

# Enantioselective Addition of Organozinc to Aldehydes and Ketones Catalyzed by Immobilized Chiral Ligands

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**Abstract:** Catalytic enantioselective addition of organozinc reagents to carbonyl groups is a valuable method for the synthesis of optically active alcohols. Such asymmetric organozinc additions allow the synthesis of chiral alcohols ubiquitous in the structures of natural and manmade compounds. Recent interest in green chemistry has led to active research in the immobilization of catalysts, and their application to asymmetric reactions. Besides simplifying compound separation and recycling, immobilized catalysts offer easier handling of toxic reagents, and convenient operation in continuous flow reactors. Thus, industrial applications of even expensive and complex chiral catalysts can be achieved in an economical and environmentally benign way.

**Keywords:** Dialkylzinc addition, benzaldehyde, chiral secondary alcohol, immobilized catalyst.

## INTRODUCTION

Enantioselective addition of organometallic reagents to aldehydes and ketones yields optically active alcohols. The relevant literature focuses mainly on the addition to aldehydes, in order to obtain chiral secondary alcohols. This reaction is one of the most important and fundamental asymmetric reactions. The optically

unsuccessful due to the highly reactive nature of the reagents. The breakthrough for the controlled enantioselective addition to the carbonyl group came from organozinc reagents, discovered by Oguni's group [2]. Following this, a plethora of ligands involved in the catalytic dialkylzinc addition to aldehydes under homogeneous conditions has been reported [3] (Fig. 1).

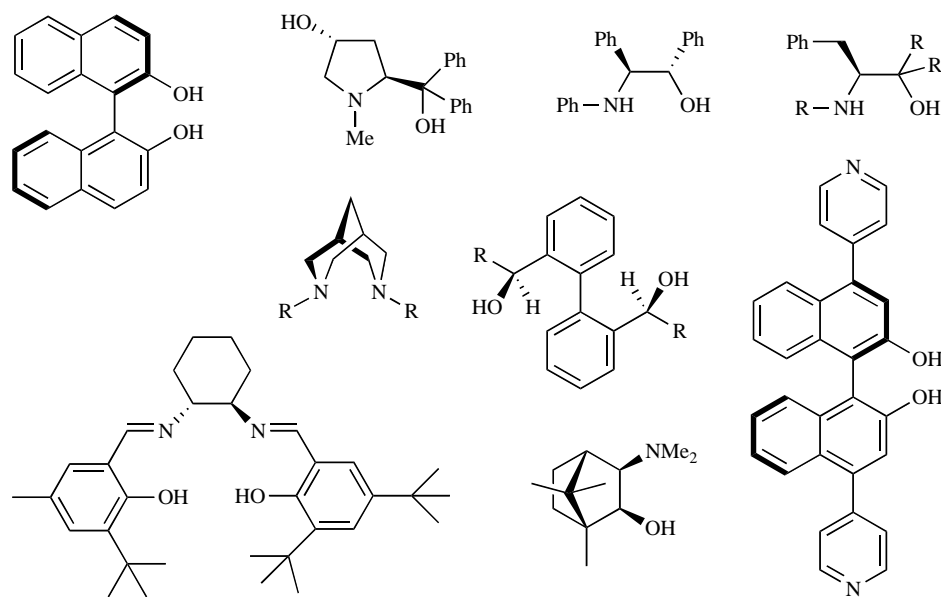


Fig. (1). Ligands used to catalyze the dialkylzinc addition to aldehyde under homogeneous conditions.

active secondary alcohols are components of many naturally occurring and biologically active compounds, as well as materials such as liquid crystals. They are also important as synthetic intermediates of functionalities such as halide, amine, ester, ether, and others.

Two major methods for the enantioselective synthesis of optically active secondary alcohols are the enantioselective reduction of ketones and the enantioselective alkylation of aldehydes (i.e. addition of organometallic reagents to aldehydes). Enantioselective carbonyl reduction has been extensively studied and reviewed [1]. Enantioselective addition of alkyl groups to aldehydes and ketones as organomagnesium and organolithium reagents has been largely

Subsequently, many of these ligands were immobilized on polymer, silica gel and dendrimers, and were applied as catalysts in the diethyl zinc addition to aromatic aldehydes in heterogeneous conditions. Immobilized catalysts have been of great interest because they offer advantages such as simplification of product work-up, straightforward separation and isolation, and re-use of the catalyst. However, their use in organic synthesis has been rather limited because in many cases immobilized catalysts are less active than the original catalysts. More importantly, recent interest in environmentally benign chemical processes, reducing waste and high-throughput organic synthesis has triggered renewed interest in the chemistry of immobilization of homogeneous catalysts.

The earlier work in the area of immobilization of catalysts for alkyl addition has been summarized in three review articles by Soai and Niwa [3a] Pu and Yu [3b], and Clapham *et al.* [4]. The objective of this review is to describe the immobilization of catalysts

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used in the diethylzinc addition to aldehydes from 2001 to the present.

### TYPES OF SUPPORT

Four distinct methodologies have been developed for the heterogenization of homogeneous catalysts: adsorption, encapsulation, covalent tethering and electrostatic interaction. The main supports used for the immobilization of homogeneous catalysts fall into two broad categories: organic and inorganic. The organic supports used for immobilization are generally soluble or insoluble polymer resins [5] or dendrimers [6]. Very often catalysts immobilized on soluble polymer can be recovered by precipitation using a non-polar solvent and then reused in the reaction. The inorganic supports described herein involve amorphous silica and mesoporous silica, such as MCM-41 and SBA-15, with well defined pore structures [7]. In these cases the chiral ligand-metal catalyst is immobilized on the silica through covalent bonding or by electrostatic interaction. At the end of the reaction the immobilized catalyst is easily recovered by simple filtration and reused in the reaction [8].

### IMMOBILIZATION OF LIGANDS ON POLYMER

Most ligand studies involve polymers, since a variety of polymers can be synthesized (e.g., linear, cross-linked) with different functional groups that can be used to tether the ligands. Polymers also provide microenvironments that may enhance the enantioselectivity of the reactions. The early discovery by Oguni and coworkers [2], in which (*S*)-leucinol catalyzed the enantioselective dimethylzinc addition to benzaldehyde, led Noyori and coworkers to report (-)-3-exo-dimethylaminoisoborneol (DAIB) (**1**) [9] as an excellent ligand (Fig. 2), with 98% ee and 98% yield.

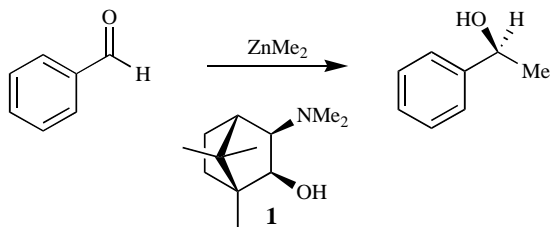


Fig. (2). Enantioselective dimethylzinc addition to benzaldehyde catalyzed by DAIB (**1**).

Fréchet, Itsuno and Soai [3a, 10a] pioneered the use of polymer-anchored chiral catalysts for the asymmetric organozinc addition to aldehydes. Following that work, a tremendous variety of amino alcohols have been synthesized and used as catalysts in the diethylzinc addition to aldehyde. Fréchet and Itsuno [10] immobilized DAIB on 1-2% cross-linked polystyrene (**2**, Fig. 3), which catalyzed the diethylzinc addition to benzaldehyde to give the chiral alcohol in 91% yield and 92% ee.

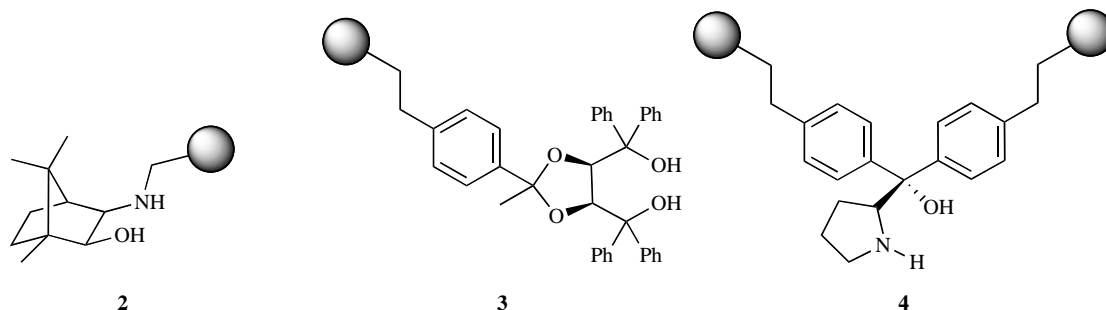


Fig. (3). Polymer-anchored chiral catalysts.

Leino and coworkers [11] reported an elegant method to immobilize chiral ligands on polymer fibers. Styrenic TADDOL (**3**) and L-prolinol (**4**) polymers (Fig. 3) were derived from monomers that were immobilized on polyethylene fibers by electron beam induced pre-irradiation grafting, using styrene as co-monomer. The polymer-supported chiral ligands catalyzed the asymmetric addition of diethylzinc to benzaldehyde to give a quantitative conversion with 94% ee. Both polymer-supported catalysts were successfully recycled after quenching with HCl, filtration and subsequent washes with solvents. Yields decreased slightly on regeneration while the enantioselectivity remained unchanged.

In subsequent work, the same authors [12] immobilized L-prolinol on polymer fibers by electron beam-induced pre-irradiation grafting using styrene as a co-monomer. The resulting polymer-supported catalyst was used in the asymmetric addition of diethylzinc to benzaldehyde. The corresponding alcohol was obtained in 98% yield and 40% ee.

Jayaprakash and Sasai [13] reported the synthesis of a soluble polymer containing the BINOL (**5**) residue (Fig. 4) and the application as a catalyst with  $\text{Ti}(\text{O}^i\text{Pr})_4$  to add diethylzinc to benzaldehyde in moderate yields (56%) and ee (84%).

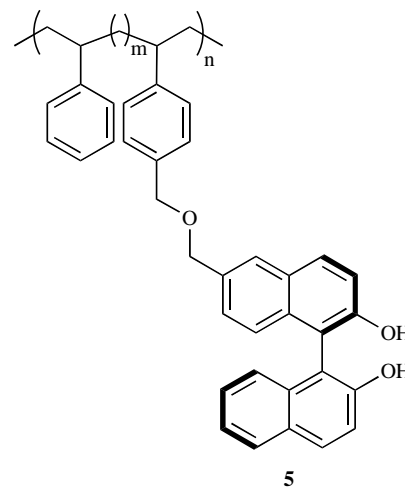


Fig. (4). Soluble polymer containing BINOL (**5**).

Martens and coworkers [14] used (*R*)-2-azabicyclo [3.3.0]octane-3-carboxylic acid, a waste product from the synthesis of the ACE inhibitor Ramipril at Aventis, as a starting material and grafted it Merrifield resin. The heterogenized ligand **6** (Fig. 5) catalyzed the diethylzinc addition to benzaldehyde to give the alcohol in 83% yield and 89% ee, slightly lower than with the homogeneous catalyst. When they reused the heterogeneous ligand **6**, the yield and ee dropped to 74% and 80%, respectively.

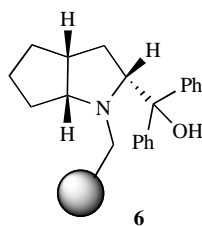


Fig. (5). Heterogeneous ligand grafted to Merrifield resin (6).

Chan and coworkers [15] reported BINOL supported on polymer (Fig. 6) and its use in the diethylzinc addition to a variety of substituted aromatic aldehydes. Better enantioselectivity was obtained with ligand 7, at 87-97% yield and 83-99% ee, vs. 82-94% yield and 41-82% ee with 8. These results were attributed to better steric control and higher conformational rigidity. Additionally, the same authors attached BINOL to a Fréchet-type dendrimer 9 and used it in the diethylzinc addition to benzaldehyde, finding lower enantioselectivity than with polymer 7. Ligands derived from the first-generation dendrimer ( $n=0$ ) gave the best yield (98%) and enantioselectivity (62%). Second and third-generation dendrimers gave lower yield (78%) and enantioselectivity (49%).

Bedekar and coworkers [16] reported polymer-anchored chiral amino-oxazolanyl ligands (10, 11, Fig. 7) as catalysts for the enantioselective addition of diethylzinc to benzaldehyde with moderate to high enantioselectivity (21-89%) and yields (46-90%). When the catalysts were recycled, a slight decrease in yield and enantioselectivity was detected.

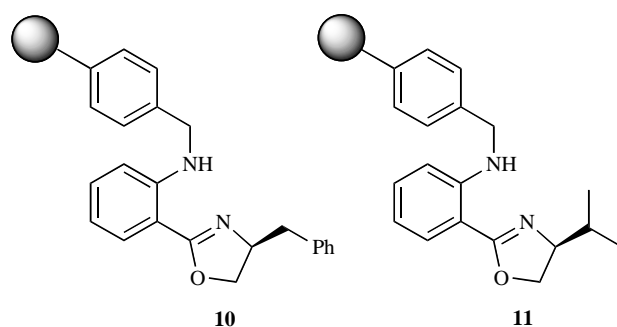


Fig. (7). Polymer anchored chiral amino-oxazolanyl ligands.

Bolm *et al.* [17] reported chiral MeO-PEG-supported ferrocenyl oxazoline ligands (Fig. 8), and successfully employed them in the enantioselective phenyl and ethyl transfer to aldehydes. The insoluble resin-bound ferrocene 12 proved to be unsuitable for the catalysis of the asymmetric phenyl transfer reaction, and only racemic product was obtained. In contrast, the addition of diethylzinc to benzaldehyde gave 87% ee with 93% yield. The addition product of phenylzinc with the MeO-PEG-bound ferrocene 13 was obtained in 97% yield and 97% ee, while diethylzinc addition was obtained with only 93% yield and 86% ee. When 13 was recycled five times in the phenyl transfer reaction, the yield and enantioselectivity remained unchanged.

The same group [18] polymerized (2*S*,4*R*)-diphenyl-(1-methyl-4-hydroxypyrrolidin-2-yl)methanol on ROMP monomers derived from *endo*-norbornene anhydride. Treatment of various mixtures of chiral and achiral monomer with Grubb's ROMP catalyst afforded

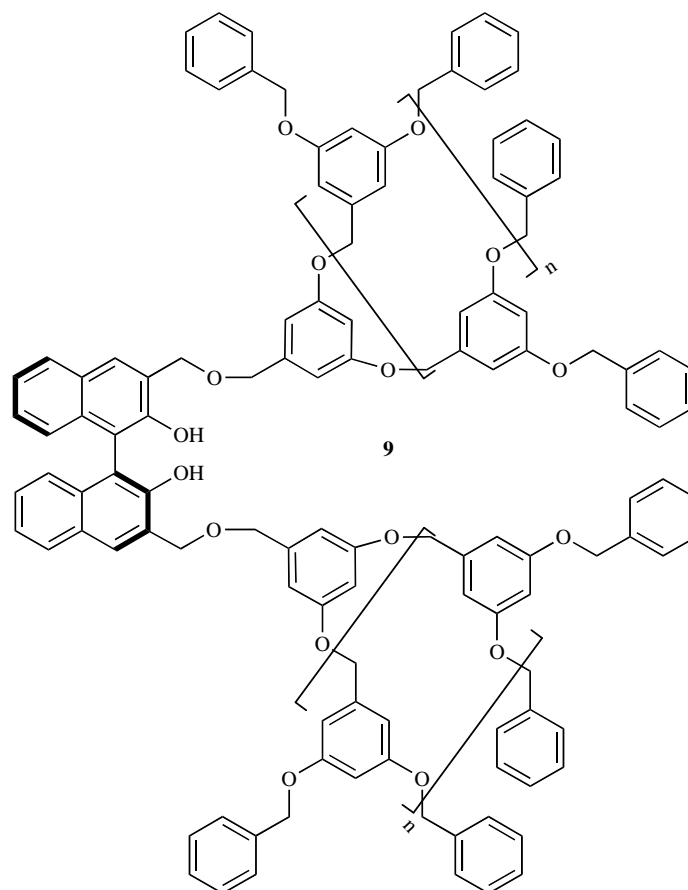
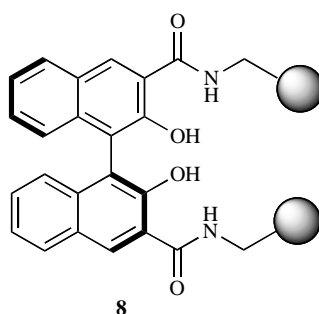
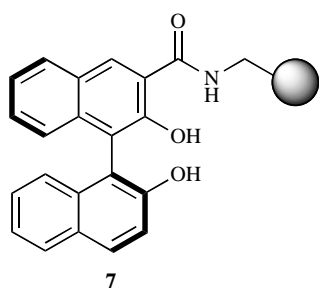


Fig. (6). BINOL catalysts supported on polymer.

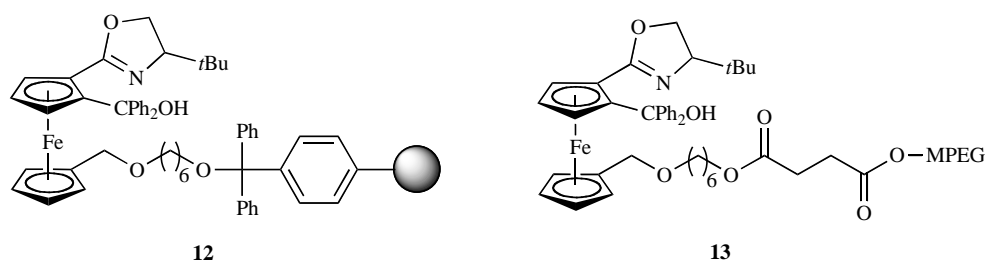


Fig. (8). Chiral MeO-PEG-supported ferrocenyl oxazoline ligands.

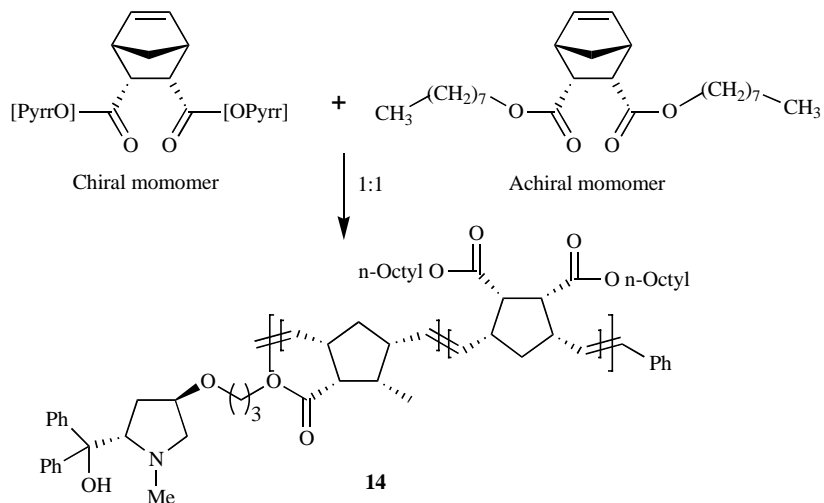


Fig. (9). Highly functionalized polymer obtained by ROMP.

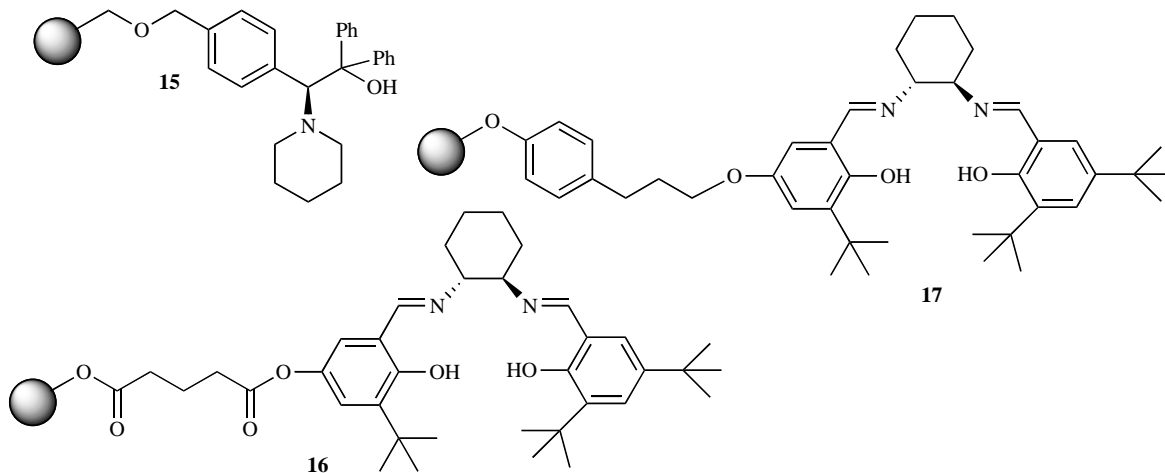


Fig. (10). Chiral ligands supported on polymer.

different macromolecules. Of the various polymers explored, product **14** (Fig. 9) gave the best enantioselectivity in the diethylzinc addition to benzaldehyde (87% ee). This polymer was obtained with co-polymer derived from 1:1 mixtures of chiral and achiral monomers. The results suggest that only some polymers create the distinct microenvironments that lead to high enantioselectivity.

Pericàs' group [19] anchored (*R*)-2-piperidino-1,1,2-triphenylethanol on different polymeric supports **15** (Fig. 10) and used them as a catalysts in the diethylzinc addition to various aromatic aldehydes. Overall, excellent yields (95-99%) and enantioselectivities (90-96%) were obtained.

Anyanwu and Venkataraman [20] anchored a salen ligand on soluble polymer support (**16**, Fig. 10) and used it as catalyst in the diethylzinc addition to benzaldehyde. The chiral alcohol was ob-

tained in 90% yield and 82% enantioselectivity. Catalyst **17** was more reactive but less selective than **16**, with 91% yield and 68% ee. The authors suggested that the difference in reactivity between these two ligands is due to the nature of the spacer unit and not a result of the polymer support.

Lesma and coworkers [21] synthesized amino alcohol ligands anchored on polymer (**18**, **19**, Fig. 11) and used them as catalysts in the diethylzinc addition to benzaldehyde. The final chiral alcohol was obtained in 95% yields, and 25 and 5% ee with **18** and **19**, respectively.

The same authors [22] reported anchoring chiral amino-amide-9-keto-bispidines on three different types of polymer supports, and used them as catalysts in the diethylzinc addition to benzaldehyde.

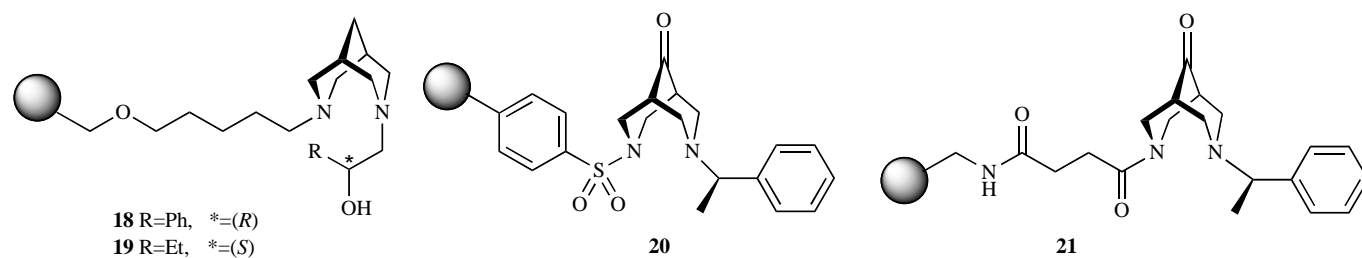


Fig. (11). Bispidine ligands anchored to polymer.

Bispidine ligands **20** and **21** (Fig. 11) gave the alcohol in 81% yield, 46% ee and 89% yield, 43% ee, respectively.

Moreau and coworkers [23] reported two types of reticulated polystyrene networks containing (*R*)-BINOL entities at each junction of the polystyrene chains (**22** and **23**, Fig. 12). When used as catalysts in the diethylzinc addition to benzaldehyde, yields >99% and enantioselectivities in the range 20-78% were obtained. Later, they demonstrated that the catalytic properties of polystyrene gels incorporating (*R*)-BINOL entities are highly dependent on the degree of reticulation [24].

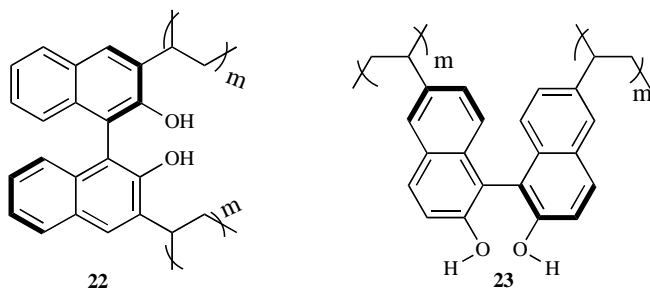


Fig. (12). Reticulated polystyrene catalyst containing BINOL.

Kim and Jin [25] reported the enantioselective addition of diethylzinc to aldehydes catalyzed by polymer-supported amino thioacetate **24** (Fig. 13). The alcohols were obtained in 71-97% yields and 51-91% ee. Amino thioacetate with 1% crosslinking gave better enantioselectivity (91% ee, 83% yield) than the 2% crosslinked polymer (82% ee, 84% yield).

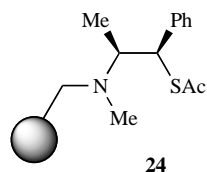


Fig. (13). Polymer-supported amino thiol ligands.

Gau and coworkers [26] reported the synthesis of polystyrene-supported *N*-sulfonylated amino alcohols **25** (Fig. 14) and their application to in the diethylzinc addition to aldehydes in the presence of titanium tetraisopropoxide. Polystyrene made with 20%

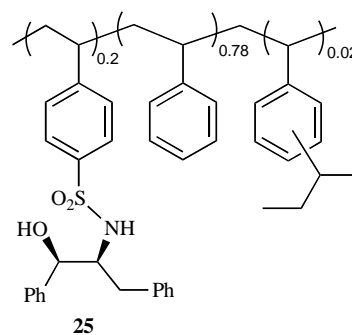


Fig. (14). Polystyrene-supported *N*-sulfonylamino alcohol ligand.

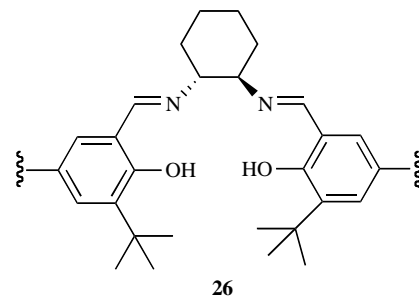


Fig. (15). Polymeric salen ligand.

amino alcohol gave the best results in the alkylation of aldehydes, with 90-95% yield and 89-95% ee.

Abdi and coworkers [27] reported the enantioselective phenylacetylene addition to aldehydes and ketones, catalyzed by recyclable polymeric salen ligand **26** (Fig. 15) complexed with Zn. The corresponding chiral secondary propargylic alcohols were obtained in 96% yield and 72% enantioselectivity. The catalyst was recycled four times with retention of enantioselectivity.

Gros and coworkers [28] reported that pyridine-based tridentate chiral ligand *N*-picolylvalinol, anchored on Merrifield resin with 2% divinylbenzene crosslinking **27** (Fig. 16), catalyzed diethylzinc addition to benzaldehyde to give the chiral secondary alcohol in >99% yield and 93% enantioselectivity.

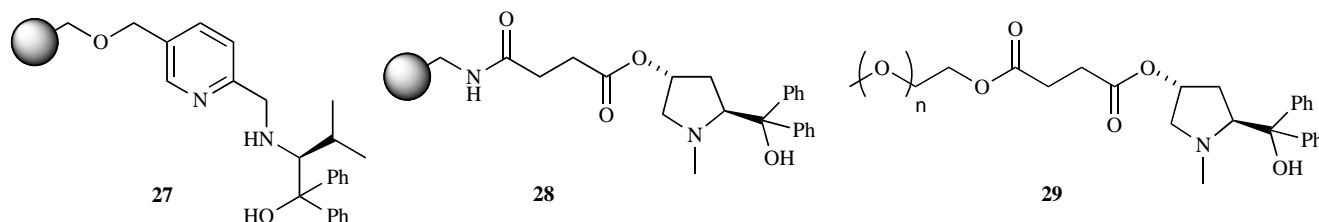


Fig. (16). Pyridine and proline based ligands.

Wang and coworkers [29] attached proline to aminomethylated polystyrene and MEO-PEG and used the supported ligands as catalysts in the diethylzinc addition to aromatic aldehydes. Ligands **28** and **29** (Fig. 16), proved to be highly active with good enantioselectivity (up to 90% ee) and yields (up to 96%). The insoluble polymer supported catalysts were easily recovered and used in several consecutive catalytic runs without significant loss of enantioselectivity.

Rosling and coworkers [30] reported soluble polymer-supported TADDOLs by copolymerizing styryl derivatives of TADDOL with styrene or *N*-isopropylacrylamide (NIPAAm). They compared the efficiency of these two ligands, in the presence of Ti(IV) as the catalyst in the enantioselective addition of Et<sub>2</sub>Zn to benzaldehyde. The copolymer with styrene **30** (Fig. 17) gave very high yield (>90%) and excellent enantioselectivity (98%), while the copolymer with NIPAAm **31** afforded a lower yield (55%) but high ee (90%).

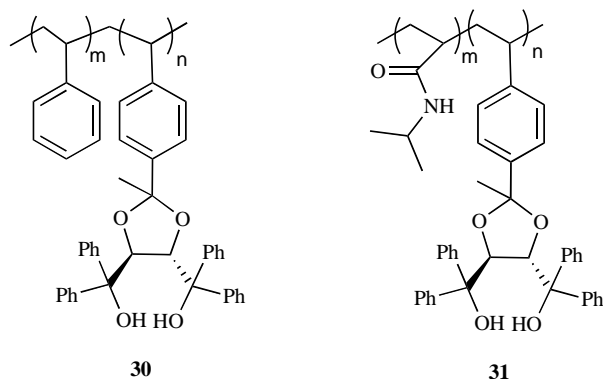


Fig. (17). Polymer supported TADDOLs.

Habaue *et al.* [31] reported a novel route to chiral polymer chain containing BINOL **32a,b** (Fig. 18) by oxidative coupling of 1,1-bi-2-naphthol units to a polymer using a copper catalyst. The polymeric BINOL was evaluated as catalyst in the diethylzinc addition to benzaldehyde. The final chiral alcohol was obtained in 98% yield and 15% ee.

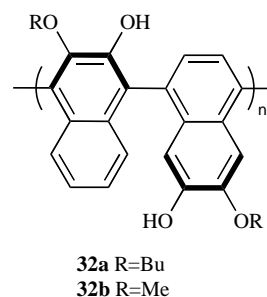


Fig. (18). Chiral polymeric BINOL.

#### LIGANDS IMMOBILIZED ON SILICA GEL

Compared to polymeric matrices that are often used for anchoring organometallic complexes, silica supports have the advantage of high mechanical strength, chemical robustness, and thermal stability. Heckel and Seebach [32] described the immobilization of TADDOLs on hydrophobic controlled-pore-glass silica gel and their use as catalysts in the addition of diethylzinc or dibutylzinc to benzaldehyde. They reported that the results obtained with immobilized ligand **33** (Fig. 19) were comparable to those under standard homogeneous conditions, >95% yield and up to 98% ee.

Chung and Rhee [33] reported the silica-supported dendrite chiral catalyst **34** (Fig. 10) in the addition of diethylzinc to benzaldehyde. The introduction of a long alkyl spacer at the periphery of the dendrimer was found to be effective in improving the conversion. The new silica-supported dendritic chiral catalyst gave 84% yield and 36% ee. Soai and coworkers [34] immobilized chiral ephedrine on silica gel **35** (Fig. 19) and used it as a catalyst in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde, obtaining the alcohol in 93% yield and 93% ee.

Recently Jin *et al.* [35] grafted ephedrine to mesoporous silica SBA-15 (**36**) and used it as a catalyst to add diethylzinc to aldehydes. The final chiral alcohols were obtained in 71-85% yield and 25-71% ee. In collaborative work, Huang *et al.* [36] grafted chiral  $\beta$ -hydroxyamide derived from L-phenylalanine, to amorphous silica

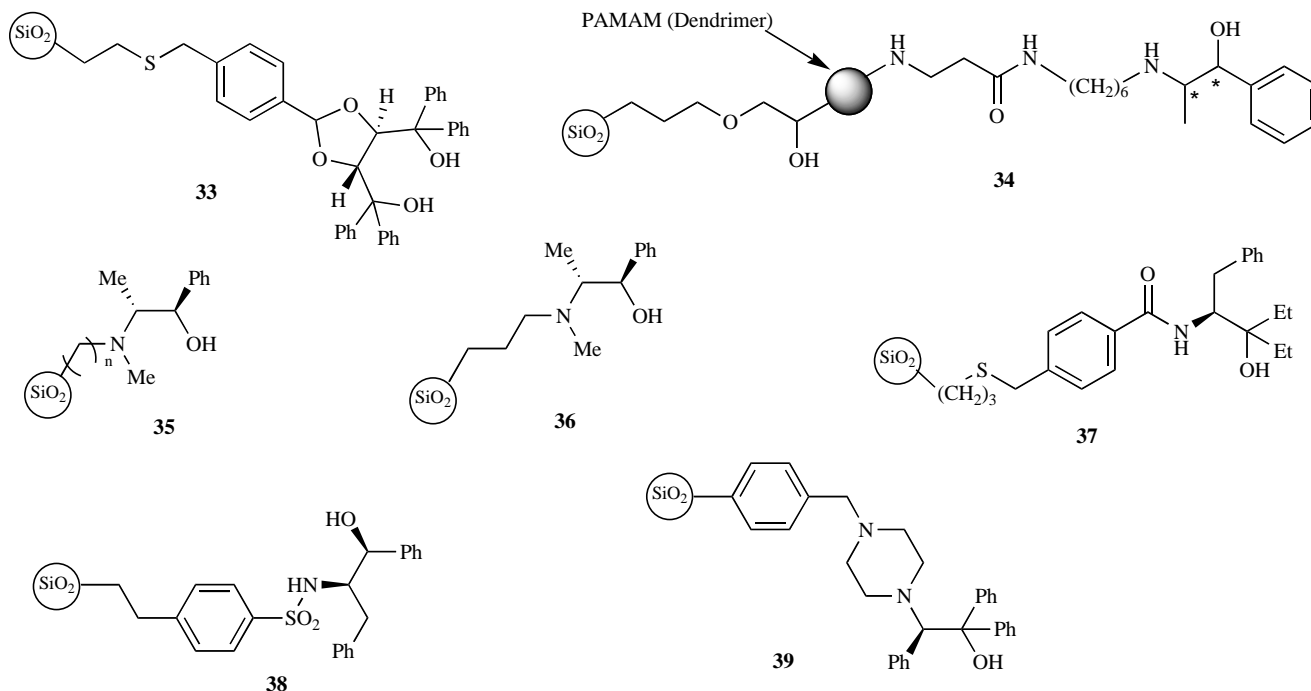
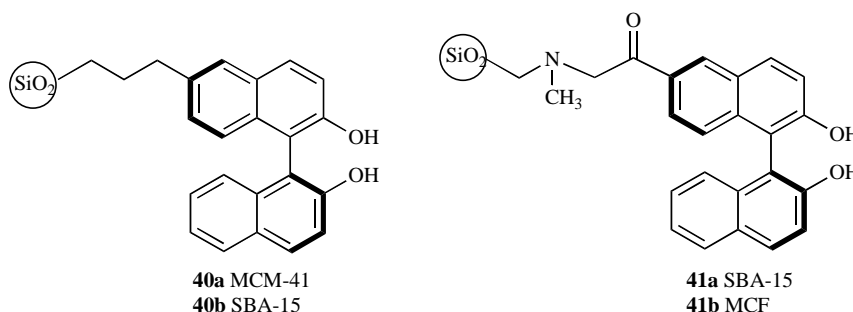


Fig. (19). Chiral ligands immobilized on Silica Gel.



**Fig. (20).** Anchored chiral (*S*)-BINOL to mesoporous MCM-41, SBA-15 and MCF.

gel **37** (Fig. **19**) and used it as a catalyst along with Ti(IV) and diethylzinc to add phenylacetylene to benzaldehyde. The chiral alcohol was obtained in 95% yield and 81% ee.

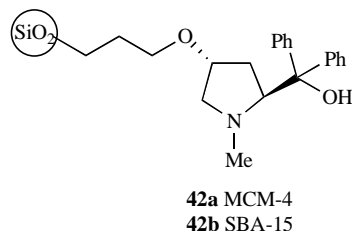
Hui and coworkers [37] grafted chiral amino alcohol to amorphous silica gel and mesoporous (MCM-41) (**38**, Fig. **19**) and used it as a catalyst with Ti(IV) to add diethylzinc to benzaldehyde. The silica gel-grafted catalyst gave 98% yield and 80% ee. The mesoporous (MCM-41) grafted silica gave 86% yield and 55% ee. The catalyst was reused in multiple catalytic runs (up to 10 times) without loss of enantioselectivity and just a slight decrease in yield.

Mayoral's group [38] reported the immobilization of chiral amino alcohol on silica **39** (Fig. **19**) by sol-gel and grafting methods, and used it as the catalyst in the diethylzinc addition to benzaldehyde. The alcohol was obtained in 99% yield and 77% ee when using amino alcohol grafted to silica gel in the presence of BuLi. The amino alcohol immobilized on silica formed by sol-gel synthesis gave much lower enantioselectivity than the solid prepared by the grafting method.

Abdi and coworkers [39] anchored chiral (*S*)-BINOL to mesoporous MCM-41 and SBA-15. The immobilized ligands **40a,b** (Fig. **20**) were used with Ti(IV) as catalysts to add diethylzinc enantioselectively to aldehyde. The immobilized ligand **40a** (MCM-41) gave 82% yield and 45% ee, whereas ligand **40a** (SBA-15) gave 94% yield and 69% ee, with benzaldehyde as the substrate.

The same group [40] anchored BINOL covalently to two different pore sizes of silica SBA-15, (7.5 nm, **41a**) and MCF (14 nm, **41b**) (Fig. **20**). These heterogenized ligands were used in the Ti-catalyzed asymmetric addition of diethylzinc to aldehydes. 94% enantioselectivity was obtained using MCF-supported chiral BINOL **41b**. The catalyst was reused in multiple catalytic runs without loss of enantioselectivity and with a slight decrease on yield.

Hyeon and coworkers [41] immobilized chiral proline on two different types of mesoporous silica, MCM-41 and SBA-15 (**42a,b**, Fig. **21**) and used these as catalysts to add diethylzinc enantioselectively to benzaldehyde. The reaction enantioselectivity was reported to be largely dependent on the pore size of the mesoporous silica, on capping of the free silanol and on the use of *n*-BuLi. When both TMS capping and *n*-BuLi addition were used with **42a** (MCM-41), 75% ee was achieved with 98% yield.



**Fig. (21).** Immobilized chiral proline on mesoporous silica.

## IMMOBILIZATION OF LIGANDS WITH DENDRIMERS AND THEIR APPLICATION AS CATALYSTS

A widely studied approach to facilitate catalyst-product separations is the attachment of homogeneous catalysts to organic or inorganic polymers. In this category, homogeneous catalysts immobilized on dendrimers are receiving much attention, due to their solubility in organic solvents and ease of separation from products by filtration or precipitation [42].

Ma and coworkers [43] reported the synthesis of BINOL grafted to Fréchet-type dendritic polymer ligands **43a,b** (Fig. **22**) and their application in the asymmetric addition of diethylzinc to benzaldehyde. The chiral alcohol was obtained in 95% yield and 89% ee.

Fan and coworkers [44] reported two kinds of dendrite chiral BINOL ligands, grafting 2,2'-dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylic acid to Fréchet-type polyether dendrons with primary and secondary amine functionality (**44a,b**, Fig. **22**). When used as the catalyst in the diethylzinc addition to benzaldehyde, yields of 96-99% and enantioselectivities of 66-70% were reported.

The same group [45] reported three new chiral BINOL ligands bearing dendrite wedges by coupling derivatized BINOL with Fréchet-type polyether dendrite benzyl bromide (**45a,b** and **46**, Fig. **22**). These new ligands were assessed in enantioselective Lewis acid-catalyzed addition of diethylzinc to benzaldehyde. The highest enantioselectivities (up to 87% ee) were obtained with the dendritic wedges at the 6,6' position of the BINOL ligand **46**.

Zhu and coworkers [46] reported a series of pyrrolidinylmethanol-based dendritic ligands (**47**, Fig. **23**) which were used with phenylboronic acid and diethyl zinc as the catalyst in aryl transfer to aldehydes. The secondary alcohols were obtained in high yields (91-98%) and excellent enantioselectivities (94-98%)

Chung and Rhee [47] reported the use of silica-supported dendritic chiral auxiliaries **48** (Fig. **23**) for the enantioselective addition of diethylzinc to benzaldehyde. The chiral alcohol was obtained in 63-92% yield and 8-60% ee with various generations of dendrimers.

Harada and Nakatsugawa [48] reported the treatment of titanium tetraisopropoxide and tris-BINOL with a rigid aromatic tether to give an insoluble polymeric aggregate (**49**, Fig. **24**), which acted as a catalyst in the asymmetric addition of diethylzinc to aldehydes. With benzaldehyde, >98% yield and 74% ee was obtained. The recovered catalyst gave 83% yield and 58% ee on the second run. Asymmetric alkylation reactions of other aromatic aldehydes gave relatively high enantioselectivities (74-84% ee) and with high yields (95->98%).

Recently El-Shehawy *et al.* [49] reported the application of well-defined chain-end functionalized polystyrenes with dendritic chiral ephedrine moieties (Fig. **24**) as reagents for highly catalytic enantioselective addition of dialkylzincs to 3-phenylpropanal. The chiral secondary alcohol was obtained in yields of 63-95% and

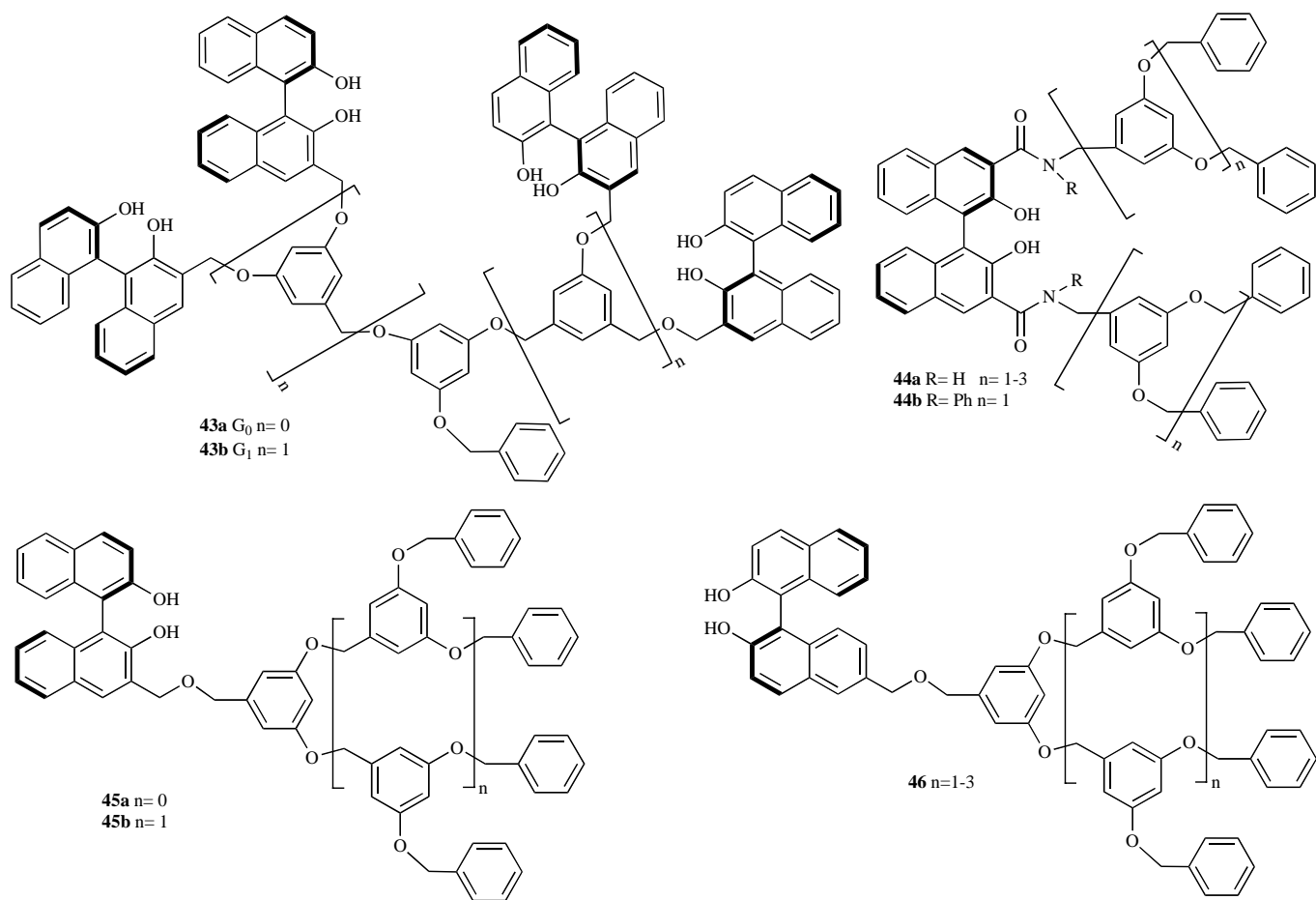


Fig. (22). BINOL grafted to Fréchet-type dendritic polymer ligands.

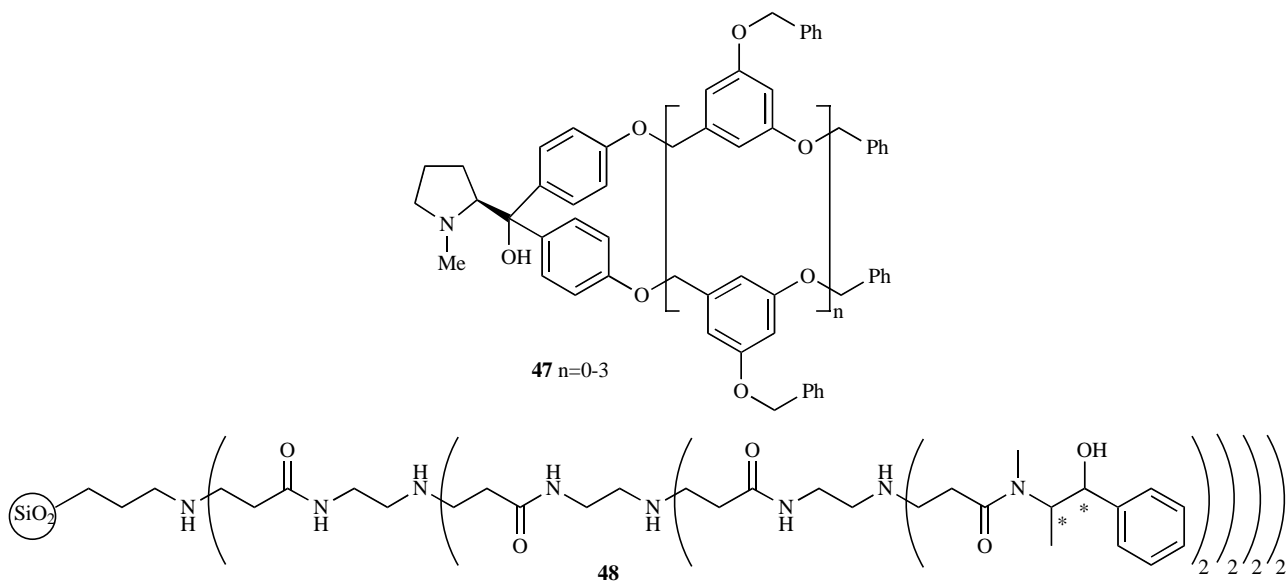


Fig. (23). Dendritic ligands.

enantioselectivities ranging from 72 to 90% with various generations of dendrites. PS(Ephed)<sub>8</sub> generation (**50**) gave the best results at 95% yield and 90% enantioselectivity.

Miscellaneous immobilization of ligands and their application in the diethylzinc addition to aldehydes.

In addition to polymer, silica gel, and dendrimers as solid supports, a variety of other novel systems have been also employed. Wu and Lin [50] reported the synthesis of a rigid, 3D grid "metal-organic framework" from Cd(NO<sub>3</sub>)<sub>2</sub>·4H<sub>2</sub>O and (*R*)-6,6'-dichloro-2,2'-dihydroxy-1,1'-binaphthyl-4,4'-bipyridine (**51**, Fig. 25). The



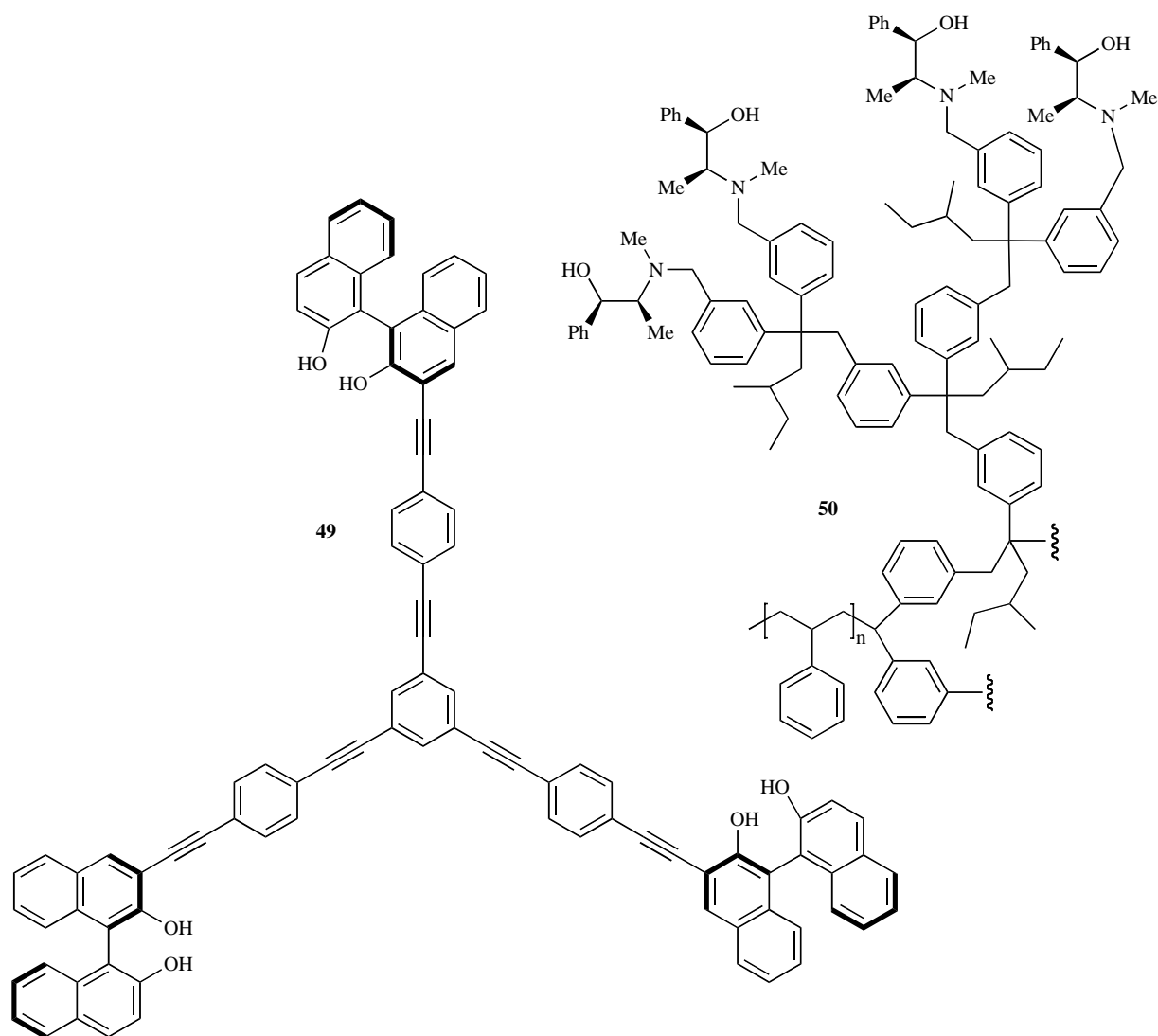


Fig. (24). Insoluble dendritic polymeric aggregates.

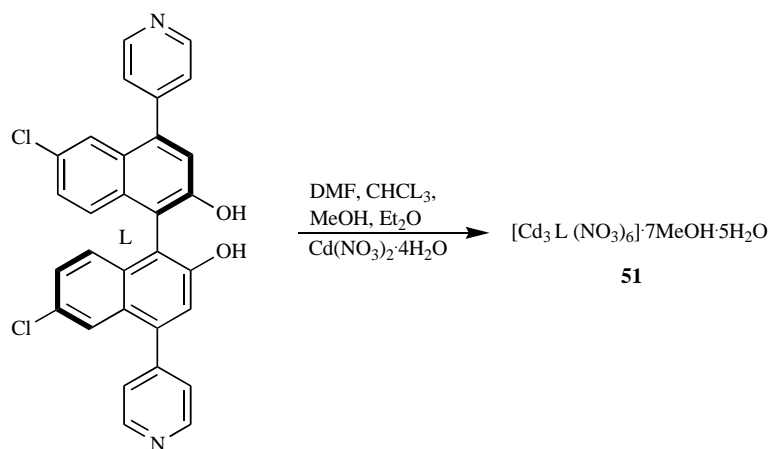
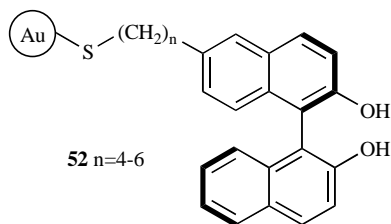


Fig. (25). Homochiral metal-organic framework structure.

authors used this heterogeneous network structure as a catalyst with Ti(O*i*Pr)<sub>4</sub> to add diethylzinc to aromatic aldehydes in an enantioselective manner. The corresponding alcohols were obtained in >99% yield and 45-90% enantioselectivity.

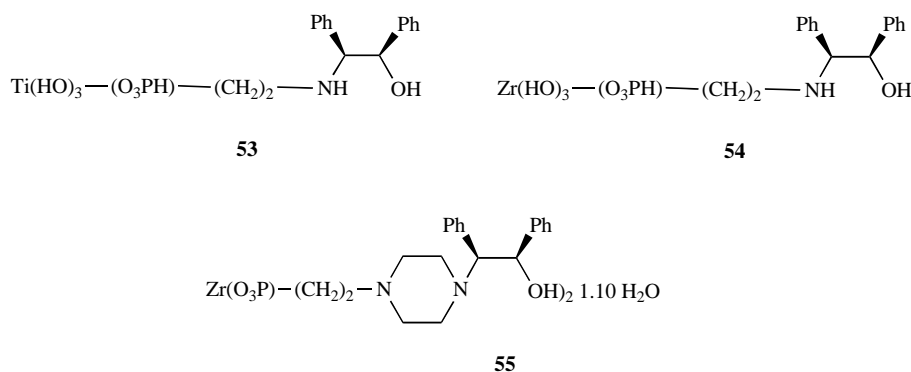
Sasai and coworkers [51] reported the immobilization of (*R*)-BINOL on the surface of Au clusters. Treatment of the ligand **52** (Fig. 26) generated from the Au cluster, with titanium tetraisopropoxide resulted in a complex that promoted catalytic asymmetric

alkylation of benzaldehyde with diethylzinc. The chiral alcohol was obtained in 98% yield and 88% ee.



**Fig. (26).** (*R*)-BINOL on the surface of Au clusters.

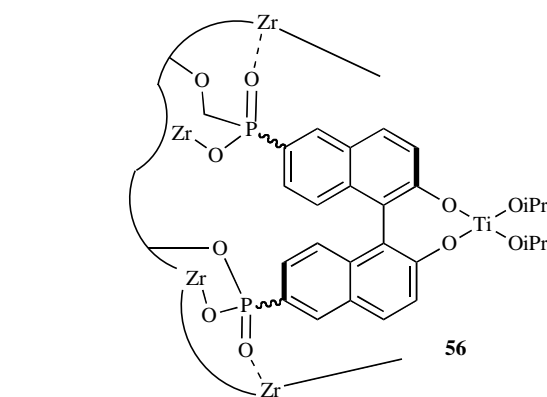
Ma and coworkers [52] immobilized (1*R*,2*S*)-(+)-2-amino-1,2-diphenylethanol on the layered titanium phosphonates **53** (Fig. 27) and used this as a heterogeneous catalyst in the enantioselective addition of diethylzinc to benzaldehyde. The final chiral alcohol was obtained in 89% yield and up to 41% ee.



**Fig. (27).** Immobilized amino alcohols on layered phosphonates.

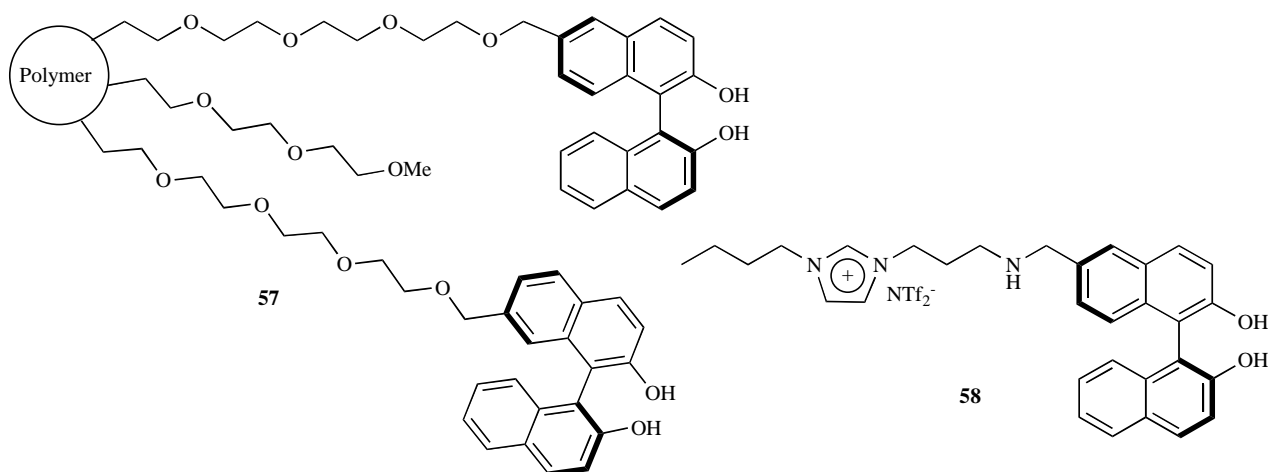
The same group [53] reported the zirconium phosphonate-immobilized amino alcohol **54** and **55** (Fig. 27) and used them as catalysts in the enantioselective addition of diethylzinc to benzaldehyde. The alcohol was obtained in 80% yield and 54% ee.

Lin and coworkers [54] reported the synthesis of porous zirconium phosphonates containing chiral BINOL **56** (Fig. 28). The nanoporous material **56** was used as a heterogeneous catalyst along with  $\text{Ti}(\text{O}i\text{Pr})_4$  to add diethylzinc to aldehydes. The chiral alcohols were obtained in 68-99% yield and 29-72% ee.



**Fig. (28).** Nanoporous zirconium phosphonate containing chiral BINOL.

Sasai and coworkers [55] reported the immobilization of chiral BINOL on the surface of a micelle-derived polymer **57** (Fig. 29).



**Fig. (29).** Chiral BINOL derivatives as ligands.

Ti-BINOLate complex derived from the polymer with  $\text{Ti}(\text{O}i\text{Pr})_4$  catalyzed the enantioselective addition of diethylzinc to benzaldehyde. The alcohol was obtained in 96% yield and up to 84% enantioselectivity.

Moreau and coworkers [56] in pioneering work attached chiral camphorsulfonamide units to ionic liquids, using this as a ligand in the titanium isopropoxide-catalyzed asymmetric diethylzinc addition to benzaldehyde. The ionic catalysts showed catalytic properties similar to those of related nonionic counterparts in terms of activity and enantioselectivity (40-64% ee), with conversions >99%.

In subsequent work, Moreau and coworkers [57] reported the synthesis of the chiral (*S*)-BINOL ligand tethered to the ionic liquid **58** (Fig. 29), and used it as a catalyst along with  $\text{Ti}(\text{O}i\text{Pr})_4$  to enantioselectively add diethylzinc to benzaldehyde. The chiral alcohol was obtained in higher yield (>99%) and better enantioselectivity (82%).

Recently, Trombini and coworkers [58] ion-tagged diphenylprolinol by converting it to trialkylammonium ion catalyst **59** (Fig. 30), and used as catalyst in the diethylzinc addition to benzaldehyde in various ionic liquids. The secondary alcohol was obtained in good enantioselectivities (69-92%) and yields (75-92%).

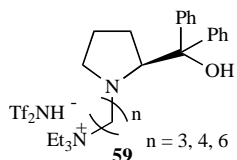


Fig. (30). Diphenylprolinol ion-tagged to trialkylammonium salt as a catalyst.

Mastalir and Király [59] immobilized (*1R,2S*)-(-)-*N*-dodecyl-*N*-methylphedrinium bromide (DMEB) on montmorillonite **60** (Fig. 31) via cation exchange and used it to catalyze the enantioselective diethylzinc addition to benzaldehyde. The alcohol was obtained in 43% yield and 32% ee.

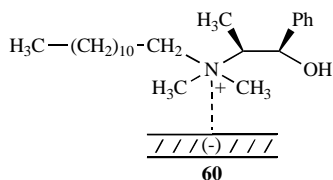


Fig. (31). Surfactant immobilized on montmorillonite via cation exchange.

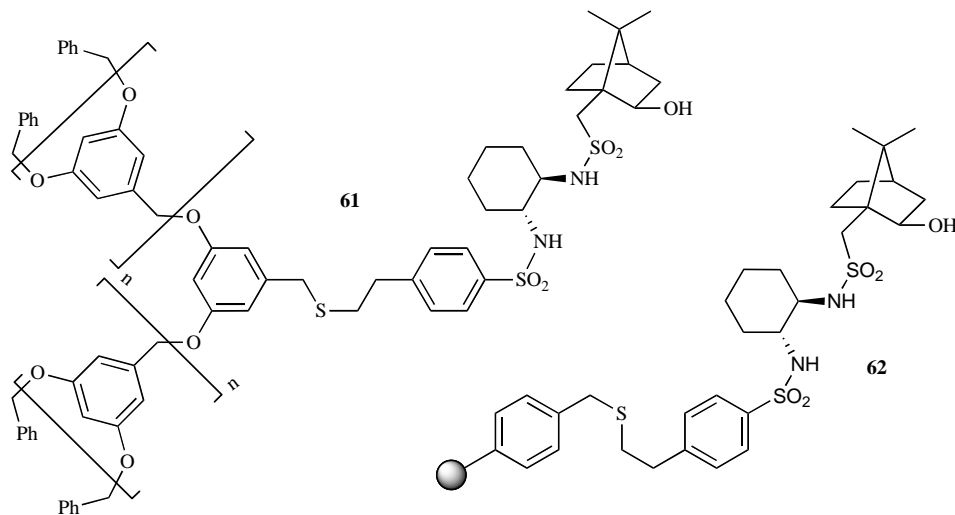


Fig. (32). Ligands used to catalyze the dialkylzinc addition to ketones.

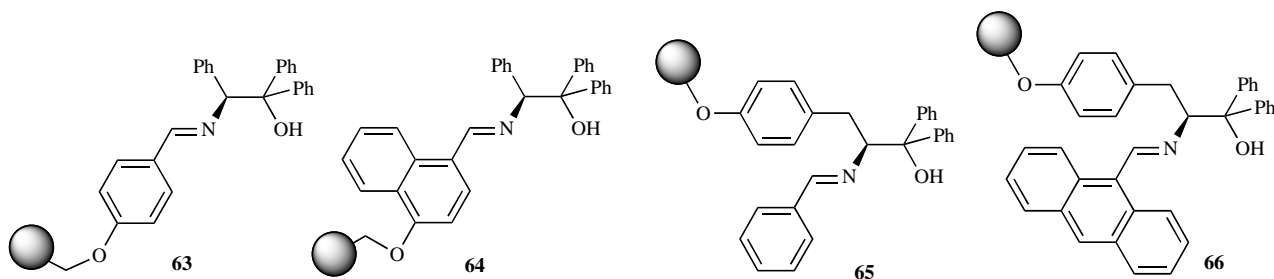


Fig. (33). Polymer-supported Schiff-base ligands used to catalyze the dialkylzinc addition to ketones.

## ASYMMETRIC DIALKYLZINC ADDITION TO KETONES

Asymmetric addition of dialkylzinc to aldehydes in combination with titaniumisopropoxide has led to excellent enantioselectivities and yields of the chiral secondary alcohol. However, the situation is more complicated when the electrophilic counterpart of the reaction is a ketone. Addition process never takes, even at high temperatures, yielding only, either the starting unchanged ketone or products arising from the reduction of the carbonyl group. The first ligand that was successfully used for the dialkylzinc addition to ketone was derived from isoborneosulfonamide [60a,b].

Recently, Yus and coworkers [61] reported the enantioselective addition of organozinc reagents to ketones using nanosize isoborneol ligands derived from *trans*-1-arenesulfonylamino-2-isoborneosulfonylamidocyclohexane and Fréchet-type dendrons (**61**, Fig. 32), giving the corresponding tertiary alcohols with enantioselectivities up to >99%.

The same authors [62] grafted *trans*-1-arenesulfonylamino-2-isoborneosulfonylamidocyclohexane to polymer (**62**, Fig. 32) and used in combination with titaniumisopropoxide to add diethylzinc to ketones in high enantioselectivities (>99%) and moderate yields (40-90%).

Wang and coworkers [63] reported the synthesis of polymer-supported Schiff base ligands derived from optically active amino alcohols **63-66** (Fig. 33) and used them as catalysts with  $\text{Et}_2\text{Zn}$  to add phenylacetylene to ketones with moderate to good enantioselectivities (up to 89% ee) and yields up to 74%. The system does not require the addition of other Lewis acids except diethylzinc, the alkynylzinc reagent (prepared separately) and simple ketones.

## CONCLUSION AND PERSPECTIVES

Asymmetric catalytic C-C bond formation commonly presents a challenging problem to synthetic organic chemists, but organozinc

addition to aldehydes offers a reliable, mild, and controlled addition to form alkylated products with excellent enantioselectivities. In this review we have shown the transformation of homogeneous catalysts into recoverable heterogeneous systems, with the advantages of easy recovery and reusability of the catalyst. Several examples of heterogenized catalysts immobilized on polymers, dendrimers, and inorganic material supports were discussed; data indicate the polymer-supported catalysts are generally superior to the latter two systems. Based on these studies, new effective immobilized ligands and new supports will continue to be developed for applications in the fine chemical industry.

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