-R^1 = -$(CH_2)_4$-
22b: R^1 = Ph

Figure 7. Dendritic Mn- and Cr-salen complexes **20–22** (M = Mn or Cr) by Seebach et al.[49]



Scheme 2. Preparation of silica gel-supported salen complexes **24a – n** by Seebach et al.[50]

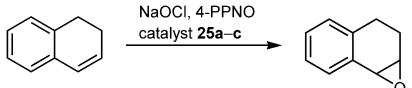
Figure 8. Soluble and polymer-bound Katsuki-type Mn-salen complexes **25a – c** by Smith and Liu.[51]

tioselectivities and yields were comparable with the soluble Mn-salen complex-catalyzed reaction (up to 75% ee, yield up to 95%). The reuse of the catalysts showed only a small difference of the selectivity (around 10% lower), but the yields decreased in some cases from quantitative to 60% after the seventh run.

Very recently, Smith and Liu reported on a polymer-bound Katsuki-type Mn-salen complex **25c** introduced in asymmetric epoxidation reactions (Figure 8).[51]

They were used in asymmetric epoxidation reactions of 1,2-dihydronaphthalene (**26**).[51] The polymer-sup-

Table 2. Asymmetric epoxidation reaction of 1,2-dihydronaphthalene (**26**) using catalysts **25** by Smith and Liu.[51]



Catalyst[a]	Number of uses	Catalyst amount [mmol Mn]	Alkene amount [mmol]	Time [h]	Yield [%][b]	ee [%][c]
25b	1st	0.010	0.20	7.5[d]	100	≥ 94
25a	1st	0.010	0.20	6.5[d]	100	≥ 94
25c	1st	0.018	0.18	24	37	94
25c	2nd	0.017	0.17	24	30	94
25c	3rd	0.010	0.10	48	70	94
25c	4th	0.009	0.09	48	38	93
25c	5th	0.006	0.06	48[e]	70[e]	90[f]
25c	6th	0.005	0.05	48[e]	50[e]	90[f]

[a] Polymer **25c** was allowed to swell in CH_2Cl_2 (2 mL) for 1 h. A solution containing the alkene **26** (1 equiv.), 4-PPNO (0.25 equiv.) and hexadecane as internal standard in CH_2Cl_2 (2 mL) was added and the mixture was cooled to 0 °C. A solution of NaOCl in phosphate buffer (0.588 M, 5 equiv., pH = 11.4) was added and the mixture was stirred at 0 °C. The progress of the reaction was monitored by GC. After the appropriate time the suspension was filtered off and washed with CH_2Cl_2, H_2O and MeOH. After being dried in a vacuum oven (50 °C/10 mm Hg) for 24 h the polymer was available for reuse.

[b] The yield of epoxide was determined by GC using hexadecane as an internal standard. Estimated error limit ± 5%.

[c] The enantiomeric excess was determined by integration of peak areas in ^1H NMR spectra using the chiral shift reagent $Eu(hfc)_3$ and the absolute configuration of the resulting epoxide, according to Katsuki, should be 1*S*,2*R*.[62]

[d] The total volume of solvent in these reactions was 2.5 mL.

[e] For these reactions the amount of solvent was reduced to 2 mL (from 4 mL).

[f] The amount of product was so small that the ee values are less reliable.

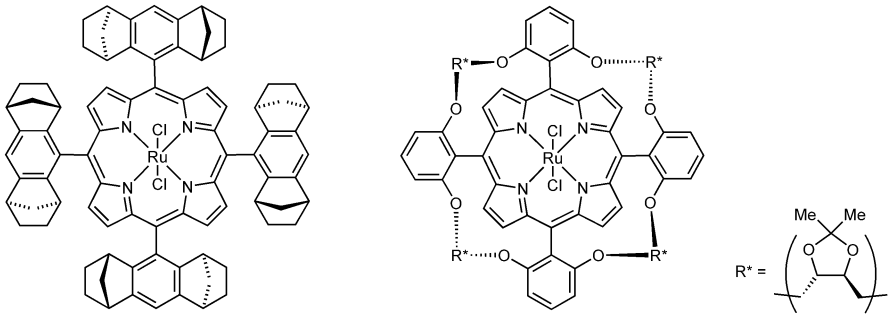
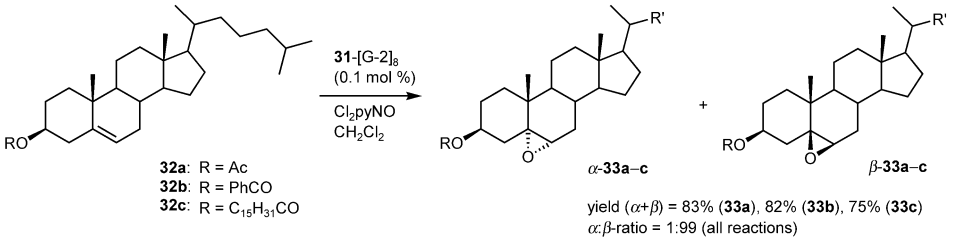


Figure 9. D_4-symmetric chiral dichlororuthenium(VI) porphyrin catalysts **28** and **29** by Che et al.[63]



Scheme 3. Epoxidation catalysis using porphyrin **31**-$[G-n]_m$ by Che et al.[67]

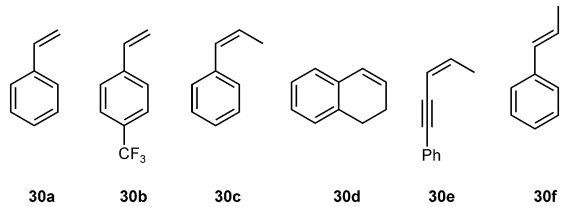


Figure 10. Olefins **30a–f** used in epoxidation reactions by Che et al.[63]

ported catalyst **25c** exhibited lower rate-enhancement than homogeneous **25a** and **25b** (Table 2). This will be partly a result of the somewhat more dilute conditions for the soluble reagents when the polymer was used, and partly the result of slow diffusion. However, enantioselectivities with the polymeric catalyst **25c** were entirely analogous to those obtained with the homogeneous ones **25a** and **25b**. Furthermore, there was no significant decrease in enantioselection on reuse of the catalyst.

In 1998, Che et al. developed a D_4-symmetric ruthenium(VI) tetrakis(dinorbornabenzene)-substituted porphyrin 28 as a catalyst for the olefin epoxidation (Figure 9).[63] One year later the same authors reported on a D_2-symmetric threithol-strapped dioxoruthenium (VI) porphyrin complex **29**.[64] Recently, a new heterogeneous catalyst by encapsulating the complex **28** within the sol-gel silica was reported.[65] Inorganic sol-gel supports are superior to organic supports in their thermal stability, inertness towards the entrapped molecules, high porosity and large surface areas.[66]

Epoxidation reactions with styrene (**30a**), 4-trifluoromethyl-styrene (**30b**), *cis*-β-methylstyrene (**30c**), 1,2-dihydronaphthalene (**30d**), pent-3-en-1-ynylbenzene (**30e**) and *trans*-β-methylstyrene (**30f**) (Figure 10) resulted in yields up to 96% (related to the conversion) and enantioselectivities up to 72% ee.

Very recently, Che et al. reported the achiral dendritic ruthenium porphyrin catalysts **31**-$[G-n]_m$ ($m=4, n=1$; $m=8, n=0-2$; Figure 11) which showed no selectivity in epoxidation reactions with small olefins but high selectivity with chiral systems.[67] An excellent diastereoselectivity in epoxidation reactions of cholesteryl esters **33** was observed with Cl_2pyNO catalyzed by dendritic ruthenium(II) porphyrin catalysts **31**-$[G-n]_m$ as shown in Scheme 3. The low catalyst amount of 0.1 mol % is, besides the excellent diastereoselectivity, a second advantage of using the dendrimer **31**-$[G-n]_m$ in epoxidation reactions of steroids like the chloresteryl esters **32**. A similar selectivity in epoxidation reactions of unsaturated steroids had been realized only in the "[Ru(IV)tmp(O_2)] + air or dioxygen" system developed by Marchon et al.[68]

Sherrington et al. are working on the immobilization of tartrate ester catalysts in a polymeric framework for the Sharpless epoxidation reaction.[69] The most active polymeric tartrate derivative **34** is shown in Figure 12.

The catalyst **34** was used in epoxidation reactions of different allylic alcohols (Table 3)[69b] leading to good enantioselectivities, but moderate yields. Additionally, high loadings of polymeric tartrate (20–100 mol %) were required. The reuse of the heterogeneous catalyst was not investigated.

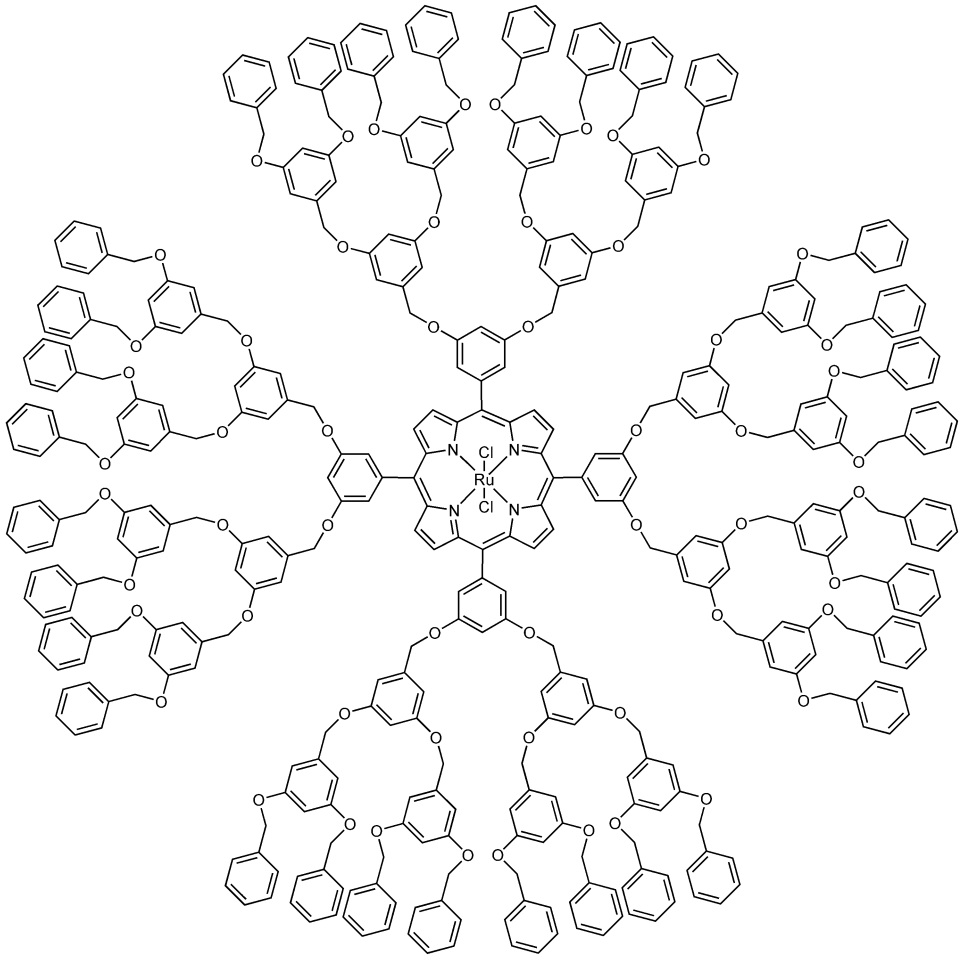


Figure 11. Schematic structures of a dendritic ruthenium porphyrin **31**-[G – *n*]$_8$ by Che et al.[67]

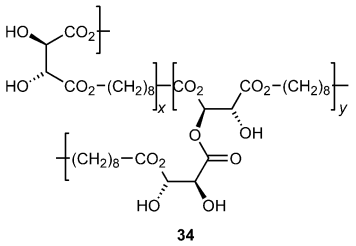
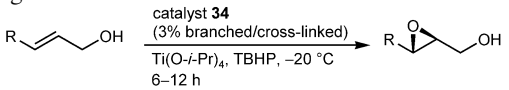


Figure 12. Chiral tartrate ester incorporated within a polymeric framework **34** by Sherrington et al.[69]

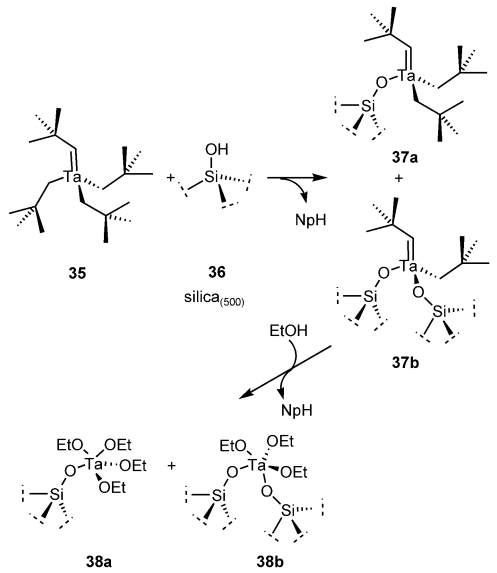
Table 3. Asymmetric Sharpless epoxidation reaction by Sherrington et al.[69b]



R	Equiv. **34**	Yield [%]	ee [%]
C_3H_7	0.5	55	87
C_8H_{17}	1.0	50	88
phenyl	0.2	48	80

In 1991, Sharpless and Finn postulated a mechanism for the Sharpless epoxidation reaction.[70] The four *d*-electrons of the titanium form two σ-bounds with the tartaric group. The metal center is also chelated by two σ-bound oxygen atoms, an allylalkoxy group and a σ/π-coordinated *tert*-butylperoxo group. If the titanium(IV) species is immobilized *via* an Si–O–Ti bond, it might be impossible to coordinate all necessary ligands to the metal center. Thus, de Mallmann, Basset et al. introduced tantalum in the heterogeneous asymmetric Sharpless epoxidation reaction, although tantalum is known as a low active catalyst in homogeneous catalytic processes.[71]

The tantalum species synthesized by this pathway (Scheme 4) are designated as $[Ta]_1 - [Ta]_3$ (for explanation see footnotes of Table 4). The catalytic activity was tested in Sharpless epoxidation reactions of 2-propen-1-ol (**39a**) and *trans*-2-hexen-1-ol (**39b**) as shown in Table 4. The results showed that the catalytic activity of silica-supported tantalum is caused by reaction centers on the surface and not by solvated species, because molecular $Ta(OEt)_5$ is catalytically inactive.



Scheme 4. Synthesis of the silica-supported alkoxytantalum compounds **37a**,**b** and **38a, b** by de Mallmann, Basset et al. (NpH = neopentane).[71]

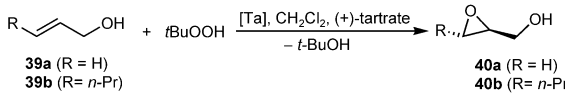
The analysis of the reaction mixture and the solids before and after the reaction showed no leaching of the metals (less than 2% of the immobilized metal). A third reason confirms this theory. The solvents showed no catalytic activity when the solid catalyst was separated by filtration before the last reactant was added.[72]

In 1980, Juliá and Colonna reported that polymeric amino acids catalyze the Weitz–Scheffer epoxidation of chalcone in a highly enantioselective and intriguingly simple manner (Scheme 5).[73]

Juliá and Colonna could show good yield and a high enantioselectivity from 93% ee.

Recently, Berkessel et al. immobilized such amino acids on TentaGel S NH_2 and inspected the minimum chain length of a catalytically active and selective peptide.[74] A maximum enantioselectivity (96–98% ee) was achieved with as little as five L-leucine residues, whereas the yield of the epoxide increased gradually and leveled off around the 14-mer. Since four amino acid residues are required to form one turn of an α-helix,[75] the authors conclude that one intact helical turn is the minimum structural element necessary for efficient asymmetric induction. Peptides containing β-amino acids like **43** and **44** (Figure 13) are known to form

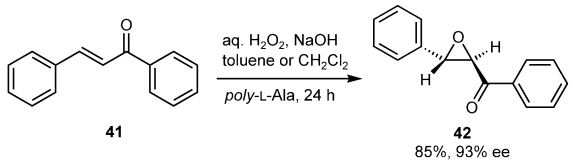
Table 4. Catalytic asymmetric epoxidation reaction of allylic alcohols **39a, b** in presence of silica-supported tantalum catalysts [Ta], Ti(O-*i*-Pr)$_4$ and Ta(OEt)$_5$ by de Mallmann, Basset et al.[71]



39a (R = H)
39b (R= *n*-Pr)
40a (R = H)
40b (R= *n*-Pr)

Entry	Catalyst[a, b]	R	Metal/Alcohol[c]	c (Substrate **39**) [M]	Conversion [%][d]	Yield [%][d]	ee [%][d, e]
1	Ti(O*i*Pr)$_4$	H	5/100	1.0[f, g]	76	72	80 (*S*)
2	[Ti]	H	5/100	0.4[f, g]	17	14	–9 (*R*)
3	Ta(OEt)$_5$	H	2/100	1.0[f, h]	0.5	0.4	–45 (*R*)
4	[Ta]$_2$	H	2/100	0.1[f, h]	60	56	85 (*S*)
5	[Ta]$_1$	H	2/100	0.1[h]	31	30	84 (*S*)
6	[Ta]$_1$	H	2/100	0.1[i]	30	29	–83 (*R*)
7	[Ta]$_3$	H	2/100	0.4[h]	20	19.5	84 (*S*)
8	[Ta]$_1$	H	19/100	0.1[h]	79	77	94 (*S*)
9	Ti(O-*i*-Pr)$_4$	*n*Pr	5/100	1.0[f, j]	99	80	96 (*S,S*)
10	[Ta]$_2$	*n*Pr	4/100	0.1[f, h]	48	40	90 (*S,S*)
11	[Ta]$_2$	*n*Pr	4/100	0.1[j]	35	34	89 (*S,S*)
12	[Ta]$_2$	*n*Pr	4/100	0.1[j, k]	35	31	93 (*S,S*)

[a] [Ta]$_1$: 4.92 w% Ta, C/Ta = 8.9 ; [Ta]$_2$: 5.40 w% Ta, C/Ta = 7.2 ; [Ta]$_3$: 5.63 w% Ta, C/Ta = 7.1. A theoretical value C/Ta of 7 is expected for a 1 : 1-mixture of **38a** and **38b**. This is correct for [Ta]$_2$ and [Ta]$_3$, the difference in case of [Ta]$_1$ is caused by the presence of SiOEt species.
[b] The [Ti] catalyst was synthesized from Ti(O*i*Pr)$_4$ and silica$_{(500)}$ (1.8 wt % Ti).
[c] Molar ratio.
[d] Determined after 48 h by GC with a Lipodex E column and with *n*-dodecane as internal standard.
[e] Main enantiomer in brackets.
[f] With pulverized molecular sieve (3 Å) dried at 300 °C in vacuum.
[g] At 0 °C; reagents for chiral induction: (+)-DIPT; oxidation reagents: CHP.
[h] At 0 °C; reagents for chiral induction: (+)-DIPT; oxidation reagents: TBHP.
[i] Like entry 5, but (–)-DIPT.
[j] At –20 °C; reagents for chiral induction: (+)-DIPT; oxidation reagents: TBHP.
[k] Like entry 11, but recycled catalyst.



Scheme 5. Weitz–Scheffer epoxidation catalyzed by polymeric amino acids reported by Juliá and Colonna.[73]

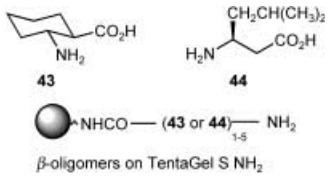


Figure 13. β-Amino acids **43**, **44** and TentaGel-bound oligomers *poly*-**43** und **44** by Berkessel et al.[74]

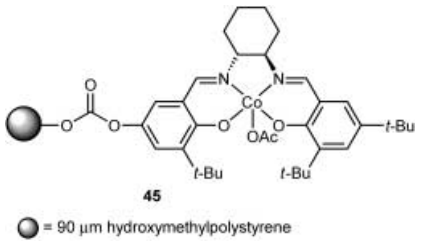


Figure 14. Polymer-supported chiral Co(salen) complex **45** by Jacobsen et al.[77]

stable helices much more readily than the corresponding α-amino acid-derived peptides.[76] Based on these findings, Berkessel et al. used β-peptides for the Juliá – Colonna epoxidation with the result that a hydrogen bonding at the *N*-terminus is crucial because the Fmoc-protected amino acid oligomers of **43** and **44** immobilized on TentaGel S NH_2 did not show catalytic activity ($\leq 1-2\%$ conversion after 24 h).

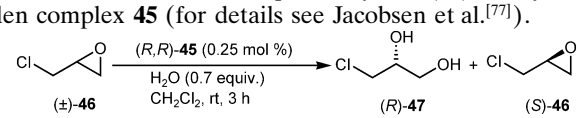
2.2 Ring Opening of Epoxides

The ring opening of achiral or racemic chiral epoxides to generate enantiopure materials such as secondary alcohols is an economic efficient entry to this class of compounds. In 1999 Jacobsen et al. published the solid-supported chiral Co(salen) complex **45** for the enantioselective epoxide opening (Figure 14).[77] The activity of catalyst **45** was proved to be successful in a hydrolytic kinetic resolution (HKR) of terminal epoxides as shown in Table 5.

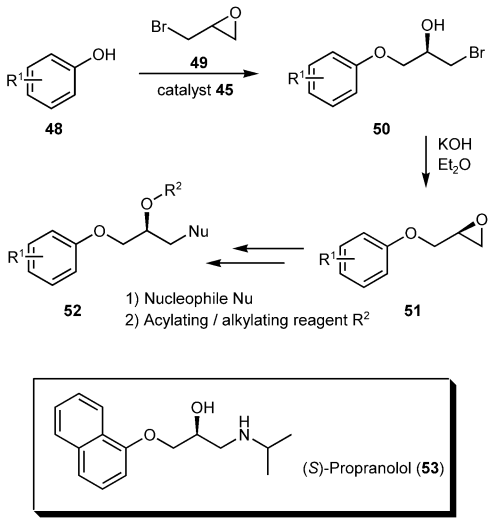
The HKR is efficient to use for epoxide opening of terminal epoxides with other alkyl nucleophiles (ee up to 94%) or by using 1.5 equivalents of water (full conversion to the diols, ee up to 96%). The catalyst **45** shows very good results in epoxide opening reactions of epibromohydrin using phenols as nucleophiles. The subsequent intramolecular ring closure to a new terminal epoxide, another epoxide opening with a different nucleophile and interception with an acylating or alkylating reagent provides a possible application in combinatorial synthesis giving access to propanolol type structures (see Table 5 and Scheme 6).[77]

Jacobsen et al. tested also a silica-bound Co(salen) complex **54** (Figure 15) in a continuous-flow system for HKR with good enantioselectivities for the opening

Table 5. HKR of racemic epichlorhydrin (**46**) catalyzed by salen complex **45** (for details see Jacobsen et al.[77]).



Cycle	Conversion [%]	ee (**47**) [%]	ee [(*S*)-**46**] [%]	k_{rel}
1	52	> 99	92	133
2	51	> 99	95	206
3	51	> 99	94	159
4	51	> 99	93	154
5	52	> 99	93	145



Scheme 6. Possible application of salen complex **45** in combinatorial synthesis.[77]

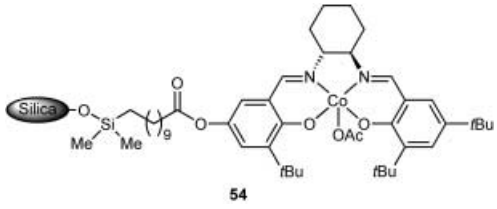
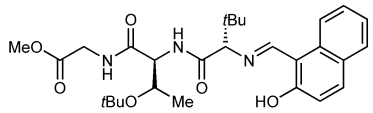
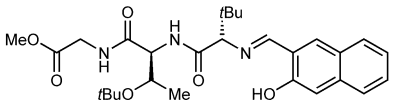


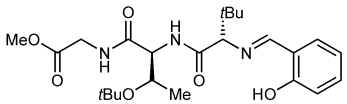
Figure 15. Silica-supported Co(salen) complex **54** for continuous-flow HKR by Jacobsen et al.[77]



55



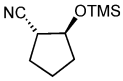
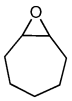
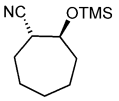
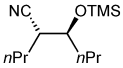
56



57

Figure 16. Optimized ligands **55 – 57** for catalytic enantioselective addition of TMSCN to *meso*-epoxides by Hoveyda et al.[78]

Table 6. Catalytic enantioselective addition of TMSCN to *meso*-epoxides by Hoveyda et al.[78]

Substrate[a]	Product	ee [%]	Yield [%]	Optimized ligand
		83	72	**55**
		84	68	**56**
		78	69	**57**

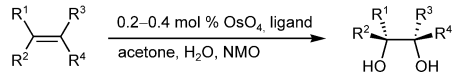
[a] Conditions: 20 mol % Ti(O-*i*-Pr)$_4$, 20 mol % ligand, 4 °C, 6 – 20 h.

product, but only fair results in the enantioselectivity of the epoxide and yield.[77]

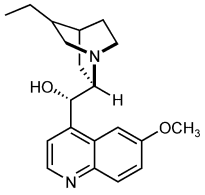
In 1998, Hoveyda et al. introduced peptide-based helical chiral ligands **55 – 57** as effective catalysts for asymmetric opening of *meso*-epoxides (Figure 16).[78] This kind of compound can be immobilized very easy, for example, by polymerization.

2.3 Dihydroxylation Reactions

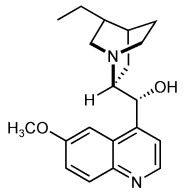
The catalytic asymmetric Sharpless dihydroxylation (AD) of olefins is a very efficient method for the catalytic preparation of chiral vicinal diols (Scheme 7).[79] Since the seminal report in 1988 by Sharpless et al., the AD reaction was so thoroughly investigated that nearly all classes of diols can be



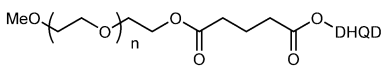
Scheme 7. Asymmetric dihydroxylation reaction by Sharpless et al.[79]



58
DHQD ligand
Dihydroquinidine



59
DHQ ligand
Dihydroquinine



60

Figure 17. Alkaloid ligands DHQD **58** and DHQ **59** by Sharpless et al.[82,83] and soluble (MeO-PEG)-DHQD ligand **60** by Janda et al.[84]

synthesized in good yield and in high enantiomeric excesses.[80,81]

The first example for heterogeneous asymmetric dihydroxylation catalysis was reported by Kim and Sharpless in 1990[82,83] using polymer-bound cinchona alkaloid derivatives as ligands **58** and **59** (Figure 17) and *trans*-stilbene as substrate. Thus, the corresponding chiral diol was obtained in high yields ranging from 81 – 87% and excellent enantioselectivies from 85 – 93% ee using 1 mol % OsO_4 and NMO as a secondary oxidant within 2 – 3 d at 10 °C.

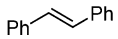
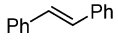
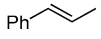
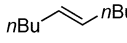
In 1996, Janda et al. reported a soluble (MeO-PEG)-DHQD ligand **60** (Figure 17).[84] It was possible to recover the ligand in > 98% yield after addition of diethyl ether for precipitation and subsequent filtration. the soluble (MeO-PEG)-DHQD ligand **60** can be reused for five times with no loss of activity or selectivity as shown in Table 7.

One year later, Janda et al. reported an MeO-PEG-[(DHQD)$_2$PHAL] ligand, which resulted in high enantioselection with up to 98% ee using *trans*-cinnamic acid esters as olefins.[85]

Bolm et al. reported in 1997 on an asymmetric dihydroxylation reaction with a soluble polyethylene glycol monomethyl ester-anchored (MeO-PEG)-DHQD **61a, b** or DHQ **62** as ligand (Figure 18).[86] The soluble ligands could be recovered by easy filtration after precipitation with methyl *tert*-butyl ether (> 98% yield).

The results are summarized in Table 8. The reaction time was 5 h in maximum with $K_3[Fe(CN)_6]$ as cooxidant.

Table 7. Asymmetric dihydroxylation reaction[a] with ligand **60** by Janda et al.[84]

	Olefin	Ligand	Time [h]	Yield [%]	ee [%]
1		**60**	5	89	88
2		**60**[b]	5	87	87
3		**60**	5	80	60
4		**60**	5	80	84
5		**60**	10	62	42

[a] General conditions employed NMO and acetone/water (10/1, v/v).

[b] The ligand **60** was reused five times; the average yield and ee for these five runs are listed here.

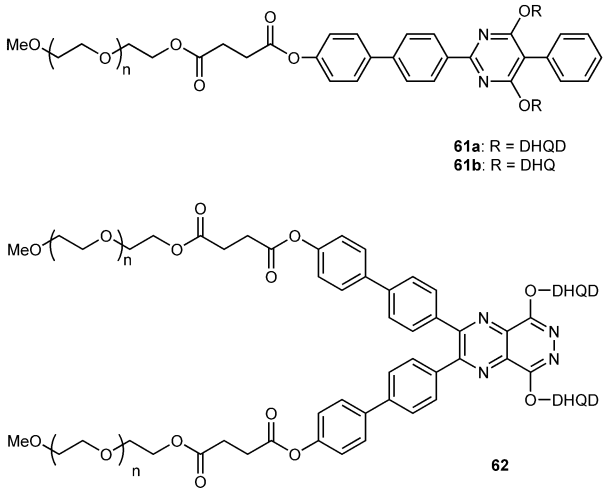


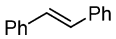
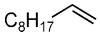
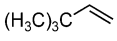
Figure 18. DHQD and DHQ ligands on a MeO-PEG chain **61a, b** and **62** by Bolm et al.[86]

The results (Table 8) showed that the enantioselectivities obtained with the (MeO-PEG) system favorably compare with the results from the homogeneous system.[87] The ligand **62** can be reused six times in the reaction with styrene as a substrate while the enantioselectivity remained nearly constant between 96 and 98% ee.

In another example, Bolm et al. used insoluble inorganic silica-anchored alkaloids as heterogeneous ligands.[88] The polysiloxane-anchored bis(9-*O*-dihydroquinidinyl)pyrazinopyridazines **63a, b** and bis(9-*O*-dihydroquinidinyl)pyrimidines **64a, b** were used in the catalytic reaction (Figure 19).

The asymmetric dihydroxylation reactions were performed in *t*BuOH-H_2O (1:1) using $K_3[Fe(CN)_6]$-K_2CO_3 as cooxidant, 0.5–1 mol % of $K_2OsO_2(OH)_4$ and 2 mol % of immobilized ligand. The results are shown in Table 9.

Table 8. Asymmetric dihydroxylation reaction[a] with ligands **61a**, **b** and **62** by Bolm et al.[86]

	Alkene	Ligand	Yield [%]	ee [%][b]	Config.
1		**62**	91	99 (99)	*R,R*
2		**62**	92	98 (99)	*R*
3		**62**	89	95 (96)	*R*
4		**61a** **61b**	86 88	87 (89) 74 (76)	*S*
5		**61a**	84	90 (92)	*R*

[a] Conditions: see ref.[85]

[b] In parenthesis: the results with not modified and immobilized DHQ and DHQD ligands.[87]

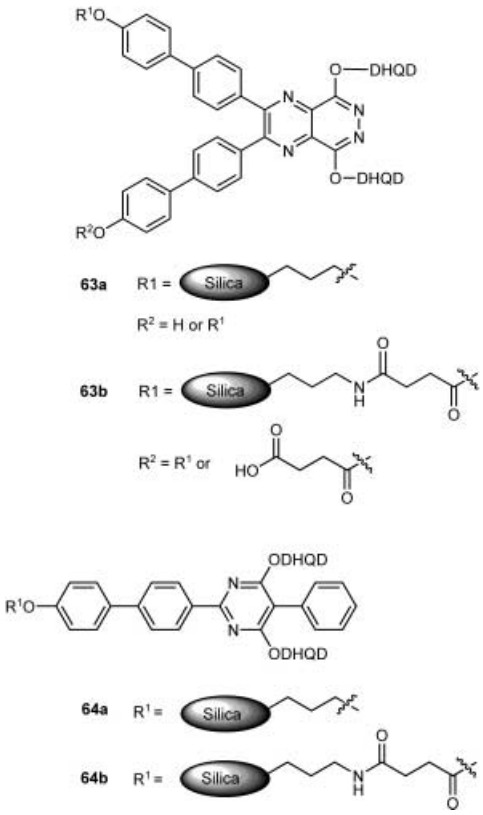
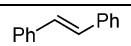
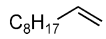
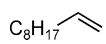
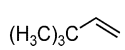


Figure 19. Modified cinchona alkaloids on an insoluble inorganic support **63a, b** and **64a, b** by Bolm et al.[88]

The problem by using osmium tetroxide as oxidant is beside its costs and the highly toxic and volatile properties, also the contamination of the products with this heavy metal, which restricts its use in industrial processes. Some groups tried to circumvent this problem.[89]

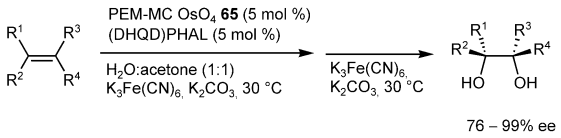
Kobayashi et al. reported in 1998 a microencapsulated osmium tetroxide in non-asymmetric dihydroxylation

Table 9. Asymmetric dihydroxylation reaction[a] with ligands **63a**, **b** and **64a, b** by Bolm et al.[88]

	Alkene	Ligand	Yield [%]	ee [%][b]	Config.
1		**63a**	77	99 (99)	*R,R*
2		**63a**	93	98 (99)	*R*
3		**63b**	93	90	*R*
4		**64a**	51	84 (89)	*R*
5		**64b**	53	61	*R*
6		**64b**	62	70 (92)	*R*

[a] Conditions: see ref.[88]

[b] In parenthesis: the results with not modified and immobilized DHQ and DHQD ligands.[87]



Scheme 8. Asymmetric dihydroxylation of olefins using PEM-MC OsO_4 **65** by Kobayashi et al.[92]

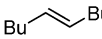
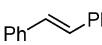
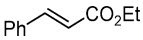
reactions, which could be completely recovered and reused without leaching of the osmium tetroxide.[90] The microencapsulated technique allowed the use of the reactive osmium tetroxide for the reaction with the advantage of safe and easy handling demonstrated in asymmetric dihydroxylation.[91]

Another version of the asymmetric catalytic dihydroxylation reaction was based on phenoxyethoxymethyl-polystyrene (PEM)-based microencapsulated osmium tetroxide (PEM-MC OsO_4) **65** prepared by standard methods.[92] The phenoxyethoxymethyl-polystyrene (PEM) was synthesized from Merrifield resin by etherification. The best conditions for this system are shown in Scheme 8.

The osmium catalyst **65** was recovered quantitatively by simple filtration, preventing the leaching of the osmium ion from **65**, and reused several times without loss of activity. The results are summarized in Table 10. Due to the fact that a complete conversion was not obtained, the addition of another equivalent of $K_3[Fe(CN)_6]$ and K_2CO_3 within 3 h led to the best results.

The group of Choudary developed an ion exchange technique for a recoverable and reusable osmium catalyst.[93] Osmium catalysts on layer double hydroxides (LDH) were immobilized by ion exchange with OsO_4^{2-} to yield the heterogeneous osmate **66** (Figure 20). As cooxidant NMO was used; when using

Table 10. Asymmetric dihydroxylation reaction[a] of olefins using PEM-MC OsO_4 **65** by Kobayashi et al.[92]

	Alkene	Time [h]	Yield [%]	ee [%]
1		3 + 2	85	78
2		3 + 2	86	94
3		3 + 2	85	76
4		5 + 4	85	95
5		3 + 2	41	91
6		3 + 2 + 2 + 2	66	> 99
7		3 + 2	51	> 99

[a] Conditions: see ref.[92]

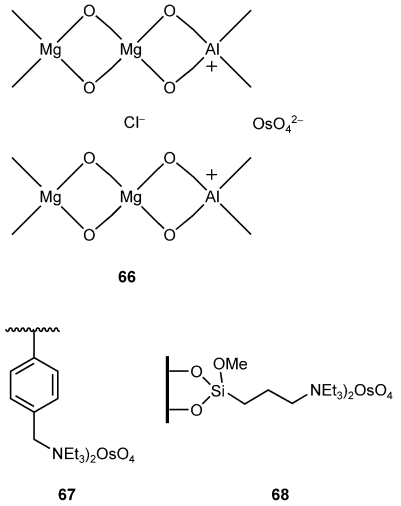


Figure 20. The structures of a) LDH-OsO_4 **66**, b) resin-bound OsO_4 **67** and c) SiO_2-OsO_4 **68** by Choudary et al.[93]

$K_3Fe(CN)_6$ or molecular oxygen a deactivation was observed.

Resin-bound OsO_4 **67** and SiO_2-OsO_4 **68** catalysts were also prepared. The structures of LDH-OsO_4 **66** and the immobilized OsO_4 are shown in Figure 20.

The results of the LDH-OsO_4 **66** catalyzed AD reactions using *trans*-stilbene as substrate are shown in Table 11.

Very high yields and excellent enantioselectivities were obtained with the resin-bound catalyst **66** for a range of substrates and different cooxidants. The resin-bound OsO_4 catalyst **66** is reusable for five times with no loss of selectivity and with complete recovery of osmium

Table 11. Results of solvent effect on the LDH-OsO_4 **67** catalyzed asymmetric dihydroxylation of *trans*-stilbene[a] reported by Choudary et al.[93]

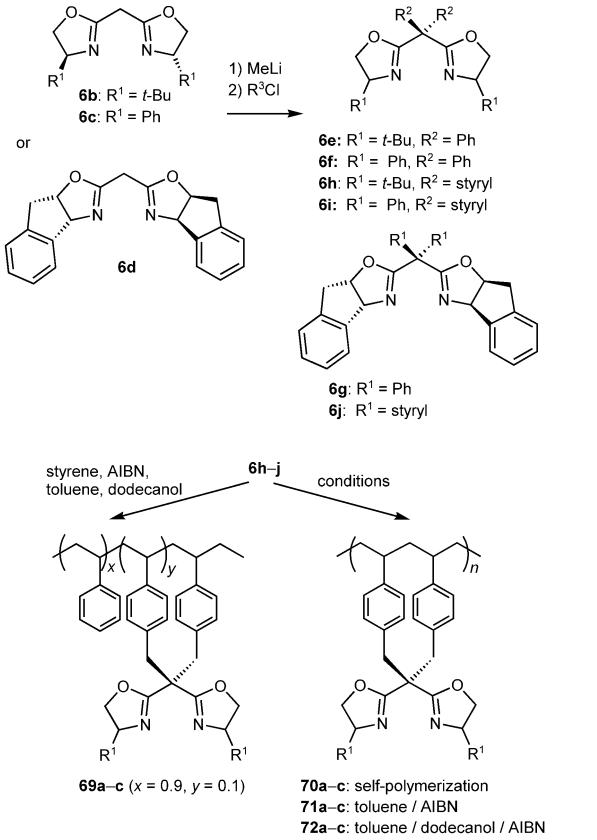
	Solvent	Yield [%]	ee [%]
1	H_2O-acetone (1:3)	96	93
2	H_2O-CH_3CN-acetone (1:1:1)	93	91
3	H_2O-CH_3CN (1:3)	58	90
4	H_2O-*t*BuOH (1:3)	62b	99

[a] NMO (1.3 equiv.), *trans*-stilbene (1 mmol), $(DHQD)_2$PHAL (1 mol %), and LDH-OsO_4 **66** in 6 mL solvent for 2 h at rt.
[b] 95% yield after 6 h.

and 95% recovery of the $(DHQD)_2$PHAL ligand by acid/base extraction.

The group of Jacobs reported a heterogeneous *cis*-dihydroxylation reaction with stable site-isolated osmium.[94] displaying high conversion and selectivity, however, with the typical chiral alkaloid ligands no noticeable enantiomeric excess was observed.

For a recent review of microencapsulated catalysts in asymmetric dihydroxylation reactions see Kobayashi and Akiyama.[95]



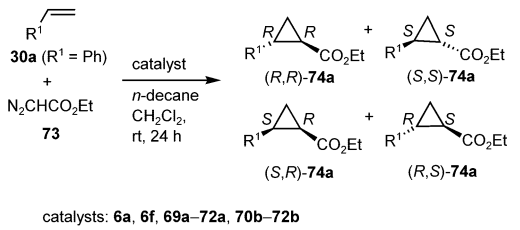
Scheme 9. Immobilization of bis(oxazolines) to give organic polymers **69**–**72** by Mayoral et al.[41]

2.4 Cyclopropanation Reactions

The asymmetric cyclopropanation of alkenes is an efficient method for the introduction of up to three new stereogenic centers. The bis(oxazoline) ligands **6** form catalytic complexes with copper(II) which are highly efficient catalysts for asymmetric cyclopropanation reactions.[33] Immobilized box-copper(II) complexes are known as enantioselective catalysts not only in asymmetric cyclopropanation and liquid-phase aziridination reactions,[36] but also for liquid-phase hetero-Diels–Alder reactions in the presence of Florisil.[37]

Mayoral and coworkers showed that cationic complexes bearing bis(oxazoline) ligands **69**–**72** can be immobilized onto anionic supports, and examined the scope and limitations of these solids as catalysts in enantioselective cyclopropanation[36a,39] and also Diels–Alder reactions.[40] The immobilization of bis(oxazoline) ligands onto organic supports proceeded through a copolymerization process (Scheme 9).

The copper complexes of **69a**–**72a** and the corresponding monomeric species were used as catalysts in cyclopropanation reactions of substituted styrenes and ethyl diazoacetate (**73**) to give *cis*- and *trans*-2-arylcyclopropanecarboxylic acid ethyl esters (**74**) (Scheme 10).[41] The *cis/trans*-ratio depended on the R^1 substituent (Table 12). With a phenyl group as the R^1 substituent, the reactions gave rise to the *trans*-product



Scheme 10. Cyclopropanation reaction catalyzed by immobilized catalysts **6a, 6f, 69a**–**72a** and **70b**–**72b** by Mayoral et al.[41]

in the presence of the catalysts **6a**, **69a**, **71a** and **72a** (up to 70:30 for *trans*).

An exception was resin **70a** that preferred the *cis*-product (53:47 for *cis*). In addition, the yield by using resin **70a** (45%) was better than with the other catalysts **6a**, **69a**, **71a** and **72a** (24–40%).

This classifies the influence of the polymeric matrix to the stereochemical behavior of this catalysts.[96] If the R^1 substituent is a *t*-Bu-group (**6f**, **69b**, **71b** and **72b**), the selectivity is reversed to the *cis*-product (up to 68:32 for *cis*). This was an unpredicted result, since a bis(oxazoline) ligand with an isopropylidene bridge shows a selectivity with a preference of 72:28 for the *trans*-product.[97] However, the enantioselectivities using

Table 12. Cyclopropanation reaction[a] between styrene (**30a**) and ethyl diazoacetate (**73**) catalyzed by the immobilized catalysts **69a – 72a** and **70b – 72b** by Mayoral et al.[41]

Entry	Ligand	Cu [mmol g^{-1}]	S/C	Run	Yield [%][b]	*trans*/*cis*[b]	ee [*trans*] [%][c, d]	ee [*cis*] [%][c, e]
1	**6a**		10	1	32	70 : 30	50	40
2	**69a**	0.39	185	1	28	60 : 40	46	42
3				2	24	60 : 40	43	41
4	**70a**	0.21	330	1	45	47 : 53	51	52
5				2	39	46 : 54	50	52
6	**71a**	0.01	6900	1	28[f]	66 : 34	61	55
7				2	27[f]	64 : 36	58	52
8	**72a**	0.14	510	1	40	53 : 47	57	53
9				2	20	53 : 47	47	50
10	**6f**		50	1	46	32 : 68	70	79
11	**70b**	0.13	490	1	51	35 : 65	75	72
12				2	56	37 : 63	74	70
13	**71b**	0.07	910	1	34	39 : 61	77	73
14				2	36	39 : 61	77	73
15	**72b**	0.03	2630	1	35	44 : 56	69[g]	75[h]
16				2	22[i]	44 : 56	69[g]	75[h]

[a] Using equimolar amounts of styrene and diazoacetate at rt. Results after 24 h.
[b] Determined by GC. Total conversion of ethyl diazoacetate.
[c] Determined by GC with a cyclo-B column.
[d] (*S,S*)-**74a** is the major isomer.
[e] (*R,S*)-**74a** is the major isomer.
[f] At 60 °C.
[g] (*R,R*)-**74a** is the major isomer.
[h] (*S,*R)-**74a** is the major isomer.
[i] After 36 h.

resins **6f**, **69b**, **71b** and **72b** are diminished compared with the result obtained with the bis(oxazoline) ligand **6a** with an isopropylidene bridge.[97 h] In all cases, the reuse of the catalysts meant a loss of activity. Yields and selectivities could be increased by the use of a five-fold excess of the styrene.

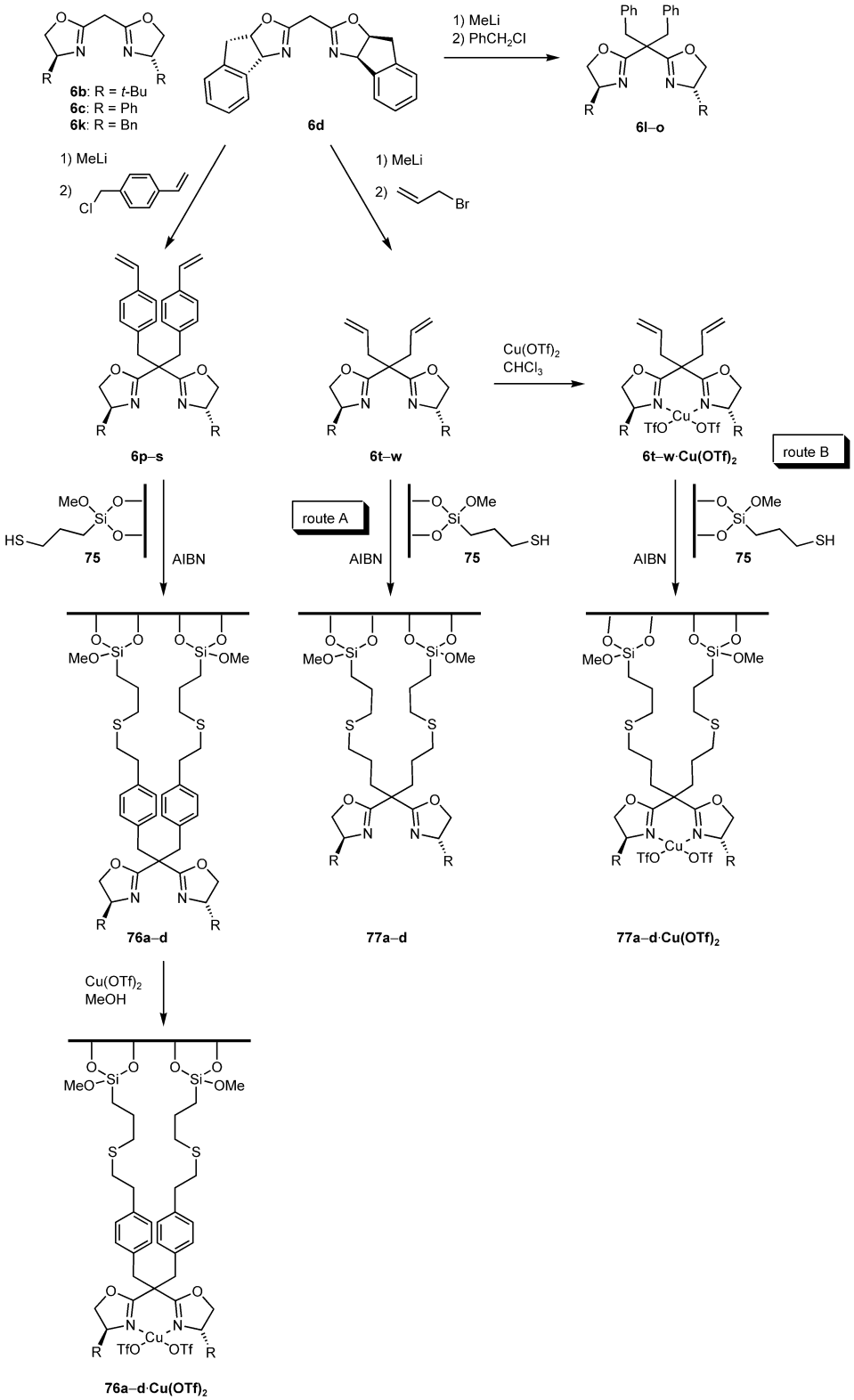
In 2001, Mayoral et al. succeeded in immobilizing bis(oxazoline) copper complexes **76a – d** · $Cu(OTf)_2$ and **77a – d** · $Cu(OTf)_2$ covalently bound to an insoluble support by grafting on silica (Scheme 11).[42]

They demonstrated the catalytic activity of this bis(oxazoline) copper complexes in the cyclopropanation reaction of styrene with ethyl diazoacetate to the *cis*- and *trans*-2-phenylcyclopropanecarboxylic acid ethyl esters.[42] In all cases (shown in Table 13), a full conversion of ethyl diazoacetate was observed with formation of diethyl fumarate and maleate as main side products. The insoluble catalysts obtained by route B (entries 6 – 8) gave similar yields to those obtained with the soluble catalysts (entries 1 – 3). The enantioselectivities by using "route A catalysts" (entries 4 and 5) were similar but the yields were lower, which may be due to diffusion limitations.

As mentioned above, the use of a *t*Bu-substituent in the bis(oxazoline) moiety of the soluble catalyst **6b** caused a selectivity reversal from *trans* to *cis* which was already observed one year before by the same authors.[41]

The results using the solid-supported catalysts **79a – d**, and **80 – 88** in cyclopropanation reactions prompted the authors to continue the route of immobilizing bis(oxazoline) ligands onto organic polymers (Schemes 12 and 13).[41,42] All the polymers are cross-linked since the functionalization of the chiral monomer makes it act as a cross-linker.

The results using these ligands in cyclopropanation reactions with styrene and ethyl diazoacetate are shown in Table 14. The activities and the enantioselectivities of the polymers **80a – d** and **83a – d** bearing the chiral bis(oxazolines) **6b – d** and **6k** as the only cross-linker are higher than those of the polymers **85 – 88** with an achiral cross-linker. They are similar to those obtained with the homogeneous catalysts. The results obtained using the achiral cross-linker are in strong contrast with the high enantioselectivities obtained when bis(oxazolines)[98] or azabis(oxazolines)[44] are bound to soluble PEG. With regard to the low copper amount, the polymers **84b – d** promote the cyclopropanation reaction similarly, or even better, than their soluble counterparts **6m – o**. The recycling of the catalysts **80d – 83d** and **84b – d** is also possible without a loss of activity. The *trans*/*cis*-selectivities are comparable to those obtained before.



Scheme 11. Immobilization of bis(oxazoline) copper complexes **76a – d** · $Cu(OTf)_2$ and **77a – d** · $Cu(OTf)_2$ onto silica by Mayoral et al.[42]

In 2000, Glos and Reiser introduced another kind of bis(oxazoline) ligand for the asymmetric cyclopropanation reactions, the aza-bis(oxazolines) **94a – c** (Scheme 14) and their polymer-supported ligand equivalent **95**.[44] In contrast to the known methylene bridged oxazolines like **6**, the oxazoline units of the new aza-

Table 13. Cyclopropanation reaction[a] between styrene (**30a**) and ethyl diazoacetate (**73**) catalyzed by silica-based catalysts reported by Mayoral et al.[42]

	Ligand	S/C	Yield [%][b]	*trans/cis*	ee [%][c] (*trans*[d])(*cis*[e])	
1	**6 t**	100	40	62:38	29	29
2	**6u**	100	36	68:32	60	60
3	**6v**	100	58	67:33	80	80
4	**77a** (A)[f]	100	29	62:38	15	15
5	**77b** (A)[f]	100	28	64:36	29	29
6	**77a** (B)[f]	100	36	63:37	9	9
7	**77b** (B)[f]	100	37	66:34	10	10
8	**77c** (B)[f]	100	47	68:32	26	26
9	**6 m**	10	32	70:30	50	50
10	**6n**	50	46	33:67	70	70
11	**6o**	125	49	58:42	83	83
12	**76b**	1720	24	62:38	33	33
13	**76c**	983	19	60:40	6	6
14	**76d**	1720	35	47:53	52	52

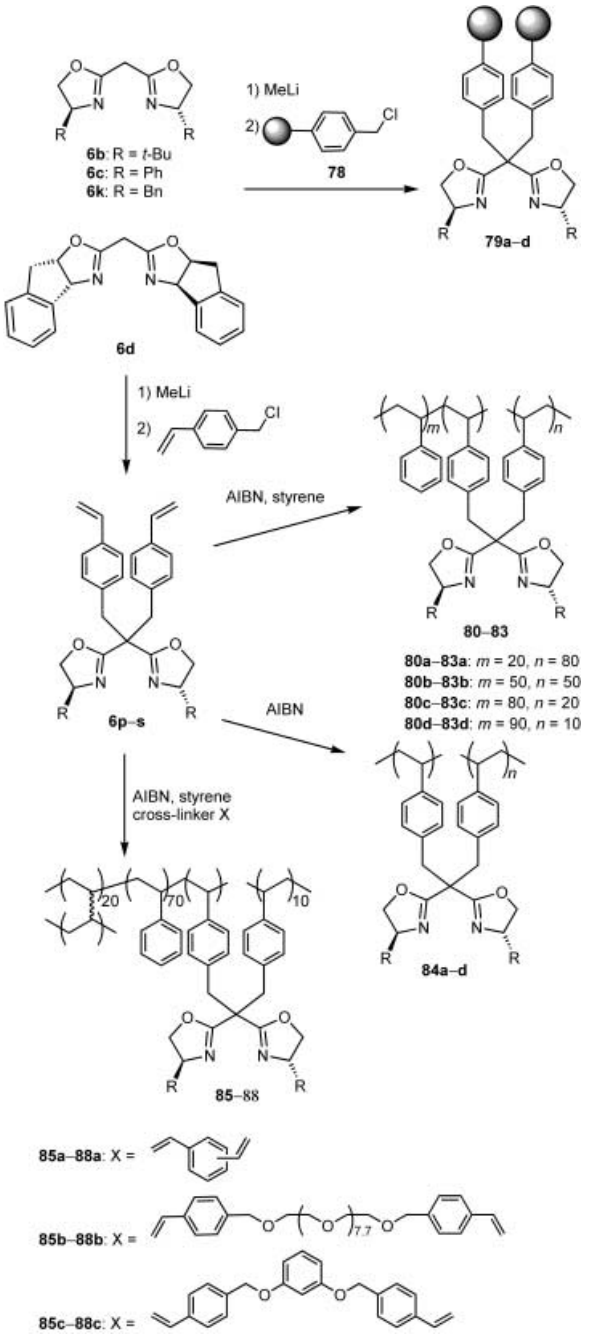
[a] Using equimolecular amounts of styrene and ethyl diazoacetate at rt in CH_2Cl_2.
[b] Determined by GC. Total conversion of ethyl diazoacetate.
[c] Determined by GC with cyclodex-B column.
[d] (*R,R*)-**74** is the major isomer.
[e] (*S,R*)-**74** is the major isomer.
[f] A = route A, B = route B, see Scheme 11.

Table 14. Cyclopropanation reaction between styrene (**30a**) and ethyl diazoacetate (**73**) catalyzed by polymeric catalysts[a] by Mayoral et al.[41,42]

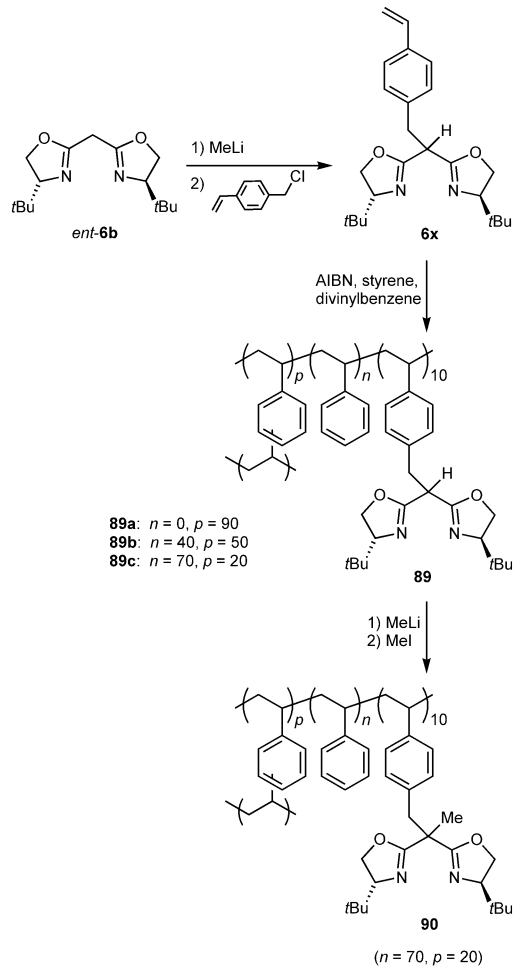
	Ligand	S/C	Yield [%]	*trans/cis*	ee [%] (*trans*) (*cis*)	
1	**6m**	10	32	70:30	50	40
2	**6n**	50	46	33:67	70	79
3	**6o**	125	49	58:42	83	86
4	**79b**	122	18	66:34	26	21
5	**85a**	176	11	71:29	18	18
6	**85b**	95	32	67:33	8	8
7	**85c**	428	12	58:42	50	46
8	**81a**	208	26	57:43	56	51
9	**81b**	371	18	57:43	57	51
10	**81c**	304	20	60:40	46	42
11	**81d**	86	28	60:40	46	42
12	**81d**[b]		24	60:40	43	41
13	**84b**	510	40	52:48	57	53
14	**84b**[b]		19	53:47	47	49
15	**84c**	796	36	37:63	78	72
16	**84c**[b]		33	36:64	75	72
17	**84d**	2630	35	44:56	69	75
18	**84d**[b]		22	44:56	69	75
19	**89a**	417	11	58:42	28	33
20	**89b**	417	15	56:44	45	44
21	**89c**	477	21	57:43	29	34
22	**90**	550	16	60:40	23	22

[a] For reaction conditions and analysis see ref.[42b]
[b] Reused catalyst.

bis(oxazoline) ligand **93a, b** are bridged by a nitrogen atom. The soluble ligands **93a, b** and **94a – c** were introduced in asymmetric palladium-catalyzed asymmetric allylic substitution reactions in solution phase with excellent results (yields up to 99% and enantioselectivities up to 97% ee). Besides to the allylic sub-



Scheme 12. Preparation of polymeric bis(oxazoline) ligands **80 – 88** by grafting and polymerization by Mayoral et al.[41,42]



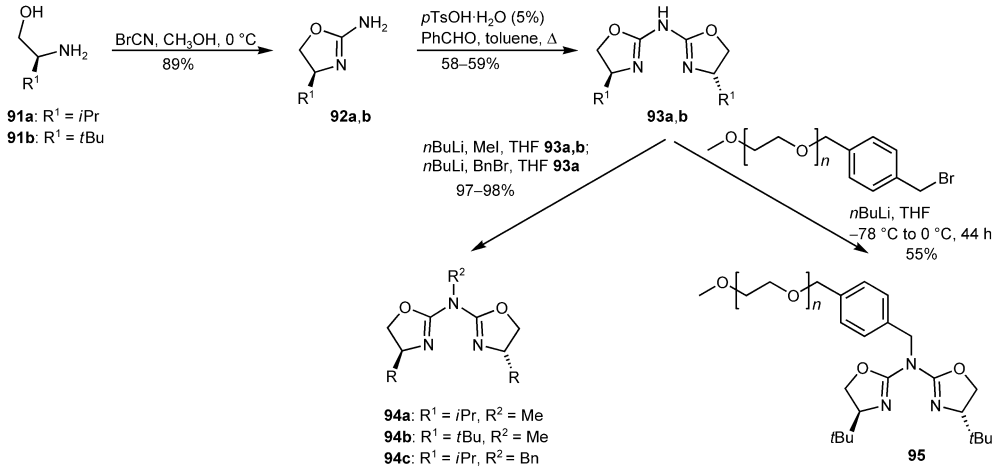
Scheme 13. Preparation of polymers with bis(oxazoline) ligands in the polymers chain **89** and **90** by Mayoral et al.[41,42]

stitution reactions, the ligands **39a – c** and the polymer-supported ligand **95** were used in asymmetric cyclopropanation reactions (Scheme 15).

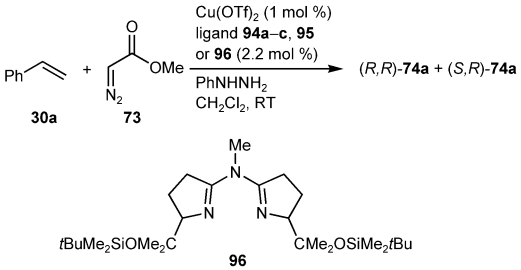
The cyclopropanation reaction of styrene **30a** and ethyl diazoacetate (**73**) using the aza-semicorrin **96** as chiral ligand (Scheme 15).[97c] was performed according to the protocols of Evans et al.. The results are shown in Table 15. The most effective ligand turned out to be **94b** (entry 5). This ligand compared well in terms of selectivity and yield to the best-reported results of **96** (entry 7) and **6** (entry 8), although somewhat lower enantioselectivities were obtained. Furthermore, it is interesting to note that catalysis also proceeded well with the non-alkylated ligand **93b** (entry 4), since only alkylated aza-semicorrins **96** have been reported as ligands for asymmetric catalysis. Most importantly, the polymer-bound ligand **95** (entry 6) gave similar yields and selectivities compared to **94b**, indicating that the immobilization of aza-bis(oxazolines) has no detrimental effects on their ability to serve as catalysts.

Reiser and Glos obtained similar results in the cyclopropanation reaction of and 1,1-diphenylethylene (**97**) with ethyl diazoacetate (**73**) (Table 16), this time, however, the non-alkylated ligand **93b** (entry 3) was superior to the alkylated **94b** (entry 4) in terms of both yield and enantioselectivity. In accord with the expectations that polymer-bound catalysts would improve the efficiency of these reactions, the polymeric catalyst derived from **95** (entry 5) gave the best results of all aza-bis(oxazolines).

The reuse of the immobilized ligand **95** was also examined. The enantioselectivities were nearly constant



Scheme 14. Synthesis of new aza-bis(oxazoline) ligands **93a, b** and **94a – c** and the immobilization of **93b** by Reiser and Glos.[44]



Scheme 15. Asymmetric cyclopropanation reaction of styrene (**30a**) with the ligands **94a – c** and **95** by Reiser and Glos.[44]

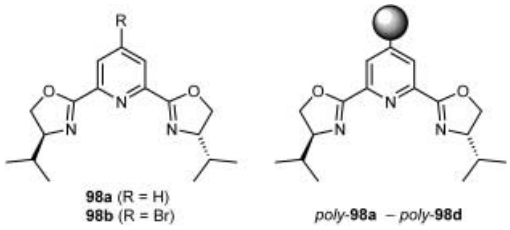


Figure 21. Monomer and polymer-supported pybox ligands **98a**, **b** and *poly*-**98a, b** (Table 17) synthesized by Mayoral et al.[100]

Table 15. Asymmetric cyclopropanation reaction[a] of styrene (**30a**) by Reiser and Glos.[44]

Entry	Ligand	Yield [%]	*(R,R)*:*(S,R)*-**74a**[b]	ee [*(R,R)*-**74a**] [%][c]	ee [*(S,R)*-**74a**] [%][c]
1	**93a**	85	62 : 38	56	42
2	**94a**	78	66 : 34	66	44
3	**94c**	44	64 : 36	62	47
4	**93b**	75	67 : 33	87	80
5	**94b**	82	73 : 27	92	84
6	**95**	69	71 : 29	91	87
7[d]	**96**	45	75 : 25	95	90
8[e]	**6**	77	73 : 27	99	97

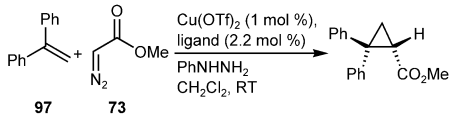
[a] All reactions were carried out under nitrogen.
[b] Determined by GC using a DB 1301 column.
[c] Determined by GC using a CP-Chiralsil DEX CB column.
[d] Entry taken from ref.[99]
[e] Entry taken from ref.[97]

around 87 – 90% ee for the *trans*-product (*R,R*)-**74a** and 81 – 85% ee for the *cis*-product (*S,R*)-**74a**. After the tenth cycle the addition of phenylhydrazine for catalyst activation was necessary.

In 2002, Mayoral et al. reported polymer-supported pyridine-bis(oxazoline) ligands *poly*-**98a – d** for the asymmetric cyclopropanation reaction of olefins (Figure 21).[100] The ligand was immobilized by chiral monomer polymerization with different ratios of pybox monomer **98b**, styrene (**30a**) and DVB (Table 17).

The catalytic activity of the pybox ligands **98a**,**b** and *poly*-**98a – d** were tested in the cyclopropanation reaction of styrene (**30a**) and ethyl diazoacetate (**73**) as shown in Scheme 10. The results summarized in Table 18 were moderate in yield (up to 39%) and good in enantioselectivity (up to 85% ee).

Table 16. Asymmetric cyclopropanation reaction[a] of **97** and **73** by Glos and Reiser.[43]



97 73

Entry	Ligand	Yield [%]	ee [%][b]
1	**93a**	70	47
2	**94a**	49	56
3	**93b**	63	86
4	**94b**	41	83
5	**95**	78	90
6[c]	**6**	70	99

[a] All reactions were carried out under nitrogen.
[b] Determined by HPLC using a Chiralpak AD column.
[c] Entry taken from ref.[99]

Very recently Che et al. reported a non-chiral dendritic ruthenium porphyrin system **31**-$[G-n]_m$ catalyzing selective alkene epoxidation and cyclopropanation reactions (Figure 11).[67] The results obtained in cyclopropanation reactions with several styrenes, ethyl diazoacetate and catalyst **31**-$[G-2]_8$ are shown in Table 19. The use of 0.1 mol % catalyst **31**-$[G-2]_8$ yielded cyclopropanecarboxylates **74** in 65–98%. The *trans*/*cis* ratio was found to be up to 16, which is comparable to those reported for ruthenium-pybox[101] or non-dendritic ruthenium porphyrin catalysts[102] but much higher than those obtained for semi-corrin or bis(oxazoline) copper catalysts.[97c,103]

In the same year, Davies and Nagashima reported catalytic asymmetric cyclopropanation reactions using bridged dirhodium tetraprolinates on a solid support.[104] The first chiral dirhodium catalysts for cyclopropanation reactions, dirhodium tetracarboxamidate com-

Table 17. Polymerization conditions[a] used by Mayoral et al.[100]

Polymer	polymerization mixture [%]			Porogen	mmol/g	
	pybox **98b**	styrene (**30a**)	DVB		pybox[b]	Ru[c]
poly-**98a**	7	42	51	toluene	0.443	0.274
poly-**98b**	7	63	30	toluene/dodec[d]	0.426	0.258
poly-**98c**	7	42	51	toluene/dodec[d]	0.405	0.143
poly-**98d**	7[e]	42	51	toluene		0.247

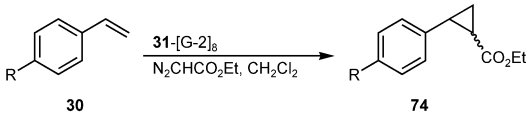
[a] Polymerization conditions: porogen/monomers mixture = 1.5 (w/w), 80 °C, 24 h. Polymers were crushed and washed with THF in a Soxhlet.
[b] Calculated from nitrogen analysis.
[c] Ru content after treatment with a stoichiometric amount of $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2 for 24 h.
[d] Mixture of toluene/1-dodecanol = 1.5 (w/w).
[e] Polymerization with the complex prepared with pybox (**98**) and $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2.

Table 18. Results obtained in the cyclopropanation reaction[a] catalyzed by pybox ligands **98a**,**b** and *poly*-**98a–d** by Mayoral et al.[100]

Cat.-Ru[b]	Run	Yield [%][c]	*trans*/*cis*[c]	*trans*-ee [%]	*cis*-ee [%][d]
poly-**98a**	1	31	85/15	85	41
	2	28	84/16	84	40
	3	11	75/25	45	20
poly-**98b**	1	32	78/22	76	41
	2	35	85/15	75	42
	3	28	75/25	44	18
poly-**98c**	1	26	77/23	54	18
	2	39	72/28	30	13
poly-**98d**	1	17	81/19	80	29
	2	9	78/22	84	30
98b	1	45	87/13	92	71
98a	1	34	90/10	88	70

[a] Reaction conditions: 5 mmol styrene (**30a**), 1 mmol of ethyl diazoacetate (**73**) (slow addition), 3 mol % Ru, CH_2Cl_2, rt. Catalyst was filtered, washed and dried before reuse.
[b] Catalysts were prepared by treatment of the ligand with $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2.
[c] Determined by GC at total conversion of diazoacetate.
[d] Determined by GC with a cyclodex-B column. Compounds (*R,R*)-**74a** und (*S,R*)-**74a** were the major products.

Table 19. Cyclopropanation reaction of substituted styrenes with ethyl diazoacetate catalyzed by dendritic ruthenium(II) porphyrin **31**-$[G-2]_8$ by Che et al.[67]



30 **74**

	Substrate	R	Product	Conversion [%]	Yield [%]	*trans*/*cis*
1	**30a**	H	**74a**	51	77	12
2	**30j**	Me	**74b**	54	98	14
3	**30g**	OMe	**74c**	81	80	16
4	**30h**	Cl	**74d**	40	65	8
5	**30i**	Br	**74e**	33	71	10

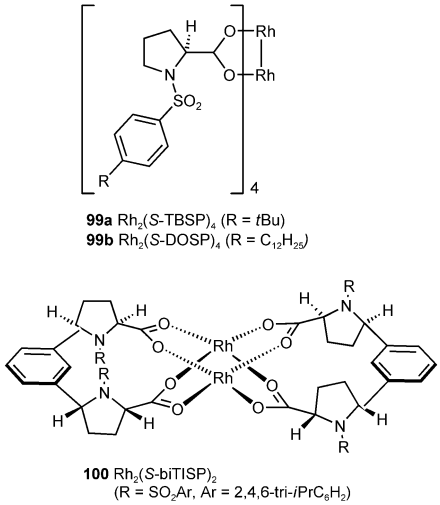
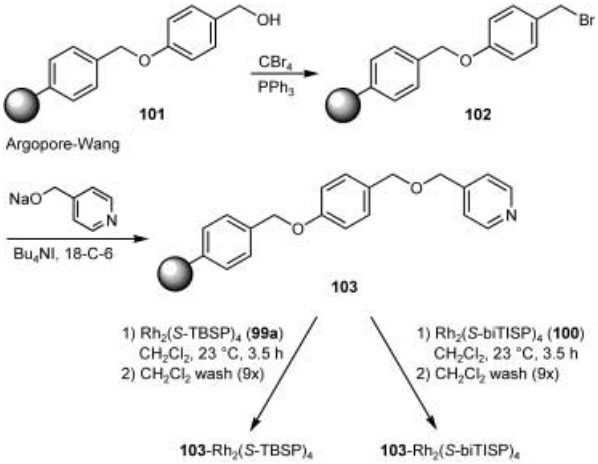


Figure 22. Chiral dirhodium complexes **100** for asymmetric cyclopropanation reactions by Davies and Nagashima.[104,107]



Scheme 16. Immobilization of dirhodium complexes **100** onto polymer-supported pyridines **103** by Davies and Nagashima.[104,107]

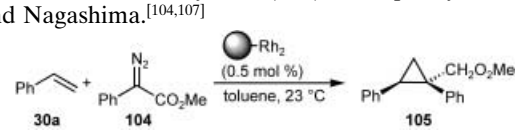
plexes, were published by Doyle and Bergbreiter et al. in 1992.[105] Considering that the dirhodium tetracarboxylates are the most generally used catalysts for carbenoid transformations, the immobilization of such catalysts is highly desirable.[106] The dirhodium complexes **99a**,**b**[107] as well as the conformationally restricted complex **100** (Figure 22) are well known as efficient catalysts for cyclopropanation reactions.[108]

Because of the broad utility of these catalysts and the high price of rhodium, Davies and Nagashima investigated the immobilization of analogous chiral catalysts on solid supports. The resultant systems are dirhodium tetraprolinates on polymer-supported pyridines **103**-Rh_2(*S*-TBSP)$_4$ and **103**-Rh_2(*S*-biTISP)$_2$ (Scheme 16). The catalytic activity of the catalysts **103**-Rh_2(*S*-TBSP)$_4$ and **103**-Rh_2(*S*-biTISP)$_2$ were evaluated in a standard cyclopropanation reaction of styrene with ethyl diazophenylacetate (**104**) (Table 20).

The authors found a dependence of the reaction rate on the rate of stirring, so all reactions were run with approximately the same stirring rate. As shown by using both catalysts **103**-Rh_2(*S*-TBSP)$_4$ and **103**-Rh_2(*S*-biTISP)$_2$ the yields were very good, even after the 15th run, but in the case of complex **103**-Rh_2(*S*-TBSP)$_4$ the enantioselectivity dropped steadily from 82% ee to 70% ee. Similar results were obtained in solution-phase cyclopropanation reactions using Rh_2(*S*-TBSP)$_4$ as catalyst.[109] In contrast, the catalyst **103**-Rh_2(*S*-biTISP)$_2$ cient even after the fifteenth cycle (nearly constant yields around 90% and selectivities from 85% ee in the first run to 88% ee in the last run). The only change is the reaction time increasing by a factor of 6 after 15 cycles. As is well established with corresponding soluble catalysts,[108,110] **103**-Rh_2(*S*-TBSP)$_4$ gave the (*S,S*)-cyclopropane **105** and G′-Rh_2(*S*-biTISP)$_2$ the (*R,R*)-cyclopropane **105**. In further reactions, Davies and Nagashima investigated the influence of different diazo compounds and using lower amounts of the catalyst **103**-Rh_2(*S*-biTISP)$_2$ (Table 21).

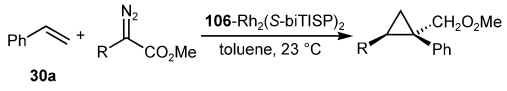
First it could be said that a catalyst amount down to 0.04 mol % is possible. The yields depended only slightly on the diazoacetate substrate, but the reaction

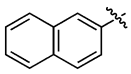
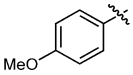
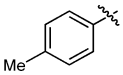
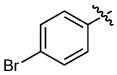
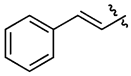
Table 20. Asymmetric cyclopropanation reaction of styrene (**30a**) with phenyldiazoacetate **104** using polymer-supported dirhodium catalysts **103** by Davies and Nagashima.[104,107]



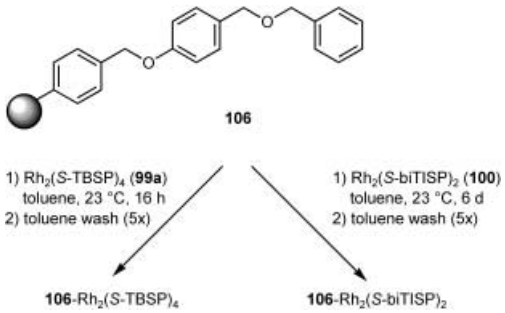
103-Rh_2(S-TBSP)$_4$				**103**-Rh_2(S-biTISP)$_2$			
Cycle	Time [min]	Yield [%]	ee [%]	Cycle	Time [min]	Yield [%]	ee [%]
1	10	92	82	1	18	91	85
2	17	91	78	2	23	91	86
3	14	89	73	3	26	90	87
4	14	89	70	4	36	90	87
				10	60	87	88
				15	92	89	88

Table 21. Asymmetric cyclopropanation reactions of styrene (**30a**) with aryl- and vinyldiazoacetates by Davies and Nagashima.[104,107]



Entry	R	Time [min]	Catalyst [mol %]	Yield [%]	ee [%]
1		180	0.04	88	88
2		120	0.1	89	74
3		60	0.1	90	80
4		60	0.1	89	93
5		60	0.1	87	90
6		420	0.1	82	68

times did so strongly. In addition, the recycling of catalyst **103**-Rh_2(*S*-biTISP)$_2$ was addressed with different styrenes in every cycle. Yields up to 94% and enantioselectivities up to 90% ee can be obtained. These results suggest that coordination of pyridine to Rh_2(*S*-biTISP)$_2$ greatly decreases its catalytic activity, and that in the **103**-Rh_2(*S*-biTISP)$_2$ catalyst, the "active" catalyst is not Rh_2(*S*-biTISP)$_2$ coordinated to the pyridine.[104] To prove this concept, the cyclopropanation reactions catalyzed by Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-biTISP)$_2$ with



Scheme 17. Dirhodium complexes on pyridine-free solid support **106** by Davies and Nagashima.[104,107]

additional 4-[3-(4-methyl-benzyloxy)propyl]pyridine were investigated. While good enantioselectivies were achieved, moderate to low yields were observed. Therefore, dirhodium complexes were immobilized onto a polymeric support **106** without a pyridyl residue (Scheme 17).

Using catalysts **106**-Rh_2(*S*-TBSP)$_4$ and **106**-Rh_2(*S*-biTISP)$_2$ the results obtained in cyclopropanation reactions with styrene were very good (yields up to 92% and enantioselectivities up to 85% ee). These experiments suggest that the catalyst in the pyridine-resin **103** is not the pyridine-coordinated dirhodium complex.

2.5 Asymmetric Hydroformylation Reactions

The hydroformylation of olefins is an efficient reaction leading to a C–C bond formation and addition of a valuable functional group ready for further transformation (Scheme 18).[111] The hydroformylation reaction is extensively used to obtain linear and branched aldehydes from the reaction of alkenes with hydrogen and carbon monoxide in the presence of a catalyst. The asymmetric hydroformylation of olefins is a direct route to optically active aldehydes, which are valuable pre-

cursors for a variety of pharmaceuticals and agrochemicals.

Stille et al. reported already in 1979 a very early case of an asymmetric hydroformylation reaction on a solid support[112] using transition metals and polymer-attached optically active phosphine ligands. 4,5-Bis[(diphenylphosphino)methyl]-1,3 dioxolane (DIOP) (**12**) and the corresponding dibenzophosphole (DIPHOL) derivatives were chosen as chiral ligands. In the first step copolymerization of ditosylates, styrene and divinylbenzene resulted in cross-linked beads which contained 10% incorporation of the ditosylate **110** (Figure 23).

In the next step, the ditosylate copolymer **110** was treated with either an excess of sodium diphenylphosphide or the sodium salt of dibenzophosphole. The corresponding polymer contained the optically active DIOP **109** or DIPHOL **111** derivatives. The active hydroformylation catalyst was prepared by addition of $[HRh(CO)(PPh_3)_3]$ to the polymeric diphosphine ligands. For the hydroformylation reaction, styrene was chosen as substrate. The *branched*/*normal* ratio of the aldehydes for the Rh-PS-DIOP catalyst **109** was about 6, for the homogeneous Rh-DIOP catalyst in liquid phase reactions it was 2. The Rh-PS-DIPHOL gave a ratio of up to 20. However, the enantioselectivities obtained were mediocre (up to 11%).

In 1986, Stille et al. showed a platinum-catalyzed asymmetric hydroformylation reaction with a polymer-attached optically active phosphine ligand **112b** (Figure 24).[113]

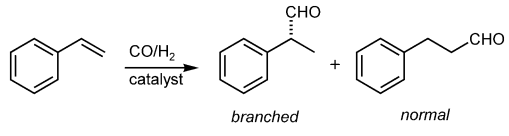
The copolymerization proceeds in the same procedure as in the example before. Both the soluble **112a** and the cross-linked polystyrene ligand **112b** were tested. Styrene, vinyl acetate, *N*-vinylphthalimide and norbornene were chosen as substrates. Stille et al. demonstrated that the polymer-supported catalysts showed in the presence of stannous chloride comparable rates and gave nearly the same optically yields as the homogeneous analogues, which is up to 65% ee for styrene, up to 58% ee for the vinyl acetate, up to 62% ee for *N*-vinylphthalimide and up to 20% ee for norbornene. Only lower branched to normal ratios were obtained by the use of polymer-supported ligands.

One year later, Stille et al. reported another phosphine ligand, the [(−)-BPPM] system which was immobilized by cross-linked polystyrene.[114] Treatment of the cross-linked polystyrene *poly*-[(−)-BPPM] with bis(acetonitrile)dichloroplatinum (II) gave *poly*-[(−)-BPPM]$PtCl_2$ **113**, which was used in the presence of stannous chloride to generate the active catalyst (Figure 25).

This catalyst results in a mediocre conversion for styrene of 22% in 10 days but a very high enantioselectivity of greater than 98% ee.

Nozaki, Hiyama et al. reported polymer-immobilized chiral phosphine-phosphite Rh(I) complexes **114b – d** (Figure 26).[115,116]

The vinyl-BINAPHOS derivatives **114b – d** were copolymerized with styrene derivatives to yield *poly*-**114b – d** and subsequently, these polymer-supported ligands were reacted with $Rh(acac)(CO)_2$. These complexes were used in the asymmetric hydroformylation



Scheme 18. Hydroformylation of olefins.[111]

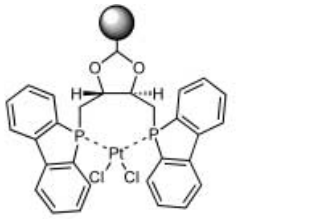


Figure 24. Polymer-bound chiral platinum complexes **112a**,**b** by Stille et al.[113]

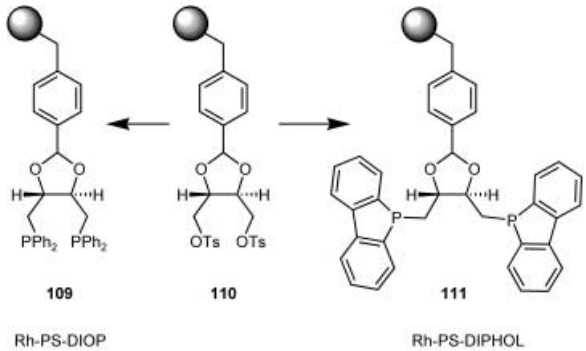


Figure 23. C_2-Symmetrical phosphine ligands **109 – 111** on polymeric support by Stille et al.[112]

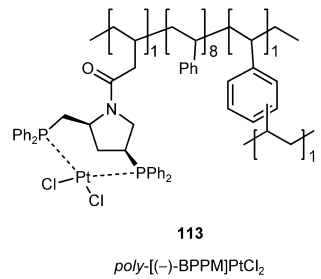


Figure 25. (2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)-methyl]pyrrolidine [(−)-BPPM] (**113**) cross-linked with polystyrene reported by Stille et al.[114]

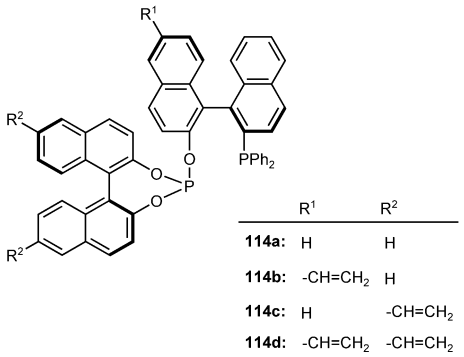


Figure 26. Phosphine-phosphane ligands **114a – d** by Nozaki, Hiyama et al.[115,116]

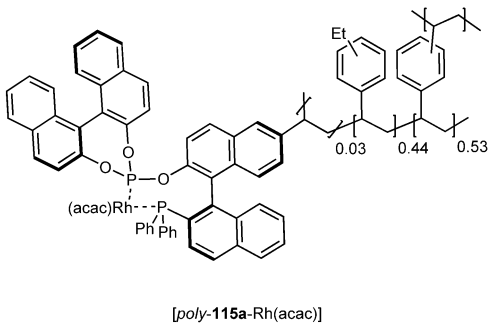


Figure 27. Catalyst [*poly*-**115a**-Rh(acac)] for the vapor-phase catalysis by Nozaki et al.[117]

Table 22. Asymmetric hydroformylation reaction[a] of styrene catalyzed by polymer-supported (*R,S*)-BINAPHOS derivatives *poly*-**114** by Nozaki, Hiyama et al.[115]

Run	Catalyst	*b*/*n*	ee [%]
1	Rh(acac) **114a**	89/11	92
2	[*poly*-**114b**-Rh(acac)]	84/16	89
3[b]	[*poly*-**114b**-Rh(acac)]	83/17	89
4[c]	[*poly*-**114b**-Rh(acac)]	80/20	81
5	[*poly*-**114c**-Rh(acac)]	90/10	87

[a] Substrate/catalyst ratio 2000: CO_2 10 atm, H_2 10 atm, 60 °C, 12 h, 6.2 mmol of styrene in 0.35 mL benzene in the present of the polymer catalyst ($3.1 \cdot 10^{-3}$ mmol of Rh), conversion of styrene to aldehydes > 99% over all runs.
[b] The polymeric ligand was prepared from a 3:87:10 mixture of **114b**, styrene and divinylbenzene (55% content).
[c] Hexane was used as solvent.

reaction with styrene and vinyl acetate as substrates. The results are shown in Table 22.

All runs were repeated at least three times without any loss of activity or selectivity. The results in Table 22 show that the activity and selectivity of the polymer-supported catalyst are comparable to the results with the corresponding homogeneous system. The group of Nozaki and Hiyama obtained similar results for vinyl acetate. While the conversion was moderate, the enantioselectivity was up to 92% ee.

Nozaki, Hiyama et al. reported[117] a polystyrene-supported (*R,S*)-BINAPHOS-Rh(acac) complex [*poly*-**115a**-Rh(acac)] for application in a vapor-phase asymmetric hydroformylation of gaseous substrates in a non-solvent system (Figure 27). Although vapor-phase reactions over heterogeneous catalysts are most widely used in industrial processes, the report by Nozaki was the first report of asymmetric vapor-phase catalysis.

For the vapor-phase catalysis highly volatile substrates such as 3,3,3-trifluoropropene, (*Z*)-butene and the less volatile olefin styrene were used. To compare the results, the polystyrene-supported (*R,S*)-BINAPHOS-Rh(acac) complex [*poly*-**115a**-Rh(acac)] and the corresponding soluble (*R,S*)-BINAPHOS-Rh(acac) **115b** were tested in two apparatuses. In apparatus A the catalyst [*poly*-**115a**-Rh(acac)] is placed at the center of a stainless autoclave without touching the liquid phase. In the apparatus B, the catalysts are used in the liquid phase. This method demonstrated a process to save solvents and the potential application of this catalyst for use in a flow system.

With the BINAPHOS ligand, Nozaki, Hiyama et al reported studies of the effect on the position of

Table 23. Asymmetric hydroformylation reactions with different olefins using immobilized catalysts *poly*-**115a** by Nozaki et al.[117]

	Substrate	Catalyst	Medium	Apparatus	H_2/CO [atm/atm]	*T* [°C]	t [h]	TOF [h^{-1}]	*i*/*n*	ee [%]
1	$CF_3CH{=}CH_2$	*poly*-**115a**	none	A	40/40	40	18	114	93/7	90 (*S*)
2		*poly*-**115a**	none	B	37/37	40	18	156	91/9	88 (*S*)
3		*poly*-**115b**	none	B	40/40	40	18	1.9	85/15	81 (*S*)
4		*poly*-**115b**	benzene	B	40/40	40	18	64	95/5	93 (*S*)
5	(*Z*)-2-butene	*poly*-**115a**	none	A	16/16	60	8	27	100/0	80 (*S*)
6		*poly*-**115a**	none	B	16/16	60	8	24	100/0	80 (*S*)
7		*poly*-**115b**	none	B	16/16	60	8	6.5 – 31	100/0	80 (*S*)
8		*poly*-**115b**	benzene	B	16/16	60	8	23	100/0	82 (*S*)
9	styrene	*poly*-**115a**	none	A	37/37	60	6	157	85/15	91 (*R*)
10		*poly*-**115b**	benzene	B	37/37	60	6	1050	87/13	91 (*R*)

Table 24. Hydroformylation reactions using catalysts **116** by Nozaki et al.[118]

Entry	Olefin	Ligand	S/C	Conv. [%]	*i/n*	ee (*iso*) [%]
1[a]	$PhCH{=}CH_2$	**116e**	2000	> 99	85/15	92
2[a, d]	$PhCH{=}CH_2$	**116a**	2000	> 99	89/11	92
3[a, e]	$PhCH{=}CH_2$	**116b**	2000	> 99	93/7	95
3[a, d]	$PhCH{=}CH_2$	**116c**	2000	> 99	85/15	90
4[b]	$AcOCH{=}CH_2$	**116e**	500	87	84/16	86
5[c, d]	$AcOCH{=}CH_2$	**116a**	500	98	84/16	92
6[c, d]	$AcOCH{=}CH_2$	**116c**	500	67	87/13	92

[a] $H_2/CO = 10$ atm/10 atm, 12 to 13 h.
[b] $H_2/CO = 40$ atm/40 atm, 25 h.
[c] $H_2/CO = 50$ atm/50 atm, 42 h.
[d] Ref.[115]
[e] Ref.[119]

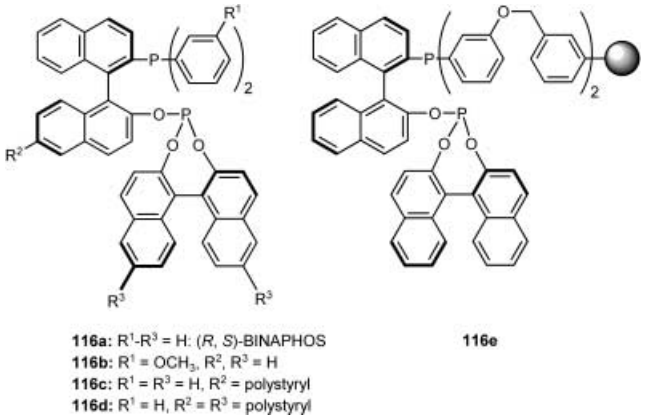


Figure 28. The derivatives of the chiral phosphine-phosphite ligand (*R*,*S*)-BINAPHOS **116a – e** by Nozaki et al.[118]

immobilization.[118] For these studies, different BINAPHOS ligands **116a – e** were synthesized, which are illustrated in Figure 28.

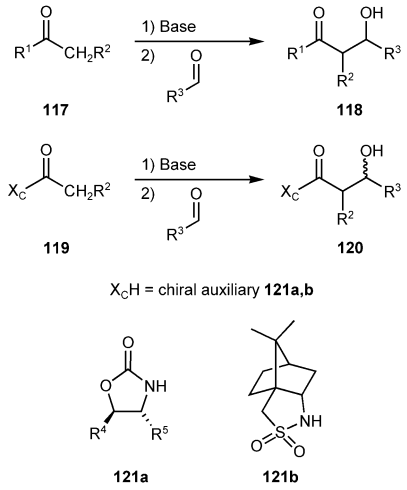
The best results were obtained using the ligand **116b**, which is immobilized only on one position on a polystyrene resin. Results are shown in Table 24.

3 Aldol and Aldol-Like Reactions

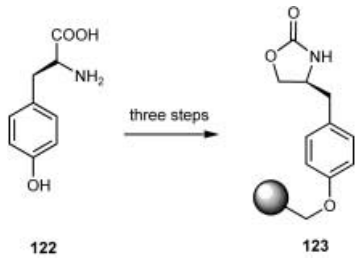
3.1 Classical Aldol Reactions

The aldol reaction is one of the oldest C–C bond formation reactions used in organic synthesis[120] and consequently the asymmetric aldol reaction is also one of the best examined methods for enantioselective synthesis (Scheme 19).[121]

Before we address the catalytic asymmetric aldol reaction with polymer-bound catalysts, some issues of the diastereoselective aldol reaction will be discussed. One of the most important chiral auxiliaries for the asymmetric aldol reaction is the oxazolidinone **121a**

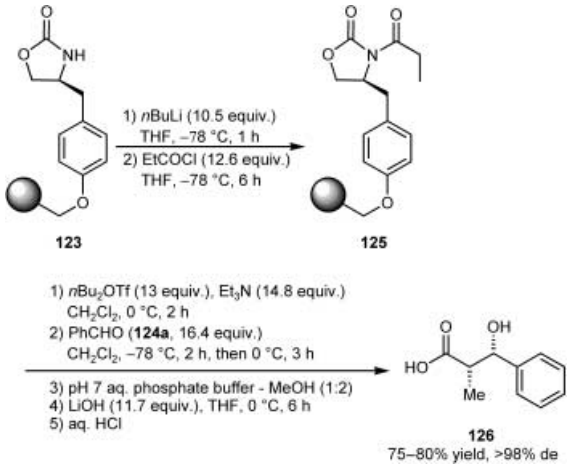


Scheme 19. Classical and asymmetric aldol reactions.[121]

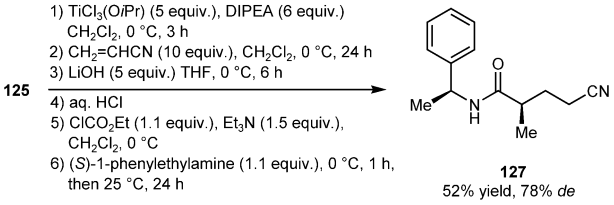


Scheme 20. Three-step synthesis of the resin-bound Evans' oxazolidinone **123** by Abell et al.[127]

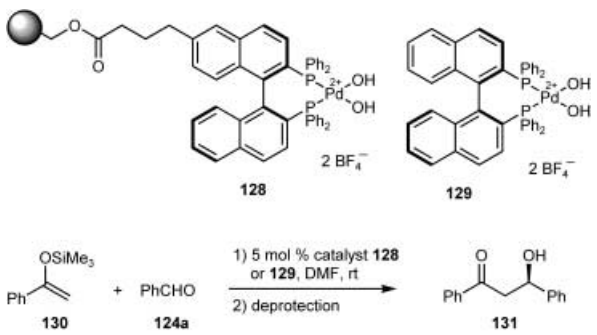
introduced by Evans.[121a] It works efficiently in alkylation reactions, conjugate addition reactions[122] and of course, in aldol reactions.[123] Resin-bound Evans' auxiliaries have been reported by Shuttleworth et al. for alkylation reactions in 1996,[124] Burgess et al. in 1997[125] and Davies et al.[126] In 1998, Abell et al. reported about a resin-bound Evans' oxazolidinone in aldol and conjugate addition reactions[127] synthesized on a solid support in three steps starting with tyrosine (**122**, Scheme 20).



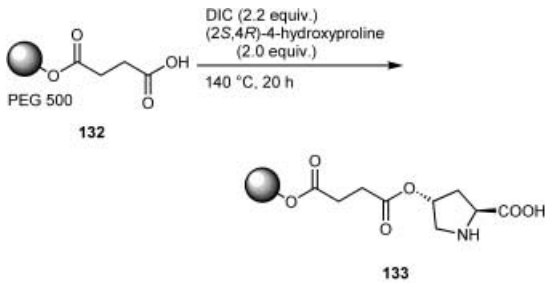
Scheme 21. Resin-supported asymmetric aldol reaction by Abell et al.[127]



Scheme 22. Conjugated addition on a resin-supported Evans' auxiliary.[122]



Scheme 23. Asymmetric aldol reaction catalyzed by BINAP complexes **128** and **129** by Fujii and Sodeoka.[128]



Scheme 24. Immobilization of proline ligand **133** by Cozzi et al.[132]

After propionalating the oxazolidinone part of the resin, the aldol reaction with benzaldehyde (**124a**) proceeds with a high degree of diastereoselectivity. The authors found only the *syn* diastereomer of 3-hydroxy-2-methyl-3-phenylpropionic acid (**126**) which is identical with the results reported by Evans et al. for the reaction in solution (Scheme 21).[123]

This solid phase-supported Evans' auxiliary can also be used in conjugated addition reactions (Scheme 22).[122]

In 1999, Fujii and Sodeoka introduced a polystyrene-supported BINAP-Pd(II) complex **128** in asymmetric aldol reactions.[128] In comparison with the soluble complex **129**[129] good yields and enantioselectivities in asymmetric aldol reactions of benzaldehyde (**124a**) and the enol silyl ether **130** were obtained as shown in Scheme 23 and Table 25.

Compounds with a proline backbone are well known as efficient catalysts in aldol[130] and asymmetric amination reactions.[131] Cozzi et al. reported recently on the immobilization of a 4-hydroxyproline catalyst on polyethylene glycol using PEG_{500} monomethyl ether (MeO-PEG) (Scheme 24).[132]

In aldol reactions with acetone and the four aldehydes **124a–d**, the β-hydroxyketones **135a–d** were obtained with good to excellent enantioselectivities (up to 98% ee, Scheme 25 and Table 26).

The best results were achieved with cyclohexanecarbaldehyde (**124d**) in DMSO (reaction time 130 h, rt) with a yield of 81% and $\geq$98% ee. After eight times of

Table 25. Asymmetric aldol reaction using aqua Pd complexes **128** and **129** by Fujii and Sodeoka.[128]

Entry[a]	Catalyst	H_2O (equiv.)	Time [h]	Yield [%]	ee [%]
1	**128**	–	17	65	74
2	**128**	–	35	35	76
3	**129**[b]	0.2	20	94	74
4	**129**[c]	0.2	40	81	71

[a] A solution of the catalyst (5 mol %), benzaldehyde (**124a**) and enol silyl ether **130** in dry or wet DMF was stirred at rt for indicated time. The product **131** was isolated after acid treatment. The ee was determined by HPLC analysis using DAICEL Chiracel OJ.[129a]

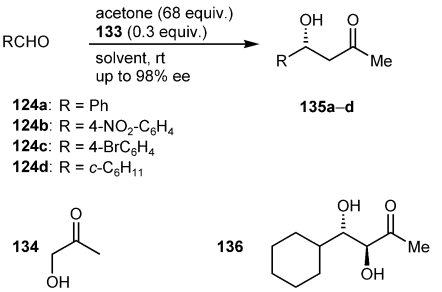
[b] Catalyst prepared from $[PdCl_2((R)\text{-BINAP})]$ and $AgBF_4$.

[c] Recovered catalyst from reaction of entry 3 was used.

Table 26. Catalytic enantioselective synthesis of aldol products **135a – d** by Cozzi et al.[132]

Entry	Aldehyde[a]	Solvent/Time [h]	Product	Yield [%][b]	ee [%]
1	**124b**	DMF/24	(*R*)-**135b**	35	67
2	**124b**	DMF/48	(*R*)-**135b**	68	77
3	**124b**	DMSO/48	(*R*)-**135b**	73	62
4	**124b**	acetone/48	**135b**	23	Not determined
5	**124b**	CH_2Cl_2/48	**135b**	8	Not determined
6	**124b**	toluene/48	**135b**	15	Not determined
7	**124c**	DMF/60	(*R*)-**135c**	45	59
8	**124d**	DMF/60	(*R*)-**135d**	55	63
9	**124d**	DMSO/130	(*R*)-**136**	81	$\geq$98
10	**124b**[c]	DMF/48	(*R*)-**135b**	63	77
11	**124b**[d]	DMF/48	(*R*)-**135b**	58	77
12	**124b**[e]	DMSO/130	(*R*)-**135b**	77	98

[a] All reactions were carried out with acetone, only entry 9 was carried out with hydroxyacetone (**134**).
[b] Yields of isolated products.
[c] Carried out with a catalyst sample recycled after use in entry 2.
[d] Carried out with a catalyst sample recycled after use in entry 2 and 10.
[e] Carried out with a catalyst sample recycled after use in entry 8.



Scheme 25. Asymmetric aldol reaction catalyzed by immobilized proline catalyst **133** reported by Cozzi et al.[132]

catalyst recycling, the yield decreased to 77%, but the enantioselectivity remained nearly on a constant level.

The substrates **124a, b** and **d** gave yields between 35% and 68% with enantioselectivities up to 77%. A high degree of diastereoselection by using the immobilized catalyst **133** was found in the aldol reaction of aldehyde **124d** with hydroxyacetone (**134**) to result in diol **136** in a yield of 48% with an *anti/syn*-ratio $>$20/1 and an ee $\geq$98% (non-supported proline: 60% yield, $>$99% ee, *anti/syn*-ration $>$20/1).

Very recently, Cozzi et al. reported new polymer (ethylene glycol)-supported proline ligands **137** and **138** as versatile catalysts for the enantioselective aldol and iminoaldol reactions (see below).[133] A comparison of the results of the aldol reaction shown in Table 27 with those obtained with non-supported proline derivatives at the same catalyst loading (0.3 – 0.4 mol %)[130c] showed that the use of PEG-prolines achieved similar yields and enantioselectivities. Among the non-supported catalysts, the best item for comparison is perhaps represented by (2*S*,4*R*)-4-acetoxyproline, which features an ester linkage at C-4 as in **137**.

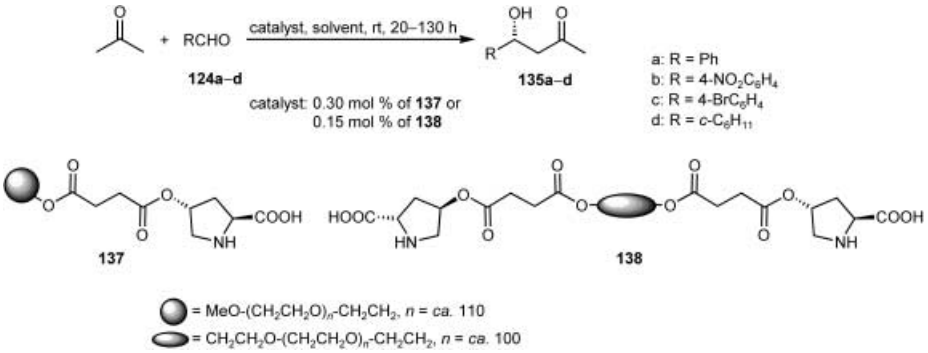
3.2 Iminoaldol Reactions

As mentioned before, Cozzi et al. reported the use of poly(ethylene glycol)-supported proline ligand **137** in iminoaldol reactions.[133] A comparison of the results shown in Table 28 with those obtained under similar conditions with non-supported proline[134] is difficult, since the reported syntheses of **140b** involved samples of the corresponding imines **139a** generated *in situ*. It must be noted, however, that the use of the *ortho*-methoxy isomer of **139**,[134b] led to the corresponding adduct in 50% yield and 40% ee. The reported results for the proline-catalyzed three-component synthesis of **140b**[134] differ slightly. List, working with 0.35 mol % of catalyst (DMSO, 48 h), claimed a 50% yield for a product having 94% ee;[134a] Barbas, working with 0.2 mol % of catalyst (DMSO, 24 h), isolated **140b** in 52% yield and 89% ee.[134b] In both cases the yields and enantioselectivities were lower than those observed with catalyst **137** in the two-component reaction. In addition, undisclosed amounts of aldol product **135b** and of the corresponding α,β-unsaturated ketone were also obtained in the proline-catalyzed three-component procedure.[134]

Cozzi et al. introduced the proline catalyst **137** also in aldol reactions using hydroxyacetone (**134**) as aldol donor.[133] It was found that the supported catalyst **137** efficiently promoted these synthetically relevant reactions in good yields and enantioselectivities (Table 29).

Condensation of hydroxyacetone (**134**) with cyclohexanecarboxyaldehyde (**124d**) carried out in DMF in the presence of 0.25 mol % of catalyst **137** afforded adduct (3*S*,4*S*)-**136** in 48% yield, $>$20:1 *anti*-diastereoselectivity and 96% ee. The use of DMSO as solvent resulted in identical stereoselectivities and yield. The latter was slightly lower than that observed in the

Table 27. Enantioselective synthesis of β-hydroxyketones **135a – d** catalyzed by polymer-supported proline derivatives **137** and **138** by Cozzi et al.[133]



Entry	Aldehyde	Solvent	Time [h]	Product	Yield [%][a]	ee [%][b]
1	**124b**	DMSO	20	(*R*)-**135b**	36	60
2	**124b**	DMSO	48	(*R*)-**135b**	73	62
3	**124b**	DMF	20	(*R*)-**135b**	35	67
4	**124b**	DMF	48	(*R*)-**135b**	68	77
5	**124b**	CH_2Cl_2	48	**135b**	8	Not determined
6	**124b**	toluene	48	**135b**	15	Not determined
7	**124b**	acetone	48	(*S*)-**135b**	23	21
8	**124b**	CH_3CN	48	(*R*)-**135b**	50	41
9	**124a**	DMF	60	(*R*)-**135a**	45	59
10	**124c**	DMF	60	(*R*)-**135c**	55	63
11	**124d**	DMF	60	(*R*)-**135d**	33	93
12	**124d**	DMSO	130	(*R*)-**135d**	81	≥ 98
13	**124b**[c]	DMSO	24	(*R*)-**135b**	67	74
14	**124b**[d]	DMF	48	(*R*)-**135b**	63	77
15	**124b**[e]	DMF	48	(*R*)-**135b**	58	77
16	**124b**[f]	DMF	48	(*R*)-**135b**	51	75
17	**124b**[g]	DMSO	130	(*R*)-**135b**	77	96
18	**124b**[h]	DMSO	24	(*R*)-**135b**	60	74

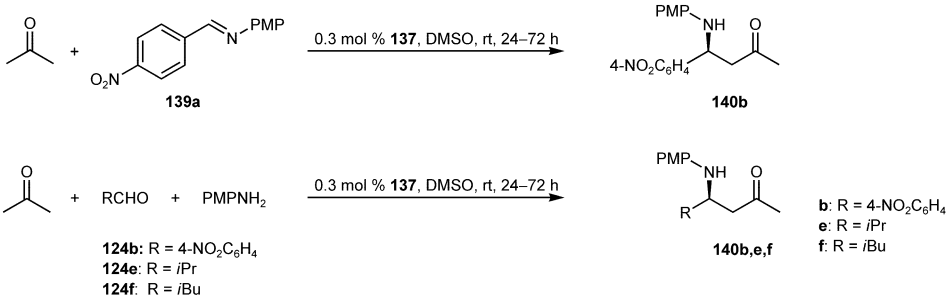
[a] Isolated yields. For each aldehyde, the highest yields were average values of at least duplicate experiments run on different scales. The variation in yield was ≤ 4%.
[b] As determined by HPLC on a chiral stationary phase. The ee values for the highest yielding reactions were average values of at least duplicate experiments run on different scales. The variation in ee was ≤ 2%.
[c] With catalyst **138**.
[d] Carried out with a catalyst sample recycled after use in entry 4.
[e] Carried out with a catalyst sample recycled after use in entries 4 and 14.
[f] Carried out with a catalyst sample recycled after use in entries 4, 14 and 15.
[g] Carried out with a catalyst sample recycled after use in entry 10.
[h] Carried out with a sample of catalyst **138** recycled after use in entry 13.

proline-catalyzed reaction carried out under identical conditions.[130c,135] The condensation reactions between hydroxyacetone (**134**) and imines **139a** and **139b** catalyzed by **137** were also investigated. Best conditions were established exploiting the synthesis of **141a**, that was obtained in 71% yield and as a 9:1 mixture of diastereomers after reaction in DMSO for 72 h. The relative configuration at the stereocenters of the major isomer was determined as *syn* by its conversion into the corresponding *trans*-oxazolidinone. The comparison with the results using the non-supported proline catalyst shows that in these condensation reactions **137** is a chemically less efficient catalyst than proline.[130c]

3.3 Mukaiyama Aldol Reactions

The Mukaiyama aldol reaction between enolsilanes and α,β-unsaturated carbonyl compounds catalyzed by Lewis acids has been known since 1974.[136] Recently, Salvadori et al. reported an insoluble polymer-bound bis(oxazoline) **6x** as a highly efficient heterogeneous catalyst precursor for the enantioselective Mukaiyama aldol reaction of ketene acetal **142a** and α-ketoester **143**.[38] Cu(II)-catalyzed reactions with the supported box **6x** were quite efficient. The reaction shown in Scheme 26 gave up to 90% yields, even after catalyst recycling for seven times (only the reaction time

Table 28. Enantioselective synthesis of β-aminoketones **140b, e, f** catalyzed by polymer-supported proline **137** by Cozzi et al.[133]



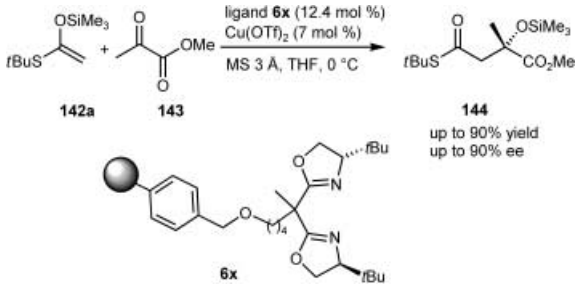
Entry	Imine[a]	Time [h]	Product	Yield [%][b]	ee [%][c]
1	**139a**	12	**140b**	18[d]	Not determined
2	**139a**	12	**140b**	29	Not determined
3	**139a**	24	(*S*)-**140b**	43	60
4	**139a**	48	(*S*)-**140b**	57	93
5	**139a**	72	(*S*)-**140b**	81	96
6	**124b** + $PMPNH_2$	48	**140b** + **135b**	10 + 10	Not determined
7	**124b** + $PMPNH_2$	48	**140b** + **135b**	29 + 7	Not determined
8	**124b** + $PMPNH_2$	48	**140b** + **135b**	16 + 11	Not determined
9	**124e** + $PMPNH_2$	24	(*S*)-**140e**	41	78
10	**124e** + $PMPNH_2$	48	(*S*)-**140e**	35	73
11	**124e** + $PMPNH_2$	72	(*S*)-**140e**	38	55
12	**124f** + $PMPNH_2$	24	(*S*)-**140f**	45	83
13	**124f** + $PMPNH_2$	48	(*S*)-**140f**	51	83
14	**124f** + $PMPNH_2$	72	(*S*)-**140f**	37	40
15	**139a**[e]	72	(*S*)-**140b**	71	96
16	**139a**[f]	72	(*S*)-**140b**	64	97

[a] In the reactions of entries 6–14 the imines were generated *in situ*.
[b] Isolated yields for reactions in DMSO (unless otherwise stated). Yields of entries 9–14 are for pure iminoalcohols. For each imine the highest yields were average values of at least duplicate experiments run on different scales. The variations in yield were $\leq 4\%$.
[c] As determined by HPLC on a chiral stationary phase or by comparison of optical rotation values. The ee values for the highest yielding reactions were average values of at least duplicate experiments run on different scales. The variations in yield were $\leq 2\%$.
[d] In DMF.
[e] Carried out with a catalyst sample recycled after use in entry 5.
[f] Carried out with a catalyst sample recycled after use in entries 5 and 15.

increased from 60 to 240 min. and, after the fifth cycle, the molecular sieve was renewed). The enantioselectivity was always around 90% ee.

3.4 Michael Addition Reactions

The Michael addition reaction is another very useful C–C bond forming reaction. A very efficient ligand for several reactions including the Michael addition reaction is 1,1′-bi-2-naphthol (BINOL) (**1a**)[22] forming chiral catalysts with main group elements,[137] transition metals[138] and rare earth elements.[139] It can be used in asymmetric hydrogenation,[140] dihydroxylation,[83,84] epoxidation,[141] or Diels–Alder[142] reactions. The first results to immobilize BINOL have been achieved by

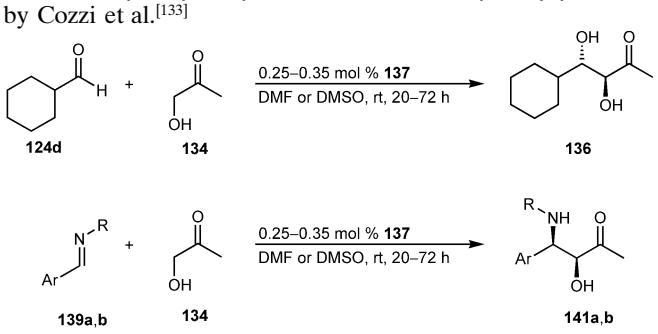


Scheme 26. Mukaiyama aldol reaction catalyzed by solid-supported bis(oxazoline) **6x** by Salvadori et al.[38]

grafting onto a sterically irregular polymer backbone (Figure 29)[23] or by cross-linking copolymerization.[24]

Shibasaki et al. employed this immobilized (*R,R*)-La-BINOL complex *poly*-**145a** (Figure 29) in an asymmet-

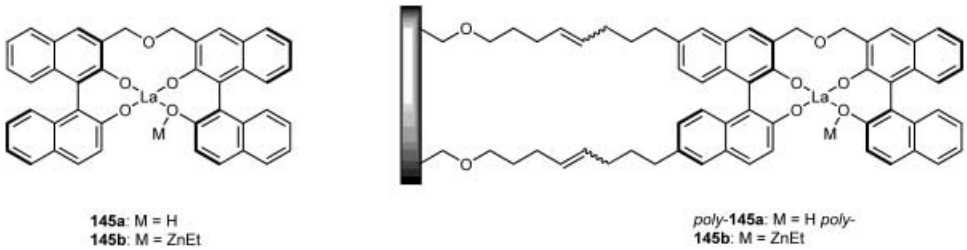
Table 29. Enantioselective synthesis of α,β-dihydroxyketone **136** and α-hydroxy-β-aminoketones **141a**,**b** catalyzed using polymer-supported proline **137** by Cozzi et al.[133]



139a, **141a**: Ar = 4-$NO_2C_6H_4$, R = PMP
139b, **141b**: Ar = Ph, R = 4-ClC_6H_4

Entry	Acceptor	Time [h]	Product	Yield [%][a]	*anti*/*syn*[b]	ee [%][c]
1	**124d**	48	(3*S*,4*S*)-**136**	48[d]	20:1	96
2	**124d**	60	(3*S*,4*S*)-**136**	45	>20:1	96
3	**124d**[e]	60	(3*S*,4*S*)-**136**	37	>20:1	96
4	**124d**[f]	60	(3*S*,4*S*)-**136**	28	>20:1	96
5	**139a**	48	(3*S*,4*S*)-**141a**	21[d]	1:4	96
6	**139a**	20	(3*S*,4*S*)-**141a**	33	1:5.6	76
7	**139a**	48	(3*S*,4*S*)-**141a**	73	1:8	83
8	**139a**	72	(3*S*,4*S*)-**141a**	71	1:9	94[g]
9	**139a**[h]	72	(3*S*,4*S*)-**141a**	69	1:9	92
10	**139b**	72	(3*S*,4*S*)-**141b**	70	1:5.6	93[i]

[a] Isolated yields for reactions in DMSO (unless otherwise stated). For products **136** and **141a**, the highest yields were average values of at least duplicate experiments run on different scales. The variations in yield were $\leq 4\%$.
[b] As determined by 300 MHz ^{1}H-NMR analysis of the crude reaction products.
[c] Reported values refer to the major isomer and were determined by HPLC on a chiral stationary phase. Highest ee values for **136** and **141a** were average values of at least duplicate experiments run on different scales. The variations in yield were $\leq 2\%$.
[d] In DMF.
[e] Carried out with a catalyst sample recycled after use in entry 2.
[f] Carried out with a catalyst sample recycled after use in entry 2 and 3.
[g] The ee of the *anti*-isomer was 40%.
[h] Carried out with a catalyst sample recycled after use in entry 8.
[i] The ee of the *anti*-isomer was 40%.



145a: M = H
145b: M = ZnEt

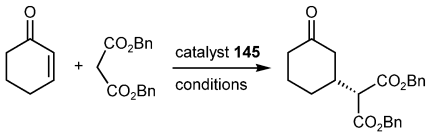
poly-**145a**: M = H *poly*-
145b: M = ZnEt

Figure 29. Polymer-supported La-BINOL catalyst *poly*-**145a**,**b** for asymmetric Michael addition reactions by Shibasaki et al.[23c]

ric Michael addition between the cyclohexenone (**146**) and dibenzyl malonate (**147**). The results depend on the reaction conditions (Table 30). With 10 mol % catalyst in THF for 45 min at 0 °C, a yield of 53% with an enantioselection of 85% ee was observed. Increasing the catalyst loading, temperature and reaction time showed a decrease of the enantioselectivity, but a slight increase of the yield. However, the problem using this immobilized BINOL systems is the diffusional limitation to generate catalytic complexes in which two or three BINOL ligands are bound to a central metal ion.[23c]

Sasai et al. synthesized a BINOL species attached on a soluble polymer (Scheme 27).[27] First, a BINOL deriv-

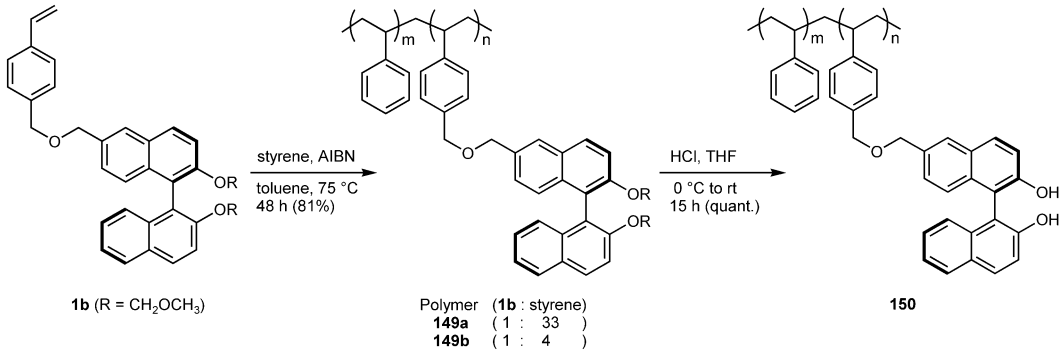
Table 30. Asymmetric Michael addition reaction by Shibasaki et al.[23c]



146 147 148a

Entry	Cat.[a] [mol%]	Solvent	T	Time [h]	Yield [%]	ee [%]
1[b]	**145a** [10]	THF	0 °C	45	53	85
2	*poly*-**145a** [20]	THF	rt	72	45	66
3	*poly*-**145a** [50]	DME	rt	87	56	78
5	*poly*-**42b** [20]	THF	rt	45	72	66

[a] **145a**: homogeneous La-linked BINOL; *poly*-**145a**: Polymer-supported La-linked BINOL; *poly*-**145b**: Polymer-supported La-Zn-linked BINOL.
[b] Ref.[143]



Scheme 27. Immobilized BINOL ligands **150** by Sasai et al.[27]

ative was coupled with a styryl tether by etherification affording monomer **1b** that was subsequently converted to the polymers **149a** [$M_w = 124000$ (PDI = 1.7)] and **149b** [$M_w = 9585$ (PDI = 1.4)], respectively, by free radical copolymerization with an excess of styrene.

Deprotection of the hydroxy groups furnished the BINOL ligand **150**. The catalyst can be separated from the reaction mixture with solvents like methanol or hexane. The catalytic activity of the BINOL ligands **150** was examined in the aluminum-lithium complex-catalyzed asymmetric Michael addition. The catalytic activity of polymer-supported BINOL **150** (Figure 30) was investigated in the aluminium-lithium complex-catalyzed asymmetric Michael addition. The enantioselectivity of AlLi-bis(binaphthoxide) catalyst **150** (ALB, probably a monomeric structure as shown in Figure 44 based on the results of the liquid phase catalyst)[28] supports the Michael addition between 2-cyclohexenone and dibenzyl malonate (**147**) with up to >99% enantiomeric excess, while the yield was 42% (68 h).

Attempts to increase the yield resulted in a decrease of the selectivity (down to 45% ee) and longer reaction times. The best ratio between yield and reactivity was

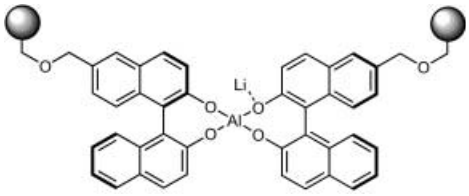
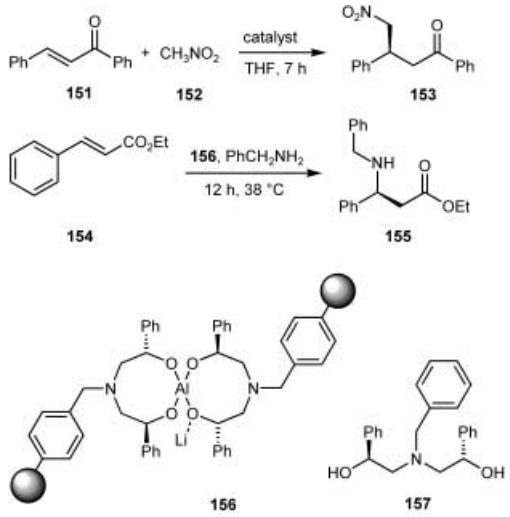


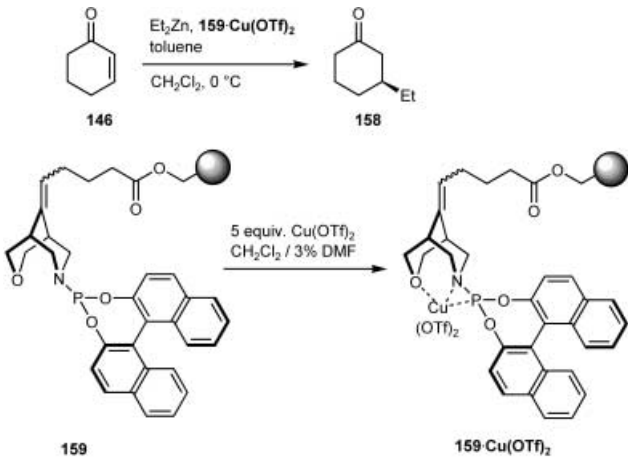
Figure 30. Plausible structure of the active polymeric catalyst **150** by Sasai et al.[27]

79% yield and 81% ee and 72% yield and 90% ee (for reaction conditions see Sasai et al.[27]).

In 2001, Sundararajan and Prabagaran reported a polymeric chiral aminodiol ligand (prepared by free radical copolymerization) and introduced it to generate a chiral aluminium-containing catalyst **156**.[144] The catalytic activity were explored in the Michael addition of 1,3-diphenylpropenone (**151**) and nitromethane (**152**) like shown in Scheme 28. The yields obtained were excellent (up to 92%) while the enantioselectivity was 51% ee. By using ethyl 3-phenylacrylate (**154**) and benzylamine with the same catalyst **156**, the enantiose-



Scheme 28. Asymmetric Michael reaction catalyzed by the aluminium-containing catalyst **156** of Sundararajan and Prabagaran (in all cases the ratio, [Al]/[Michael acceptor] was kept at 0.5).[144]



Scheme 29. Asymmetric conjugate addition reaction catalyzed by solid-supported phosphoramidate ligand **159** by Waldmann et al.[145]

lectivity increased up to 81% ee, but the yield decreased to 75%.

Recently, Waldmann et al. reported new solid-supported chiral phosphoramidite ligands like **159** for enantioselective conjugate addition reactions.[145] The enantioselectivities in 1,4-addition reactions of cyclohexenone (**146**) with diethylzinc (Scheme 29) were up to 40% ee (full conversion).

Very recently, Benaglia et al. introduced the PEG-supported *Cinchona* alkaloid **160** into 1,4-Michael addition reactions of cyclohexenone and thiophenol. The product was obtained in 75% yield and an enantioselectivity of 22% ee.[146]

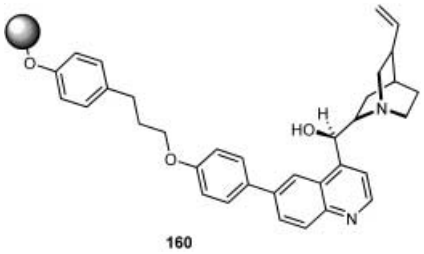
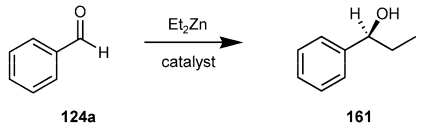


Figure 31. PEG-supported *Cinchona* alkaloid **160** by Benaglia et al.[146]

4 Asymmetric 1,2-Addition Reactions

4.1 Addition of Alkyl- and Phenylzinc Species to Carbonyl Compounds

One of the best, if not the most, studied asymmetric C–C bond formation reaction in the liquid phase is the reaction of dialkylzinc reagents, particularly diethylzinc, with aldehydes.



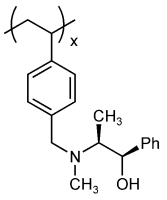
Scheme 30. Enantioselective addition of diethylzinc to benzaldehyde (**124a**).[147]

A wide range of various catalysts, substrates, conditions and other literature precedents with detailed experimental results and mechanistic studies is known (Scheme 30).[147] In addition, this reaction is often the first proof of a new ligand concept. Based on the elegant studies of Noyori,[148] it was known that the dimerization of the ligands plays an important role in liquid phase.

It was only a question of time when this reaction was carried out with ligands immobilized on a solid support.

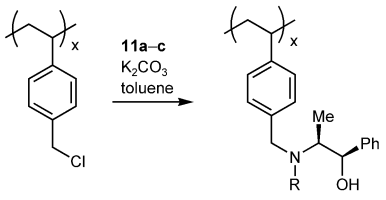
One of the first publications stems from the group of Soai et al. in the years 1988 and 1989.[149] Since in particular amino alcohols like ephedrine derivatives are efficient catalysts for this reaction, polymer-bound *N*-alkylephedrine analogues (Figure 32) were synthesized as efficient chiral catalysts for the enantioselective addition of dialkylzinc reagents to both aromatic and aliphatic aldehydes. Using these catalysts, up to 89% ee for aromatic and up to 80% ee for aliphatic aldehydes were obtained.

The synthesis of the chiral ligands starts with the preparation of the required *N*-alkylnorephedrines (Scheme 31). They were easily prepared from (1*S*,2*R*)-norephedrine hydrochloride (**163**) in two steps. The acylation with acid chlorides under alkaline reaction conditions (Schotten–Baumann) was followed by treat-



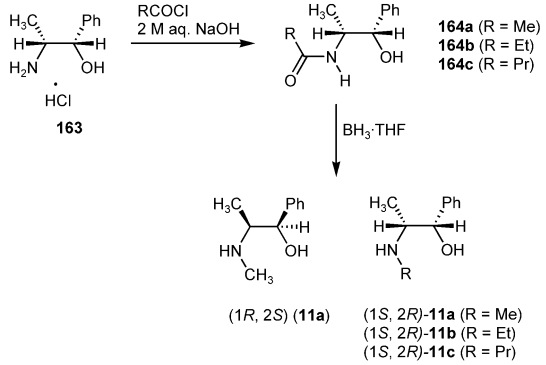
162a

Figure 32. Polymer-bound *N*-methyl-norephedrine **162a** as a chiral catalyst.[148]



162a (R = Me)
162b (R = Et)
162c (R = Pr)

Scheme 32. Synthesis of polymer-bound ephedrine catalysts **162a – c** by Soai et al.[149]



163

164a (R = Me)
164b (R = Et)
164c (R = Pr)

(1*R*, 2*S*) (**11a**)

(1*S*, 2*R*)-**11a** (R = Me)
(1*S*, 2*R*)-**11b** (R = Et)
(1*S*, 2*R*)-**11c** (R = Pr)

Scheme 31. Synthesis of ephedrine **11a** and the derivatives **11b**,**c** by Soai et al.[149]

ment of the corresponding amides with borane-THF complex to afford (1*R*,2*S*)-*N*-alkylnorephedrines.

The catalyst **162a** was then prepared in one step from (1*R*,2*S*)-*N*-alkylnorephedrines and chloromethylated polystyrene (1% divinylbenzene, chlorine content 0.8 mmol/g) under alkaline conditions (Scheme 32).

In the enantioselective addition of diethylzinc to aldehydes, the catalysts **162a – c** were used in the reaction of diethylzinc with benzaldehyde (**124a**) using 10 mol % catalyst loading in hexane at room temperature to afford (*R*)-1-phenylpropanol (**161**) in 83% chemical yield and in 89% enantiomeric excess (Table 31).

It is interesting to note that the immobilized ephedrine works better than the reported monomeric *N*-alkylephedrine (maximum 80% ee for benzaldehyde and nearly no enantioselection for aliphatic aldehydes).[150] Soai modified the monomeric chiral ligand with a methylene spacer to give 99% ee in liquid phase.[151]

Another ligand used in asymmetric liquid phase 1,2-addition reactions and Diels–Alder reactions is the TADDOL (**3a**) system.[30] The immobilization of TADDOL systems on polymer support **3f** was first reported by Seebach et al. in 1996 (Figure 33).[31] In 1999, Seebach et al. employed also dendritically cross-linked Ti-TADDOLate *poly*-**3b – e** as efficient catalysts under diffusion control in these reactions (Figure 33).[33] In the first step, dendritic extended TADDOLs **3b – e** with copolymerizable end groups were synthesized.[33] The next step includes the copolymerization with styrene and the loading with Ti(O-*i*-Pr)$_4$. The polymer-bound Ti-TADDOLates *poly*-**3b – e** were used for enantioselective

Table 31. Asymmetric addition of dialkylzinc derivatives to aldehydes[a] by Soai et al.[149]

	Aldehyde		Yield [%]	ee [%]	Configuration
1	C_6H_5CHO	Et_2Zn	83	89	*R*
2	*p*-ClC_6H_4CHO	Et_2Zn	78	83	*R*
3	*p*-$MeOC_6H_4CHO$	Et_2Zn	75	54	*R*
4	*o*-$MeOC_6H_4CHO$	Et_2Zn	79	51	*R*
5	2-naphthylCHO	Et_2Zn	78	56	*R*
6	$CH_3(CH_2)_5CHO$	Et_2Zn	71	21	*R*
7[b]	$CH_3(CH_2)_5CHO$	Et_2Zn	67	61	*S*
8	C_6H_5CHO	Me_2Zn	43	33	*R*
9[c]	$Me(CH_2)_7CHO$	Et_2Zn	88	80	*S*
10[d]	$MeCHCH_2CHO$	Et_2Zn	49	57	*S*
11[c]	*cyclo*-$C_6H_{11}CHO$	Et_2Zn	55	50	*S*

[a] Conditions: see ref.[148]
[b] Catalyst was prepared from (1*S*,2*R*)-2-(*N*-ethylamino)-1-phenylpropan-1-ol instead of (1*R*,2*S*)-(–)-ephedrine.
[c] Catalyst **162b**.
[d] Catalyst **162c**.

addition reaction of diethylzinc (X) to benzaldehyde (**124a**) with enantioselectivities up to 98% ee.[31–33] TADDOL ligands can also be immobilized on hydrophobic controlled-pore glass (CPG) silica gel giving rise to structures like **165** (Figure 33).[13]

The use of hydrophobic controlled-pore glass (CPG) has some advantages over organic supports; they are form stable and do not swell in solvents. For this reason, CPG supports could be used at non-ambient temperatures and at higher pressure. The solid support is chemically inert, only strong alkaline conditions and fluoride ions are not compatible.

Polymer-bound catalysts with low loading (0.1 mmol TADDOL/g polymer) gave the best rates. The enantioselectivity was always better than 80% ee. Quite remarkable is the fact that only the dendritic polymer makes over 20 cycles with a constant enantiomeric excess of 96% ee. The efficiency of the catalyst decreases if the length of the not branched chain is longer between the TADDOL unit and the polymeric backbone.

The polymer-bound catalyst *poly*-**3b** gave 1-phenylpropanol (**161**) in consistently $>96\%$ ee with rates which are comparable with low molecular-weight catalysts.

The immobilization of a TADDOL ligand was also performed on hydrophobic controlled-pore glass (CPG) silica gel (**165**) (Figure 33).[13] After loading with Ti(O-*i*-Pr)$_4$, the corresponding ligand was tested in the addition of diethylzinc on benzaldehyde (**124a**) giving rise to a 95% yield and $\leq 98\%$ ee. The immobilized chiral catalysts were used 20 times with only minor loss of selectivity. After 20 cycles the catalyst were washed with HCl, H_2O, and acetone, then reloaded with the titanate source and used again. It is remarkable that the same selectivity was observed as for the first run. These examples demonstrate that there is only a slight leaching of the center metal.

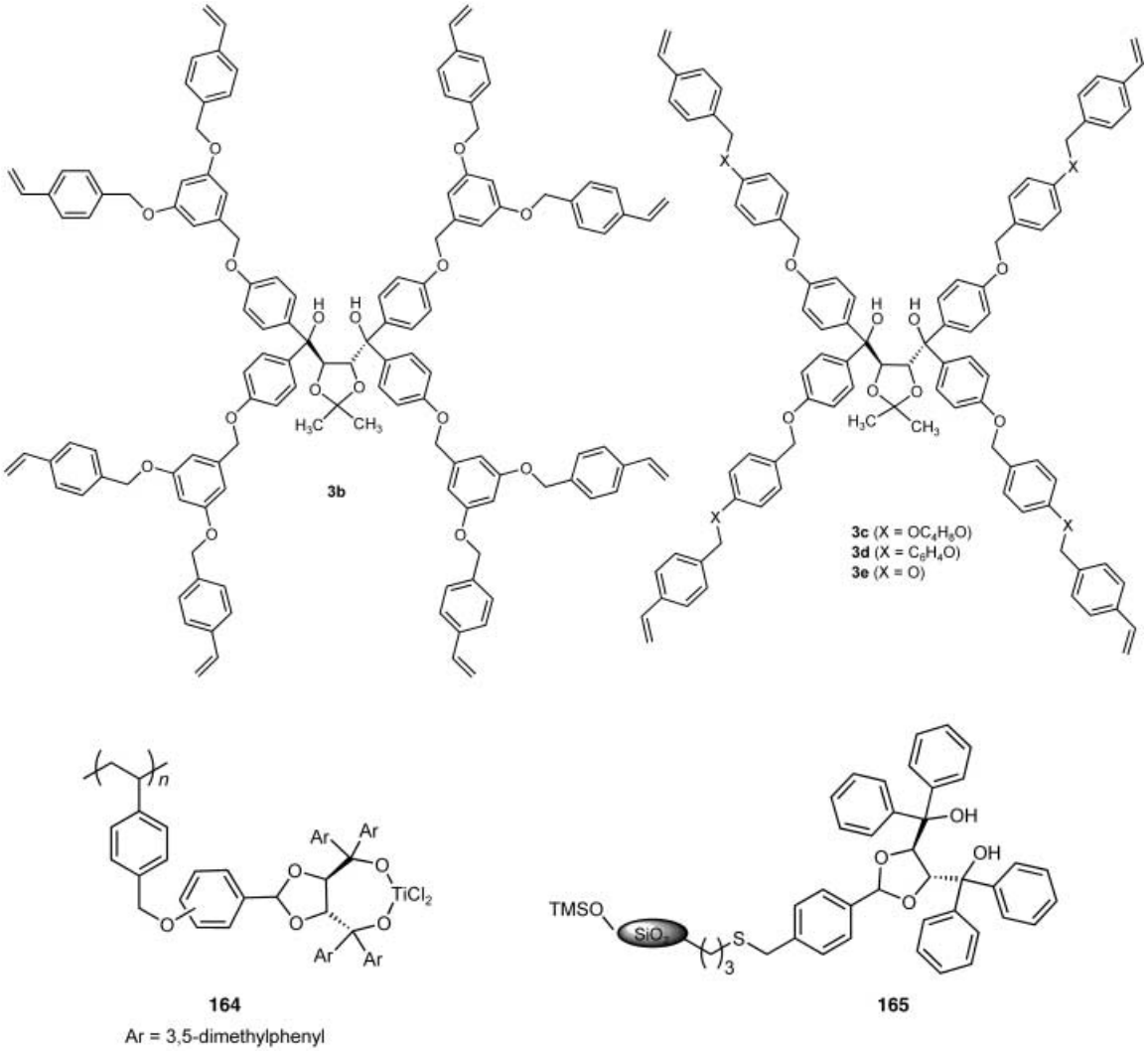
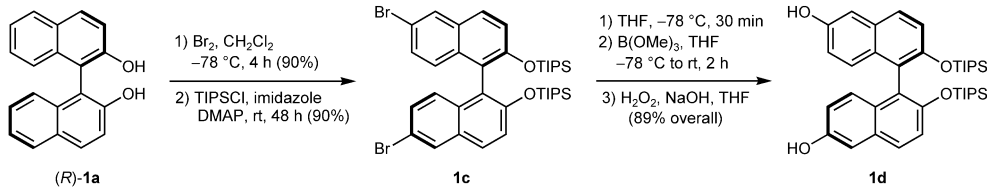


Figure 33. First polymer-supported TADDOL-system **164**,[31] styryl-substituted TADDOL derivatives **3b – e** for copolymerization[33] and TADDOL ligand **165** immobilized on hydrophobic controlled-pore-glass silica gel by Seebach et al.[13]



(*R*)-**1a** **1c** **1d**

Scheme 33. Synthesis of modified BINOL derivatives **1a, c, d** used for the preparation of polymeric catalyst by Seebach et al.[24]

Table 32. Addition of Et_2Zn to PhCHO (**124a**) catalyzed[a] by soluble BINOLs **1e – h** by Seebach et al.[24]

BINOL	Conversion [%]	ee [%]
1e	87	85
1f	79	83
1g	88	87
1h	78	86

[a] Conditions: 1 equiv. of PhCHO, 3 equiv. of Et_2Zn, 0.2 equiv. of Ti(O-*i*-Pr)$_4$ BINOLate, 1 equiv. Ti(O-*i*-Pr)$_4$, toluene, – 20 °C, 2 h.

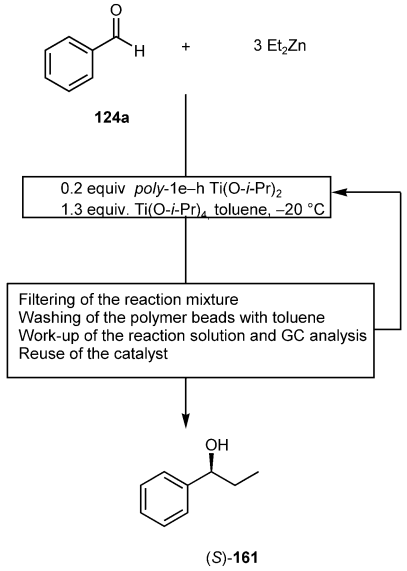
Table 33. Addition of Et_2Zn to PhCHO (**124a**) catalyzed[a] by solid-supported BINOLs *poly*-**1e – h** reported by Seebach et al.[24]

BINOL	Loading [mmol/g]	Time [h]	Conver. [%]	ee [%]
poly-**1e**	0.13	4	82	84
poly-**1f**	0.13	3	31	87
poly-**1g**	0.13	4	96	83
poly-**1h**	0.07	4	66	83

[a] Conditions: 1 equiv. PhCHO, 3 equiv. Et_2Zn, 0.2 equiv. Ti(O-*i*-Pr)$_2$ BINOLate, 1 equiv. Ti(O-*i*-Pr)$_4$, toluene, – 20 °C.

Recently Seebach et al. reported an immobilized BINOL ligand by cross-linking copolymerization of styryl derivatives with styrene for the enantioselective titanium-catalyzed addition of diethylzinc to aldehydes.[24] The preparation of the BINOL ligands **1e – h** started from BINOL. Bromination in the 6,6′-position and following protection of the hydroxy groups with the TIPS group (TIPS = triisopropylsilyl) resulted in dibromide **1c**. The next step was a replacement of the Br atoms by hydroxy groups. After copolymerization with cross-linkers (Figure 34), four solid-supported BINOL species were obtained.

The four BINOL ligands **1e – h** (Figure 34) were used in the addition of diethylzinc to benzaldehyde (**124a**) mediated by Ti complexes (Table 32).[24] Prior to immobilization of the BINOL cross-linkers on polystyrene, the effect of branching and spacers on the catalytic performance in homogeneous solution was explored.



(*S*)-**161**

Scheme 34. Multiple use of polymer-bound BINOLate *poly*-**1e – h** by Seebach et al.[24]

The selectivities and the conversions are comparable with the simple unsubstituted BINOLate (88% ee, 90% conversion after 2 h). Copolymerization of the BINOL cross-linkers (Figure 34) with styrene furnished the ligands *poly*-**1e – h** suitable for the addition of diethylzinc to benzaldehyde (**124a**) (Scheme 34).

The reuse of the catalyst is one of the important issues to be addressed in the use of immobilized catalysts. Seebach et al. showed that 20 catalytic runs proceeded with only minor loss of activity at a low loading of 0.13 mmol BINOL per gram of polymer.

With these results in hand, Seebach et al. showed that the immobilized catalysts have an activity comparable with the soluble analogues and that the multiple use of the catalyst is possible without or with only minor loss of activity.

Independently, Wang, Chan et al. also used polymer-supported BINOL ligand **1i** for the titanium-catalyzed diethylzinc addition to both aromatic and aliphatic aldehydes (Figure 35)[152] discovering that the new ligand works better than its "free" analogue [Ti(BINOL)-(O-*i*-Pr)$_2$]. A range of 57 – 99% ee as well as 78 – 97% yields was obtained.

In 1997, Pu et al. employed the sterically regular chiral polybinaphthol **1j** (Figure 36) in catalytic alkylation

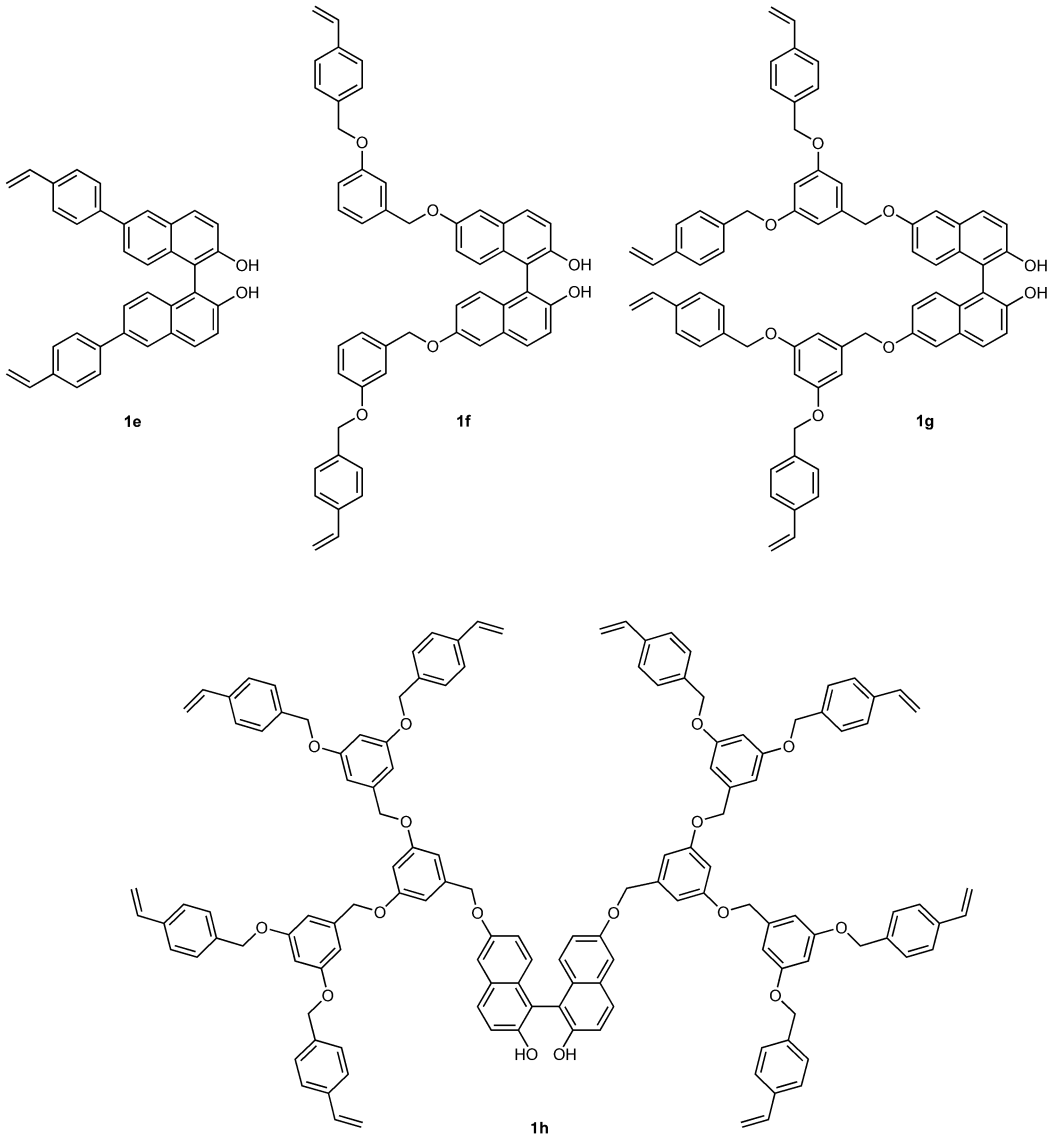


Figure 34. BINOL cross linkers **1e** – **1 h** by Seebach et al.[24]

reaction.[25] All the catalytic reactions were carried out at 0 °C in the presence of 5 mol % (based on the binaphthyl unit) of the chiral ligand. The soluble polymer was easily recovered by simple addition of methanol causing precipitation. The results are listed in Table 34.

The reactions are completed within 12 – 16 hours for aromatic aldehydes and 3 – 4 days for aliphatic aldehydes.

Another soluble optically active polymer-bound BINOL system **1k** was published by Pu et al. in 1999 (Figure 36).[153] The new soluble dendrimer **1k** was tested in enantioselective reactions of aldehydes with diethylzinc and is particularly effective in the presence of Ti(O-*i*-Pr)$_4$.

In the case of 20 mol % ligand and 1.4 equivalents of Ti(O-*i*-Pr)$_4$ in toluene at 0 °C and 5 h, complete conversion and 90% ee for 1-naphthaldehyde and complete conversion and 89% ee for benzaldehyde (**124a**) were observed. This soluble dendrimer **1k** is also reusable. In these catalytic reactions, the soluble dendrimer ligand could be easily recovered from the reaction mixture by

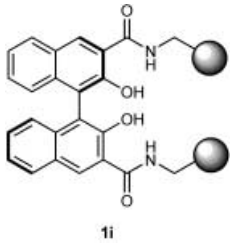
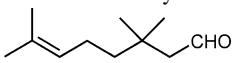


Figure 35. Polymer-supported BINOL ligand **1i** by Wang, Chan.[152]

Table 34. Addition of diethylzinc to aldehydes[a] with catalyst **1j** reported by Pu et al.[25]

Aldehyde	Yield [%]	ee [%]	Configuration
benzaldehyde	89	92	*R*
p-methylbenzaldehyde	90	93	*R*
p-chlorobenzaldehyde	94	93	*R*
p-anisaldehyde	84	88[c, d]	*R*
cinnamic aldehyde	86	90[c]	*R*
	67	83[c]	$[\alpha]_D$: −13.25 (*c* 1.95, THF)
n-$C_8H_{17}CHO$	89	74	*R*
cyclohexanecarbaldehyde	70	83[c]	*R*
n-$C_5H_{11}CHO$	65	74[c]	*R*

[a] Conditions: see ref.[42]
[b] All ee values were determined by GC with a chiral stationary phase.
[c] The recycled polymer was used.
[d] The ee was measured by HPLC on chiral stationary phase.

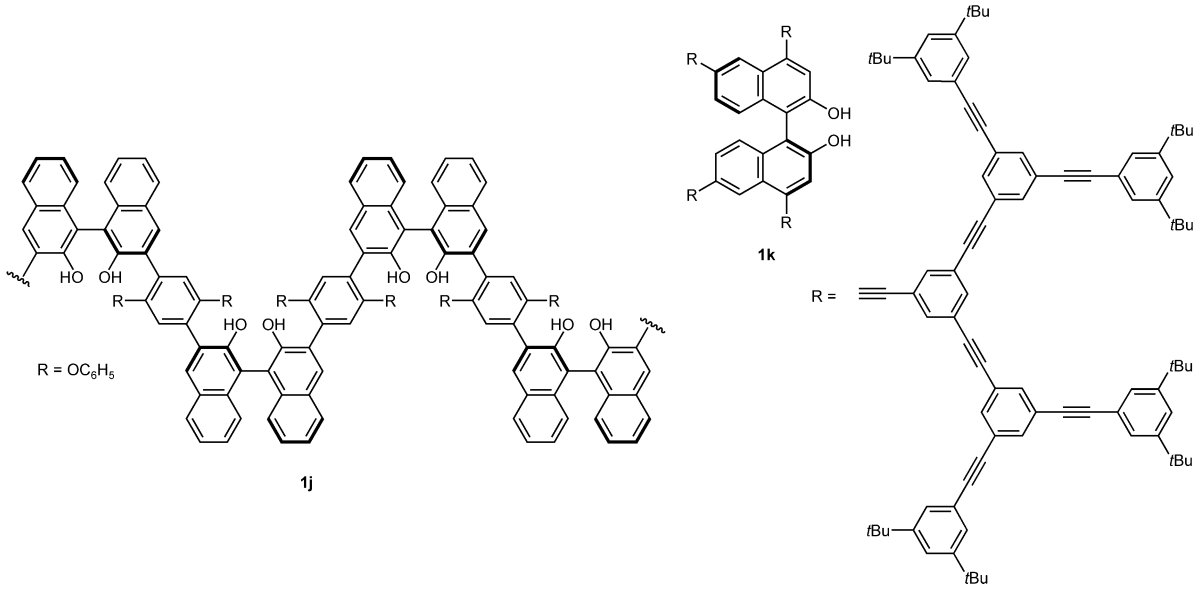


Figure 36. Sterically regular chiral polybinaphthol **54**, and the soluble dendrimer **1k** based on BINOL by Pu et al.[25,153]

precipitation with methanol. The product and other reagents remain in solution due to the large size differences between them and the dendritic molecule.

While Fan et al. reported a soluble dendritic BINOL ligand,[154] Sasai et al. introduced a soluble polymer-supported BINOL ligand.[153]

Very recently, Chan et al. established the dendrimeric BINOL-catalyst **1l–n** (Figure 37) into asymmetric diethylzinc addition reactions to aldehydes and obtained moderate to very good yields (77–97%) and moderate enantioselectivities (up to 62% ee).[29]

In a cooperation between the groups of Leadbeater and Bräse, polymer-bound 1-aryl-3-alkyltriazenes **167a–h** were investigated as modular ligands for catalysis (Figure 38).[155] A range of di- and trisubstituted triazenes

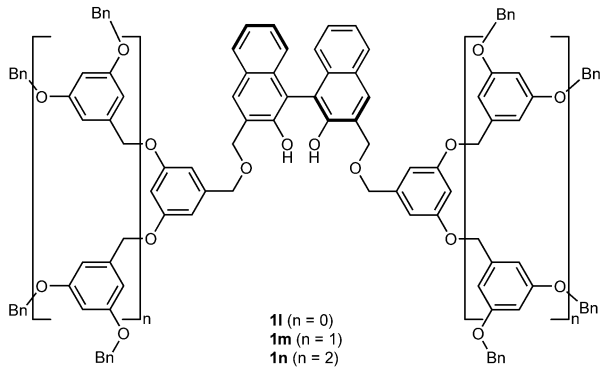


Figure 37. BINOL-catalyst **1l–n** synthesized by Chan et al.[29]

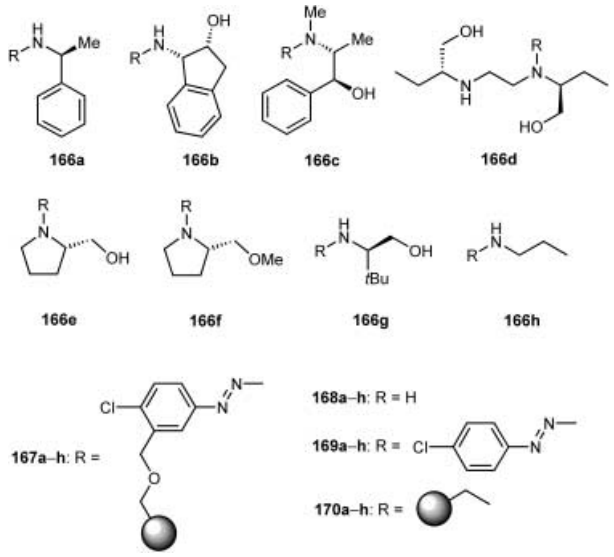


Figure 38. Polymer-bound 1-aryl-3-alkyltriazenes by Bräse, Leadbeater et al.[155]

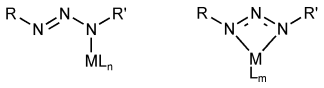
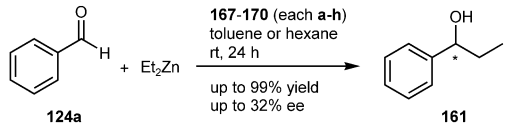


Figure 39. Binding modes in metal triazenes.[155]



Scheme 35. Activity of the polymer triazenes and metal complexes used by Bräse, Leadbeater et al.[155]

have been synthesized from a polymer-supported diazonium salt and various achiral and chiral primary and secondary amines **168a – h**. The new triazenes obtained were treated with transition metal salts to form polymer-supported metal complexes (Figure 39) first in a general screen and then in a specific manner.

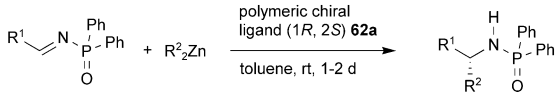
A range of transition metal salts, namely $Co(acac)_3$, $Cu(OTf)_2$, $FeCl_2$, $Pd(OAc)_2$, $Ti(O\text{-}i\text{-}Pr)_4$ and $Zr(acac)_4$ were used and screened.

The polymer-supported triazenes **167a – h** showed that metal coordination was possible and that stable complexes were formed.

The initial reaction of choice for assessing the activity of the polymer triazenes and metal complexes derived from them was the addition of diethylzinc to benzaldehyde (**124a**). In this case, an enantioselection of up to 32% ee was obtained (Scheme 35).

Polymer-supported norephedrine derivatives **162a** are suitable for the addition of diethylzinc on aldehydes (Scheme 32),[149,151] and the enantioselective addition of

Table 35. Enantioselective ethylation of imines with dialkylzinc by Soai et al.[156]



Entry	R^1	R^2	Yield [%]	ee [%]
1	Phenyl	Et	70	84
2	1-Naphthyl	Et	65	62
3	2-Naphthyl	Et	61	85
4	2-Furyl	Et	31	69
5	Phenyl	Me	46	86

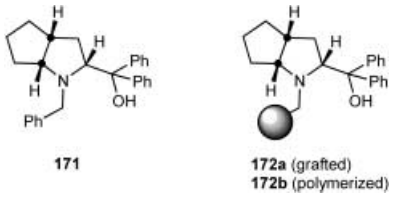


Figure 40. New supported β-amino alcohols **172a**,**b** by Luis and Martens et al.[157]

dialkylzinc reagents giving rise to *N*-diphenylphosphinylimines.[156]

Recently, Luis and Martens et al. reported on newly supported β-amino alcohols like **172a**,**b** for the enantioselective addition of diethylzinc to benzaldehyde (**124a**) under flow conditions (Figure 40).[157] The synthesis started from grafting of the ligand **171** on Merrifield resin and subsequent polymerization with divinylbenzene and vinylbenzene in the presence of AIBN. Ligand amounts from 2 to 20 mol % were introduced in the diethylzinc addition reaction to benzaldehyde (**124a**) catalyzed by **171** with yields ranging from 74 to 88% and enantioselection from 70 to 90% ee for the *R*-benzyl alcohol. The results achieved by using catalyst **172a** (10 mol %) were also very good (yield 83% and enantioselectivity 89% ee), even after recycling.

With these results in hand, Luis and Martens developed flow-bed reactors. The chiral macroporous monolithic column allowed the design of a flow system in which the column was attached to a pump and the reaction mixture was pumped continuously through the chiral column over a period of 24 h. After this period, the pump was stopped and the reaction was quenched and analyzed. Yields between 80 and 85% and enantioselectivities of 99% ee were observed, even after the fourth cycle of the chiral column.

Very recently, Bedekar et al. reported polymer-anchored chiral amino oxazolines **173a**,**b** (Figure 41) as effective catalysts for enantioselective addition of diethylzinc to aldehydes.[158] Moderate to good enantioselectivities in addition reactions of diethylzinc to

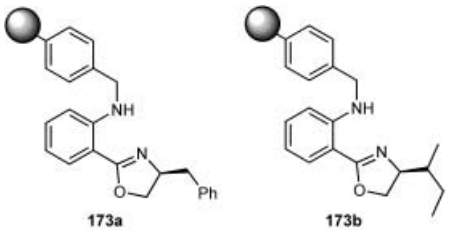


Figure 41. Polymer-anchored chiral amino oxazolines **173a**,**b** introduced by Bedekar et al.[158]

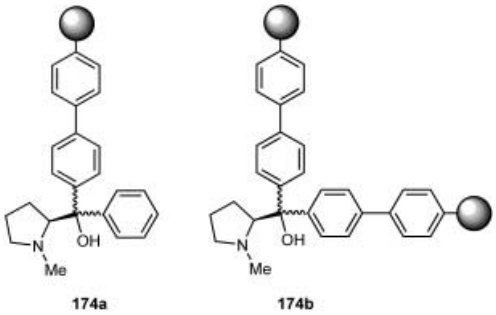


Figure 42. Polymer-supported prolinol catalysts **174a, b** introduced for asymmetric diethylzinc addition reactions to aldehydes by Hodge et al.[159]

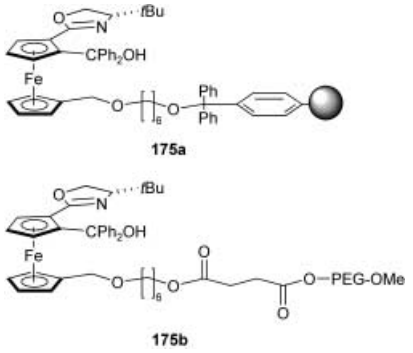


Figure 43. Immobilized ferrocenyl ligands **175a, b** reported by Bolm et al.[160]

benzaldehyde (**124a**) and good enantioselectivities (ee up to 95%) were obtained in addition reactions of diethylzinc to different aromatic aldehydes.

Good to excellent enantioselectivities in diethylzinc addition reactions to aldehydes catalyzed by polymer-supported prolinol catalysts **174a**,**b** were reported by Hodge et al. (Figure 42).[159] The difference between catalyst **174a** and **174b** is that prolinol **174b** is immobilized by "double binding" onto the polymer support while prolinol **174a** is immobilized by "mono binding" onto the polymer support. Hodge et al. obtained slightly lower enantioselection by using catalyst **174b**, nevertheless, the results were very good for the enantioselective diethylzinc addition to aldehydes.

Recently, Bolm et al. reported the immobilization of chiral ferrocenyl ligands **175a**,**b** and their application in enantioselective phenyl transfer reactions to different

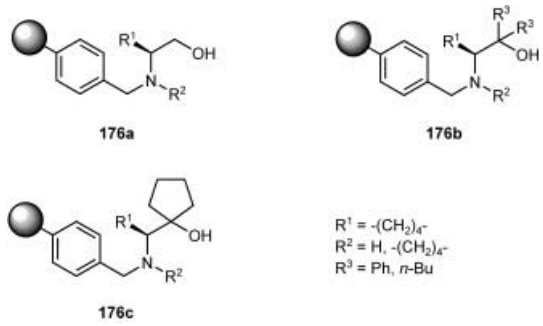


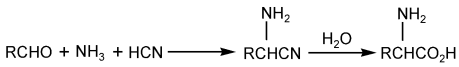
Figure 44. Immobilized amino alcohols **176a–c** by Martens et al.[161]

aldehydes (Figure 43)[160] causing excellent enantioselectivities (up to 97% ee) which decreased after recycling (four times) only very slightly.

Very recently, Martens et al. reported the development of small focused libraries of supported amino alcohols as an efficient strategy for the optimization of enantioselective heterogeneous catalysts for the diethylzinc addition to benzaldehyde.[161] The amino alcohols **176a–c** shown in Figure 44 were introduced to 1,2-addition reactions with yields up to 99% and enantioselectivities up to 80% ee. Martens et al. showed that the activity and stereoselectivity depends on the substituents.

4.2 Strecker Reactions

The Strecker reaction is one of the oldest three-component reactions giving rise to the valuable α-amino acids after hydrolysis (Scheme 36).



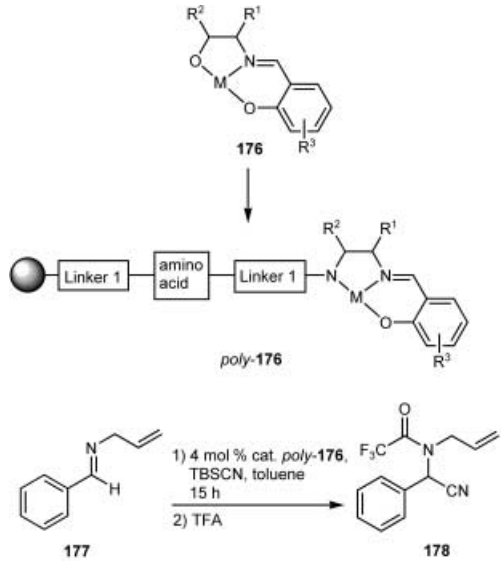
Scheme 36. Strecker synthesis leading to racemic α-amino acids.

For a long period, essentially no efficient asymmetric Strecker reaction was reported. However, within the last decade this challenging problem was tackled successfully by various groups.

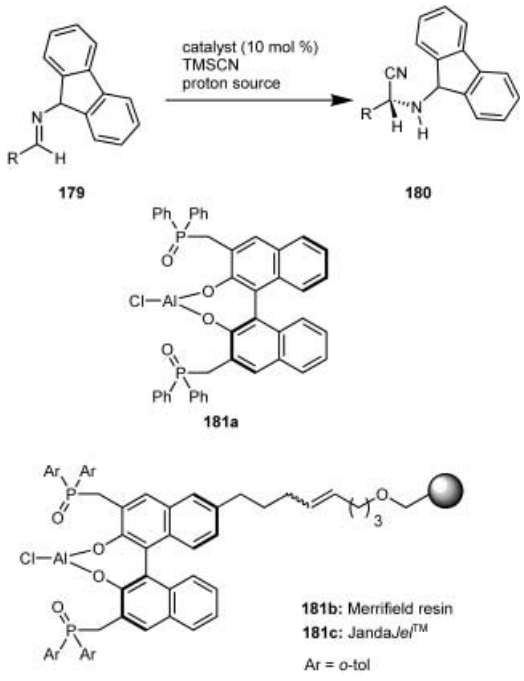
Sigman and Jacobsen reported polymer-bound catalysts **176** for the asymmetric Strecker reaction (Scheme 37).[162] Immobilized Schiff bases optimized by a parallel synthesis library were used as catalysts for the hydrocyanation of imines.

Three libraries were synthesized by this strategy. In the first library, different metal ions were tested. However, the best result (19% ee) was observed in the absence of any metal ion.

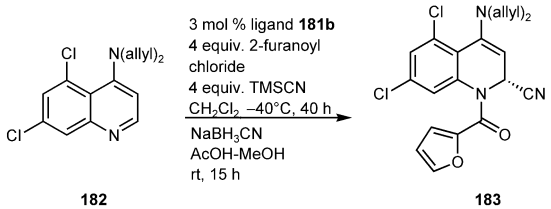
Two libraries with 48 and 132 members were then synthesized and screened in the absence of any metal ion. In this case, enantioselectivities up to 80% ee were



Scheme 37. The concept for the immobilization of the tridentate Schiff base ligands **176** and asymmetric Strecker type reaction with immobilized Schiff base ligands *poly*-**176** by Jacobsen et al.[162]



Scheme 38. Enantioselective Strecker type reaction with polymer-supported bifunctional catalyst **181c**.[163]



Scheme 39. Enantioselective Reissert-type reaction by Shibasaki et al.[164]

Table 36. Enantioselective Strecker reaction catalyzed by **181c** by Shibasaki et al.[163]

Entry	Imine; R =	Time [h]	Yield [%]	ee [%]
1	Phenyl	60	98	87
2	*p*-MeC_6H_4	64	100	83
3	*p*-ClC_6H_4	59	98	85
4	*p*-$MeOC_6H_4$	41	98	83
5	3-Furyl	66	97	86
6	(*E*)-PhCH=CH	66	96	83

Table 37. Enantioselective Reissert-type reaction using homogeneous **181a** and solid-supported catalyst **181b** by Shibasaki et al.[164]

Entry	Cycle	Catalyst	Yield [%]	ee [%]
1	–	**181a**	91	93
2	1	**181b**	92	86
3	2	**181b**	93	84
4	3	**181b**	93	79
5	4	**181b**	92	64

observed while the soluble counterpart resulted in 91% enantiomeric excess.

Shibasaki et al. showed an enantioselective Strecker type reaction of α,β-unsaturated imines **179** promoted by a Janda*Jel*™-supported bifunctional catalyst **181c** on a level of 10 mol % (Scheme 38) in the presence of *t*-BuOH (110 mol %).[163] The amino nitriles **180** were produced in excellent yields and 83 – 87% enantiomeric excess. The substrates and the results are shown in Table 36.

It is possible to reuse the catalyst in five cycles with a slight loss of activity and selectivity (98 – 83% yield and 77 – 87% enantiomeric excess).

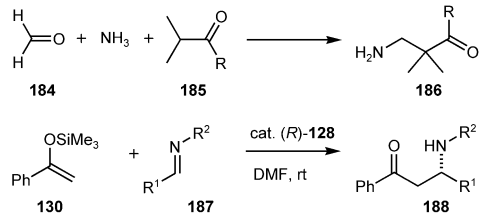
With the ligand **181b** a variant of a Strecker-type reaction, specifically a Reissert-type reaction, was explored as a key step in the synthesis of NMDA receptor antagonist (–)-L-689,560.[164] Treatment of the quinoline **182** with 2-furanoyl chloride and TMSCN gave rise to the *N*-acyldihydroquinoline **183** (Scheme 39).

The immobilized ligand **181b** showed comparable yields to the homogeneous ligand **181a**, while a slightly lower enantioselectivity occurred (Table 37).

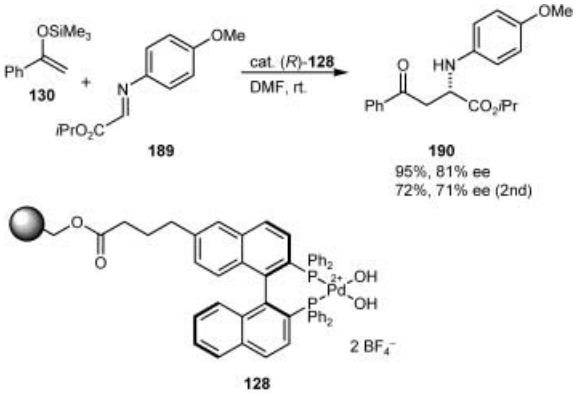
The solid-supported ligand **181b** is reusable with up to four cycles (Table 37), while the enantioselectivity of the product is slightly decreasing.

4.3 Mannich Reactions

Less elaborated asymmetric C–C bond forming reactions on solid supports are Mannich and Mannich-type reactions (Scheme 40).



Scheme 40. Classical Mannich reaction and asymmetric Mannich-type reaction.



Scheme 41. Asymmetric Mannich-type reaction with solid-supported BINAP ligand **128** by Sodeoka et al.[128]

To our knowledge, the only example was reported by Fujii and Sodeoka in the year 1999.[128] Based on the Mannich-type addition of enol ethers to imines derived from glyoxylates to yield acylalanates, Sodeoka used a polymer-supported BINAP-Pd(II) complex **128** (Scheme 41).[165]

Starting from enol silyl ether **130** and the imine **189** in the presence of the solid-supported BINAP-Pd(II) complex **128** (20 mol % Pd calculated as 0.41 mmol/g), the amino acid derivatives **190** are produced in good yields and enantioselectivities. The reuse the ligand is possible (Scheme 43), but with concomitant lower activity and selectivity. This ligand is also suitable for aldol reactions (see Aldol and Aldol-like Reactions above).

4.4 Carbonyl Ene Reactions

Another important enantioselective Lewis acid-catalyzed carbonyl addition reaction of π-nucleophiles is the carbonyl ene reaction.[166] In 1998, Evans et al. introduced C_2-symmetric copper(II) complexes of bis(oxazolines) **6a** (Figure 45) in the asymmetric glyoxylate ene reaction of olefin and carbonyl components resulting in very good yields (up to 99%) and enantioselectivities (up to 98% ee).[167] In the same year, Vederas et al. reported also on the use of similar copper(II) complexes of bis(oxazolines) **6c** (Figure 45) in the carbonyl ene reaction with high selectivity.[168] To our knowledge,

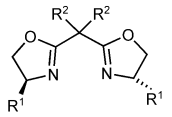


Figure 45. Cu-BOX complexes **6a** by Evans et al.[167] and **6c** by Evans et al.[168]

Table 38. Carbonyl ene reaction[a] of ethyl glyoxylate **191** and isopropenyl-benzene **192** by Ikegami et al.[169]

Catalyst	Solvent	Time [h]	Yield [%][b]	ee [%][c]
194a	CH_2Cl_2	48	49	49
194b	CH_2Cl_2	60	55	58
194c[d]	CH_2Cl_2	14	87	56
194b	THF	60	trace	n.d.[e]
194b	PhMe	60	56	59
194b	Et_2O	60	68	84

[a] Conditions: 5 mol % catalyst, solvent, rt.
[b] Isolated yield after purification by column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK AS.
[d] Compound **193** was obtained in 26% yield with 36% ee using a reused catalyst **194c**, which was recovered after the reaction.
[e] Not determined.

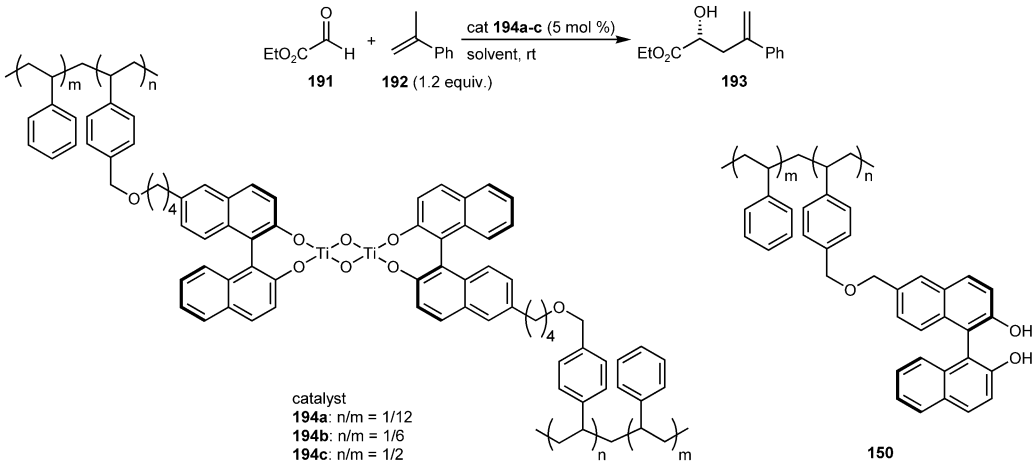
there is no example of the introduction of immobilized bis(oxazoline) complexes in asymmetric carbonyl ene reactions, although the results with the soluble box-complexes are very good.

In 2002, Ikegami et al. introduced catalysts with titanium and non-cross-linked chiral copolymers on the base of BINOL **150** like those synthesized by Sasai et al. (Scheme 42)[27] for an enantioselective carbonyl ene reaction.[169] The catalytic activities of the three polymer-supported catalysts **194a–c** are shown in Scheme 42 and Table 38. By optimization, diethyl ether in conjunction with catalyst **194b** caused the highest enantioselectivities. The catalytic activity of **194b** was even after the fifth run as good as in the first.

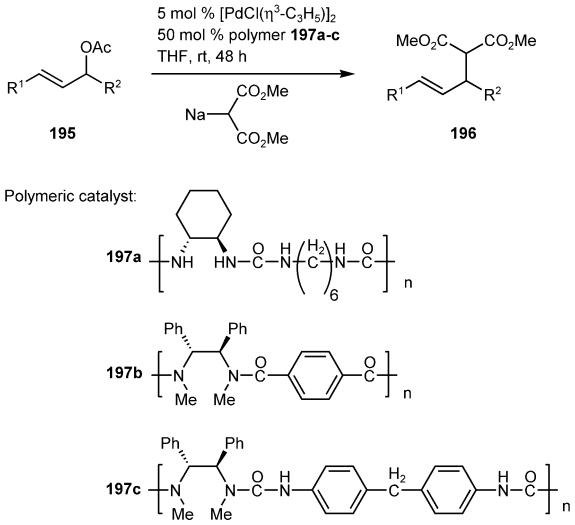
5 (Metal-Catalyzed) Substitution Reactions

5.1 Allylic Substitution Reactions

The enantioselective allylic substitution, although a well-established catalytic asymmetric C–C bond forming reaction using homogeneous chiral catalysts, has rarely been studied in its heterogeneous version.



Scheme 42. Immobilized BINOL ligands **150** by Sasai et al.[27] and asymmetric carbonyl ene reaction catalyzed by polymer-supported Ti-BINOL complexes **194a – c** by Ikegami et al.[169]

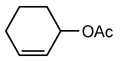
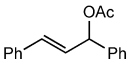
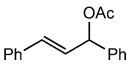


Scheme 43. Heterogeneous substitution of allylic acetates[a] by Lemaire, Fache et al.[170]

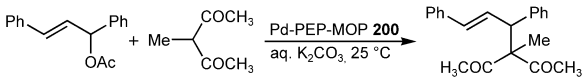
The group of Lemaire, Fache et al. presented a solid-supported C_2-symmetric chiral nitrogen ligand **197** for this useful reaction.[170] Treatment of a chiral, enantiopure diamine with a diisocyanate or with a diacid chloride resulted in polyaddition or polycondensation reaction to give insoluble poly(ureas) or poly(amides). After reaction of both polymeric catalysts with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ asymmetric allylic substitution reactions of allylic acetates with malonates have been performed (Scheme 43). The results are presented in Table 39. There is no possibility to reuse the heterogeneous catalyst. After the reaction, palladium precipitates on the polymer causing a black color with the catalyst loosing its activity. Both polymeric catalysts are also less reactive than the homogeneous one.

In 1998, the group of Hayashi and Uozumi reported resin-supported 2-diphenylphosphino-1,1′-binaphthyl-Pd(0) catalysts **200** (Figure 46).[171]

Table 39. Asymmetric allylic substitution by Lemaire, Fache et al.[170]

Allylic acetate	Polymer	Conversion [%]	ee [%]
	**197a**	80	25 (*R*)
	**197b**	38	80 (*R*)
	**197c**	72	38 (*R*)

[a] See Scheme 43.



Scheme 44. Asymmetric substitution of acetate **201** with 3-methyl-2,4-pentanedione **202** by Hayashi and Uozumi.[171]

The PEG-MOP ligand was synthesized starting from (*S*)-MOP (**199**) and tethers **198**. The active resin-supported palladium-phosphine complexes **200a – f** were prepared by treatment of the PEG-MOP ligand with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (Figure 46). The allylic substitution reaction was carried out in aqueous media with 1,3-diphenyl-2-propenyl acetate (**201**) with 3-methyl-2,4-pentanedione **202** and 2 mol % palladium of the catalyst resins **200** at 25 °C for 12 h (Scheme 44). The best catalyst was the complex **200f**, which includes L-Leu as tether. Results are shown in Table 40.

A new class of ligands suitable for asymmetric catalysis are helical chiral polymers without additional stereogenic units reported first by Reggelin et al.[172] The helical chiral ligands were produced by helix-sense selective anionic polymerization reaction. For the

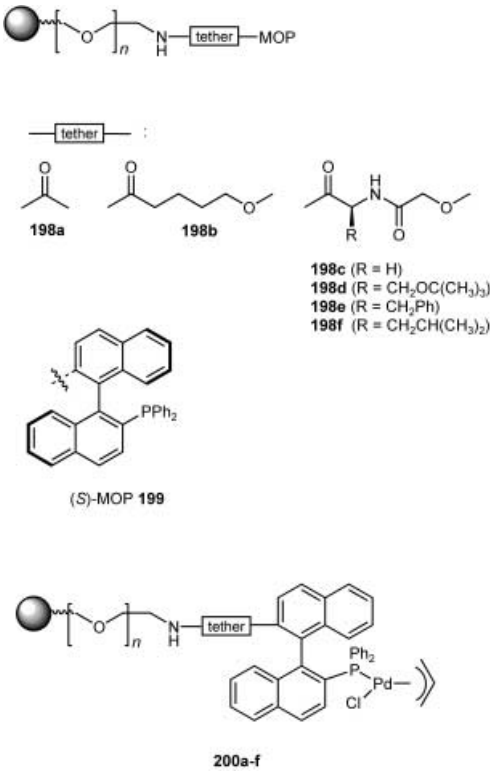


Figure 46. Resin-supported MOP ligands (PEG-MOP) **200a – f** by Hayashi and Uozumi.[171]

Table 40. Asymmetric allylic substitution[a] by Hayashi and Uozumi.[171]

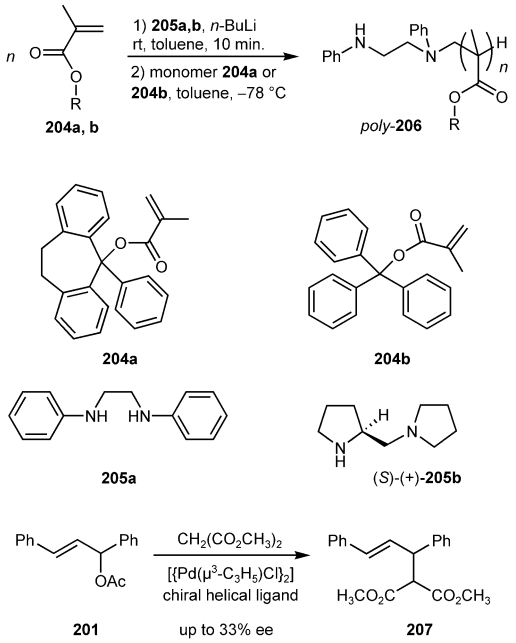
Entry	Catalyst	Base	Yield [%]	ee [%]
1	(*R*)-**200a**	K_2CO_3	< 5	14
2	(*R*)-**200b**	K_2CO_3	56	55
3	(*R*)-**200c**	K_2CO_3	58	74
4	(*R*)-**200d**	K_2CO_3	68	81
5	(*R*)-**200e**	K_2CO_3	75	81
6	(*R*)-**200f**	K_2CO_3	75	81
7	(*R*)-**200f**	Li_2CO_3	45	84
8	(*R*)-**200f**	Na_2CO_3	58	77
9	(*R*)-**200f**	Cs_2CO_3	62	77
10	(*S*)-**200f**	K_2CO_3	49	78

[a] Conditions: 1 equiv. **201**, 1 equiv. **202**, base, catalyst.

polymerization of sterically congested methacrylates **204a**,**b** chiral base mixtures were used as initiator (Scheme 45).

The helical chiral polymer ligands were used in an allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate **201** with dimethyl malonate (Scheme 45). First results show enantioselectivities up to 33%.

In 2000, Reiser and Glos introduced the aza-bis(oxazoline) ligands **93a, b** (Scheme 14) into the asymmetric palladium-catalyzed allylic substitution reaction in



Scheme 45. Synthesis of helical sense selective polymers *poly*-**206** by polymerization of methacrylates **204a, b** with the additives **205a** and (*S*)-(+)-**205b** by Reggelin et al.[172]

solution phase with excellent results (yields up to 99% and enantioselectivities up to 97% ee).[44]

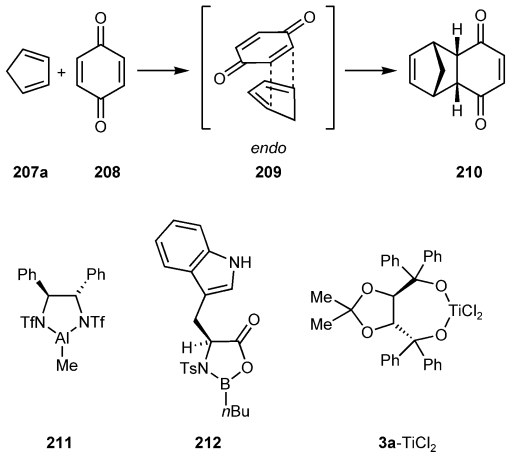
6 Cycloaddition Reactions

6.1 Diels–Alder and other Cycloaddition Reactions

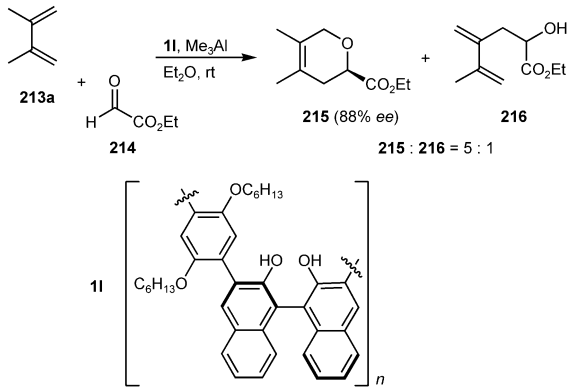
The Diels–Alder reaction was discovered in the beginning of the 20th century[173] and is one of the best examined and well appreciated reactions (Scheme 46).[174] There are many variants of this reaction, for example intramolecular [4 + 2] cycloaddition or hetero-Diels–Alder reactions. It has been reported that this reaction can be accelerated by (high) pressure or Lewis acids. Enantioselective Diels–Alder reactions with chiral catalysts, for example, chiral diazaaluminolidine or oxaborolidine catalysts are well known. For an overview, see the review of E. J. Corey on the occasion of the 100th birthday of Kurt Alder in 2002.[175] Meanwhile the Diels–Alder reaction has been featured to be an excellent tool to build up (chiral) cyclic systems.[176,177]

The hetero Diels–Alder reaction is a particularly advantageous pathway to get heterocyclic compounds. These reactions have been used in the total synthesis of various natural products.[175,177]

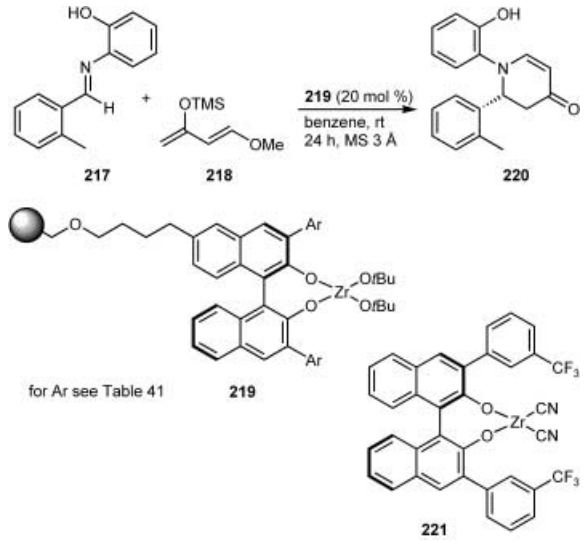
Asymmetric Diels–Alder reactions, the "normal" or the hetero version, are also well known.[175] The use of chiral diazaaluminodines like **211**[178] or chiral oxazaborolidines like **212**[179] have been described by Corey et al.



Scheme 46. Diels–Alder reaction with *endo* transition state[172] and homogeneous chiral catalysts for Diels–Alder reactions.[178–180]



Scheme 47. Asymmetric hetero Diels–Alder reaction with a solid-supported BINOL ligand **1l** by Pu et al.[25,26]



Scheme 48. Optimized soluble zirconium-binaphthol catalyst **221** for Diels-Alder reactions and aza-Diels–Alder reaction catalyzed by polymer-supported zirconium-binaphthol catalyst **219** by Kobayashi et al. (Table 41).[23a,185]

(Scheme 46). The enantioselectivities obtained by using these ligands are up to 99% ee. Other very efficient ligands for asymmetric Diels–Alder reactions are the chiral Ti-TADDOL systems like **3a**-$TiCl_2$.[180] Other chiral systems are also good chiral promoters for this reaction type (see below).

Diels–Alder reactions catalyzed by zeolites or Lewis acids on modified silica or alumina have previously been described.[181]

In 1997, Pu et al. employed immobilized BINOL complexes **1l** (Scheme 47) in asymmetric hetero-Diels–Alder reactions with selectivities up to 88% ee.[25,26]

Anwander et al. reported hetero-Diels–Alder reactions using the Danishefsky diene mediated by organolanthanide-modified mesoporous silicate MCM-41, but without an asymmetric aspect.[182] Abbenhuis used oligometallasilsesquioxanes as heterogeneous catalysts.[183]

In 1996, Kobayashi et al. reported the first examples of catalytic asymmetric aza-Diels–Alder reactions using a chiral ytterbium catalyst.[184] The same authors disclosed reactions of azadienophiles (imino dienophiles) with Danishefsky's diene using chiral zirconium-binaphthol complexes like **221** (Scheme 48).[185] While high yields and selectivities were obtained, the catalyst loading was rather high (10–20 mol %). Kobayashi et al. reported the optimization of their catalyst system.[23] During the progress of optimizing the soluble zirconium catalyst, the authors succeeded to immobilize it on solid supports (but not the optimized one).[23a] The optimized version of the soluble zirconium-binaphthol catalyst, compound **221**, and the reaction results of the polymer-supported zirconium-binaphthol catalyst **219** in an aza-Diels–Alder reaction are shown in Scheme 48 and Table 41.

While the 4-*tert*-butylphenyl group on the BINOL fragment gave lower enantioselectivities, higher enantioselectivities were obtained when 3,5-xylyl, 4-biphenyl, 4-fluorophenyl and 3-trifluoromethylphenyl groups were introduced at the 3,3′-positions of the BINOL.

Among them, the 4-fluorophenyl and 3-trifluoromethylphenyl groups were the most promising in both yields and selectivities. Kobayashi et al. tested the recovery of the catalyst **219** (Ar = 3-trifluoromethylphenyl). The results after the third run were nearly as good as in the first run.

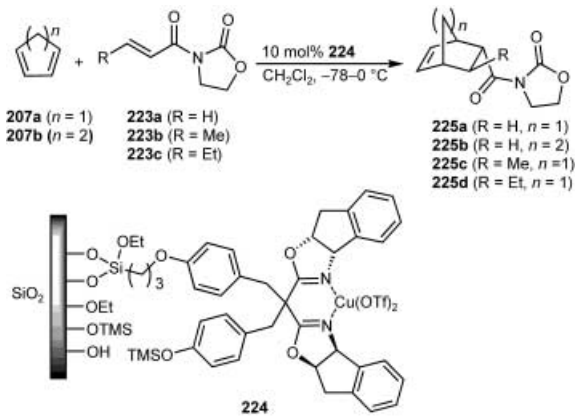
Seebach et al. employed the dendritic Cr-salen complexes **20c**, **22a** and corresponding monomeric species **8c** in the hetero-Diels–Alder reaction (Scheme 49).[49] As shown in Table 42, the selectivities achieved were only slightly lower than in homogeneous solution under identical conditions. In all cases the lowest selectivities were obtained with *poly*-**20** · Cr(Cl).

The authors also investigated the reusability of the catalysts in the Diels–Alder reaction. Surprisingly, in the case of *poly*-**8c** · Cr(Cl) and *poly*-**20c** · Cr(Cl), the enantioselectivity in which the dihydropyranones **222a–c**

Table 41. Catalyst optimization of polymer-supported zirconium-binaphthol catalyst **219** in the aza-Diels–Alder reaction[a] by Kobayashi et al. (Scheme 48).[23a]

Ar	Yield [%]	ee [%]
phenyl	61	77
m-tolyl	80	73
o-tolyl	80	72
4-*tert*-butylphenyl	58	48
3,5-xylyl	70	82
4-biphenyl	59	80
2-naphthyl	74	74
6-methoxy-2-naphthyl	61	70
4-fluorophenyl	80 (78)[b]	83 (88)[b]
3,4-difluorophenyl	82	71
3-trifluoromethylphenyl	87 (>99)[b]	80 (91)[b]
3,5-bis(trifluoromethyl)phenyl	92	60
3-methoxyphenyl	75	76
4-methoxyphenyl	75	41
3,4-dimethoxyphenyl	82	60
4-ethoxyphenyl	63	59
2-thienyl	61	44

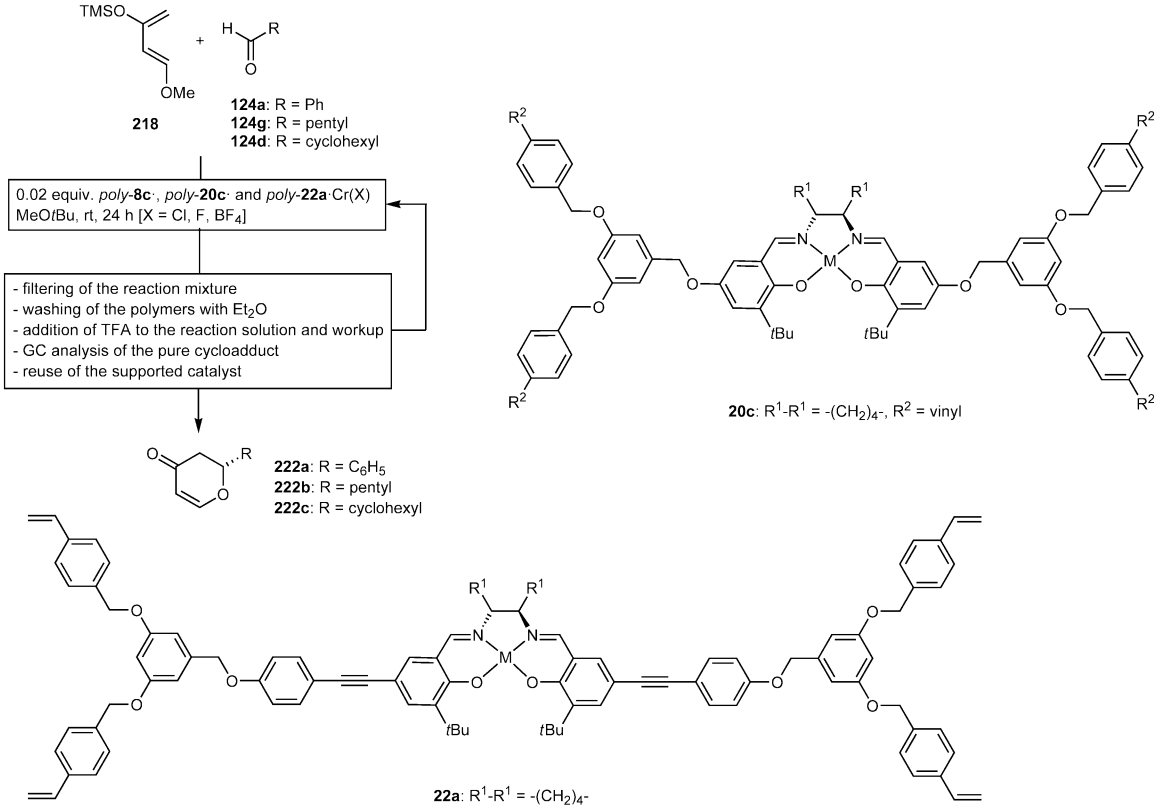
[a] Conditions: 20 mol% **219**, benzene, MS 3 Å, rt, 24 h.
[b] 1-Methoxy-2-methyl-3-trimethylsiloxy-1,3-butadiene was used instead of **218**.



Scheme 50. Diels–Alder reaction catalyzed by silica-indabox **224** by Hyeon and Kim et al.[186]

were formed, steadily increased during multiple use to reach the values of the homogeneous reaction. In contrast to these results, the conversion gradually dropped. Catalyst *poly*-**22a**·Cr(Cl) could be recycled up to ten times without decrease of conversion and with nearly constant enantioselectivity.

In the same year, Hyeon and Kim et al. immobilized a copper-chiral bis(oxazoline) complex on mesoporous silica and employed it as catalyst **224** in a Diels–Alder reaction (Scheme 50).[186]



Scheme 49. Hetero-Diels–Alder reaction catalyzed (non) dendritic using Cr-salen complexes *poly*-**8c**, *poly*-**20c** and *poly*-**22a**·Cr(X) by Seebach et al. (Table 42).[49]

Table 42. Hetero-Diels–Alder reaction[a] (Scheme 49) by Seebach et al.[49] The enantioselectivities obtained with simple unsubstituted Cr(Cl)-salen are the following: **222a** 60% ee; **222b** 78% ee; **222c** 74% ee.

Substrate	Catalyst	Loading [mmol g^{-1}]	Cycloadduct	Conversion [%]	ee (*S*) [%]
124a	*poly*-**8c** · Cr(Cl)	0.20	**222a**	74	56
124a	*poly*-**20c** · Cr(Cl)	0.13	**222a**	67	58
124a	*poly*-**22a** · Cr(Cl)	0.13	**222a**	82	50
124g	*poly*-**8c** · Cr(Cl)	0.20	**222b**	79	70
124g	*poly*-**8c** · Cr(F)	0.20	**222b**	58	70
124g	*poly*-**8c** · Cr(BF_4)	0.20	**222b**	27	70
124g	*poly*-**20a** · Cr(Cl)	0.13	**222b**	70	72
124g	*poly*-**22a** · Cr(Cl)	0.13	**222b**	73	70
124d	*poly*-**8c** · Cr(Cl)	0.20	**222c**	60	70
124d	*poly*-**20c** · Cr(Cl)	0.13	**222c**	41	72
124d	*poly*-**22a** · Cr(Cl)	0.13	**222c**	36	64

[a] Conditions: 1 equiv. **218**, 1 equiv. **124a, d, g**, 0.02 equiv. *poly*-**8c** · , *poly*-**20c** or *poly*-**22a** · Cr(X), MeO-*t*-Bu, rt, 24 h (X = Cl, F, BF_4).

Table 43. Asymmetric Diels–Alder reaction between cyclopentadiene **207a** and acrylamide **223a** using 10 mol% of **224** by Hyeon and Kim et al. (Scheme 50).[186]

	Cu(OTf)$_2$ [mol %]	*T* [°C]	Yield [%]	*endo*/*exo*	ee (*endo*) [%]
1	10[a]	−78	96	9:1	88
2	6[b]	0	99	10:1	15
3	6[b]	0	99	8:1	39
4	10[c]	0	99	9:1	11
5	10[b]	−50	99	9:1	50
6	10[b]	−70	97	12:1	65
7	30[b]	−70	97	11:1	65
8	–	−70	22	10:1	–
9	10	−78	99	13:1	75

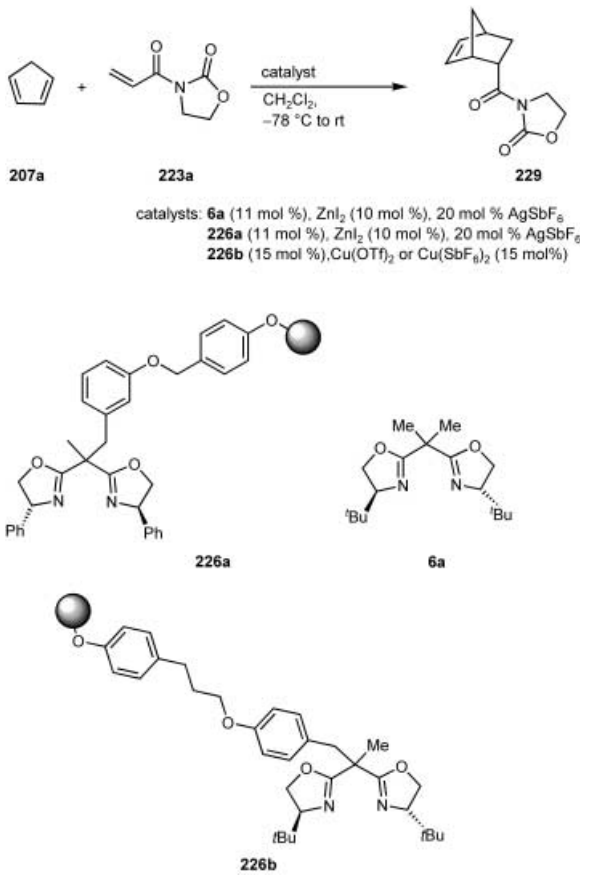
[a] Reaction was carried out in solution phase.
[b] The copper complex was washed with CH_2Cl_2 before the reaction.
[c] The copper complex was washed with acetone twice.

As shown in Table 43, the optimum amount of the copper catalyst is 10 mol % at −78 °C (entry 1). By increasing or decreasing the copper content the yields are also up to 99% and the *endo*-selectivity is 10:1, but the enantioselectivity is decreasing dramatically (entry 7).

It is also shown that the reaction temperature is an important point. Upon a small increase of the temperature from −78 °C to −70 °C the enantioselectivity decreased from 75% ee to 65% ee. An explanation for these effects might be some uncomplexed copper reagent in the mixture lowering the enantioselectivity of the reaction. Even washing of the copper complex improved the results only slightly. By using the catalyst without trimethylsilyl protection the *endo*/*exo*-ratio increased up to 17:1 but the enantioselectivity stayed nearly constant. The catalyst **224** is recyclable. The yields in the Diels–Alder reaction between cyclopentadiene (**207a**) and acrylamide **223a** at −78 °C varied between 48% and 75% in five runs. After the third run an additional amount of Cu(OTf)$_2$ was added. The *endo*/*exo*-ratio remained constant at 13:1.

Chiral C_2-symmmetric bis(oxazolines) have also been shown to serve as successful ligands in copper-catalyzed Diels–Alder reactions.[34e,37b,187] Moberg et al. used such polymer-supported bis(oxazolines) as ligands in zinc-catalyzed Diels–Alder reaction of 3-(2-propenoyl)-2-oxazolidone **223a** and cyclopentadiene (**207a**) (Scheme 51).[188] While using the corresponding soluble ligand **6a** (Figure 45), the *endo*-product (*endo*/*exo* ratio 94:6) with an enantioselectivity of 85% ee was formed after 15 h at −78 °C, the reaction with the solid phase-bound ligand **226a** was very slow at this temperature. Only traces of product were formed after 48 h. Increasing the reaction temperature to −40 °C showed only a small effect (13% conversion overnight). This low reactivity might be explained by the fact that the polymer is probably more rigid and less swollen at lower temperatures, causing the surface area of the polymer to be decreased, and thereby preventing exposure of a large fraction of the ligands.

In the same year, Cozzi et al. used polyethylene glycol-supported bis(oxazoline) ligand **226b** in a Diels–



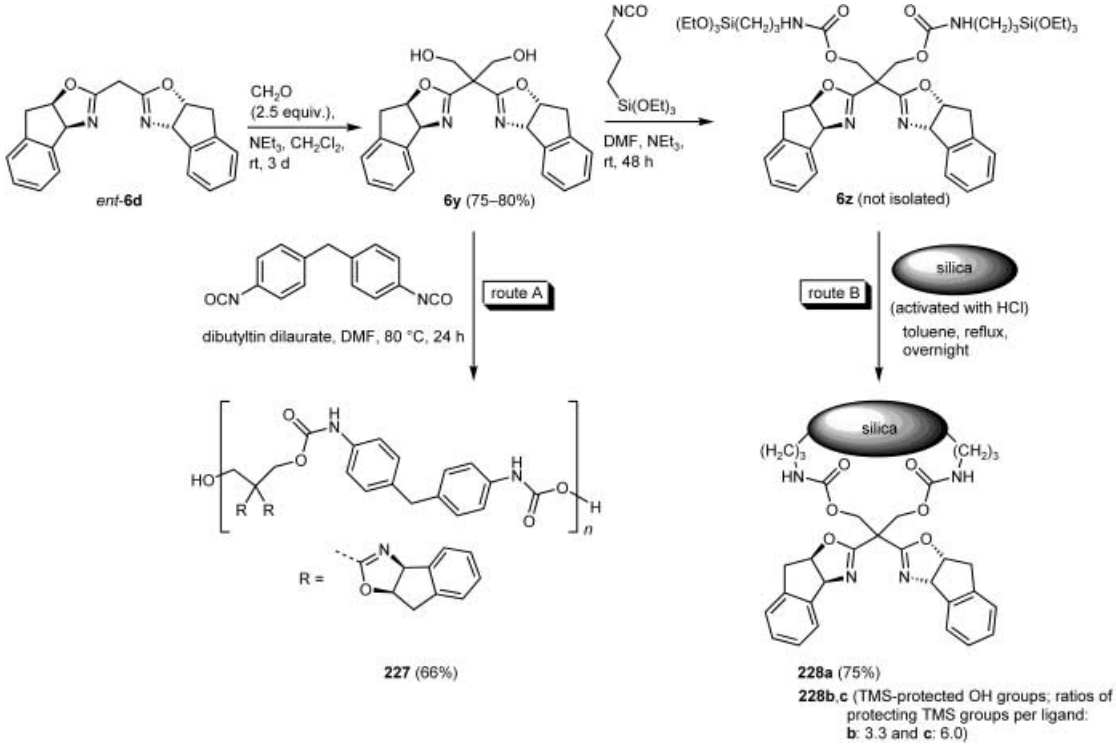
Scheme 51. Enantioselective Diels–Alder reaction by Moberg et al.[188] and Cozzi et al.[98]

Alder reaction (Scheme 51).[97] Using $Cu(OTf)_2$ or $Cu(SbF_6)_2$ as metal sources the isolated yields were up to 91%. The diastereomeric ratio was excellent (> 98:2) while the enantioselectivity reached 45% ee. Many factors can be responsible for the inferior enantioselectivity observed. For instance, the supported ligand **226b** lacks the C_2-symmetry common to the most effective box ligands for the Diels–Alder reaction.[187]

In 2002, Lemaire and Rechavi immobilized a chiral bis(oxazoline) by polymerization as part of the ligand main chain of a polyurethane backbone **227** (route A in Scheme 52) and by grafting onto silica **228a** (route B in Scheme 52). These heterogeneous catalysts were applied to Diels–Alder reactions.[43] The silica-supported catalyst was investigated with free hydroxy groups of the silica and with trimethylsilyl protected hydroxy groups. The two different immobilized box ligands **227** and **228a** were used in asymmetric Diels–Alder reactions of dienes **207** and acrylamide **223a** (Scheme 51).[43] The results are shown in Tables 44 and 45.

The first three reaction cycles gave enantioselectivities up to 56% ee, but the fourth cycle showed a complete loss of enantioselectivity. In addition, the polymer's appearance changed, and it looked worn out. IR spectra also indicated that the polymer composition had changed.

The catalyst **228a** grafted on silica gave 87% ee at – 78 °C (entry 1, Table 45). Even at higher temperature it gave better enantioselectivities than the polymer-supported catalyst **227**. The enantioselectivity de-



Scheme 52. Immobilization of bis(oxazoline) ligand **6d** by polymerization as part of the main chain of a polyurethane backbone **227** (route A) and by grafting onto a silica surface **228a** (route B) by Lemaire et al.[43]

Table 44. Recycling of catalyst **227** (polyurethane), using $Cu(OTf)_2$ as metal precursor[a] by Lemaire and Rechavi.[43]

Entry	Cycle[b]	*endo* [%]	ee [%][c]
1	1	89	51
2	2	90	56
3	3	90	56
4	4	87	0

[a] Temperature: $-78\,^{\circ}C$ (4 h) to rt (overnight).
[b] Conversions in all cases quantitative.
[c] % ee of the *endo* isomer. The ee was determined by HPLC on Chiralcel-OD column with heptane:2-propanol 95:5 as eluent.

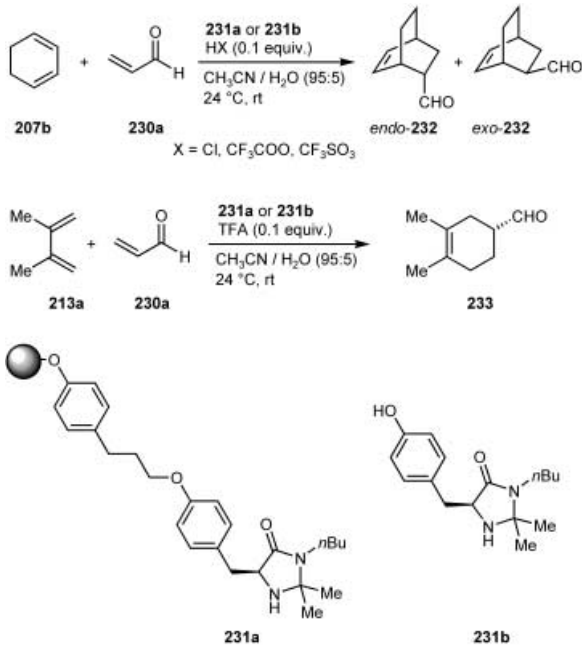
Table 45. Diels–Alder reactions catalyzed by reused silica-supported catalyst **228a** by Lemaire and Rechavi.[43]

Entry[a]	Cycle	Conv. [%]	*endo* [%]	ee [%][b]
1[c]	1[e]	82	96	87
2[c]	1[f]	97	89	65
3[c]	2[f]	53	90	73
4[c]	3[f]	65	88	69
5[c]	4[f]	19	89	26
6[d]	1[f]	96	86	70
7[d]	2[g]	97	85	65
8[d]	3[h]	97	90	85
9[d]	4[f]	100	88	79

[a] Reaction time 1 h, except entry 1: 48 h.
[b] The ee of the *endo* product was determined by HPLC on Chiralcel-OD column with 95% heptane: 5% 2-propanol as eluent.
[c] The reaction was conducted under argon, in dry CH_2Cl_2 with $Cu(OTf)_2$ as metal precursor. The catalyst (8 mol %) was separated by centrifuge. The catalyst was dried in vacuum before reuse.
[d] $Cu(ClO_4)_2 \cdot H_2O$ as metal precursor. The catalyst (10 mol %) was separated by centrifuge. The catalyst was dried in vacuum before reuse.
[e] Reaction temperature $-78\,^{\circ}C$.
[f] Reaction temperature $0\,^{\circ}C$.
[g] Reaction performed at rt.
[h] Reaction temperature $-15\,^{\circ}C$.

creased also on the fourth reaction cycle. A reason for the decrease in enantioselection after several reaction cycles might be the high sensitivity to water of both supported Cu-ligand complexes. Gosh et al. have recently shown that, when $Cu(ClO_4) \cdot 6\,H_2O$ is used as the metal precursor, the reaction is not sensitive to water.[189] Using this metal precursor Lemaire and Rechavi obtained better enantioselectivities without a decrease after the third cycle.

Furthermore the free silanol groups of catalyst **228a** were protected with $SiMe_3$. Two ratios of protecting TMS groups per ligand were obtained, 3.3 for **228b** and 6.0 for **228c**. The catalytic activity was proved in the same reaction as before. The best enantioselectivity



Scheme 53. Enantioselective Diels–Alder reactions with a metal-free polymer-supported ligand **231a** and **231b** by Cozzi et al.[190]

observed was 92% ee for the *endo* product at a reaction temperature of $-78\,^{\circ}C$ (quantitative conversion). Furthermore, the authors introduced other substrates in the Diels–Alder reaction catalyzed by the silica-supported ligand **228a** with enantioselectivities only somewhat lower compared with the homogeneous catalyst.

Very recently, Cozzi et al. reported enantioselective Diels–Alder reactions with a chiral imidazolidin-4-one on a polyethylene glycol support, **231a**.[190] The Diels–Alder reactions shown in Scheme 53 are metal-free reactions. Chiral metal-free organic catalysts[191] seem particularly attractive for placing on polymers, since they cannot suffer from metal leaching upon recycling, a major drawback associated with the use of polymer-bound metal-based catalysts.[38a]

The results are presented in Table 46. The same reaction was performed with the soluble, non-polymer-bound catalyst **231b** for comparison. The acid employed to generate the catalyst was crucial, with **231a**/HCl securing better yields and **231a**/TFA a higher stereocontrol. A longer reaction time increased the yield independently from the catalyst counter ion. A decrease of the catalyst loading to 5 mol % slowed down the reaction, but preserved the stereoselectivity. The use of preformed catalysts did not improve the efficiency of the process while making it less practical. The reaction was successfully extended to the acyclic 2,3-dimethylbutadiene **213a** which afforded cycloadduct **233** in 75% yield (with soluble ligand **231b** up to 75%) and 73% ee (with soluble ligand **231b** up to 84% ee) upon reaction with acrolein **230a** under the same conditions. Recovery of

Table 46. Catalytic enantioselective synthesis of cycloadduct **232** in CH_3CN/H_2O (95:5) at rt by Cozzi et al.[190]

Entry	Catalyst	Time [h]	Yield [%][a]	*endo*/*exo*	ee (*endo*) [%]
1	**231b**/HCl	22	35	90:10	68
2	**231b**/TFA	22	39	91:9	82
3	**231b**-OMe/TFA[b]	22	75	92:8	84
4	**231a**/HCl	22	63	91.5:8.5	70
5	**231a**/HCl	40	81	91:9	73
6	**231a**/TfOH	22	27	94:6	88
7	**231a**/TFA	22	50	94:6	92
8	**231a**/TFA	40	67	94:6	92
9	**231a**/TFA[c]	40	45	94:6	90
10	**231a**/TFA[d]	40	10	91:9	– [i]
11	**231a**/HCl[e]	40	61	92:8	70
12	**231a**/TFA[e]	40	52	93:7	84
13	**231a**/TFA[f]	40	61	94:6	87
14	**231a**/TFA[g]	40	50	94:6	87
15	**231a**/TFA[h]	40	38	94:6	85

[a] Yields of isolated products.
[b] The phenol OH-group of **231b** was methylated.
[c] 0.05 equiv. of catalyst.
[d] Carried out in $MeOH/H_2O$.
[e] Carried out with a preformed sample of catalyst.
[f] Carried out with a catalyst sample recycled after use in entry 8.
[g] Carried out with a catalyst sample recycled after use in entries 8 and 13.
[h] Carried out with a catalyst sample recycled after use in entries 8, 13 and 14.
[i] Enantioselectivity not determined.

Table 47. Hetero-Diels–Alder reaction[a] to form the cycloadducts **222a, b** by Seebach et al.[50]

Aldehyde	Cr-salen	T [°C]	Conv. [%]	ee [%]
124 g	**8c**	rt	97	83
124 g	**8c**	rt	91	80[b]
124 g	**8c**	0	7	84[c]
			62	83[d]
124a	**8b**	rt	–	80[f]
124a	**8b**	rt	69	74[b]
124a	**8b**	rt	72	78[e]

[a] Conditions: as shown in Scheme 54.
[b] First run.
[c] After 24 h.
[d] After another 24 h at rt.
[e] Second run.
[f] See ref.[49]

the catalysts was possible with an accompanied slight decrease of yield and nearly constant selectivity.

The manganese- and chromium-salen complexes immobilized on silica gel by radical grafting like **20–22** published by Seebach et al. are not only employed in enantioselective heterogeneous epoxidation reactions, but also in enantioselective heterogeneous hetero-Diels–Alder reactions.[49] This reaction was carried out with soluble Cr-salen complex **8c** for comparison. As shown in Table 47, the immobilized catalyst **8b** gave under identical conditions (Scheme 54) nearly the same results in enantioselectivities as the soluble catalyst **8c**. The reaction with caproaldehyde **124 g** was conducted with an eleven-times recycled catalyst **8b**. After 24 h at 0 °C, the conversion was under 10% with an enantioselectivity of 84% ee. But after another 24 h at room temperature, the conversion increased to 62% with an enantioselectivity nearly as good as before. The reaction with benzaldehyde (**124a**) and recycled catalyst **8b** gave a better yield (from 69% to 72%) and a better enantioselectivity (from 74% ee to 78% ee) in the second run than in the first run. It could be shown that the catalyst **8b** is recyclable with slightly better results after the first run.

Very recently Pihko et al. introduced a Janda*Jel*™-supported amine catalyst **236** and a silica-supported amine catalyst **237** in asymmetric Diels–Alder cycloaddition reactions of the dienes **207a, b, 213b** and the dienophiles **230a–c** with moderate to good results as shown in Scheme 55, Tables 48 and 49.[192]

6.2 1,3-Dipolar Cycloaddition Reactions

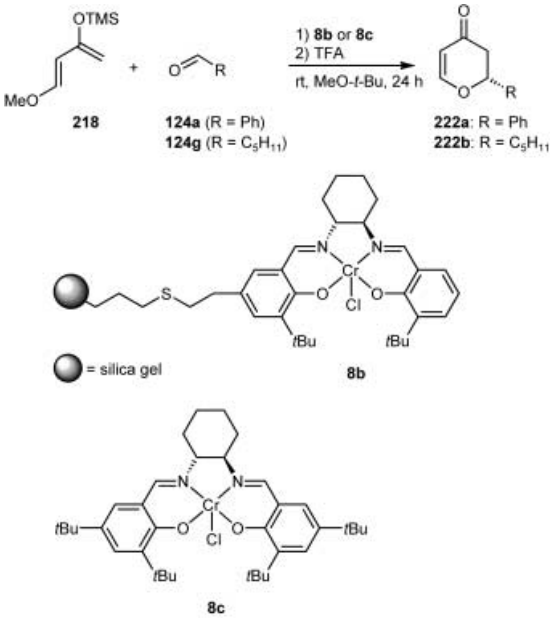
A useful approach to asymmetric 1,3-cycloaddition reactions is a permanent or temporarily linked chiral ligand on a solid support.[194]

In 1999, Jørgensen et al. reported on the 1,3-dipolar cycloaddition of diphenylnitrone to alkyl vinyl ethers using catalytic amounts of MeAl-BINOLates in solu-

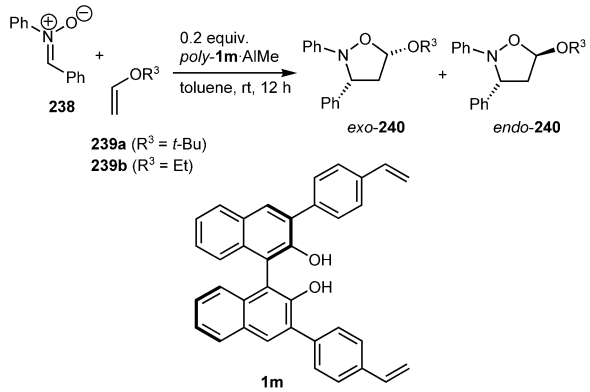
tion.[195] The *exo*-cycloadducts, which were almost exclusively formed, were obtained in enantioselectivities up to 96%. Seebach showed that cross-linked polymer-bound Al-BINOLates give rise to the same catalytic activity as their homogeneous counterparts.[24] These systems were not only employed in enantioselective titanium and aluminium Lewis acid-mediated addition reactions of diethylzinc and trimethylsilyl cyanide to aldehydes, but also in 1,3-dipolar cycloaddition reactions of diphenylnitrone **238** with enol ethers **239a** and **239b** (Scheme 56).

The selectivities obtained with *poly*-**1m** · AlMe correspond to those found in homogeneous solution.[195] There seems to be no dependence of performance of the polymer-bound catalyst from the degree of loading. It is remarkable that attachment of the polystyrene matrix to the 3,3′ position of the BINOL core, close to the catalytic site, has no negative effect on the catalytic performance. The drawback of this system is the non-recyclability.

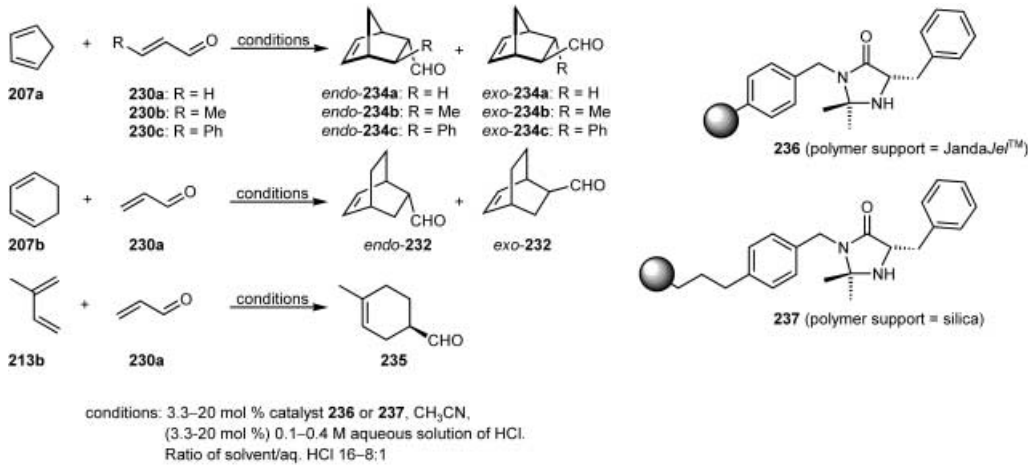
Very recently, Seebach et al. reported on the application of polymerization of TADDOL **3b** and its application in a 1,3-dipolar cycloaddition reaction of diphenylnitrone (**238** to [(*E*)-but-2-enoyl]-oxazolidinone (**223b**) (Scheme 57).[196] The polymer *poly*-**3b** was loaded with titanate by the addition of a solution of $TiCl_2(O\text{-}i\text{-}Pr)_2$ or $Ti(OTs)_2(O\text{-}i\text{-}Pr)_2$. Conversion (93%), *endo*/*exo* selectivity (82:18) and enantioselectivity (*exo* 75% ee) by using *poly*-**3b** · $TiCl_2$ were comparable with those obtained in solution phase.[197] It turned out that high conversions could only be achieved when 50 mol % of *poly*-**3b** were used, whereas the reaction in solution proceeded well in the presence of 10 mol % catalyst. Recycling of *poly*-**3b** also proved successful. The preferential formation of *exo*-cycloadduct *exo*-**241** is



Scheme 54. Enantioselective hetero-Diels–Alder reactions with the silica gel-supported Cr-salen catalyst **8b** by Seebach et al. and soluble Cr-salen complex **8c**.[50]



Scheme 56. 1,3-Dipolar cycloaddition reactions catalyzed by *poly*-**1 m** (substituted BINOL **1m** as precursor for the solid-supported ligand *poly*-**1m**) by Seebach et al.[24]



Scheme 55. Enantioselective Diels–Alder reactions catalyzed by Janda*Jel*™-bound amine catalyst **236** and silica-supported amine catalyst **237** by Pihko et al.[192]

Table 48. Enantioselective Diels–Alder reaction catalyzed by Janda*Jel*™-bound amine **235** by Pihko et al.[192]

Entry	Diene	Aldehyde	Catalyst [mol %][a]	t [h]	*endo*[a] [% ee]	*exo*[b] [% ee]	Yield [%][c]
1	**207a**	**230a**	20	24	5.1 (89)	1 (83)	73
2	**207a**	**230a**	10[d]	24	4.9 (75)	1 (75)	68
3	**207a**	**230b**	10	24	1.2 (91)	1 (89)	60
4	**207a**	**230b**	10[d]	24	1.2 (88)	1 (87)	58
5	**207a**	**230c**	20	24	1 (99)	1.2 (99)	70
6	**207a**	**230c**	10[d]	24	1 (97)	1.2 (95)	65
7	**207b**	**230a**	20	25	13 (98)	1	30
8	**213b**	**230a**	5	32	(70)	–	24

[a] Calculated based on the amine loading (mmol/g) of the supported catalyst. The loading is based on the original nitrogen loading of the support but a correction has been made for the mass gain of the catalyst during its preparation.
[b] *endo*:*exo* ratios were determined by ^{1}H NMR from the aldehyde product mixture. For determination of the ee values, the aldehyde products were first reduced to the alcohols with excess of $NaBH_4$ in EtOH, and the resulting alcohols were an analyzed by GLC using Supelco γ-DEX™ 120 column. Absolute and relative configuration were assigned by chemical correlation to compounds obtained by known solution phase methods[193] or by analogy.
[c] Yields of isolated, purified aldehydes.
[d] Reaction was performed with catalyst recovered from previous run.

Table 49. Enantioselective Diels–Alder reaction catalyzed by silica-supported amine **237** by Pihko et al.[192]

Entry	Diene	Aldehyde	Catalyst [mol %][a]	t [h]	*endo*[a] [% ee]	*exo*[b] [% ee]	Yield [%][c]
1	**207a**	**230a**	3.3	24	6.6 (91)	1 (-)	73
2	**207a**	**230a**	3.3	25	2 (52)	1 (6)	41
3	**207a**	**230a**	3.3	64	1.1 (90)	1 (90)	33
4	**207b**	**230a**	20	24	14 (90)	1	83
5	**213b**	**230a**	20	24	(90)	–	79

[a] Calculated based on the amine loading (mmol/g) of the supported catalyst. The loading is based on the original nitrogen loading of the support but a correction has been made for the mass gain of the catalyst during its preparation.
[b] *endo*:*exo* ratios were determined by ^{1}H NMR from the aldehyde product mixture. For determination of the ee values, the aldehyde products were first reduced to the alcohols with excess of $NaBH_4$ in EtOH, and the resulting alcohols were an analyzed by GLC using Supelco γ-DEX™ 120 column. Absolute and relative configuration were assigned by chemical correlation to compounds obtained by known solution phase methods[193] or by analogy.
[c] Yields of isolated, purified aldehydes.

Table 50. 1,3-Dipolar cycloaddition reactions[a] (Scheme 57) with different loadings of catalyst *poly*-**1m** by Seebach et al.[24]

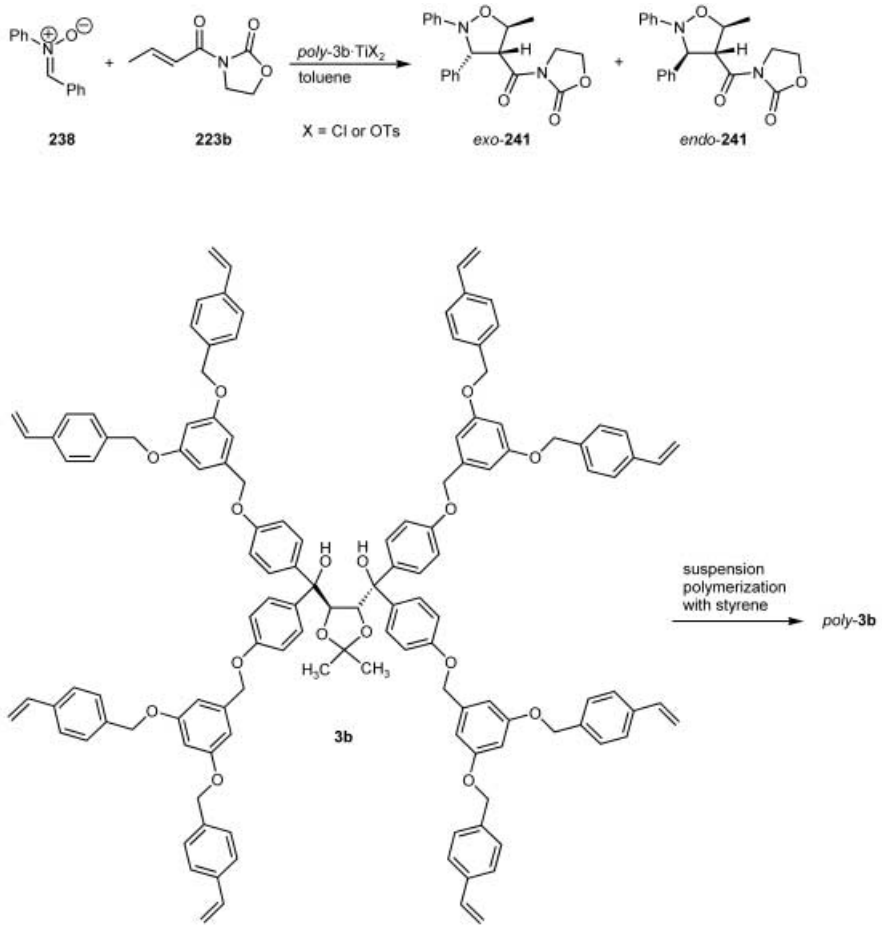
Loading [mmol g^{-1}]	Adduct	*exo*/*endo*	ee (*exo*) [%]
0.39	**241**	92:8	96
0.22	**241**	93:7	96
0.14	**241**	93:7	97
0.39	**241**	>95:5	95
0.22	**241**	>95:5	96
0.14	**241**	>95:5	95

[a] Conditions: 0.2 equiv. of *poly*-**1m** · AlMe, toluene, rt, 12 h.

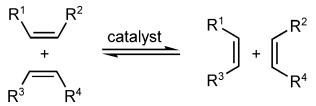
induced, as shown above, by Cl_2Ti-TADDOLates. However, the formation of the corresponding *endo*-cycloadduct *endo*-**241** is favored when $(TsO)_2$Ti-TADDOLates are employed.[198] In solution, this reaction gives rise to good results only when 50 mol % of catalyst are used. Thus, polymer *poly*-**3b** (50 mol %) was loaded with titanate by the addition of a solution of $Ti(OTs)_2$-(O-*i*-Pr)$_2$ in toluene to give *poly*-**3b** · $Ti(OTs)_2$ and a solution of the starting materials for cycloaddition reaction **238** and **223b** were added. The results observed with *poly*-**3b** · $Ti(OTs)_2$ (conversion 72%, *endo*/*exo* 88:12, enantioselectivity 86% ee for *endo*) were slightly inferior than with tetraphenyl-TADDOLate in solution.[196] Recycling was, again, possible only after hydrolysis and reloading with titanate.

7 Olefin Metathesis Reactions

The catalytic olefin metathesis became recently one of the most important methods for C–C bond formation (Scheme 58).[199] Since it relies just on a very simple and readily installable functional group, a C=C double bond,



Scheme 57. 1,3-Dipolar cycloaddition reactions catalyzed by *poly*-**3b** by Seebach et al.[196]



Scheme 58. Olefin metathesis reaction.[199]

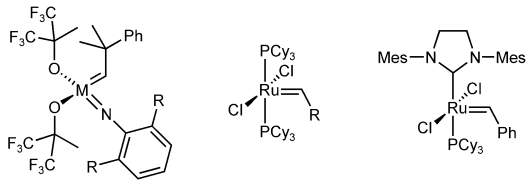


Figure 47. Metathesis catalysts **242 – 244**.[197,198,201]

this reaction is applicable to various different compounds possessing a more or less complicated molecular architecture.

Three categories of this powerful tool are known today and have been widely used: The ring closing (RCM), the ring opening (ROM) and the cross metathesis (CM). The catalysts required for these processes are still under improvement in terms of efficiency, turnover frequencies, long-term stability and tolerance toward functional groups. However, the state of the art provides the chemical community with highly active and nevertheless bench stable catalysts. In Figure 47 are shown three important metathesis catalysts.[199–202]

For more information about mechanism, substrates and conditions see various reviews by A. Fürstner, S. Blechert, R. H. Grubbs and others which offer a detailed overlook.[199] In the last few years, the immobilization of metathesis catalysts is one of the most interesting research targets in this area.[201–209]

Recently, Schrock et al. reported the first polymer-supported and recyclable chiral catalyst **248** for the enantioselective olefin metathesis reaction (Figure 48).[210] The synthesis of this chiral ligand starts with a biphenol that is anchored by a styrene unit to a poly(vinyl alcohol). In the last step, the chiral catalyst is then linked to the polymer.

The results for asymmetric olefin metathesis reactions promoted by this polymer-supported chiral catalyst **248** (Scheme 59) are nearly as good as for reaction performed in solution, but with a lower amount of metal impurities. As in the most solid phase synthesis, the

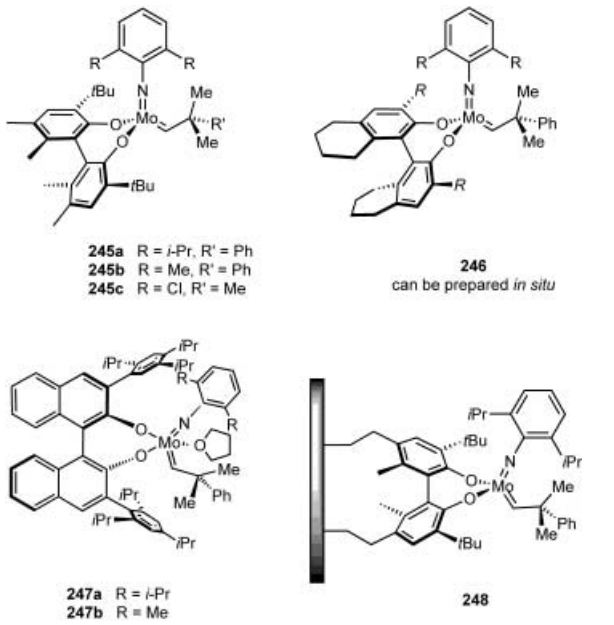
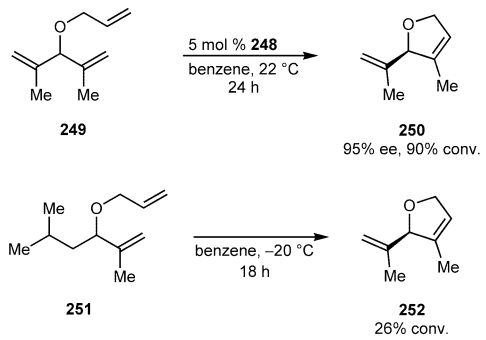


Figure 48. Some chiral metathesis catalysts **245–247**[210] and first polymer-supported chiral catalyst **248** for asymmetric olefin metathesis reactions by Schrock, Hoveyda et al.[210]



Scheme 59. Asymmetric olefin metathesis reaction catalyzed by immobilized **248** by Schrock, Hoveyda et al.[210]

reactivity depends on the polymer swelling, so the influence of the solvent to the reactivity is very high.[210]

8 Summary and Conclusions

Solid-bound chiral catalysts have been found increasing applications in the construction of chiral entities. Although these techniques are so far limited to smaller reaction scales, promising application to industrial scales are anticipated for the future.

With the advent of the discovery of new reactions types, design of novel catalysts, use of hitherto unknown reagents and application of unusual reaction conditions, asymmetric catalysis remains a frontier in modern organic synthesis. At the present time, key issues such as the synthesis, substrate specificity, product selectivity, turnover rates, leaching and recyclability of polymer-bound catalyst have to be addressed.

Acknowledgements

Our own projects were supported by the DFG (SFB 380) and the Fonds der Chemischen Industrie. We thank the DAAD for a grant (cooperation between the groups of Bräse and Leadbeater).

References and Notes

[1] W. S. Knowles, M. Sabacky, *J. Chem. Soc., Chem. Commun.* **1968**, 1445–1446.
[2] H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433.
[3] a) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1996–2007; *Angew. Chem.* **2002**, *114*, 2096–2107; b) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; *Angew. Chem.* **2002**, *114*, 2108–2123; c) K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032; *Angew. Chem.* **2002**, *114*, 2126–2135.
[4] S. C. Stinson, *Chem. Eng. News* **2001**, *79*, 45–56.
[5] a) D. E. de Vos, I. F. J. Vankelecom, A. P. Jacobs (Eds.), *Chiral Catalyst Immobilization and Recycling*, Wiley-VCH, Weinheim, **2000**; b) G. Ertl, H. Knözinger, J. Weitkamp (Eds.), *Preparation of Solid Catalysts*, Wiley-VCH, Weinheim, **1999**; c) E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis Vol. I–III*, Springer, Berlin, **1999**.
[6] a) http://www.epa.gov/opptintr/greenchemistry/; b) T. Collins, *Science* **2001**, *291*, 48–49.
[7] K. C. Nicolaou; R. Hanko, W. Hartwig (Eds.), *Handbook of Combinatorial Chemistry, Drugs, Catalysts, Materials,* Wiley-VCH, Weinheim, **2002**.
[8] C. J. Brinker, G. W. Scherer, *Sol-gel Science, the Physics and Chemistry of Sol-gel Processing,* Academic Press, London, **1990**.
[9] J. M. Thomas, S. Ramdas, G. J. Millward, J. Klinowski, M. Audier, J. Conzalec-Calbet, C. A. Fyfe, *J. Solid State Chem.* **1982**, 368–380.
[10] A. Corma, *Chem. Rev.* **1997**, *97*, 2373–2420.
[11] X. S. Zhao, G. Q. Lu, G. J. Millar, *Ind. Eng. Chem. Res.* **1996**, *35*, 2075–2090.
[12] a) A. Heckel, D. Seebach, *Chem. Eur. J.* **2002**, *8*, 559–572; b) A. Heckel, D. Seebach, *Angew. Chem. Int. Ed.* **2000**, *39*, 163–165; *Angew. Chem.* **2000**, *112*, 165–167.
[13] a) C. Saluzzo, R. te Halle, F. Touchard, F. Fache, E. Schulz, M. Lemaire, *J. Organomet. Chem.* **2000**, *603*, 30–39; b) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345–3384; c) T. J. Dickerson, N. N. Reed, K. D. Janda, *Chem. Rev.* **2002**, *102*, 3325–3344.
[14] F. Zaragoza-Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, **2000**.
[15] U. Kragl, T. Dwars, *Trends Biotech.* **2001**, *19*, 442–449.

[16] G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Molecules: Concepts, Syntheses and Perspectives*, Wiley-VCH, Weinheim, **1996**.
[17] a) S. Rissom, J. Beliczey, G. Giffels, U. Kragl, C. Wandrey, *Tetrahedron Asymmetry* **1999**, *10* , 923 – 928; b) J. Wöltinger, A. S. Bommarius, K. Drauz, C. Wandrey, *Organic Process Research & Development* **2001**, *5*, 241 – 248; c) S. Laue, L. Greiner, J. Wöltinger, A. Liese, *Adv. Synth. Catal.* **2001**, *343*, 711 – 720.
[18] a) C.-J. Li, *ACS Symp. Ser.* **2000**, *767*, 74 – 86; b) M. E. Wilson, G. M. Whitesides, *J. Am. Chem. Soc.* **1978**, *100*, 306 – 307.
[19] a) Y. Kawabata, C. U. Pittman Jr., R. Kobayashi, *J. Mol. Catal.* **1981**, *12*, 113 – 115; b) B. A. Bolto, D. E. Weiss, *Ion Exchange and Solvent Extraction*, Vol. 7, (Eds.: J. A. Marinsky, Y. Marcus), Dekker, New York, **1977**, 221 – 289; c) A. J. Moffat, *J. Catal.* **1970**, *19*, 322 – 325.
[20] P. Hodge, B. J. Hunt, E. Khoshdel, J. Waterhouse, *Nouv. J. Chim.* **1982**, *6*, 617 – 620.
[21] M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, **1998**.
[22] For the first application of BINOL: a) R. Noyori, I. Tomino, Y. Tanimoto, *J. Am. Chem. Soc.* **1979**, *101*, 3129 – 3131; b) L. Pu, *Chem. Eur. J.* **1999**, *5*, 2227 – 2232; c) S. Matsunaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.* **2002**, *344*, 3 – 15.
[23] a) S. Kobayashi, K. Kusakabe, H. Ishitani, *Org. Lett.* **2000**, *2*, 1225 – 1227; b) B. H. Lipshutz, Y.-J. Shin, *Tetrahedron Lett.* **2000**, *41*, 9515 – 9521; c) S. Matsunaga, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2000**, *41*, 8473 – 8478; d) X. W. Yang, W. Su, D. X. Liu, H. S. Wang, J. H. Shen, C. S. Da, R. Wang, A. S. C. Chan, *Tetrahedron* **2000**, *56*, 3511 – 3516.
[24] H. Sellner, C. Faber, P. B. Rheiner, D. Seebach, *Chem. Eur. J.* **2000**, *6*, 3692 – 3705.
[25] W. S. Huang, Q. S. Sheng, X. F. Zheng, J. Anderson, L. Pu, *J. Am. Chem. Soc.* **1997**, *119*, 4313 – 4314.
[26] M. Johannsen, K. A. Jørgensen, X.-F. Zheng, Q.-S. Hu, L. Pu, *J. Org. Chem.* **1999**, *64*, 299 – 301.
[27] D. Jayaprakash, H. Sasai, *Tetrahedron Asymmetry* **2001**, *12*, 2589 – 2595.
[28] T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem. Int. Ed.* **1996**, *35*, 104 – 106; *Angew. Chem.* **1996**, *108*, 103 – 105.
[29] Q.-H. Fan, R. Wang, A. S. C. Chan, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1867 – 1871.
[30] a) D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo, A. Wonnacott, *Helv. Chim. Acta* **1987**, *70*, 954 – 974; b) D. Seebach, M. Hayakawa, J. Sakaki, W. B. Schweizer, *Tetrahedron* **1993**, *49*, 1711 – 1724; c) J. Sakaki, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1993**, *76*, 2654 – 2665; d) D. Seebach, A. Pichota, A. K. Beck, A. B. Pinkerton, T. Litz, J. Karajalainen, V. Gramlich, *Org. Lett.* **1999**, *1*, 55 – 58.
[31] D. Seebach, R. Marti, T. Hintermann, *Helv. Chim. Acta* **1996**, *79*, 1710 – 1740.
[32] P. B. Rheiner, H. Sellner, D. Seebach, *Helv. Chim. Acta* **1997**, *80*, 2027 – 2032.
[33] H. Sellner, D. Seebach, *Angew. Chem. Int. Ed.* **1999**, *38*, 1918 – 1920; *Angew. Chem.* **1999**, *111*, 2039 – 2041.
[34] For reviews, see: a) A. K. Gosh, P. Mathivanan, E. Garcia-Verdugo, J. Capiello, *Tetrahedron Asymmetry* **1998**, *9*, 1 – 45; b) K. A. Jørgensen, M. Johannsen, S. L. Yao, H. Audrain, J. Thorhauge, *Acc. Chem. Res.* **1999**, *32*, 605 – 613; c) A. Pfaltz, *Synlett* **1999**, 835 – 842. d) A. Pfaltz, *J. Heterocycl. Chem.* **1999**, *36*, 1437 – 1451; e) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325 – 335; f) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159 – 2231.
[35] C. Jönsson, K. Hallman, H. Andersson, G. Stemme, M. Malkoch, E. Malmström, A. Hult, C. Moberg, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1857 – 1861.
[36] a) J. M. Fraile, J. I. Garcia, J. A. Mayoral, T. Tarnai, M. A. Harmer, *J. Catal.* **1999**, *186*, 214 – 221; b) C. Langham, S. Taylor, D. Bethell, P. McMorn, P. C. B. Page, D. J. Willock, C. Sly, F. E. Hancock, F. King, G. J. Hutchings, *J. Chem. Soc., Perkin Trans. 2* **1999**, 1043 – 1049.
[37] a) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635 – 1649; b) D. A. Evans, J. S. Johnson, E. J. Olhava, J. M. Janey, *Angew. Chem. Int. Ed.* **1998**, *37*, 3372 – 3375; *Angew. Chem.* **1998**, *110*, 3554 – 3557.
[38] a) S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, *Angew. Chem. Int. Ed.* **2001**, *40*, 2519 – 2521; *Angew. Chem.* **2001**, *113*, 2587 – 2589; b) D. A. Evans, K. A. Scheidt, J. N. Johnston, M. C. Willis, *J. Am Chem. Soc.* **2001**, *123*, 4480 – 4491.
[39] a) J. M. Fraile, J. I. Garcia, J. A. Mayoral, T. Tarnai, *Tetrahedron Asymmetry* **1997**, *8*, 2089 – 2092; b) J. M. Fraile, J. I. Garcia, J. A. Mayoral, T. Tarnai, *Tetrahedron Asymmetry* **1998**, *9*, 3997 – 4008; c) P. J. Alonso, J. M. Fraile, J. I. Garcia, J. I. Martinez, J. A. Mayoral, M. C. Sánchez, *Langmuir* **2000**, *16*, 5607 – 5612; d) A. I. Fernández, J. M. Fraile, J. I. Garcia, C. I. Herrerias, J. A. Mayoral, L. Salvatella, *Catal. Commun.* **2001**, *2*, 165 – 170.
[40] J. M. Fraile, J. I. Garcia, M. A. Harmer, C. I. Herrerias, J. A. Mayoral, *J. Mol. Catal.* **2001**, *165*, 211 – 218.
[41] M. I. Burguete, J. M. Fraile, J. I. Garcia, E. Garcia-Verdugo, S. V. Luis, J. A. Mayoral, *Org. Lett.* **2000**, *2*, 3905 – 3908.
[42] M. I. Burguete, J. M. Fraile, J. I. Garcia, E. Garcia-Verdugo, C. I. Herrerias, S. V. Luis, J. A. Mayoral, *J. Org. Chem.* **2001**, *66*, 8893 – 8901.
[43] D. Rechavi, M. Lemaire, *J. Mol. Catal.* **2002**, *182*, 239 – 247.
[44] M. Glos, O. Reiser, *Org. Lett.* **2000**, *2*, 2045 – 2048.
[45] For a general review, see: E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421 – 431, and references therein.
[46] B. B. De, B. B. Lohray, S. Sivaram, P. K. Dhal, *Tetrahedron Asymmetry* **1995**, *6*, 2105 – 2108.
[47] F. Minutolo, D. Pini, A. Petri, P. Salvadori, *Tetrahedron Asymmetry* **1996**, *7*, 2293 – 2302.
[48] a) L. Canali, E. Cowan, H. Deleuze, C. L. Gibson, D. C. Sherrington, *Chem. Commun.* **1998**, 2561 – 2562; b) L. Canali, E. Cowan, H. Deleuze, C. L. Gibson, D. C.

Sherrington, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2055 – 2066.
[49] H. Sellner, J. K. Karjalainen, D. Seebach, *Chem. Eur. J.* **2001**, *7*, 2873 – 2887.
[50] A. Heckel, D. Seebach, *Helv. Chim. Acta* **2002**, *85*, 913 – 926.
[51] K. Smith, C.-H. Liu, *Chem. Commun.* **2002**, 886 – 887.
[52] G. Sienel, R. Rieth, K. T. Rowbottom, in *Ullmanns Encyklopädie der technischen Chemie*, *Vol. A9*, 5th Ed., VCH, Weinheim, **1992**, pp. 531 – 545.
[53] a) D. E. de Vos, B. F. Sels, P. A. Jacobs, *Adv. Catal.* **2001**, *46*, 1 – 87; b) K. Fodor, S. G. A. Kolmschot, R. A. Sheldon, *Enantiomer* **1999**, *4*, 497 – 511; c) D. C. Sherrington, *Catalysis Today* **2000**, *57*, 87 – 104.
[54] S. Krijnen, H. C. L. Abbenhuis, J. H. C. van Hooff, R. A. van Santen, *Angew. Chem. Int. Ed.* **1998**, *37*, 356 – 358; *Angew. Chem.* **1998**, *110*, 374 – 376.
[55] D. E. de Vos, S. de Wildeman, B. F. Sels, P. J. Grobet, P. A. Jacobs, *Angew. Chem. Int. Ed.* **1999**, *38*, 980 – 983; *Angew. Chem.* **1999**, *111*, 1033 – 1036.
[56] a) S. B. Chang, J. M. Galvin, E. N. Jacobsen, *J. Am. Chem. Soc.* **1994**, *116*, 6937 – 6938; b) W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801 – 2803; c) T. Katsuki, *Coord. Chem. Rev.* **1995**, *140*, 189 – 214.
[57] K. B. M. Janssen, I. Laquiere, W. Dehaen, R. F. Parton, I. F. J. Vankelecom, P. A. Jacobs, *Tetrahedron Asymmetry* **1997**, *8*, 3481 – 3487.
[58] a) R. F. Parton, I. F. J. Vankelecom, D. Tas, K. B. M. Janssen, P.-P. Knops-Gerrits, P. A. Jacobs, *Mol. Cat. A: Chemical* **1996**, *113*, 283 – 292; b) I. F. J. Vankelecom, D. Tas, K. B. M. Janssen, P.-P. Knops-Gerrits, P. A. Jacobs, *Angew. Chem. Int. Ed.* **1996**, *35*, 1346 – 1348; *Angew. Chem.* **1996**, *108*, 1445 – 1447.
[59] a) P. Piaggio, C. Langham, P. McMorn, D. Bethell, P. C. Bulman-Page, F. E. Hancock, C. Sly, G. J. Hutchings, *J. Chem. Soc. Perkin Trans. 2* **2000**, 143 – 148; b) P. Piaggio, P. McMorn, D. Murphy, D. Bethell, P. C. B. Page, F. E. Hancock, C. Sly, O. J. Kerton, G. J. Hutchings, *J. Chem. Soc. Perkin Trans. 2* **2000**, *2*, 2008 – 2015.
[60] M. Palucki, G. J. McCormick, E. N. Jacobsen, *Tetrahedron Lett.* **1995**, *36*, 5457 – 5460.
[61] T. S. Reger, K. D. Janda, *J. Am. Chem. Soc.* **2000**, *122*, 6929 – 6934.
[62] T. Kuroki, T. Hamada, T. Katsuki, *Chem. Lett.* **1995**, 339 – 341.
[63] a) T.-S. Lai, R. Zhang, K.-K. Cheung, H.-L. Kwong, C.-M. Che, *J. Chem. Soc. Dalton Trans.* **1998**, 3559 – 3564; b) T. S. Lai, R. Zhang, K. K. Cheung, H. L. Kwong, C. M. Che, *Chem. Commun.* **1998**, 1583 – 1584.
[64] R. Zhang, W.-Y. Yu, T.-S. Lai, C. M. Che, *Chem. Commun.* **1999**, 409 – 410.
[65] R. Zhang, W. Y. Yu, K. Y. Wong, C. M. Che, *J. Org. Chem.* **2001**, *66*, 8145 – 8153.
[66] D. Avnir, *Acc. Chem. Res.* **1995**, *28*, 328 – 334.
[67] J.-L. Zhang, H.-B. Zhou, J.-S. Huang, C.-M. Che, *Chem. Eur. J.* **2002**, *8*, 1554 – 1562.
[68] a) J.-C. Marchon, R. Ramasseul, *J. Chem. Soc. Chem. Commun.* **1988**, 298 – 299; b) J.-C. Marchon, R. Ramasseul, *Synthesis* **1989**, 389 – 391; c) M. Tavarès, R. Ramasseul, J.-C. Marchon, B. Bachet, C. Brassy, J.-P. Mornon, *J. Chem. Soc. Perkin Trans. 2* **1992**, 1321 – 1329.
[69] a) L. Canali, J. K. Karjalainen, D. C. Sherrington, O. Hormi, *J. Chem. Soc. Chem. Commun.* **1997**, 123 – 124; b) J. K. Karjalainen, O. E. O. Hormi, D. C. Sherrington, *Tetrahedron Asymmetry* **1998**, *9*, 1563 – 1575; c) J. K. Karjalainen, O. E. O. Hormi, D. C. Sherrington, *Tetrahedron Asymmetry* **1998**, *9*, 2019 – 2022; d) J. K. Karjalainen, O. E. O. Hormi, D. C. Sherrington, *Tetahedron Asymmetry* **1998**, *9*, 3895 – 3901.
[70] M. G. Finn, K. B. Sharpless, *J. Am. Chem. Soc.* **1991**, *113*, 113 – 126.
[71] D. Meunier, A. Piechaczyk, A. de Mallmann, J.-M. Basset, *Angew. Chem. Int. Ed.* **1999**, *38*, 3540 – 3542; *Angew. Chem.* **1999**, *111*, 3738 – 3741.
[72] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 483 – 485.
[73] a) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem. Int. Ed.* **1980**, *19*, 929 – 930; *Angew. Chem.* **1980**, *92*, 968 – 969; b) S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annunziata, H. Molinari, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1317 – 1324.
[74] A. Berkessel, N. Gasch, K. Glaubitz, C. Koch, *Org. Lett.* **2001**, *3*, 3839 – 3942.
[75] C. Branden, J. Tooze, *Introduction to Protein Structure*, 2nd Ed.; Garland: New York, **1999**.
[76] a) D. H. Apella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1999**, *121*, 6206 – 6212; b) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173 – 180.
[77] D. A. Annis, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 4147 – 4154.
[78] K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885 – 1889.
[79] E. N. Jacobsen, I. Markó, S. Mungall, G. Schroeder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968 – 1970.
[80] a) H. Becker, K. B. Sharpless, *Angew. Chem., Int. Engl.* **1996**, *35*, 448 – 451; *Angew. Chem.* **1996**, *108*, 447 – 449; b) E. J. Corey, A. Guzman-Perez, M. C. Noe, *J. Am. Chem. Soc.* **1995**, *117*, 10805 – 10816.
[81] For reviews, see: a) H. C. Kolb, M. S. van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483 – 2547; b) C. Bolm, A. Gerlach, *Eur. J. Org. Chem.* **1998**, *21*, 21 – 27.
[82] For achiral polymer-bound catalysts in dihydroxylation reaction with osmium tetroxide see: G. Cianelli, M. Contento, F. Manescalchi, L. Plessi, *Synthesis* **1989**, 45 – 47.
[83] B. M. Kim, K. B. Sharpless, *Tetrahedron Lett.* **1990**, *31*, 3003 – 3006.
[84] H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, *118*, 7632 – 7633.
[85] a) H. H. Kim, K. D. Janda, *Angew. Chem. Int. Ed.* **1997**, *36*, 1731 – 1733; *Angew. Chem.* **1997**, *109*, 1835 – 1837; b) H. Han, K. D. Janda, *Tetrahedron Lett.* **1997**, *38*, 1527 – 1530.

[86] C. Bolm, A. Gerlach, *Angew. Chem. Int. Ed.* **1997**, *36*, 741 – 743; *Angew. Chem.* **1997**, *109*, 773 – 775.
[87] H. Becker, S. B. King, M. Tanguchi, K. P. M. Vanhessche, K. B. Sharpless, *J. Org. Chem.* **1995**, *60*, 3940 – 3941.
[88] C. Bolm, A. Maischak, A. Gerlach, *J. Chem. Soc. Chem. Commun.* **1997**, 2353 – 2354.
[89] For "green" versions of osmium dihydroxylation, see: A. Severeyns, D. E. de Vos, P. A. Jacobs, *Top. Catal.* **2002**, *19*, 125 – 131.
[90] S. Kobayashi, M. Endo, S. Nagayama, *J. Org. Chem.* **1998**, *63*, 6094 – 6095.
[91] S. Kobayashi, M. Endo, S. Nagayama, *J. Am. Chem. Soc.* **1999**, *121*, 11229 – 11230.
[92] S. Kobayashi, T. Ishida, R. Akiyama, *Org. Lett.* **2001**, *3*, 2649 – 2652.
[93] B. M. Choudary, N. S. Chowdari, K. Jyothi, M. L. Kantam, *J. Am. Chem. Soc.* **2002**, *124*, 5341 – 5349.
[94] A. Severeyns, D. E. D. Vos, L. Fiermans, F. Verpoort, P. J. Grobet, P. A. Jacobs, *Angew. Chem. Int. Ed.* **2001**, *40*, 586 – 589; *Angew. Chem.* **2001**, *113*, 606 – 609.
[95] S. Kobayashi, R. Akiyama, *Chem. Commun.* **2003**, 449 – 460.
[96] a) B. Altava, M. I. Burguete, J. M. Fraile, J. I. Garcia, S. V. Luis, J. A. Mayoral, M. J. Vincent, *Angew. Chem. Int. Ed.* **2000**, *39*, 1503 – 1506; *Angew. Chem.* **2000**, *112*, 1563 – 1566; b) E. Breysse, C. Pinel, M. Lemaire, *Tetrahedron Asymmetry* **1998**, *9*, 897 – 900.
[97] a) R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005 – 6008; b) R. E. Lowenthal, S. Masamune, *Tetrahedron Lett.* **1991**, *32*, 7373 – 7376; c) D. A. Evans, K. A. Woerpel, M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726 – 728; d) A. V. Bedekar, P. G. Andersson, *Tetrahedron Lett.* **1996**, *37*, 4073 – 4076; e) A. V. Bedekar, E. B. Koroleva, P. G. Andersson, *J. Org. Chem.* **1997**, *62*, 2518 – 2526; f) N. End, A. Pfaltz, *J. Chem. Soc. Chem. Commun.* **1998**, 589 – 590; g) R. Boulch, A. Scheurer, P. Mosset, R. W. Saalfrank, *Tetrahedron Lett.* **2000**, *41*, 1023 – 1026; h) J. M. Fraile, J. I. Garcia, J. A. Mayoral, T. Tarnai, *J. Mol. Catal. A* **1999**, *144*, 85 – 89.
[98] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, M. Pitillo, *J. Org. Chem.* **2001**, *66*, 3160 – 3166.
[99] U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt, A. Pfaltz, *Tetrahedron* **1992**, *48*, 2143 – 2156.
[100] A. Cornejo, J. M. Fraile, J. I. Garcia, E. Garcia-Verdugo, M. J. Gil, G. Legarreta, S. V. Luis, V. Martínez-Merino, J. A. Mayoral, *Org. Lett.* **2002**, *4*, 3927 – 3930.
[101] a) H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223 – 2224; b) H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, K. Itoh, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247 – 1262.
[102] a) E. Galardon, P. L. Maux, G. Simonneaux, *J. Chem. Soc. Chem. Commun.* **1997**, 927 – 928; b) W. C. Lo, C. M. Che, K. F. Cheng, T. C. W. Mak, *J. Chem. Soc. Chem. Commun.* **1997**, 1205 – 1206; c) M. Frauenkron, A. Berkessel, *Tetrahedron Lett.* **1997**, *38*, 7175 – 7176; d) E. Galardon, S. Roue, P. L. Maux, G. Simonneaux, *Tetrahedron Lett.* **1998**, *39*, 2333 – 2334; e) E. Galardon, P. L. Maux, G. Simonneaux, *Tetrahedron* **2000**, *56*, 615 – 621; f) C. M. Che, J. S. Huang, F. W. Lee, Y. Li, T. S. Lai, H. L. Kwong, P. F. Teng, W. S. Lee, W. C. Lo, S. M. Peng, Z. Y. Zhou, *J. Am. Chem. Soc.* **2001**, *123*, 4119 – 4129.
[103] H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem. Int. Ed.* **1986**, *25*, 1005 – 1006; *Angew. Chem.* **1986**, *98*, 1028 – 1029.
[104] T. Nagashima, H. M. L. Davies, *Org. Lett.* **2002**, *4*, 1989 – 1992.
[105] M. P. Doyle, M. Y. Eismont, D. E. Bergbreiter, H. N. Gray, *J. Org. Chem.* **1992**, *57*, 6103 – 6105.
[106] M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, 1st Ed., Wiley-Interscience, New York, **1998**.
[107] a) H. M. L. Davies, *Eur. J. Org. Chem.* **1999**, 2459 – 2469; b) H. M. L. Davies, *Adrichimica Acta* **1997**, *30*, 105 – 106.
[108] H. M. L. Davies, S. A. Panaro, *Tetrahedron Lett.* **1999**, *40*, 5287 – 5290.
[109] H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall, *J. Am. Chem. Soc.* **1996**, *118*, 6897 – 6901.
[110] a) H. M. L. Davies, P. R. Bruzinski, M. J. Fall, *Tetrahedron Lett.* **1996**, *37*, 4133 – 4136; b) M. P. Doyle, Q.-L. Zhou, C. Charnsangavej, M. A. Longoria, M. McKervey, C. F. Garcia, *Tetrahedron Lett.* **1996**, *37*, 4129 – 4132.
[111] B. Breit, W. Seiche, *Synthesis* **2001**, 1 – 36, and references therein.
[112] S. J. Fritschel, J. J. H. Ackermann, T. Keyser, J. K. Stille, *J. Org. Chem.* **1979**, *44*, 3152 – 3154.
[113] G. Parrinello, R. Deschenaux, J. K. Stille, *J. Org. Chem.* **1986**, *51*, 4189 – 4195.
[114] G. Parrinello, J. K. Stille, *J. Am. Chem. Soc.* **1987**, *109*, 7122 – 7127.
[115] K. Nozaki, Y. Itoi, F. Shibahara, E. Shirakawa, T. Ohta, H. Takaya, T. Hiyama, *J. Am. Chem. Soc.* **1998**, *120*, 4051 – 4052.
[116] K. Nozaki, F. Shibahara, Y. Itoi, E. Shirakawa, T. Ohta, H. Takaya, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1911 – 1918.
[117] K. Nozaki, F. Shibahara, T. Hiyama, *Chem. Lett.* **2000**, 694 – 695.
[118] F. Shibahara, K. Nozaki, T. Matsuo, T. Hiyama, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1825 – 1827.
[119] K. Nozaki, T. Matsuo, F. Shibahara, T. Hiyama, *Adv. Synth. Cat.* **2001**, *343*, 61 – 63.
[120] a) M. A. Wurtz, *Bull. Soc. Fr.* **1972**, *17*, 436 – 442; b) A. T. Nielsen, W. J. Houlihan, *Org. React.* **1968**, *16*, 14 – 38.
[121] a) D. J. Ager, I. Prakesh, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835 – 876; b) W. Oppolzer, *Tetrahedron* **1987**, *43*, 1969 – 2004.
[122] D. A. Evans, M. T. Bilodeau, T. C. Somers, J. Clardy, D. Cherry, Y. Kato, *J. Org. Chem.* **1991**, *56*, 5750 – 5752.
[123] J. R. Gage, D. A. Evans, *Org. Synth.* **1990**, *68*, 83 – 91.
[124] S. M. Allin, S. J. Shuttleworth, T*etrahedron Lett.* **1996**, *37*, 8023 – 8026.

[125] K. Burgess, D. Lim, *J. Chem. Soc. Chem. Commun.* **1997**, 785 – 786.
[126] S. P. Bew, S. D. Bull, S. G. Davies, *Tetrahedron Lett.* **2000**, *41*, 7577 – 7581.
[127] C. W. Phoon, C. Abell, *Tetrahedron Lett.* **1998**, *39*, 2655 – 2658.
[128] A. Fujii, M. Sodeoka, *Tetrahedron Lett.* **1998**, *39*, 8011 – 8014.
[129] a) M. Sodeoka, K. Ohrai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 2648 – 2649; b) M. Sodeoka, R. Tokunoh, F. Miyazaki, E. Hagiwara, M. Shibasaki, *Synlett* **1997**, 463 – 466; c) M. Sodeoka, M. Shibasaki, *Pure Appl. Chem.* **1998**, *70*, 411 – 414.
[130] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615 – 1621; b) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395 – 2396; c) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386 – 7387; d) T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951 – 6954; e) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573 – 575; f) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423 – 2425; g) B. List, *Tetrahedron* **2002**, *58*, 5573 – 5590; h) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254 – 6255.
[131] a) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656 – 5657; b) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 1790 – 1793; *Angew. Chem.* **2002**, *114*, 1868 – 1871.
[132] M. Benaglia, G. Celentano, F. Cozzi, *Adv. Synth. Catal.* **2001**, *343*, 171 – 173.
[133] M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, *Adv. Synth. Catal.* **2002**, *344*, 533 – 542.
[134] a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336 – 9337; b) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199 – 201.
[135] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260 – 5267.
[136] K. Narasaki, K. Soai, T. Mukaiyama, *Chem. Lett.* **1974**, 1223 – 1224.
[137] H. Yamamoto, A. Yanagisawa, K. Ishihara, S. Saito, *Pure Appl. Chem.* **1998**, *70*, 1507 – 1512.
[138] C. Roshini, L. Franzini, A. Raffaeli, P. Salvadori, *Synthesis* **1992**, 503 – 505.
[139] C. Qian, C. Zhu, T. Huang, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2131 – 2132.
[140] W. Dumont, J. C. Poulin, T. P. Dang, H. B. Kagan, *J. Am. Chem. Soc.* **1973**, *95*, 8295 – 8299.
[141] F. Minutolo, D. Pini, P. Salvadori, *Tetrahedron Lett.* **1996**, *37*, 3375 – 3378.
[142] Q. S. Hu, L. Pu, *Polym. Prep.* **2000**, *41*, 16 – 20.
[143] Y.-S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6506 – 6507.
[144] G. Sundararajan, N. Prabagaran, *Org. Lett.* **2001**, *3*, 389 – 392.
[145] O. Huttenloch, E. Laxman, H. Waldmann, *Chem. Eur. J.* **2002**, *8*, 4767 – 4780.
[146] T. Danelli, R. Annnziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Tocco, *Tetrahedron Asymmetry* **2003**, *14*, 461 – 467.
[147] a) L. Pu, H. B. Yu, *Chem. Rev.* **2001**, *101*, 757 – 824; b) M. Kitamura, S. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc.* **1986**, *108*, 6071 – 6072.
[148] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York **1994**, Chapter 5; b) R. Noyori, S. K. Kawai, S. Okada, M. Kitamura, *Pure Appl. Chem.* **1988**, *60*, 1597 – 1606; c) M. Yamakawa, R. Noyori, *Organometallics* **1999**, *18*, 128 – 133.
[149] a) K. Soai, S. Niwa, M. Watanabe, *J. Org. Chem.* **1988**, *53*, 927 – 928; b) K. Soai, S. Niwa, M. Watanabe, *J. Chem. Soc. Perkin Trans. 1* **1989**, 109 – 113.
[150] P. A. Chaloner, S. A. R. Perera, *Tetrahedron Lett.* **1987**, *28*, 3013 – 3014.
[151] K. Soai, M. Watanabe, *J. Chem. Soc. Perkin Trans. 1* **1994**, 837 – 842.
[152] X. Yang, J. Sheng, C. Da, H. Wang, W. Su, R. Wang, A. S. C. Chan, *J. Org. Chem.* **2000**, *65*, 295 – 296.
[153] Q. S. Hu, V. Pugh, M. Sabat, L. Pu, *J. Org. Chem.* **1999**, *64*, 7528 – 7536.
[154] Q. H. Fan, G. H. Liu, X. M. Chen, G. J. Deng, A. S. C. Chan, *Tetrahedron Asymmetry* **2001**, *12*, 1559 – 1565.
[155] a) S. Bräse, S. Dahmen, F. Lauterwasser, N. E. Leadbeater, E. L. Sharp, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1845 – 1848; b) S. Bräse, S. Dahmen, F. Lauterwasser, N. E. Leadbeater, E. L. Sharp, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1849 – 1851.
[156] T. Suzuki, T. Shibata, K. Soai, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2757– 2760.
[157] M. I. Burguete, E. Garcia-Verdugo, M. J. Vicent, S. V. Luis, H. Pennemann, N. G. v. Keyserling, J. Martens, *Org. Lett.* **2002**, *4*, 3947 – 3950.
[158] N. S. Shaikh, V. H. Deshpande, A. V. Bedekar, *Tetrahedron Lett.* **2002**, *43*, 5587 – 5589.
[159] R. J. Kell, P. Hodge, M. Nisar, D. Watson, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1803 – 1807.
[160] C. Bolm, N. Hermanns, A. Claßen, K. Muñiz, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795 – 1798.
[161] M. I. Burguete, M. Collado, E. Garcia-Verdugo, M. J. Vicent, S. V. Luis, N. Graf von Keyserling, J. Martens, *Tetrahedron* **2003**, *59*, 1797 – 1804.
[162] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901 – 4902.
[163] H. Nogami, S. Matsunaga, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 279 – 283.
[164] M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 6801 – 6808.
[165] E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474 – 2475.
[166] a) K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021 – 1050; b) K. Mauruoka, Y. Hoshino, T. Shirasaka, H. Yamamoto, *Tetrahedron Lett.* **1988**, *29*, 3967 – 3970; c) J. K. Whitesell, A. Bhattacharya, C. M. Buchanan, H. H. Chen, D. Deyo, D. James, C.-L. Liu, M. A. Minto, *Tetrahedron* **1986**, *42*, 2993 – 3001.
[167] D. A. Evans, C. S. Burgey, N. A. Paras, T. Vojkovsky, S. W. Tregay, *J. Am. Chem. Soc.* **1998**, *120*, 5824 – 5825.

[168] Y. Gao, P. Lane-Bell, J. C. Vederas, *J. Org. Chem.* **1998**, *63*, 2133 – 2143.
[169] Y. M. A. Yamada, M. Ichinohe, H. Takahashi, S. Ikegami, *Tetrahedron Lett.* **2002**, *43*, 3431 – 3434.
[170] P. Gamez, B. Dunjic, F. Fache, M. Lemaire, *Tetrahedron Asymmetry* **1995**, *6*, 1109 – 1116.
[171] Y. Uozumi, H. Danjo, T. Hayashi, *Terahedron Lett.* **1998**, *39*, 8303 – 8306.
[172] M. Reggelin, M. Schultz, M. Holbach, *Angew. Chem. Int. Ed.* **2002**, *41*, 1614 – 1617; *Angew. Chem.* **2002**, *114*, 1684 – 1687.
[173] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98 – 122.
[174] W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, **1990**.
[175] E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650 – 1667; *Angew. Chem.* **2002**, *114*, 1724 – 1741; and references therein.
[176] S. M. Weinreb, P. M. Scola, *Chem. Rev.* **1989**, *89*, 1525 – 1534.
[177] K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. E. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668 – 1698; *Angew. Chem.* **2002**, *114*, 1742 – 1773; and references therein.
[178] a) S. Pikul, E. J. Corey, *Org. Synth.* **1991**, *71*, 22 – 38; b) E. J. Corey, R. Imwinkelried, S. Pikul, Y. B. Xiang, *J. Am. Chem. Soc.* **1989**, *111*, 5493 – 5495; c) E. J. Corey, N. Imai, S. Pikul, *Tetrahedron Lett.* **1991**, *32*, 7517 – 7520; d) E. J. Corey, S. Sarshar, J. Bordner, *J. Am. Chem. Soc.* **1992**, *114*, 7938 – 7939; e) E. J. Corey, S. Sarshar, D.–H. Lee, *J. Am. Chem. Soc.* **1994**, *116*, 12089 – 12090; f) E. J. Corey, M. A. Letavic, *J. Am. Chem. Soc.* **1995**, *117*, 9616 – 9617.
[179] a) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986 – 2012; *Angew. Chem.* **1998**, *110*, 2092 – 2118; b) E. J. Corey, T.-P. Loh, *J. Am. Chem. Soc.* **1991**, *113*, 8966 – 8967; c) E. J. Corey, T.-P. Loh, *Tetrahedron Lett.* **1993**, *34*, 2979 – 2982; d) E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara, M. C. Noe, *J. Am. Chem. Soc.* **1992**, *114*, 8290 – 8291; e) E. J. Corey, T.-P. Loh, M. D. Azimioara, *Tetrahedron Lett.* **1992**, *33*, 6945 – 6948; f) E. J. Corey, J. J. Rhode, *Tetrahedron Lett.* **1997**, *38*, 37 – 40; g) Review: E. J. Corey, T. W. Lee, *J. Chem. Soc. Chem. Commun.* **2001**, 1321 – 1329.
[180] a) D. Seebach, A. K. Beck, M. Schiess, L. Widler, A. Wonnacott, *Pure Appl. Chem.* **1983**, *55*, 1807 – 1822; b) D. Seebach, B. Weidmann, L. Widler, *Modern Synthetic Methods, Vol. 3* (Ed.: R. Scheffold), Salle & Sauerländer, Aarau, **1983**, 217 – 353; c) D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem. Int. Ed.* **2001**, *40*, 92 – 138; *Angew. Chem.* **2001**, *113*, 96 – 142.
[181] a) R. M. Dessau, *J. Chem. Soc. Chem. Commun.* **1986**, 1167 – 1168; b) M. Conrads, J. Mattay, J. Runsink, *Chem. Ber.* **1989**, *122*, 2207 – 2208; c) C. Cativiela, J. M. Fraile, J. I. Garcia, J. A. Mayoral, E. Pires, A. J. Royo, F. Figueras, L. C. de Ménorval, *Tetrahedron* **1993**, *49*, 4073 – 4084; d) K. Narasaka, M. Inoue, T. Yamada, J. Sugimori, N. Iwasawa, *Chem. Lett.* **1987**, 2409 – 2412.
[182] P. Gerstberger, C. Palm, R. Anwander, *Chem. Eur. J.* **1999**, *5*, 997 – 1005.
[183] H. C. L. Abbenhuis, *Chem. Eur. J.* **2000**, *6*, 25 – 32.
[184] H. Ishitani, S. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 7357 – 7360.
[185] a) S. Kobayashi, S. Komiyama, H. Ishitani, *Angew. Chem. Int. Ed.* **1998**, *37*, 979 – 981; *Angew. Chem.* **1998**, *110*, 1026 – 1028; b) S. Kobayashi, K. Kusakabe, S. Komiyama, H. Ishitani, *J. Org. Chem.* **1999**, *64*, 4220 – 4221; c) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153 – 7154; d) K. Hattori, H. Yamamoto, *Tetrahedron* **1993**, *49*, 1749 – 1760; e) E. Jnoff, L. Ghosez, *J. Am. Chem. Soc.* **1999**, *121*, 2617 – 2618; f) S. Yao, M. Johannsen, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **1998**, *37*, 3121 – 3124; *Angew. Chem.* **1998**, *110*, 3318 – 3321; g) S. Bromidge, P. C. Wilson, A. Whiting, *Tetrahedron Lett.* **1998**, *39*, 8905 – 8908.
[186] J. K. Park, S. W. Kim, T. Hyeon, B. M. Kim, *Tetrahedron Asymmetry* **2001**, *12*, 2931 – 2935.
[187] a) D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, *J. Am. Chem. Soc.* **1999**, *121*, 7559 – 7573; b) S. Crosignani, G. Desimoni, G. Faita, P. Righetti, *Tetrahedron* **1998**, *54*, 15721 – 15730; c) D. A. Evans, J. S. Johnson, *J. Am. Chem. Soc.* **1998**, *120*, 4895 – 4896; d) D. A. Evans, S. J. Miller, T. Lectka, *J. Am. Chem. Soc.* **1993**, *115*, 6460 – 6461; e) D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 7582 – 7594; f) P. Carbone, G. Desimoni, G. Faita, S. Filippone, P. Righetti, *Tetrahedron* **1998**, *54*, 6099 – 6110; recent reviews: g) A. K. Gosh, P. Mathivanan, E. García-Verdugo, J. Capiello, *Tetrahedron Asymmetry* **1998**, *9*, 1 – 45; h) I. Ojima, *Catalytic Asymmetric Synthesis*; Wiley-VCH, New-York, **2000**.
[188] K. Hallmann, C. Moberg, *Tetrahedron Asymmetry* **2001**, *12*, 1475 – 1478.
[189] A. K. Gosh, H. Cho, J. Cappiello, *Tetrahedron Asymmetry* **1998**, *9*, 3687 – 3691.
[190] M. Benaglia, G. Celentano, M. Cinquini, A. Puglisis, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149 – 152.
[191] P. I. Dalko, L. Mosian, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726 – 3748; *Angew. Chem.* **2001**, *113*, 3840 – 3864.
[192] S. A. Selkälä, J. Tois, P. M. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941 – 945.
[193] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243 – 4244; b) K. Ishihara, K. Kurihara, M. Matsumoto, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 6920 – 6930.
[194] G. Faita, A. Paio, P. Quadrelli, F. Rancati, P. Seneci, *Tetrahedron* **2001**, *57*, 8313 – 8322.
[195] a) K. B. Simonsen, K. A. Jørgensen, Q.-S. Hu, L. Pu, *J. Chem. Soc. Chem. Commun.* **1999**, 811 – 812; b) K. B. Simonsen, P. Bayon, R. G. Hazell, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **1999**, *121*, 3845 – 3853.
[196] H. Sellner, P. B. Rheiner, D. Seebach, *Helv. Chim. Acta* **2002**, *85*, 352 – 387.

[197] K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1994**, *59*, 5687 – 5691.
[198] K. V. Gothelf, I. Thomsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **1996**, *118*, 59 – 64.
[199] a) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109,* 2124 – 2144; *Angew. Chem. Int. Ed.* **1997**, *36*, 2036 – 2056; b) K. J. Ivin, J. C. Mol, *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, **1997**; c) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413 – 4450; d) *Alkene Metathesis in Organic Synthesis,* (Ed.: A. Fürstner), Springer, Berlin, **1998**; e) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 – 3043; *Angew. Chem.* **2000**, *112*, 3140 – 3172; f) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* 2001, *34*, 18 – 29.
[200] a) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875 – 3886; b) J. H. Oskam, H. H. Fox, K. B. Yap, D. H. McConville, R. O'Dell, B. J. Lichtenstein, R. R. Schrock, *J. Organomet. Chem.* **1993**, *459*, 185 – 198; c) J. Feldman, J. S. Murdzek, W. M. Cavis, R. R. Schrock, *Organometallics* **1989**, *8*, 2260 – 2265.
[201] a) S. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1992**, *114*, 3974 – 3975; b) S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, *115*, 9858 – 9859; c) P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed.* **1995**, *34*, 2039 – 2041; *Angew. Chem.* **1995**, *107*, 2179 – 2181; d) Z. Wu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *117*, 5503 – 5511; e) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100 – 110.
[202] a) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.* **1999**, *121*, 2674 – 2678; b) J. Huang, H.-J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5375 – 5378; c) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247 – 2250; d) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956; e) A. K. Chatterjee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 1751 – 1753; f) A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783 – 3784; g) L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann, *Tetrahedron Lett.* **1999**, *40*, 4787 – 4790; h) T. Weskamp, F. J. Kohl, W. Hieringer, D. Gleich, W. A. Herrmann, *Angew. Chem. Int. Ed.* **1999**, *38*, 2416 – 2419; *Angew. Chem.* **1999**, *111*, 2573 – 2576; i) T. Weskamp, F. J. Kohl, W. A. Herrmann, *J. Organomet. Chem.* **1999**, *582*, 362 – 365.
[203] S. T. Nguyen, R. T. Grubbs, *J. Organomet. Chem.* **1995**, *497*, 195 – 200.
[204] M. Ahmed, A. G. M. Barrett, D. C. Braddock, S. M. Cramp, P. A. Procopiou, *Tetrahedron Lett.* **1999**, *40*, 8657 – 8662.
[205] S. C. Schürer, S. Gessler, N. Buschmann, S. Blechert, *Angew. Chem. Int. Ed.* **2000**, *39*, 3898 – 3901; *Angew. Chem.* **2000**, *112*, 4062 – 4065.
[206] J. Dowden, J. Savovic, *J. Chem. Soc. Chem. Commun.* **2001**, 37 – 38.
[207] a) M. Mayr, B. Mayr, M. R. Buchmeiser, *Angew. Chem. Int. Ed.* **2001**, *40*, 3839 – 3842; *Angew. Chem.* **2001**, *113*, 3957 – 3960; b) M. Mayr, M. R. Buchmeiser, K. Wurst, *Adv. Synth. Catal.* **2002**, *344*, 712 – 719.
[208] a) M. Kubin, P. Spacek, R. Chromecek, *Collect. Czech. Chem. Commun.* **1967**, *32*, 3881 – 3887; b) L. C. Hansen, R. E. Sievers, *J. Chromatograph.* **1974**, *99*, 123 – 133; c) S. Hjertén, J.-L. Liao, R. Zhang, *J. Chromatograph.* **1989**, *473*, 273 – 275; d) S. Hjertén, Y.-M. Li, J.-L. Liao, J. Mohammad, K. Nakazato, G. Pettersson, *Nature* **1992**, *356*, 810 – 811; e) J. A. Tripp, F. Svéc, J. M. J. Fréchet, *J. Comb. Chem.* **2001**, *3*, 216 – 223; f) J. A. Tripp, J. A. Stein, F. Svéc, J. M. J. Fréchet, *Org. Lett.* **2000**, *2*, 195 – 198; g) F. Sinner, M. R. Buchmeiser, *Angew. Chem. Int. Ed.* **2000**, *39*, 1433 – 1436; *Angew. Chem.* **2000**, *112*, 1491 – 1994; h) M. R. Buchmeiser, F. Sinner, M. Kupa, K. Wurst, *Macromolecules* **2000**, *33*, 32 – 39.
[209] a) J. B. Alexander, D. S. La, D. R. Cefalo, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 4041 – 4042; b) D. S. La, J. B. Alexander, D. R. Cefalo, D. D. Graf, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 9720 – 9721; c) S. S. Zhu, D. R. Cefalo, D. S. La, J. Y. Jamieson, W. M. Davies, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1999**, *121*, 8251 – 8259; d) D. S. La, G. J. Ford, E. S. Sattely, P. J. Bonitatebus, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 11603 – 11604; e) G. S. Weatherhead, J. H. Houser, G. J. Ford, J. Y. Jamieson, R. R. Schrock, A. H. Hoveyda, *Tetrahedron Lett.* **2000**, *41*, 9553 – 9559; f) G. S. Weatherhead, J. G. Ford, E. J. Alexanian, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 1828 – 1829; g) D. R. Cefalo, A. F. Kiely, M. Wuchrer, J. Y. Jamieson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 3139 – 3140; h) D. S. La, E. S. Sattely, J. G. Ford, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 7767 – 7778; i) A. H. Hoveyda, R. R. Schrock, *Chem. Eur. J.* **2001**, *7*, 945 – 950; j) T. J. Seiders, D. W. Ward, R. H. Grubbs, *Org. Lett.* **2001**, *3*, 3225 – 3228.
[210] K. C. Hultzsch, J. A. Jernelius, A. H. Hoveyda, R. R. Schrock, *Angew. Chem. Int. Ed.* **2002**, *41*, 589 – 593; *Angew. Chem.* **2002**, *114*, 609 – 613.

