New Approaches for Reusable Chiral Heterogeneous Catalysts for Epoxide Ring Opening Reaction

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Abstract

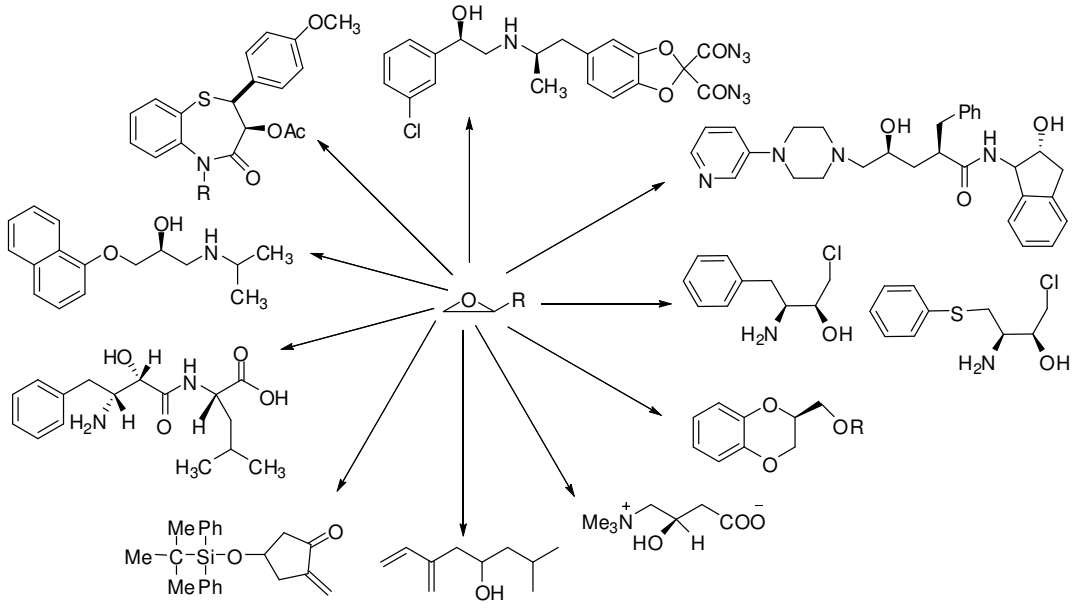
The heterogenization of chiral homogeneous catalysts, which endows homogeneous systems with attractive features such as easy product separation and catalyst recovery by simple filtration, constitutes a rapidly expanding research area in asymmetric catalysis. Among various organic transformations, chiral transition-metal complexes catalyzed asymmetric ring opening reaction is one of the most fascinating areas because the enantiopure end-products have wider application in pharmaceuticals, fine chemicals and as chiral auxillaries. In this direction attempts were made to develop highly active and enantioselective catalysts based on chiral ligands viz. BINOLs, SALENs etc., with various transition metals. As chiral catalysts are expensive, focuses on low catalyst loading and/ or their recovery and re-use are important aspects. Since various homogeneous catalysts have been found to be efficient in asymmetric catalysis their immobilization on solid supports is of great interest. This led researches to make these systems recyclable by way of supporting the catalyst on organic and inorganic polymeric materials or making use of ionic liquids or manipulating solubility of the catalyst by increasing the molecular weight of catalyst with simultaneous increase in active sites so that the catalyst is easily recovered by simple precipitation method in a post catalytic workup process. Therefore, this chapter will give an in-sight of epoxide asymmetric ring opening reaction based on chiral recyclable catalysts and would bring about the latest trends in this area of research.

Introduction

The growing demand for enantiopure compounds in pharmaceuticals, food & agrochemicals, fragrance & flavors, biochemicals and fine chemicals industries has

stimulated interest in asymmetric catalysis [1]. Asymmetric catalysis strongly relies on ready access to enantiomerically pure ligands with precious metals (metalloenzyme mimics), chirally pure organic molecules with extensive hydrogen bonding (enzyme mimics) and enzymes as catalyst. High chemo and enantioselectivity together with high turnover number are requisite properties for an efficient chiral catalyst. Last two decades have shown tremendous growth in the area of asymmetric catalysis under homogeneous condition to achieve target chiral molecules in their high optical purity. In majority of the homogeneous catalysis, a highly specialized chiral ligand is required as pre-catalyst, which is often more expensive than most precious metals. Thus recovery and recyclability of the catalyst is an unavoidable issue for such processes. On the other hand, the heterogeneous catalysis has been very successful in terms of industrial applications for the production of racemic and achiral compounds. Therefore, the heterogenization of chiral homogeneous catalyst was considered as logical option for the practical development of chiral technology.

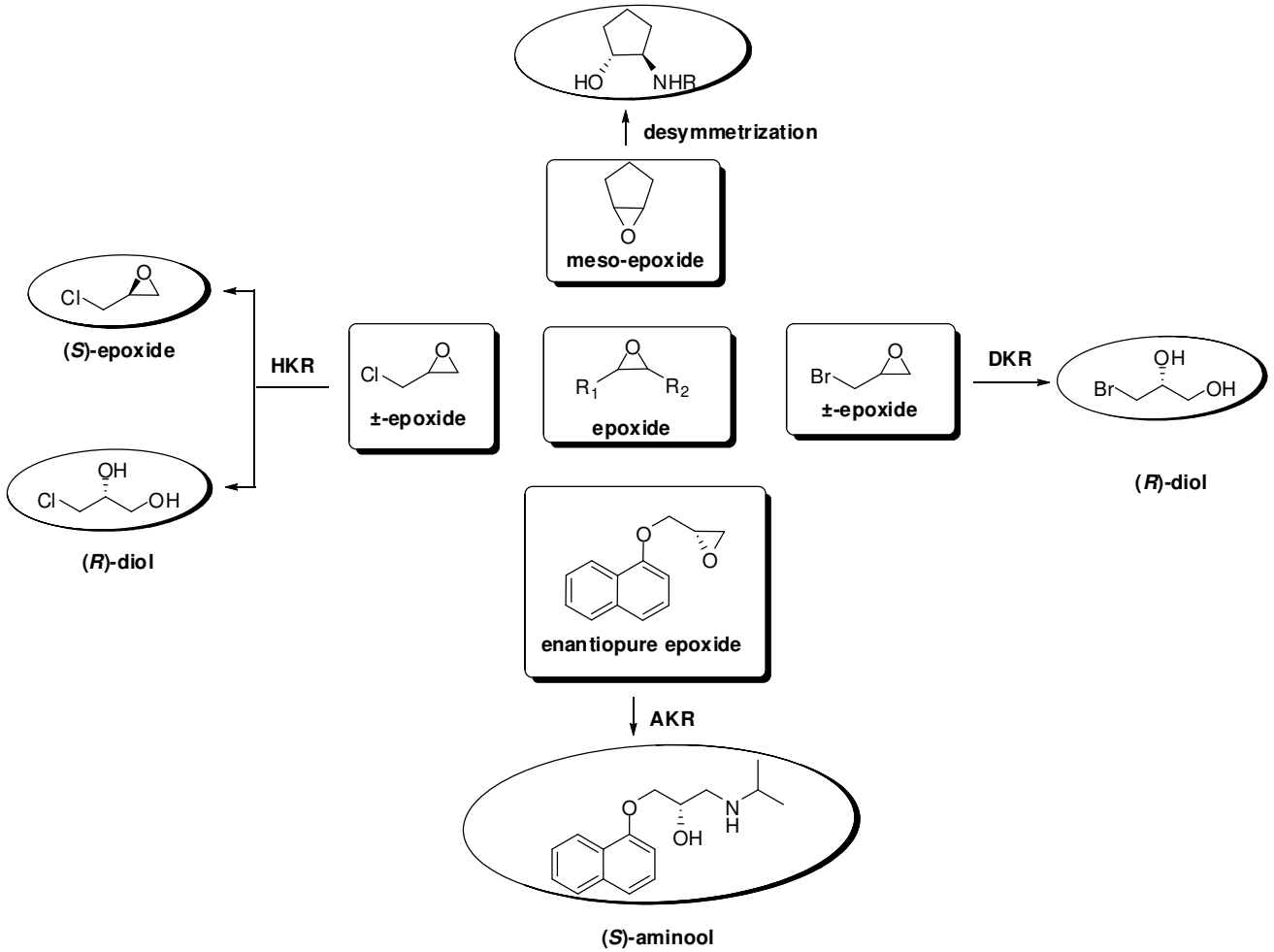
In asymmetric catalysis, the epoxide ring opening reaction provides an elegant route to develop synthetically useful and biologically interesting molecules in optically pure form [2-4]. Some of the useful racemic / *meso* epoxide ring opening reactions and their resultant end products are depicted in Scheme 1.



Scheme 1 Stereospecific ring opening of epoxide

Typically chiral metal complexes catalyzed asymmetric ring opening of achiral / racemic and chiral epoxides with various nucleophiles conveniently produce enantioenriched 1,2-bifunctional compounds viz., β-azido alcohols [5-11], β-halohydrins [12-19], β-cyanohydrins [10,20-22], β-hydroxysulfides [23-26], β-benzoyloxy alcohols [27], β-aryloxy alcohols [28, 29], and β-aminoalcohols [30-35]. The entire literature available on these transformations can be classified as under (Scheme 2).

- Kinetic resolution (KR) of racemic epoxides
- Desymmetrization of *meso*-substrates
- Dynamic kinetic resolution (DKR) of racemic epoxides
- Asymmetric ring opening (ARO) reaction of enantiopure epoxide



Scheme 2 Various strategies for enantioselective epoxide ring opening reactions

The above transformations have been extensively studied under homogeneous condition [36-41], however, their heterogeneous counter part is still in developmental stage [42-47].

Considering the importance of recoverable catalyst, this chapter, would provide an overview on asymmetric ring opening of epoxides using heterogeneous catalysis, however, we would also include some of the homogeneous chiral catalysts which are recoverable and have potential for heterogenization. Several strategies used for heterogenization/recycling of chiral catalysts discussed in this chapter include; immobilization of the soluble catalysts; on organic and inorganic polymers, on ionic liquids, use of differential solubility of the catalyst in various solvents and two-phase systems. In principle, all the methods presented here have capability of repeated use of a chiral catalyst without loss of activity and/or enantioselectivity. While the chapter will present up to the date information on epoxide ring opening reaction available in the literature, an attempt would be made to discuss highlights and limitations of the existing systems and bring about recent trends in heterogeneous catalysis.

Kinetic resolution of racemic epoxides

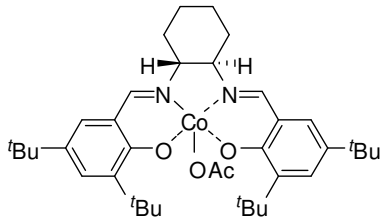
Jacobsen et al. [48], in 1997 for the first time demonstrated KR of racemic terminal epoxides with water as nucleophile for the production of optically pure epoxides and corresponding 1,2-diols. Since then, various other nucleophiles viz., carboxylic acids, phenols, thiols, amines, carbamates and indols were used in KR to produce optically pure epoxides with concomitant production of corresponding enantioenriched 1,2-bifunctional moieties [49-52].

Hydro kinetic resolution (HKR) of racemic epoxides

Kinetic resolution of racemic terminal epoxide with water (HKR) is an attractive strategy for the synthesis of valuable enantiopure terminal epoxide and corresponding diol. Easy availability of terminal epoxides at cheaper price and water as sole reagent with a recoverable chiral catalyst makes this solvent free protocol very attractive for its commercial exploitation [53, 54]. Both terminal epoxides and respective diols in their chirally pure form have wider applications in academics and industry [48, 50]. For the

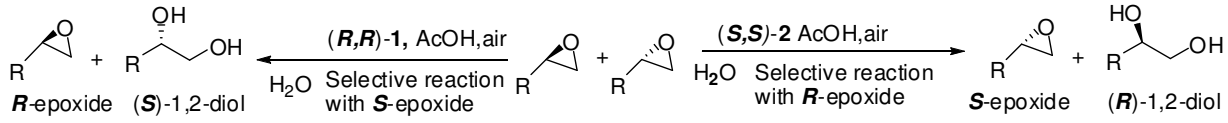
efficient resolution the reaction rates of the two enantiomers must be unequal and the reaction must be stopped when only one enantiomer reacts to give a maximum of 50% product leaving behind the other enantiomer unreacted.

In the case of Jacobsen's Co(III) salen complexes **1, 2** (Figure 1) [48], (*R, R*) form of the catalyst selectively allows water to react with (*S*)-form of epoxide to generate (*S*)-1,2-diol leaving behind (*R*)-epoxide in high enantioselectivity (ee) (Scheme 3, **PATH A**). By simply reversing the chirality of the catalyst from (*R*,*R*) to (*S*,*S*), epoxides and 1,2-diols in their respective (*S*) and (*R*) forms (Scheme 3, **PATH B**) were achieved in high optical purity. This method was found to be highly effective and economical for the low boiling racemic epoxides where catalyst separation was affected by simple distillation process. However, this process was less effective for high boiling racemic epoxides due to the decomposition of the desired products at higher temperatures.



1 (***R,R***) Co salen OAc
2 (***S,S***) Co salen OAc

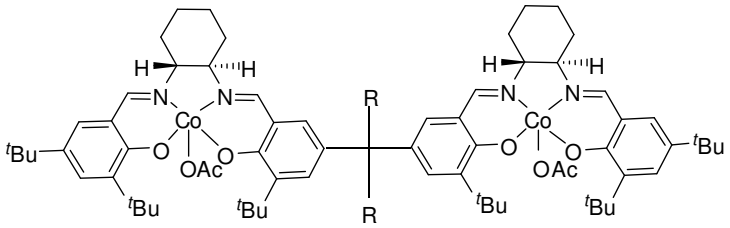
Figure 1 Structure of the catalysts **1, 2**



Scheme 3 HKR of terminal epoxide using Jacobsen Co(salen) complexes **1, 2**

To overcome this issue Kureshy et al. [55, 56] reported dimeric form of Jacobsen's catalysts **3, 4**. They used the concept of solubility modification by altering the molecular weight of the catalyst so that in a post catalytic work-up procedure the catalyst is precipitated, filtered and used for subsequent catalytic runs. The complexes **3, 4** (0.2 mol % of Co(III)–salen unit) (Figure 2) were effectively used for HKR of racemic

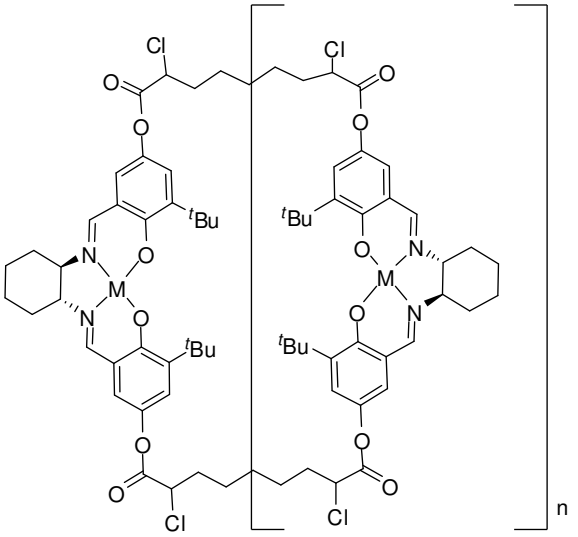
epoxides, e.g., styrene oxide, epichlorohydrin, 1,2-epoxypropane, 1,2-epoxyhexane, 1,2-epoxyoctane, and 1,2-epoxydodecane to achieve corresponding epoxides and 1,2-diols in high optical purity and isolated yields. In this process, once the catalytic reaction is complete the product epoxides were collected by reduced pressure distillation. Addition of diethylether to the residue precipitated the catalyst which was removed by filtration. However, the recovered catalyst was required to be reactivated by its treatment with acetic acid in air. The catalysts were reused 4 times with complete retention of its performance.



3 R= H
4 R=CH_3

Figure 2 Structure of dimeric Co(salen)complexes **3,4**

Ironically, oligomeric Co(III) salen complexes **5** (Figure 3) developed by Jacobsen et al. [57, 58] though highly active was non-recyclable. These complexes degraded during HKR of terminal/meso epoxides under the reaction conditions used.

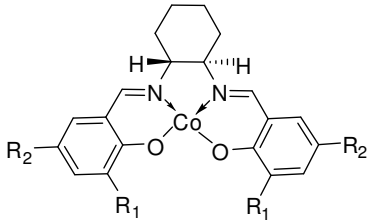


5

M = Co(OTs)
n = 1-5

Figure 3 Oligomeric Co(salen) complex **5**

Keeping in mind the recovery of the catalyst issue, Pozzi et al. [59] specifically tailored the salen ligand to suit its application in fluorous biphasic (FB) system (Figure 4). Accordingly, authors made modification at 5 and 5' position of Jacobsen catalyst by replacing *tert*-butyl group with perfluoroalkyl chain **6** or 3,5-bis heptadecafluorooctylphenyl **7, 8** [60]. The catalyst **6** afforded 46% diol with 99% ee and epoxide (ee, 91.2%) in 6h for the HKR of racemic 1-hexene oxide. The catalyst **6** was recovered by liquid-liquid extraction at room temperature in the presence of a fluorinated solvent; however there was a loss of catalyst by 16% in the first reuse experiment. Authors also tried solid phase extraction of **6** by fluorous reverse phase silica with toluene. However, only 50% of the catalyst was recovered while remaining material was adsorbed on silica. The recovered catalyst still showed catalytic activity (47% conversion with diol ee >99%) but reaction rate was reduced considerably (50h). Ironically silica-bound material which contained 0.4 mol% of **6** was inactive for HKR of 1-hexene oxide. Site isolation resulting from low catalyst loading on the fluorous silica was explained to be the main reason for the absence of catalytic activity of this material. The heavily fluorinated catalyst **7, 8** when activated with $C_8F_{17}COOH$ was found to be highly active (50% conversion in 2h) and enantioselectivity for both epoxide and diol (ee, >99%) under fluorous biphasic condition. The recycling of the catalysts **7, 8** caused sever loss of activity and enantioselectivity of epoxide however, ee of diol was retained**.** It is to be noted that recycling of the heavily fluorinated chiral complexes **7, 8** was less effective than that of the light-fluorous complex **6**.



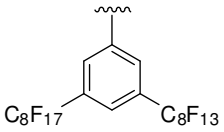
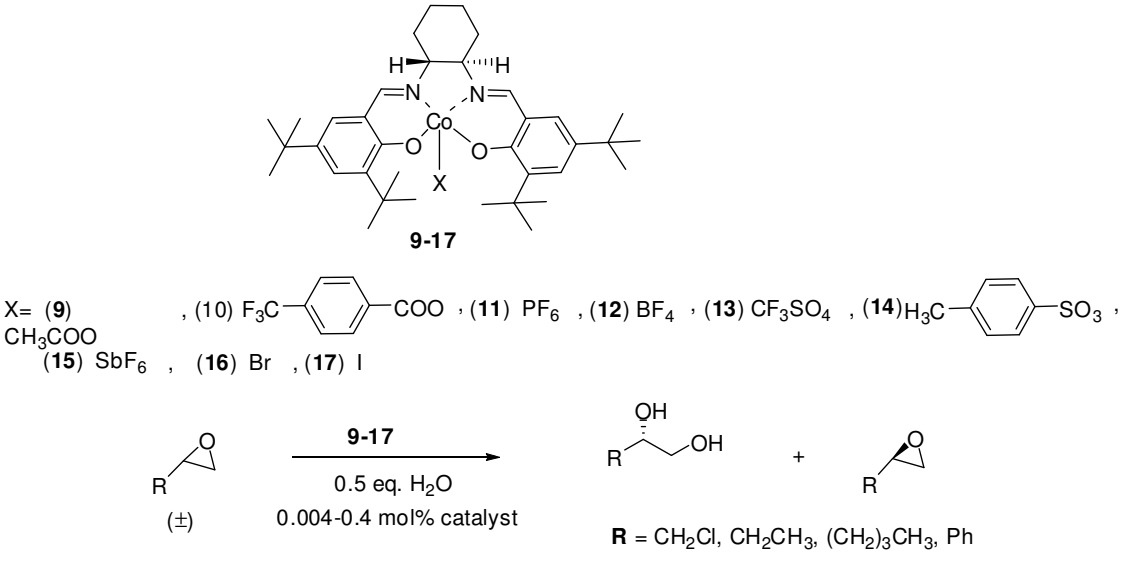
	R_1	R_2
(*R*,*R*)-**6**	Bu^t	C_8F_{17}
(*R*,*R*)-**7**	C_8F_{17}	C_8F_{17}
(*R*,*R*)-**8**	Bu^t	

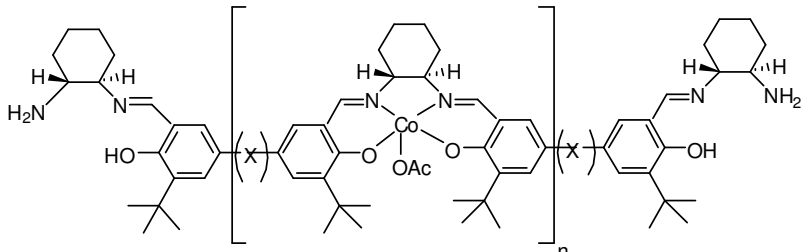
Figure 4 Structure of fluorous chiral Co(salen) catalysts **6-8**

Kim et al. [61] demonstrated that with the change in counter ion in Co(III)-X where (X= **9-17),** the catalysts could be reused ten times after simple distillation of products without observable loss in activity and enantioselectivity for HKR of epichlorohydrin. Interestingly the catalyst-regeneration step was not required with the use of PF_6 **11** and BF_4 **12** as counter ion in this system (Scheme 4).



Scheme 4 HKR of terminal epoxide using Co(salen) complexes **9-17**

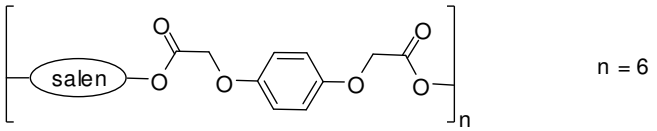
Song et al. [62] reported poly-salen Co(III) complexes **18, 19** as catalyst for HKR (Figure 5) of terminal alkene epoxides. The polymeric catalysts provided product epoxides with excellent conversion (>49%) and high chiral purity (ee's, 98%) and the catalytic system could be recycled once with retention of activity and enantioselectivity.



18 X=CH_2
19 X= $C(CH_3)$

Figure 5 Structure of the catalysts **18**, **19**

Later on same authors [63] developed several crosslinked polymeric salen-Co(III) complexes **20, 21** with different pore sizes by using the trialdehyde and the dialdehyde in different proportions with (*R*,*R*)-1,2-diaminocyclohexane (Figure 6). The molecular weight of these complexes was found to be in the range of 4000-10000 by (GPC). The crosslinked polymeric salen–Co(III) complexes **20, 21** (0.02 mol %) were employed in the HKR of terminal epoxides viz. epichlorohydrin, styrene oxide and phenyl glycidyl ether. Excellent activities and enantioselectivities were achieved with all catalysts in different ratios of trialdehyde and dialdehyde. Most of the crosslinked polymer catalysts showed better activities than oligomeric catalyst with trialdehyde:dialdehyde::0:100, which means the crosslinker had positive effect due to better cooperation between the metal centers of the salen units. Unfortunately none of these catalysts were recyclable, possibly due to the hydrolysis of ester linkage under the HKR condition.



20

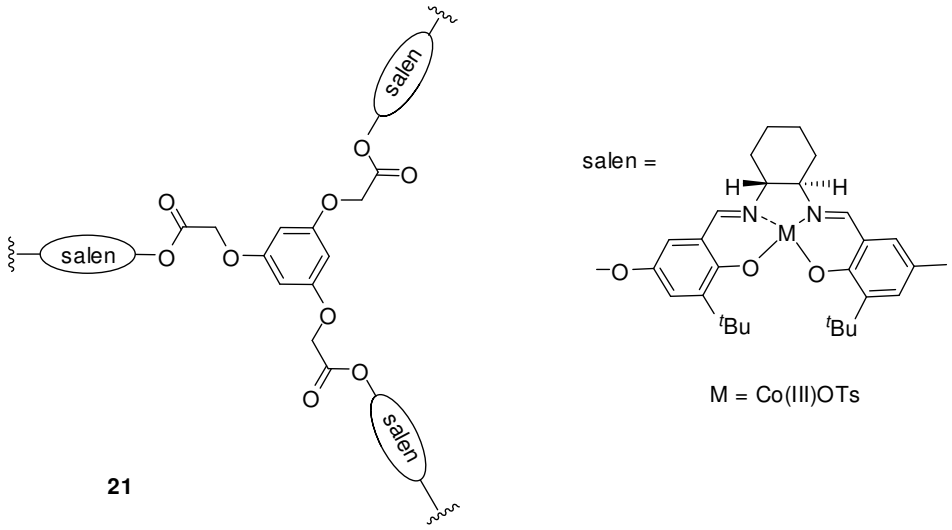
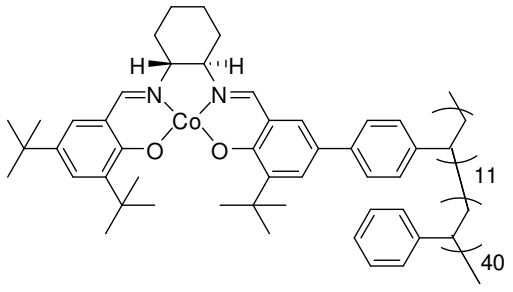


Figure 6 Structure of the crosslinked polymeric complexes **20, 21**

Weck et al. [64] reported synthesis of poly-(styrene)-supported Co-salen complexes by free-radical co-polymerization of vinyl-salen derivatives with styrene **22** (Figure 7). These catalysts (0.5 % of catalyst loading) were tested for HKR of racemic epychlorohydrin with water. The reaction was run neat since the polymers were soluble in the epoxide. Further, an improvement in the activity and selectivity was reported by diluting the Co–salen units along the polymer backbone by increasing the ratio between styrene and vinyl-salen monomer. The copolymerized catalysts showed better catalytic performance (>99% ee, 54% conversion, 1h) in comparison to the homopolymeric analogues and small molecule Co-salen complex. This difference in the performance might be due to the dilution effect or better accessibility of the reactants to the catalytic sites in more flexible co-polymeric catalysts. The polymeric catalyst could be recovered by precipitation with diethylether and was reused three times with a slight decrease on reactivity but with consistent conversion and enantioselectivity.



22

Figure 7 Structure of the complex **22**

Weck et al. [65] further reported the Co salen complex supported on norbornene polymers (**23, 24**) with stable phenylene-acetylene linker (Figure 8). The polymer-supported salen catalysts were investigated for HKR of the racemic terminal epoxides that showed outstanding catalytic activities and comparable selectivities to the original catalysts reported by Jacobsen. However, the polymeric catalyst was recycled only once after its precipitation with diethylether as the catalyst became less soluble and less reactive in subsequent catalytic runs.

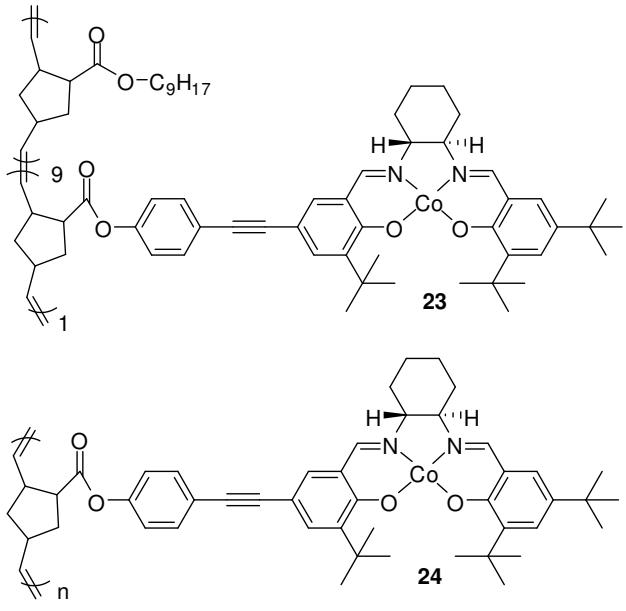
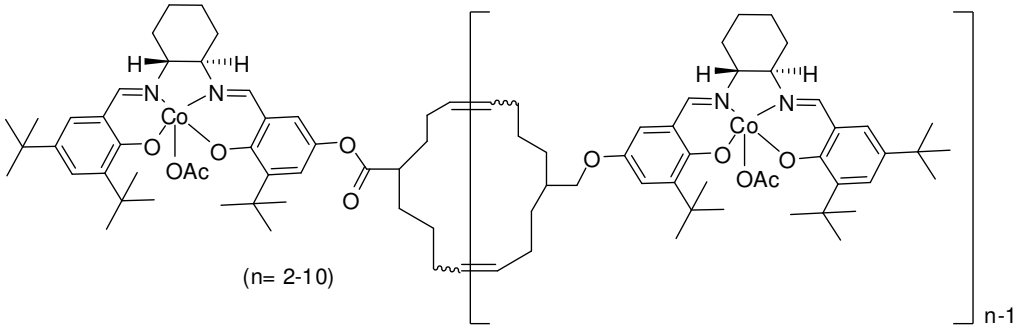


Figure 8 Structure of norbornene-functionalized Co(salen) complexes **23, 24**

Davis et al. [66] developed an oligo(cyclooctene)-supported Co-OAc salen complex **25** (Figure 9) which efficiently catalyzed HKR of epichlorohydrin. The catalyst

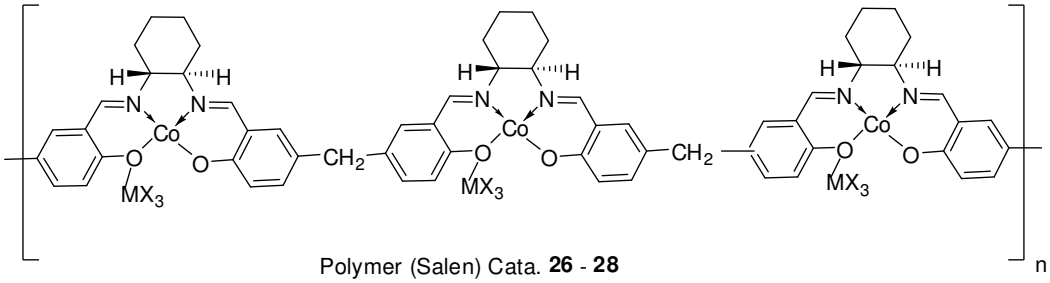
was recycled many times with negligible deactivation. The oligomeric complex was found to be 25 times more reactive than monomeric Co-salen. This study also gives possible modes of deactivation of Jacobsen's Co-salen catalyst during HKR of epichlorohydrin by spectroscopy, combined with recycling studies.



25

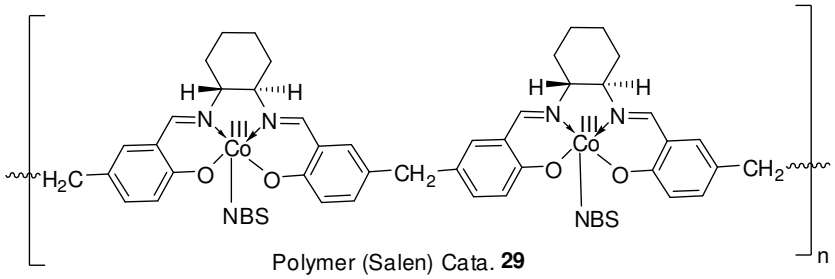
Figure 9 *R*,*R*-Oligo(cyclooctene) supported Co-OAc salen catalyst **25.**

Kim et al. [67] recently reported the synthesis of heterometallic chiral polymer (salen) Co-(Al, Ga, In)Cl_3 complexes **26-32** (Figure 10) and their use in the HKR of racemic epoxides. Polymeric salen catalysts showed very high reactivity and enantioselectivity at substantially lower catalyst loadings for the asymmetric ring opening of terminal epoxide to obtain the enantio-enriched products. The performance of catalysts is retained on multiple-use and do not suffer the problems of solubility and deactivation (Scheme 5).

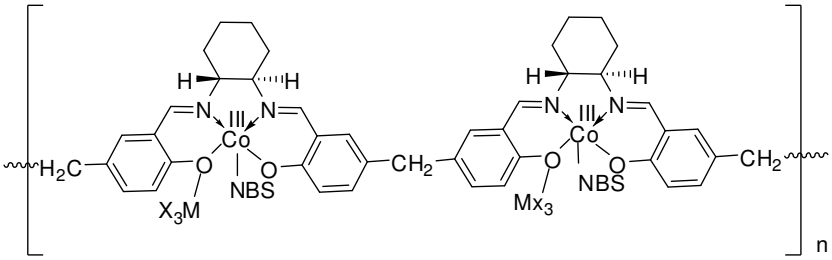


Polymer (Salen) Cata. **26** - **28**

MX_3 ; **26** = $AlCl_3$
27 = $GaCl_3$
28 = $InCl_3$



Polymer (Salen) Cata. **29**

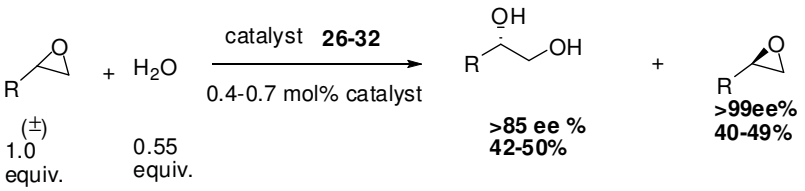


Polymer (Salen) Cata. **30** - **32**

MX_3 ; **30** = $AlCl_3$
31 = $GaCl_3$
32 = $InCl_3$

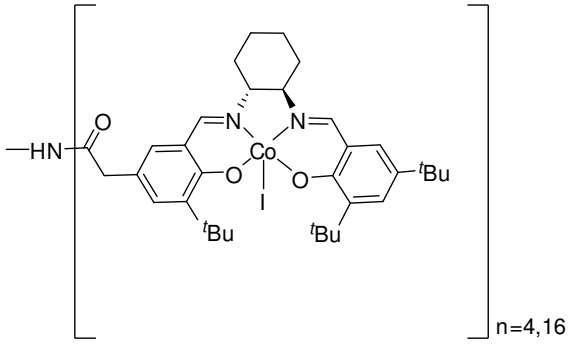
Figure 10 Structure of chiral heterometallic salen complexes **26-32**

Further, the effects of metal halide source on the catalytic activity in HKR of epichlorohydrin was also studied with the following activity trend; Co-$InCl_3$ **32>** Co-$GaCl_3$ **31>** Co-$AlCl_3$ **30>** Co-$GaCl_3$ **27>** catalyst **29>** Co-$AlCl_3$ **26**. It was claimed that neither the pre-catalyst (salen)Co **29** nor 13-group MX_3 salts alone exhibits any epoxide ring opening reactivity in the presence of nucleophiles.



Scheme 5 HKR of terminal epoxides catalyzed by polymeric salen catalysts **26-32**

Breinbauer and Jacobsen [68] reported the synthesis of dendrimer-bound Co(salen) complexes **33-35** (Figure 11) derived from commercially available NH_2-terminated PAMAM (polyamidoamine) dendrimers. The dendritic catalysts were used for HKR of (*rac*)-1,2-epoxyhexane (Scheme 6) and (*rac*)-vinylcyclohexane epoxide as substrates where highly enantioenriched (>98% ee) epoxide at 50% conversion was achieved. The best results were obtained with the first generation (4-branch) **33** metallodendrimer and the efficiency of catalyst on a per-metal basis was in the following order: 4-Co(salen)-PAMAM **33 >** 8-Co(salen)-PAMAM **34 >** 16-Co-(salen)-PAMAM **35**. This "dendrimer effect" was thought to arise from restricted conformation imposed by the dendrimer structure, which enhanced the cooperative interactions between Co-salen units (Figure 12). However, no catalyst recycle data was provided.



PAMAM-4-Co(Salen) 33
PAMAM-16-Co(Salen) 35

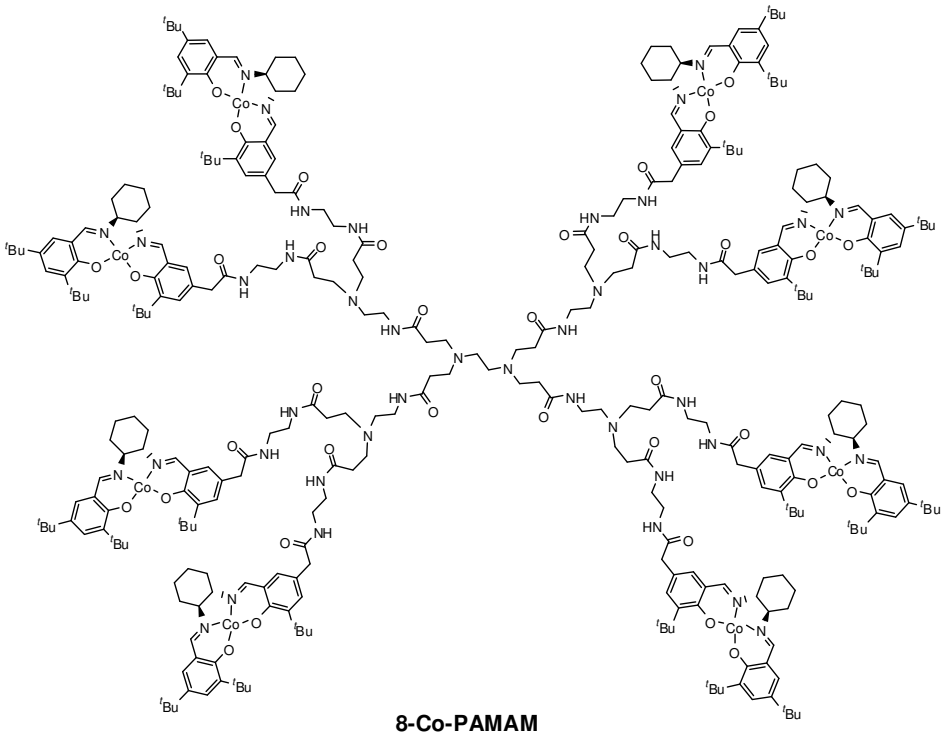


Figure 11 Structure of dendrimeric [Co(salen)] complexes **33,34**

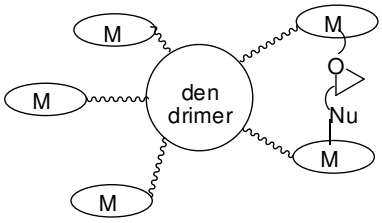
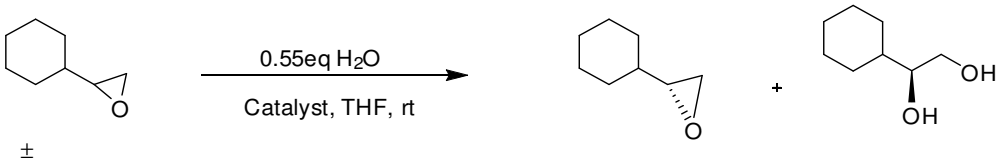


Figure 12 Proposed mechanism for cooperative catalysis in asymmetric ring opening of epoxide by dendimeric frame work



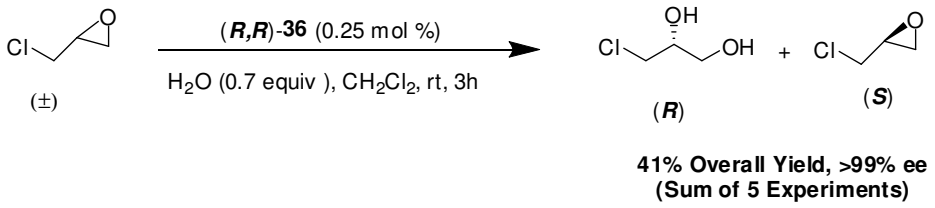
Scheme 6 Reaction for HKR of racemic cyclohexeneepoxide using dendimeric Co(salen) complex **34**

Annis et al. [69] reported the synthesis of polystyrene- **36** and silica bound Co(salen) **37** and their use in HKR of racemic epoxides (Scheme 7-9). Polystyrene bound systems **36** demonstrated highly practical solutions to certain technical difficulties associated with the isolation of reaction products from HKR especially problematic substrates like epichlorohydrin and other high boiling epoxides (Table 1).

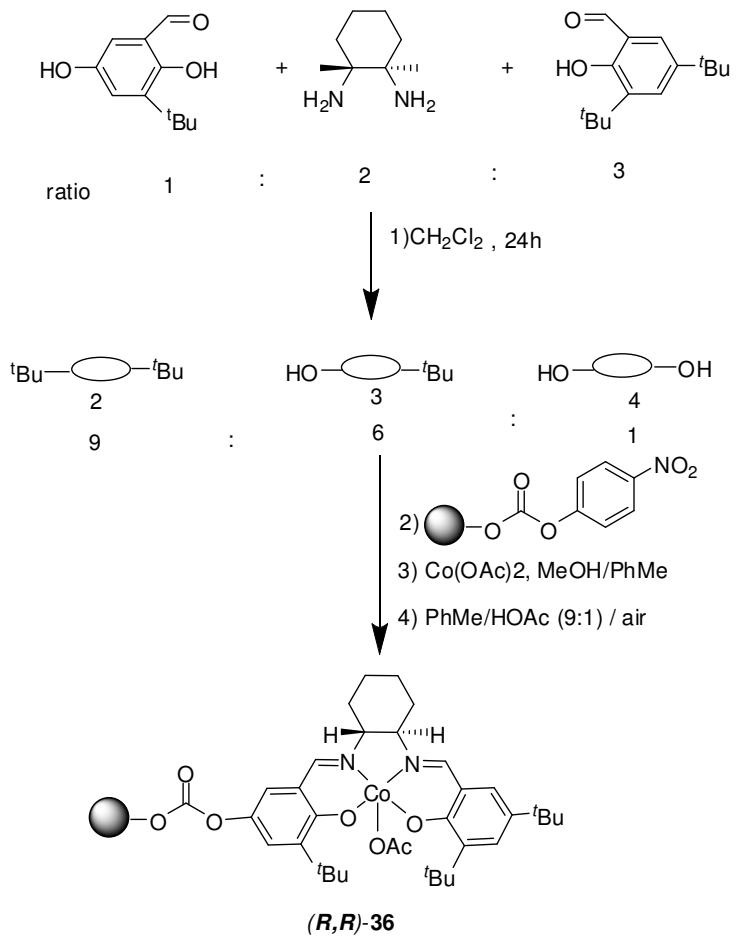
Table 1 Recycling data of HKR of epichlorohydrin using the catalyst 36

Cycle	Conversion[a] (%)	Ee epoxide(%)	Ee Diol (%)	k_{rel}
1	52	>99	92.4	133
2	51	>99	95.0	206
3	51	>99	93.6	159
4	51	>99	93.4	154
5	52	>99	93.0	145

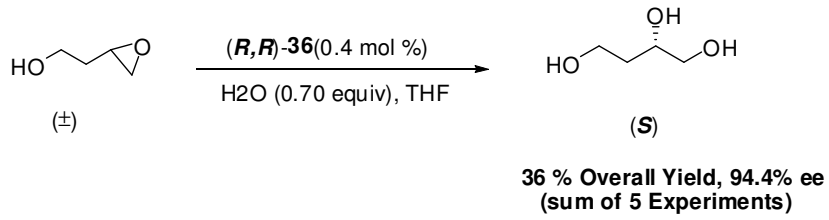
[a]Estimated based on the ee of epoxide and diol product



Scheme 8 HKR of epichlorohydrin using supported catalyst **36**

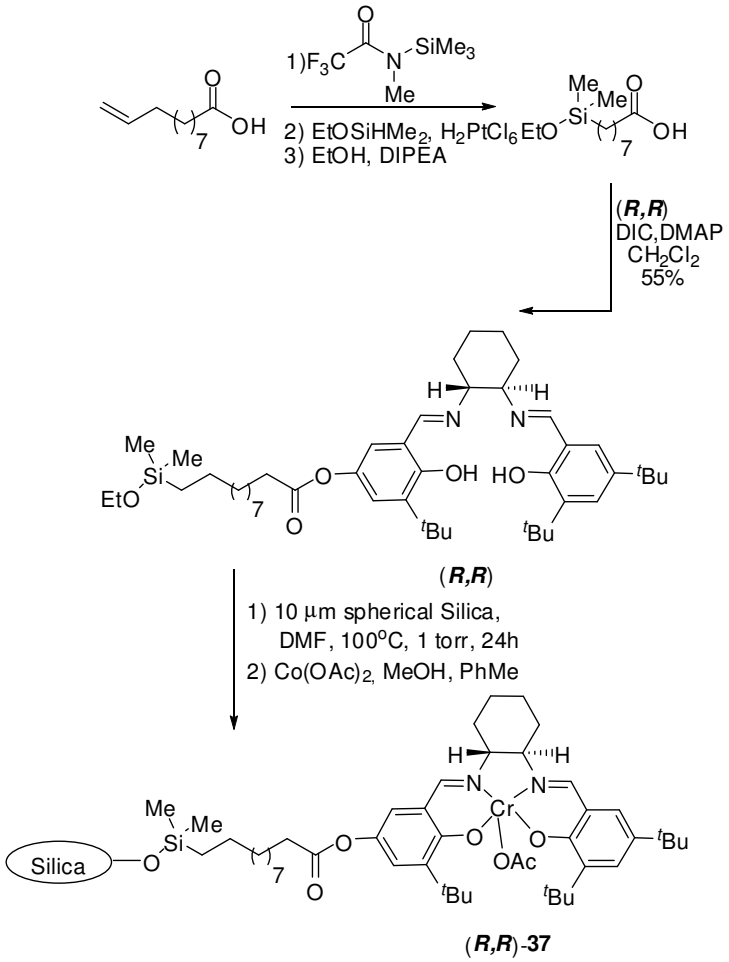


Scheme 7 Resin captured synthesis of polystyrene-bound chiral Co(salen) complex **36**

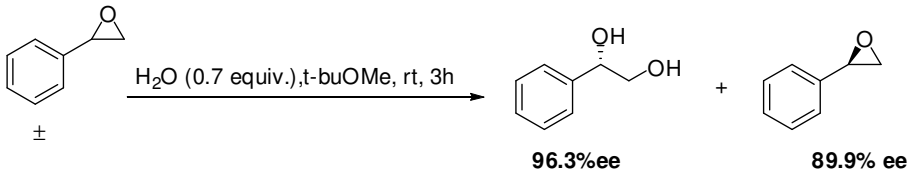


Scheme 9 HKR of 4-hydroxy-1-butene oxide with solid phase catalyst

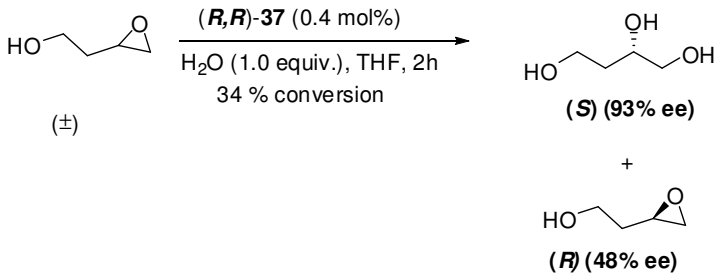
Similarly Silica-Bound Co(salen) **37** (Scheme 10) [69] was also effectively used in the HKR of styrene oxide (Scheme 11) and 4-hydroxy-1-butene oxide (Scheme 12). The immobilized catalysts were adapted to a continuous flow process for the generation of reaction products in high yield and ee, requiring only very simple techniques for product purification (Scheme 13).



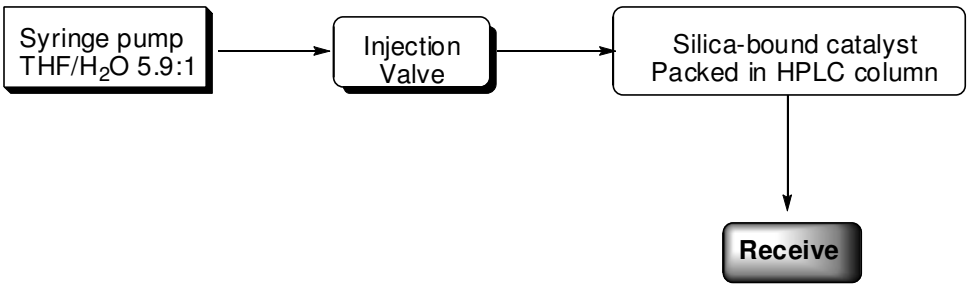
Scheme 10 Silica bound Co(salen) complex **37**



Scheme 11 HKR of styrene oxide with silica bound Co(salen) complex **37**

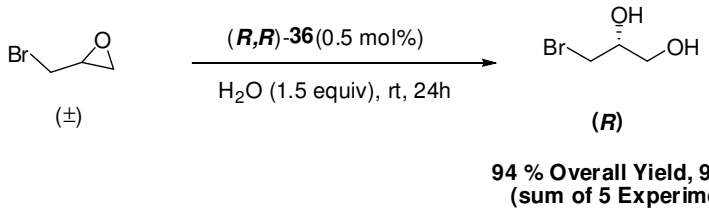


Scheme 12 HKR of 4-hydroxy butene oxide with silica bound Co(salen) complex **37**



Scheme 13 Continuous flow apparatus for the HKR of 4-hydroxy butene oxide over silica bound Co(salen) complex **37**

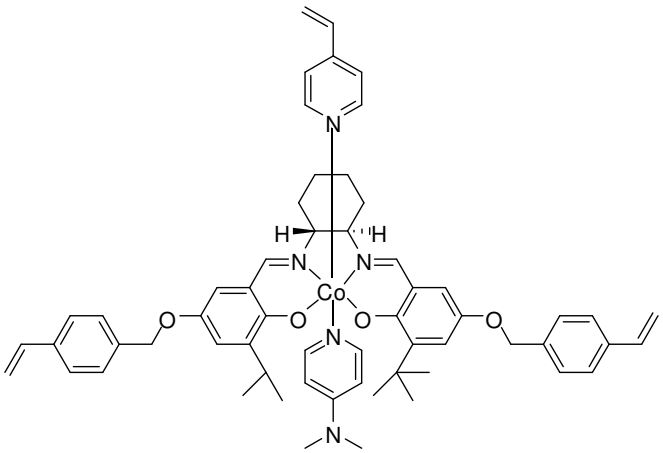
The same immobilized catalyst **36** [69] was also effectively used for dynamic hydrolytic kinetic resolution of epibromohydrin. Five reaction cycles performed with single catalyst batch provided combined yield of 94% with 96% ee and in 90% chemical purity for the product 1-bromo-2,3-propandiol (Scheme 14).



Scheme 14 Dynamic kinetic resolution of epibromohydrin with polymer bound catalyst **36**

Borovik et al. [70] prepared a highly crosslinked polymeric porous material containing Co-salen units **38** (Figure 13) by template copolymerization method. The authors reported that as the cross-linking degree increases from 5 % to 50 %, the catalyst become more efficient in terms of reactivity, possibly due to the improved proximity of

metal centers that work in cooperation. Unfortunately low enantioselectivity for the product epoxide was observed (<42 % ee) while the ee for concomitantly produced diol did not go above 86%. Reusability of the catalyst containing 50 mol% template showed consistent activity and enantioselectivity for three consecutive recycle experiments.



38

Figure 13 Structure of Co(salen) **38** supported on porous materials

Kim and Park [71] reported multi-step synthesis of various unsymmetrical chiral salen Co(III)(OAc) complexes co-valently bonded onto MCM-41 type mesoporous Al-Si material (**39-44**) (Figure 14). Authors developed a new approach of anchoring method where the reaction of a functionalized ligand, diformylphenol, was carried out with 3-aminopropyltrimethoxysilane modified Al-MCM-41. These supported catalysts were used in the HKR of racemic epichlorohydine, 1,2-epoxyhexane, epoxystyrene and epoxycyclohexane under mild conditions to produce respective epoxides and diols in high yield and ee (Table 2).

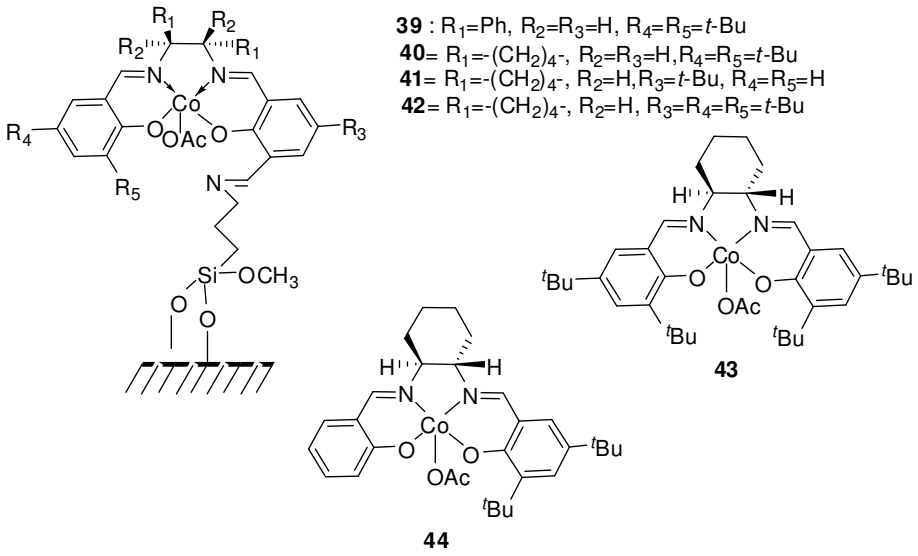
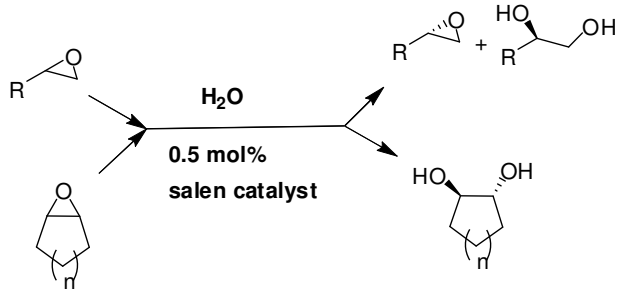


Figure 14 Structure of Co(salen) homogeneous and heterogeneous complexes **39-44**

The substituents on salen ligand have strong influence on the activity and selectivity of catalyst. It was observed that salen ligands bearing bulkier substituents are less effective, this observation is contrary to the one observed in the case of monomeric salen ligand used for the same reaction. The reaction using the Co(III)(OAc) salen catalyst immobilized on MCM-41 gave the almost same enantioselectivity as against homogeneous salen catalysts, however, the reaction rate was low (prolonged reaction time was required).

Table 2 HKR of terminal and meso epoxide catalyzed by the immobilized chiral Co(III) salens[a]



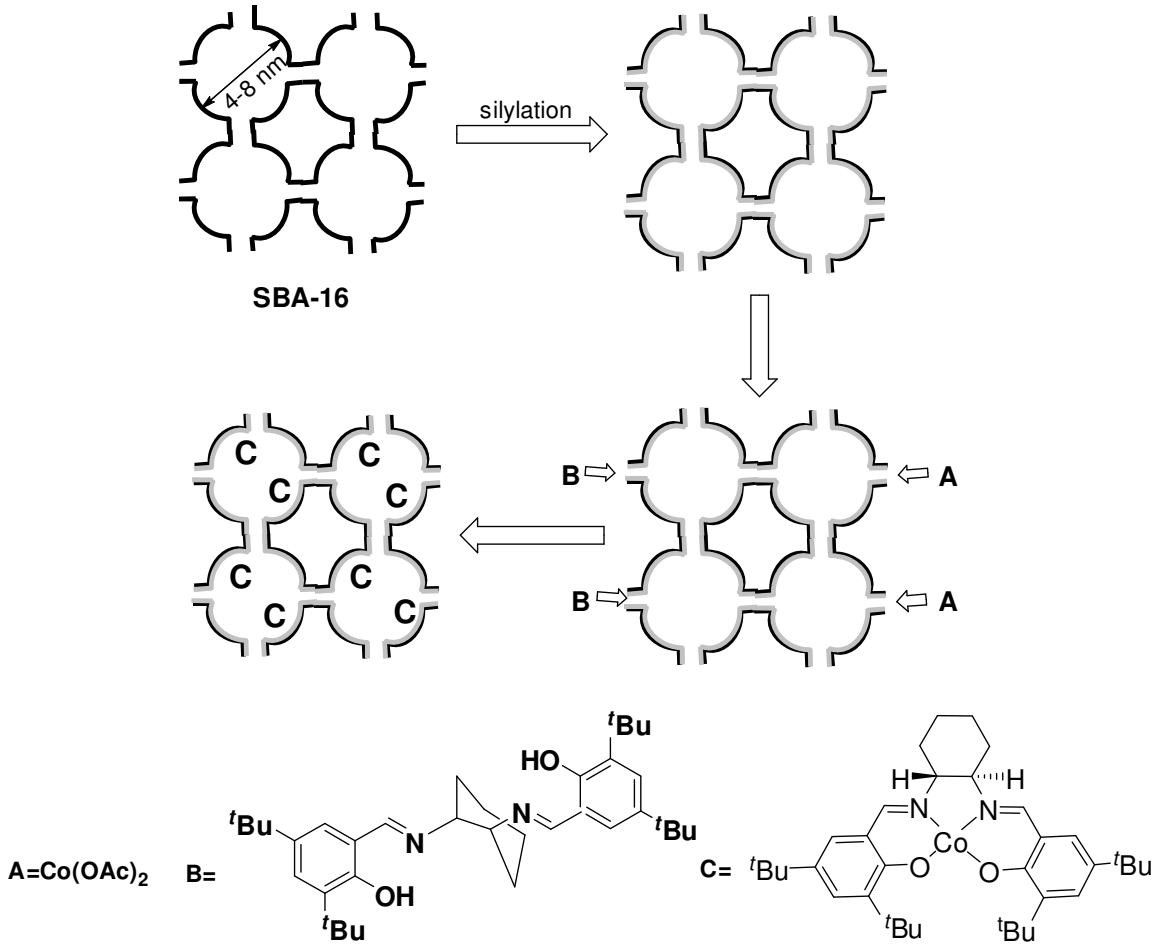
Catalyst	Substrate	Time (h)	Solvent	Diol yield (%)	Diol Ee (%)
39	Epichlorohydrin	24	None	Trace	-
40	Epichlorohydrin	24	None	34	86

41	Epichlorohydrin	24	None	35	92
42	Epichlorohydrin	24	None	31	87
43	Epichlorohydrin	12	None	35	86
44	Epichlorohydrin	12	THF	34	86
43	Epichlorohydrin	12	Acetonitrile	18	85
44	Epichlorohydrin	12	None	34	96
39	Styrene oxide	48	None	Trace	-
40	Styrene oxide	48	None	35	98
41	Styrene oxide	48	None	35	97
43	Styrene oxide	24	None	38	98
44	Styrene oxide	24	None	35	97
40	1,2 Epoxyhexane	24	None	42	97
42	1,2 Epoxyhexane	24	None	48	96
43	1,2 Epoxyhexane	12	None	46	98
40	Epoxycyclohexane	24	None	34	83
42	Epoxycyclohexane	24	None	29	83
42	Epoxycyclohexane	24	MeOH	11	82
42	Epoxycyclohexane	24	THF	37	83
44	Epoxycyclohexane	24	None	39	84
40	Epoxycyclopentane	48	None	29	61
42	Epoxycyclopentane	48	None	18	61
42	Epoxycyclopentane	48	MeOH	7	60
42	Epoxycyclopentane	48	THF	29	62
44	Epoxycyclopentane	48	None	39	64

[a]Olefins, 10mmol; water,5.5mmol; chiral catalyst, 0.5 mol%; reaction temperature 20 ^{0}C

Can Li et al. [72] synthesized a chiral Co(salen) complex in the mesoporous cage of SBA-16 through the flexible ligand method which is akin to “ship in a bottle” method. It was based on the concept that the pore entrance size should be larger than the molecular size of the fragments used for constructing the metal complex and smaller than

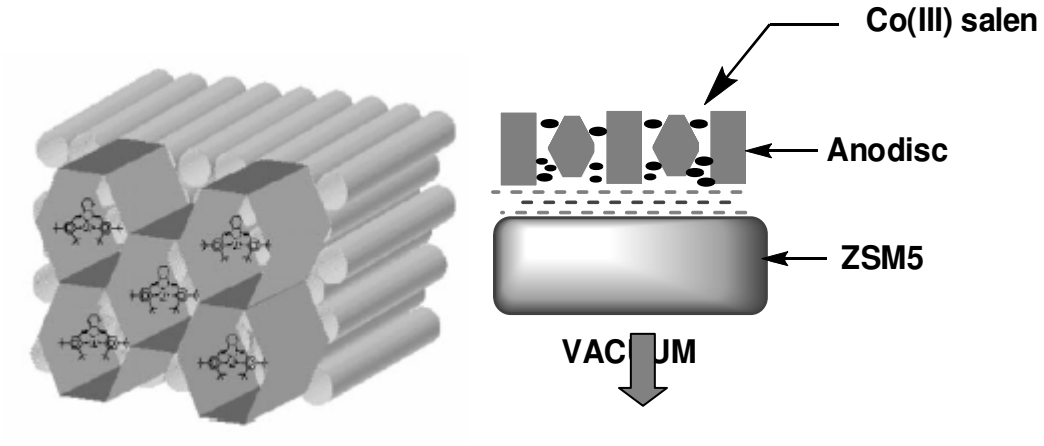
the metal complex catalyst formed inside the cage. To achieve this authors tailored the pore entrance size (4.9, 5.4, and 5.9 nm) of SBA-16 precisely by varying the autoclaving time and silylation with phenyltrimethoxysilane. Flexible chiral salen ligand was then diffused inside the pores of thus modified SBA-16 which was trapped inside the cage of SBA-16 on complexation with cobalt metal ion (Scheme 15). Chiral Co(salen) trapped in SBA-16 **45** showed high enantioselectivity (87–96% ee, at par with the homogeneous catalyst) for the asymmetric ring opening of terminal epoxides and can be recycled at least 10 times with no apparent loss of activity.



Scheme 15 Schematic description of chiral Co(salen) **45** synthesized in the cages of phenyl-modified SBA-16 through the "ship in a bottle"method

Choi and Kim [73] immobilized Co(III)-salen complexes in a ZSM-5 **46** and Anodisc membrane **47** for their use as catalyst in HKR of terminal epoxides with water.

The supported ZSM-5 film for this purpose was synthesized hydrothermally on the porous supports such as Anodisc and alumina tubes. The method for impregnation of the homogeneous complex at the interface between macroporous matrix (Anodisc **47**) and ZSM-5 film layer is shown in Figure 15. The Co(III)-salen complex **46** was loaded into the macropore of Anodisc **47** by impregnation under vacuum. The authors suggested that the salen catalyst must exist near the interface of ZSM-5 film so as the contact of the catalyst with reactants is efficient. By using the immobilized chiral salen membrane catalysts, the product separation became easier and the catalyst could be recycled without observable loss in activity. When the organic-phase feed stream containing a reactant epoxide was contacted with the catalyst at the interface of membrane, the epoxide remained in an organic phase and the converted hydrophilic diol diffused into the aqueous phase on the other side. Enantioselectivities up to 98 % were achieved in this way for several epoxides such as epichlorohydrin, styrene oxide, 1,2-epoxihexane and 1,2-epoxybutane in 27-100 h.



46 **47**

Figure 15 Representative construction of composite membrane **47** for impregnation of chiral Co(salan) **46**

Jacobsen group [74] recently reported the immobilization of chiral salen ligands into self-assembled thiolate monolayers (SAMs) on 3.4 nm gold colloids. Treatment of the immobilized ligand with $Co(OAc)_2 \cdot 4H_2O$ yielded the corresponding [(salen)Co(II)]

complex **48**, which on aerobic oxidation in the presence of triflic acid afforded the catalytically active [(salen)Co (III)] complex. The synthesis of the gold colloids was straightforward, and catalyst immobilization took place under mild conditions. A single functionalized gold colloid can carry several hundred catalyst moieties on its surface, and the thiolate chains self-assemble to minimize steric interactions, leading to a uniform catalyst distribution on the colloid surface (Figure 16). The colloid-bound catalysts were shown to catalyze the HKR of 1,2-epoxyhexane with significant rate enhancements (>99.9% ee of recovered epoxide in 5h) relative to monomeric [(salen)Co(III)] complexes which took 24h that too with higher catalyst loading for getting similar results.

Recovery of the immobilized catalyst **48** was accomplished by simple filtration, and catalyst reoxidation and repeated recycling (seven times) was possible with no loss of reactivity or enantioselectivity.

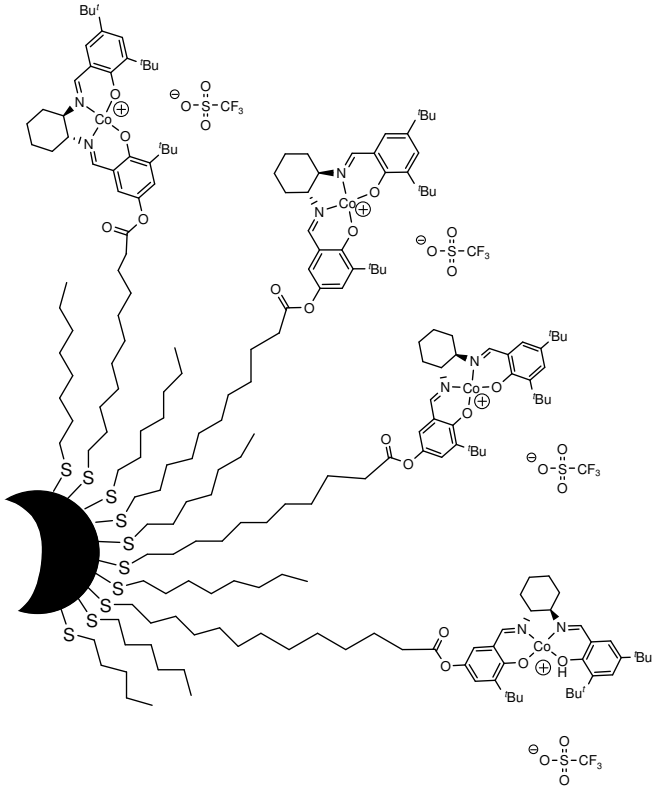


Figure 16 Structure of chiral Co(salen) **48** immobilized on gold colloids

In an another strategy for supporting chiral Co(III) salen complex **49**, ionic liquid **50** was used by Song et al. [75] to carry out HKR of racemic epoxides. They used chiral Co(III) salen complex (Figure 17) in a mixture of ionic liquid [bmim][PF_6] in THF (1:4). Excellent enantioselectivities (>99% ee) for epichlohydrin and 92% ee for its corresponding diol with 0.1 mol% catalyst was achieved with this system. Interestingly, in this system no reduction of Co(III) species was observed during HKR, which is normally the case in the HKR reactions using Jacobsen's catalyst under homogeneous condition. The supported catalyst was retained in the ionic phase, which re-used for ten more cycles without any loss in its performance. Authors also reported that Co(II)salen catalyst **49** can be directly used for the HKR and does not require oxidation in the presence of acetic acid. Very interestingly, with this system the catalytic activity of the recovered ionic liquid phase in the HKR of racemic epichlorohydrin increased upon reuse (reaction time; 22 h for the first run, 22 h for the second run, 15 h for the third run, 4 h for the fourth run, 3 h for the fifth run, 2 h for the sixth run, 2 h for the seventh run, 2 h for the eighth run, 2 h for the ninth run, 2 h for the tenth run). The reason for the increase in activity upon reuse was ascribed to increasing concentration of catalytically active Co(III) complex in the reaction mixture.

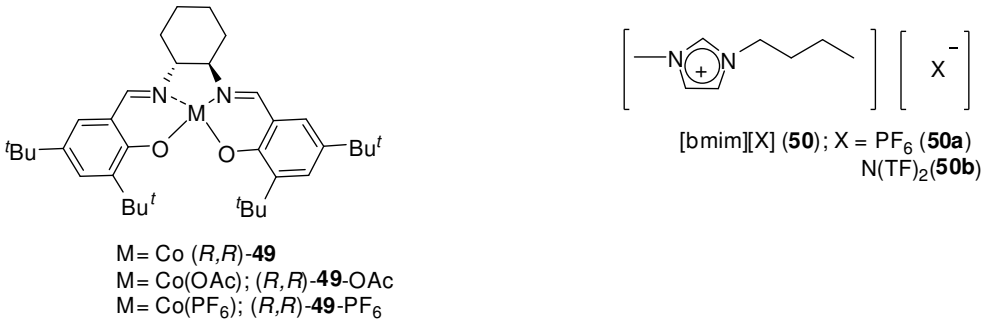
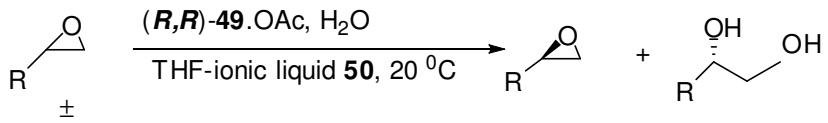


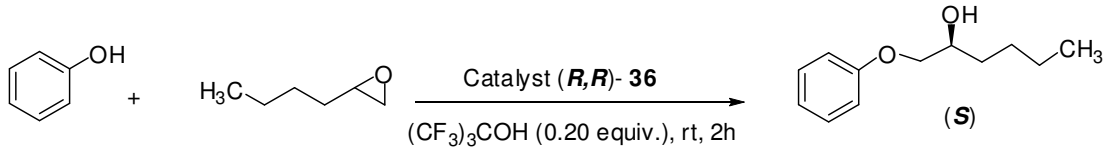
Figure 17 Structure of Co(salen) complex **49** in presence of ionic liquid **50** for HKR reaction



Scheme 16 Reaction for HKR for terminal epoxides using chiral Co(salen) **49** in presence of ionic liquid **50.**

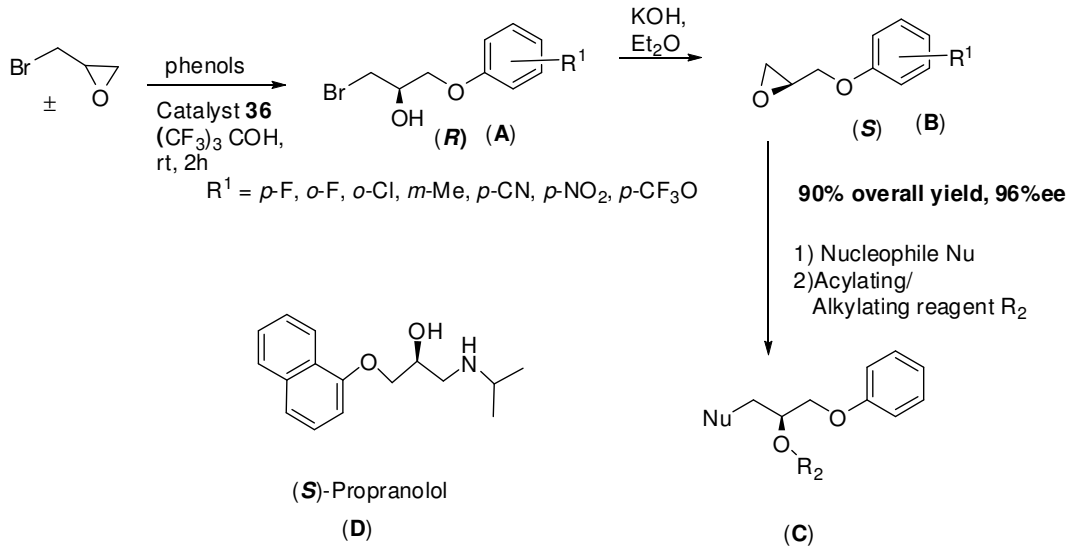
ARO of epoxides with Phenols and alcohols as nucleophiles

ARO reaction with phenols and alcohols as nucleophiles is a logical extension of HKR of epoxides to synthesize libraries of stereochemically defined ring-opened products in high optical purity. To this effect Annis and Jacobsen [69] used their polymer-supported Co(salen) complex **36** as catalyst for kinetic resolution of epoxides with phenols to give 1-aryloxy-2-alcohols in high yield, purity and ee (Scheme 17). Conducting the same reaction in the presence of tris(trifluoromethyl)methanol, a volatile, nonnucleophilic protic acid additive accelerates KR reaction with no compromise with enantioselectivity and yield. Presumably the additive helped in maintaining the Co(III) oxidation state of the catalyst.



Scheme 17 KR of racemic terminal epoxide with phenol using chiral catalyst **36**

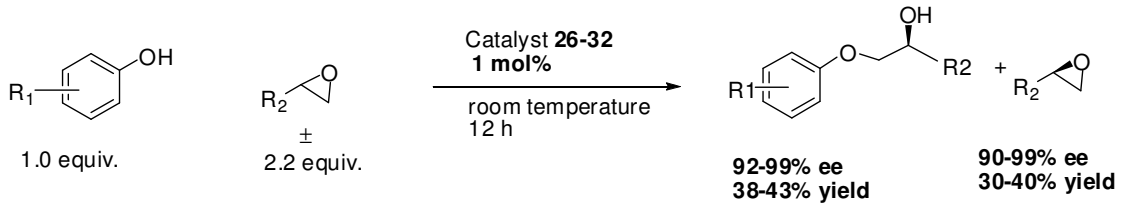
ARO of epibromohydrin with phenols using polymer-bound catalysts, **36** [69] proceeded with high efficiency and enantioselectivity, but the bromohydrin product (**A**) underwent ring-closure reaction to produce phenyl glycidyl ether **(B)** under the ring-opening reaction conditions. Incidentally, the aryl glycidyl ether thus produced is useful in the synthesis of combinatorial libraries of the general structure (**C**). For instance, Propranolol, **(D)** is commercial antihypertensive agent (Scheme 18). The catalyst **36** is recyclable and its performance was found to be persistent over 5 cycles.



Scheme 18 A possible application of the enantioselective ring opening of epibromohydrin with phenols in combinatorial synthesis using the catalyst **36**

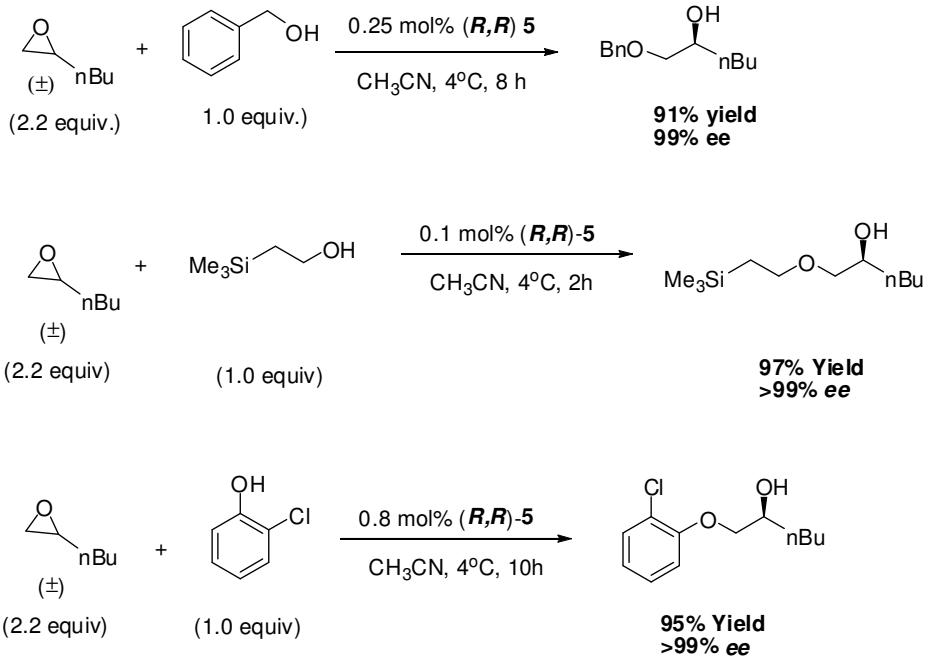
Cycle	Ee of **A** %
1	97.1
2	97.1
3	95.5
4	95.8
5	94.6

Kim et al. [67], used the self-polymerized heterometallic polymeric salen complexes **26-32** as efficient catalysts for kinetic resolution of terminal epoxides with phenols to give α-aryloxy alcohols in high yields (38-43%) and ee (92-99%) (Scheme 17). These catalysts were recycled up to three times without any loss in their performance.



Scheme 19 ARO of terminal epoxides with phenol using heterobimetallic chiral catalysts **26-32**

Unfortunately there is no report on ARO reaction of epoxides with alcohols using heterogeneous or recyclable homogeneous catalysts. In this direction, it is worth mentioning the potentiality of Jacobsen's oligomeric complex **5** [57, 58] which though not recyclable is highly active and enantioselective for ARO of *meso* and terminal epoxides with alcohols as well as phenols (Scheme 20). Stability of this oligomeric complex was the main issue, which if addressed can provide highly practical protocol for the synthesis of chirally pure alkoxy and aryloxy alcohols.



Scheme 20 ARO of terminal epoxides with phenol and alcohol using oligomeric Co(salen) complex **5**

C-C and C-S bond formation reactions are important organic reaction and are usually accomplished by Lewis acid-based catalysts. However, this reaction is rarely achieved by epoxide ring opening reaction. One such example of C-C and C-S bond formation was reported by Bandini et al. [76]. They reported polymer-supported indium Lewis acid **51** (Amberlyst 15/indium complex) (Figure 18) as catalyst for the formation of β-indolyl alcohols and β-hydroxy sulphides through the highly regio- and stereoselective ring-opening reaction of enantiomerically pure internal as well as terminal epoxides under ambient and atmospheric conditions (Scheme 21-23). This catalyst was recycled five times without a remarkable loss of activity.

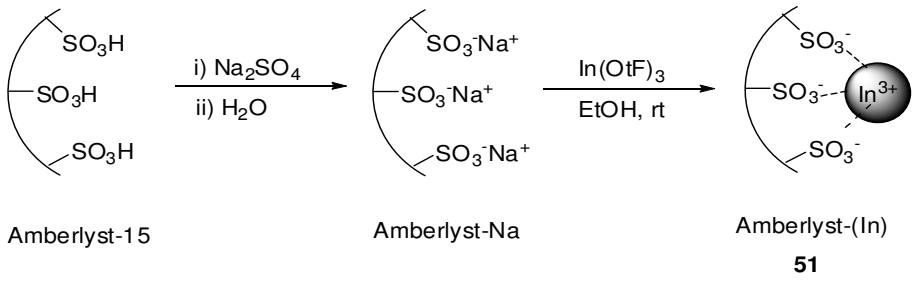
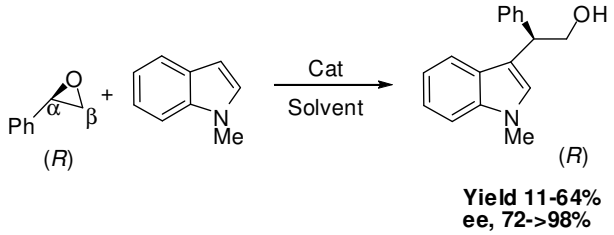
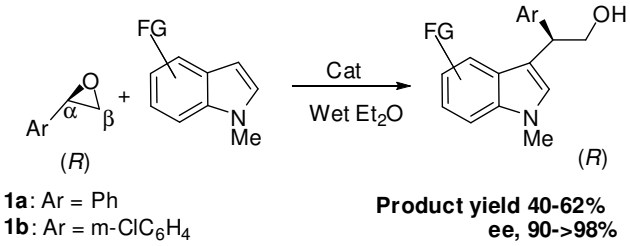


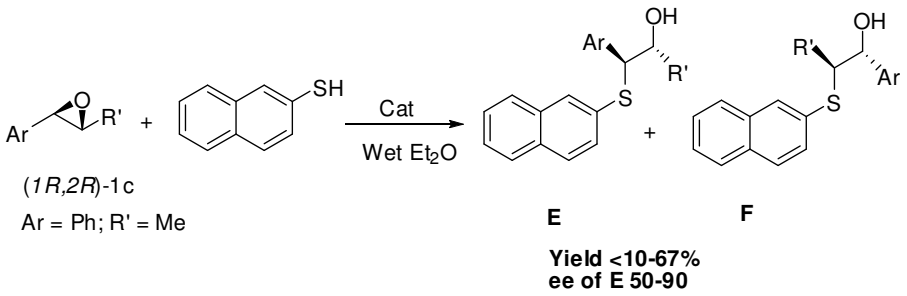
Figure 18 Synthesis of the resin-supported indium Lewis acid catalyst **51**



Scheme 21 ARO reaction for optimization of conditions using the catalyst **51**



Scheme 22 ARO of enantiomerically pure epoxide with various indoles using catalyst **51**

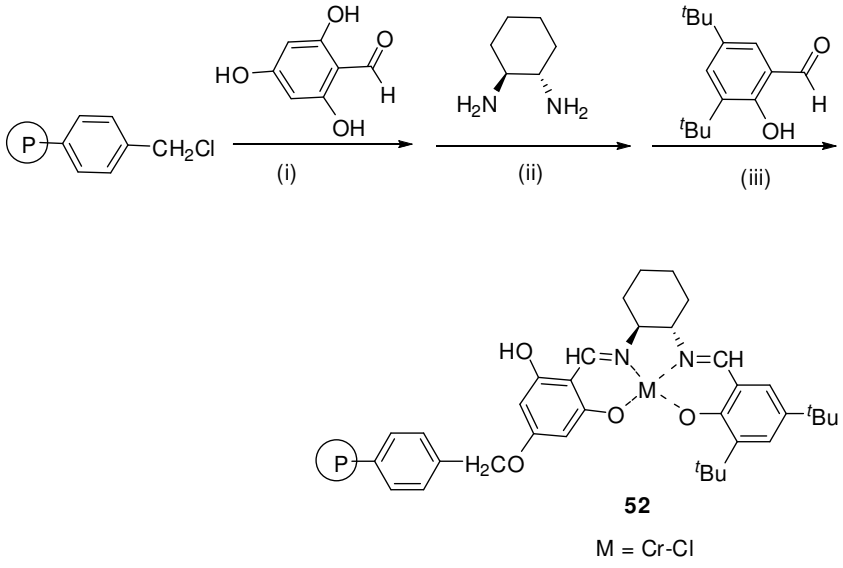


Scheme 23 Reaction for Thiolysis of enantiomerically pure epoxide mediated by **51**

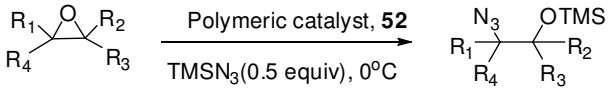
Asymmetric ring opening reaction of epoxides with trimethylsilyl azide ($TMSN_3$)

Optically pure β-amino alcohols are important structural entities in many biologically active compounds and intermediates in the preparation of many chiral auxiliaries and ligands [3, 77-79]. Among many other methods, asymmetric ring opening reaction (ARO) of epoxides with $TMSN_3$ catalyzed by Cr(salen) complex is an attractive approach for the synthesis of optically pure β-aminoalcohols. Cr(salen) complex is very stable under the homogeneous reaction condition used for ARO of epoxides and can be recycled a number of times without loss of activity and enantioselectivity. However, this catalyst recycling procedure involves the potentially hazardous distillation of neat liquid azides, which may prove a limitation for large scale applications.

Angelino and Laibinis [80] reported polystyrene-supported salen complex **52** (Scheme 24) in the asymmetric ring opening of epoxides. At 0 °C with 1 mol % catalyst loading, the asymmetric ring opening of epoxyhexane, propylene oxide, and cyclohexene oxide gave the corresponding products with 34%, 36%, and 6% ee, respectively, and in 40-47% yield (Scheme 25). The recycled catalysts were stable and were reused three times without loss of activity or enantioselectivity. However, during the reaction the leaching of Cr to the extent of <0.1% was reported, suggesting the possible use of the catalyst over hundreds of cycles before reloading the polymer-supported salen ligand with metal would be necessary.

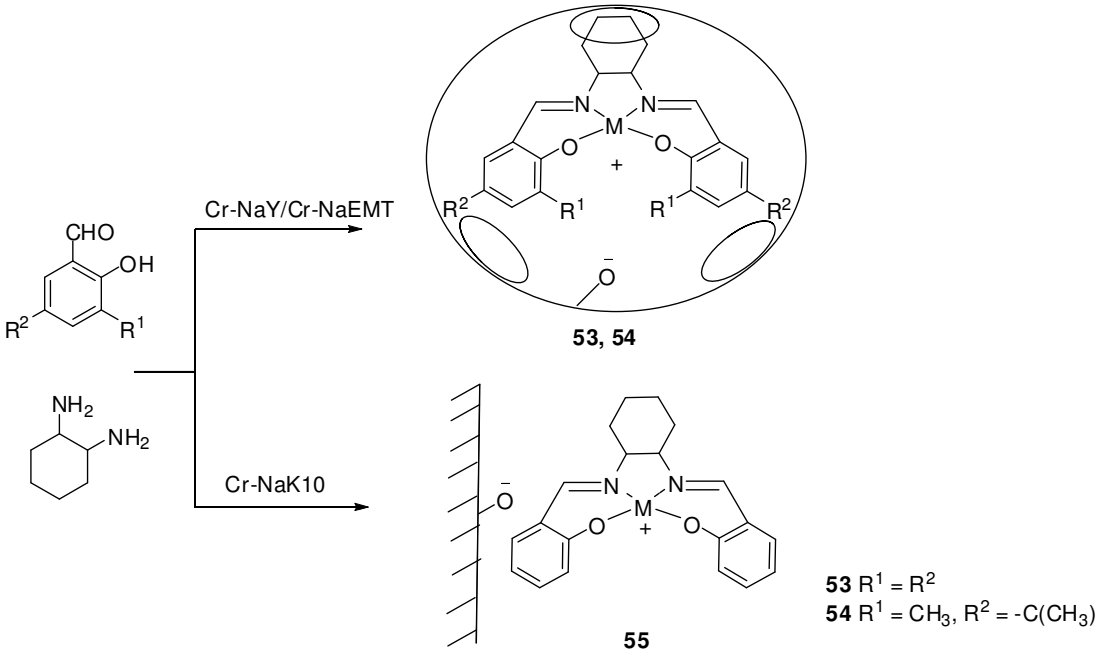


Scheme 24 Synthesis of chiral polymeric Cr(salen complex **52**

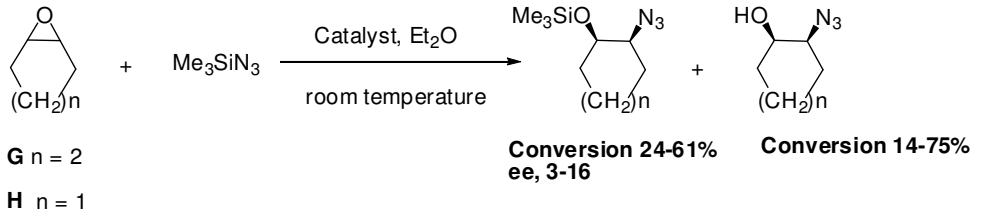


Scheme 25 ARO of epoxides with $TMSN_3$ using the complex **52**

Corma group [81] reported incorporation of different chiral Cr(III)-salen complexes within the cavities of zeolites Y **53**, EMT **54** and into the interlamellar region of K-10 montmorillonite **55** (Scheme 26). These heterogeneous catalysts promoted the asymmetric ring opening of epoxides viz., cyclohexane oxide and cyclopentene oxide with trimethylsilylazide to afford chiral azido trimethylsilyl ethers and azido alcohols with modest ees that vary depending on the inorganic support used (Scheme 27). The enantioselectivity of the ring-opened azide however, was inferior than the ees achieved with the unsupported complexes under homogeneous condition.

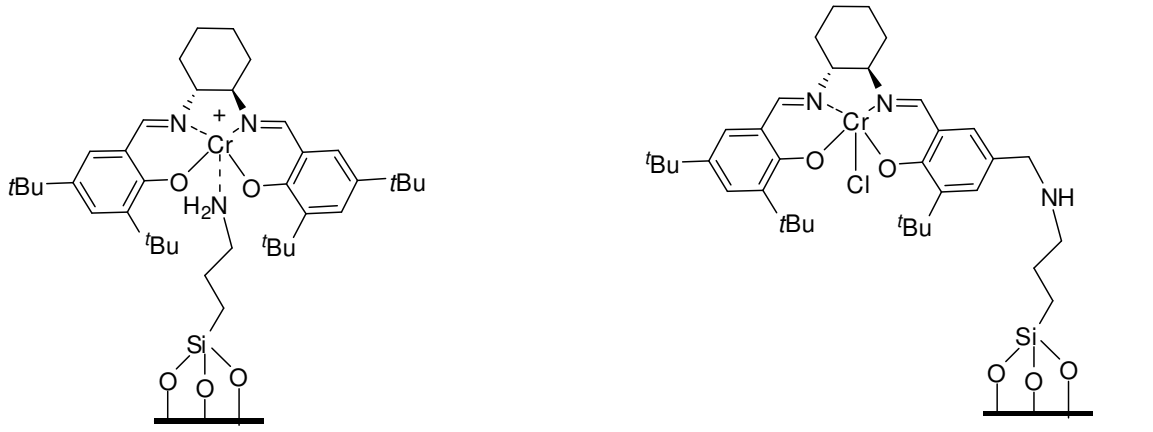


Scheme 26 Preparation of Cr(III) Schiff base complexes into the cavities of zeolites Y **53**, EMT **54** and in the montmorillonite clay K-10 **55**



Scheme 27 Enantioselective ring opening of cyclic oxides **G** and **H** by $TMSN_3$ catalyzed by chiral Cr(III) Schiff base complexes within the cavities of zeolites Y **53**, EMT **54** and into the interlamellar region of K-10 montmorillonite **55**.

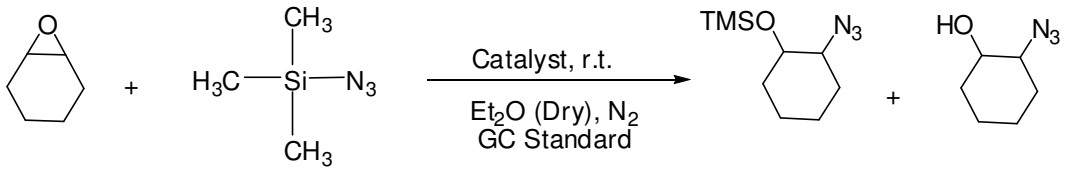
Later on, Corma et al. [82] reported covalent anchoring of chiral chromium salen complexes on SiO_2, ITQ-2 or MCM-41 via aminopropyl functionalization. The catalysts in which anchoring of the complex was accomplished through coordination with the metal **56, 57** (Figure 19) showed high enantiomeric excesses (ee up to 70%) for ARO of cycloheneoxide with $TMSN_3$ (Scheme 28), but there was considerable leaching of the complex into the reaction medium. In contrast, the complexes **58-62** which were attached to the surface of silica through covalent linkage do not leach out, but at the same time they induct modest ee (below 20%) in the products as compared to the homogeneous catalysis under comparable conditions (>50% ee) (Table 3).



Catalyst **56** Solid Silica/NH_2
57 ITQ-2/NH_2

Catalyst **58-62**

Figure 19 Structure of the catalysts **56-62**



Scheme 28 ARO of cyclohexene oxide with $TMSN_3$ using immobilized catalysts **56-62**

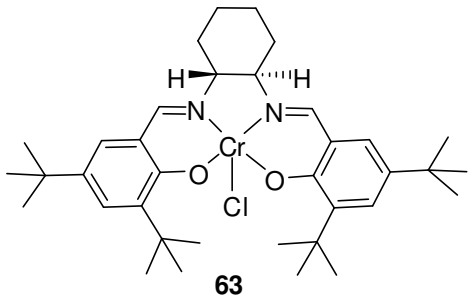
Table 3 Enantioselective ring opening of cyclohexeneoxide with $TMSN_3$ catalyzed by chromium salen complexes[a]

Catalyst	Time (h)	Conversion (%)[b,c]	E.e (%)[b.d]
Homo (2%)	18	83	84
Homo (1%)	42	56	59
Homo (0.3)	88	51	50
56	48	100(45)	70
57	48	93(20)	52
58	48	66	8
59	48	43	9
60	48	57	13
61	48	47	14
62	48	61	18

[a]All reactions were performed at room temperature with 3 mmol of cyclohexeneoxide, 3 mmol of *cis* decahydronaphthalene (internal standard), unsupported catalyst (homo) or 100 mg of heterogeneous complex and 3.15 mmol $TMSN_3$ in 1 ml of dry Et_2O.
[b]Determined by capillary GC column (Cyclodex B, 30 x 25mm).
[c]The values between brackets correspond to the percentage of leaching; no leaching was observed unless specified.
[d]Ee of azido silyl ether

Dioos and Jacobs [83] impregnated silica with a Cr(salen) complex **63** (1.25 wt%) (Figure 20) for ARO of 1,2-epoxyhexane and 1,2-epoxyoctane with $TMSN_3$ to give the ring opening products in high ees (>97%) and conversions (~50%). For other substrates like styrene oxide and the *meso* epoxides cyclohexeneoxide and cyclopenteneoxide, the ARO displayed lower diastereoselectivities. The recycling experiments with Cr(salen) impregnated with silica catalyst displayed reproducible activities for 10 consecutive ARO

reactions (Table 4) of epoxyhexane however, in every run 1.83-0.01% leaching of the complex was observed.



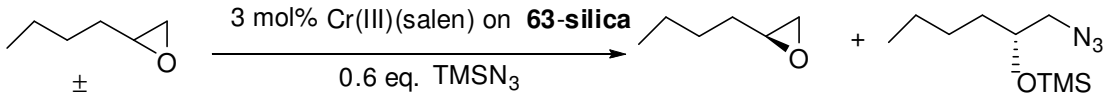
63

Figure 20 Structure of the monomeric Cr(III) salen complex **63** used for impregnation on silica

Table 4 Recycling experiments with Cr(salen) 63-silica in the ARO reaction of epoxyhexane

Run	Time (h)	E.e[a] (%)	Conversion[b] (%)	Leaching (%)
1	21	84.9	53.3	0.59
2	21	87.2	46.3	1.83
3	23	91.5	48.4	1.07
4	23	91.6	53.4	0.17
5	23	92.8	55.6	<0.01
6	23	92.9	52.8	0.01
7	24	90.9	50.2	0.08
8	26	82.3	51.4	<0.01
9	33	84.9	50.9	0.30
10	41	86.2	50.8	1.22

[a]Ee of (R)-1,2-epoxyhexane
[b]The optimum conversion should be 50%

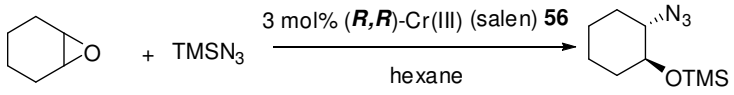


Scheme 29 ARO of 1,2 epoxyhexane using catalyst **63-silica**

Cr(salen) supported on amino-modifed silica **56** was reported by Corma at al. [82] that showed high activity and selectivity for ARO of *meso* epoxides with $TMSN_3$ but

suffered acute catalyst leaching problem. To overcome this problem, Jacobs et al. [84] made an improvement over the above catalytic system by the careful choice of the solvent for epoxide ring opening reaction. Authors found that hexane is the right choice of solvent and demonstrated that the supported catalyst worked efficiently for the ARO of cyclohexeneoxide with $TMSN_3$. Additionally, in this protocol the problem of catalyst leaching was minimal (<1%) (Table 5).

Table 5 Catalytic results of the recycling experiments using the catalyst 56

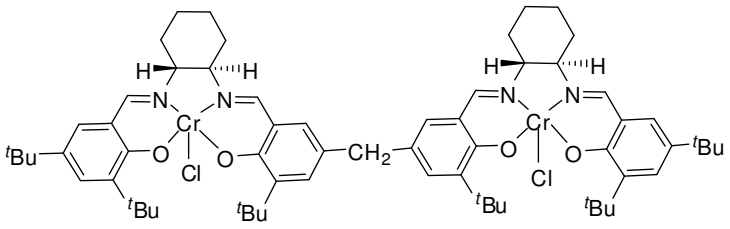


Run	Reaction time (h)	Conversion (%)	Ee (%)	Leaching (%)
1	12	99.5	65.4	0.9
2	18	100.0	67.9	0.8
3	18	100.0	68.7	0.5
4	18	100.0	73.3	1.0
5	19	99.3	73.1	1.0
6	21	99.5	75.0	0.7
7	21	99.5	75.5	0.6
8	23	99.0	76.6	0.6
9	24	99.1	77.2	0.8
10	*24*	*99.2*	*76.9*	0.9

50 mg catalyst; 3 mL hexane; toluene (75 μL) = internal standard; catalyst/substrate ratio= 3 mol%; 1.1 eq. $TMSN_3$; stirred batch reactor ar RT

To further minimize leaching of the Cr(salen) catalyst Jacobs et al. [85] impregnated relatively less soluble dimeric Cr(salen) catalyst on a silica material **64** (Figure 21)**.** The silica impregnated dimeric Cr(salen) catalyst showed high enantioselectivities for epoxide (ee, >97.5%) and ring opened product (ee, 80%) with good conversions for ARO of 1,2-epoxyhexane with trimethylsilylazide. This catalyst

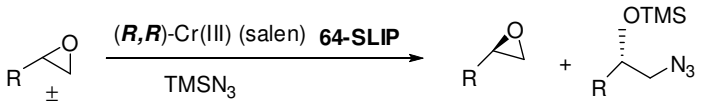
system work well both in batch (12 recycling experiments) and continuous flow experiments and suffers even less catalyst leaching problem than monomeric Cr(salen) supported on silica (**63-silica**).



64

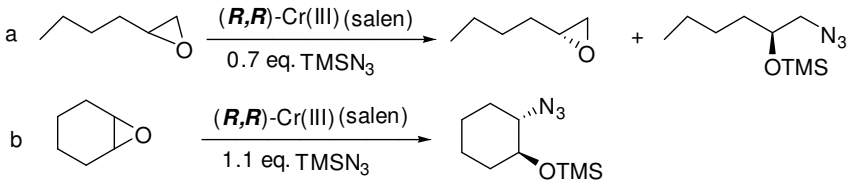
Figure 21 Structure of dimeric Cr(III) salen complex **64** used for impregnation on silica

Interestingly, the dimeric Cr(salen) catalyst **64** supported on silica showed enhanced activity for ARO of 1,2-epoxyhexane and cyclohexene oxide in the presence of ionic liquids particularly with [BMIM][PF6] (**64-IL**) [86] (Table 6). A significant increase in the product selectivity was also observed with silica supported ionic liquid (**64-SILP**) for ARO of 1,2-epoxyhexane and cyclohexene oxide (ee, of 87% and 75% respectively) as compared to silica supported catalyst minus the ionic liquid (Table 6, entries 5,6). However, after repeated recycling, the silica support material deteriorates due to the abrasive forces in the stirred reactor. As a result, silica material was non-recoverable, but the expensive dimeric Cr(salen) catalyst **64** and the ionic liquid was recovered quantitatively by Soxhlet extraction with acetone. SILP-catalyst system was also used in a continuous-flow reactor.



Scheme 30 ARO of epoxides catalysed by (***R,R***)-Cr(III)(salen) complex **64-SLIP**

Table 6 Stirred batch reactor: ARO of epoxides catalyzed by a dimeric (*R,R*)-Cr(III)(salen) complex 65 immobilized in a supported ionic liquid phase compared to the dimeric complex impregnated on silica 64-silica and the reported homogeneous reactions with the monomeric Cr(salen) complex 63.

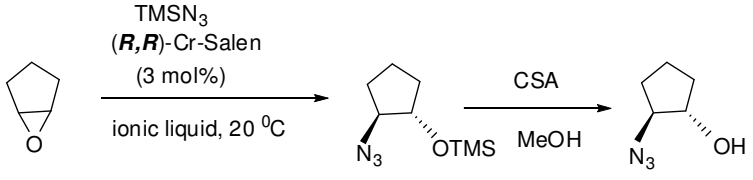


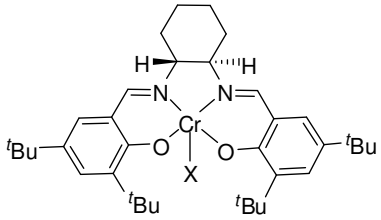
Run[a]	Reaction	Time (h)	Conversion (%)	Ee epoxide (%)	Ee product (%)	Leaching (%)
1	a	3	52	95	84	0.4
2	a	3	48	96	87	0.5
3	b	20	93	-	75	1.1
4	b	20	92	-	73	1.1
Impregnation[b]	a	10	59	96	66	1.0
Impregnation[b]	b	70	98	-	65	1.1
Homogeneous[c]	a	27	45	-	97	-
Homogeneous[d]	b	18	83	-	84	-

The catalyst/substrate ratio is 1.5 mol% for the supported ionic liquid phase (SILP) catalyst, 3 mol% for the impregnated catalyst and 2 mol% for the homogeneous reaction
[a]Runs 1-4 are consecutive experiments with the same catalyst in a stirred batch reactor.
[b]Dimeric Cr (salen) catalyst impregnated on silica
[c]Homogeneous reaction at 0-2 ^{0}C optimized for product selectivity
[d]Homogeneous reaction at room temperature optimized for product selectivity

Prior to the study of Jacobs, Song et al. [87] had already reported monomeric Cr-salen **63** catalyzed ARO of epoxides with $TMSN_3$ in ionic liquid 1-butyl-3-methylimidazolium salts [bmim][X]. The ARO reaction proceeded readily at room temperature with easy catalyst/solvent recycling and does not include hazardous workup stages such as distillation of the azide product.

Table 7 Cr-salen 63, 66 catalyzed ring opening of epoxides carried out in ionic liquids





63 $X = Cl^-$,
66 X= N_3

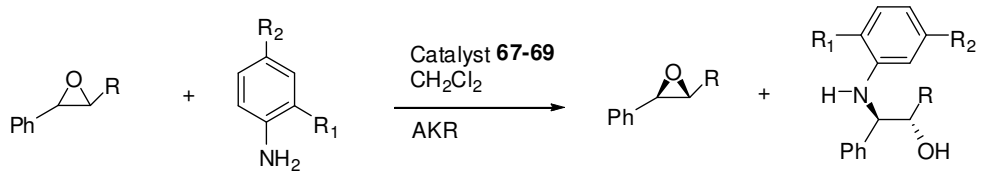
Ionic liquid	Time (h)	Yield (%)	Ee (%)
[bmim][PF_6]	28	76	94
[bmim][SbF_6]	28	75	87
[bmim][BF_4]	28	5	3
[bmim][OTf]	28	trace	-

Aminolytic Kinetic resolution of racemic epoxides with amines as nucleophile

Enantiomerically pure β-amino alcohols which are important intermediates for many bioactive compounds can be directly synthesized by the ARO reaction of readily accessible racemic and meso epoxides with appropriate amines. Indeed, some simple and multifunctional β-amino alcohols have been obtained using this strategy by the promotion of chiral BINOL [30-32,88,89], salen [35,52], bipyridine [33,40,90-94] and proline-*N,N*-dioxide based metal complexes [95]. However, none of these systems demonstrated the recyclability of the precious chiral catalyst.

Kureshy et al. [96], for the first time reported recyclable catalyst based on polymeric Cr(III)(X) salen complexes derived from (1*R*,2*R*)-(-)-cyclohexanediamine with 5,5'-methylene di-3-*tert*-butylsalicylaldehyde and X = Cl, NO_3, and ClO_4 **67-69** (Figure 22). These complexes were used in regio-, diastereo-, and enantioselective aminolytic kinetic resolution (AKR) of *trans*-stilbene oxide, *trans*-β- methyl styrene oxide, and 6-CN-chromene oxide at room temperature, providing the desired anti-β-amino alcohols in high yields (49% out of maximum 50% theoretical yield) and ee (up to 100%) leaving behind the corresponding valuable epoxide in high ee (up to 98%) (Scheme 31). These polymeric catalysts were reportedly more active than their monomeric counterparts due to higher number of repeat salen units that worked in cooperation. The polymeric

Cr(III)(X) salen catalysts were recovered by taking advantage of solubility difference and were reused 4 times in the AKR of trans-stilbene oxide without any apparent loss in its performance.(Table 8).



Scheme 31 Reaction for AKR of *trans* epoxides with anilines as nucleophiles using the catalysts **67-69**

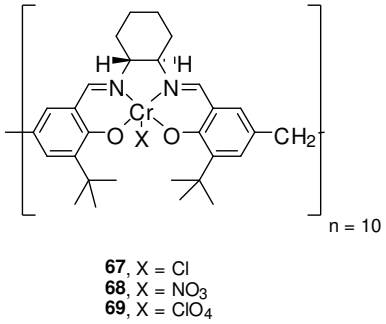


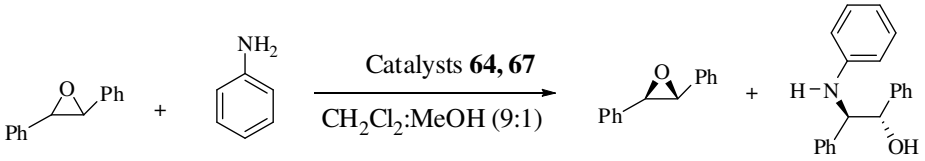
Figure 22 Structure of the catalysts **67-69**

Table 8 Recycling data of catalyst 67 for AKR of *trans* stilbene oxide using aniline as nucleophile

Catalytic run	Time (h)	Ee of epoxide	Ee of amino alcohols	Yield of amino alcohols
1	14	80	87	49
2	14	80	86	48
3	15	79	85	47
4	17	75	87	46
5	20	71	86	45

Kureshy et al. [97] in their subsequent study demonstrated the use of above polymeric **67** and analogous dimeric catalyst **64** in AKR of several epoxides under microwave (MW) irradiations in order to speed up the sluggish chemical reactions under conventional heating. Accordingly, AKR of *trans*-stilbene oxide and *trans*-*β*-methyl styrene oxide with aniline and substituted anilines were found to proceed smoothly under MW within 2 min using **67, 64** complexes as catalysts giving *anti*-*β*-amino alcohols. High yields (49%) and chiral purity (ee up to 94%) was achieved in case of 4-methylaniline. This AKR system under MW irradiation was found to be ~5 times faster than traditional oil bath heating at 70 ^{o}C and 420 times faster than the reaction conducted at room temperature with concomitant recovery of respective chirally enriched epoxides (ee, 92%) in excellent yields (up to 48%).

Table 9 Aminolytic kinetic resolution (AKR) of *trans*-stilbene epoxides using recyclable catalysts with aniline under different reaction conditions.



Temp. ^{o}C	Time (min)	MW (W)	*Trans-epoxide* Ee(%)	Yield(%)	Anti-*β*-amino Alcohols Yield(%)	Ee(%)
40	2	900	78 (73)	78 (83)	94 (81)	22 (16)
50	2	900	81 (74)	62 (65)	94 (80)	35 (30)
60	2	900	84 (72)	63 (62)	92 (78)	42 (37)
70	2	900	90 (72)	48 (48)	92 (78)	49 (49)
80	2	900	81 (69)	35 (37)	92 (67)	65 (62)
70	2	800	35 (25)	65 (67)	42 (37)	35 (32)
70	2	1000	40 (31)	37 (26)	55(55)	72(74)
70	2	900	75 (68)	65(67)	96(80)	36(32)
70	2	900	92 (79)	45(46)	68 (70)	60 (57)
70	2	900	96 (83)	39 (41)	61 (62)	69(68)
70	2	900	30	72	75	27
70	5	-	42(40)	65(68)	75 (73)	35(32)
70	10	-	79((73)	51(50)	61 (67)	48(49)
27	840	-	85(80)	47(48)	93 (87)	49(49)

70 (2nd cycle)	2.0	900	89 (70)	48 (48)	92 (78)	49(49)
70 (3rd cycle)	2.0	900	89 (71)	47 (49)	91 (78)	48(48)
70 (4thcycle)	2.0	900	90 (72)	46 (48)	92 (77)	48(48)
70 (5^{th} cycle)	2.0	900	90 (72)	46 (48)	91 (76)	47(47)

Very recently Kureshy et al. [98] further reported non-salen chiral Schiff base derived Ti complexes as catalysts **70, 71** (Figure 23) in the KR of *meso*-stilbene oxide, cyclohexene oxide, cyclooctene oxide and *cis*-butene oxide with anilines. The study deliberated upon the role of several chiral and achiral additives with these catalysts to give chiral β-amino alcohols with high enantioselectivity (*ee*, >99%) in excellent yield (>99%) at 0 ^{o}C in 10h. Unlike the monomeric version **72** the chiral catalyst **70** used in this study was recoverable and recyclable several times with retention of its performance (Table 10)

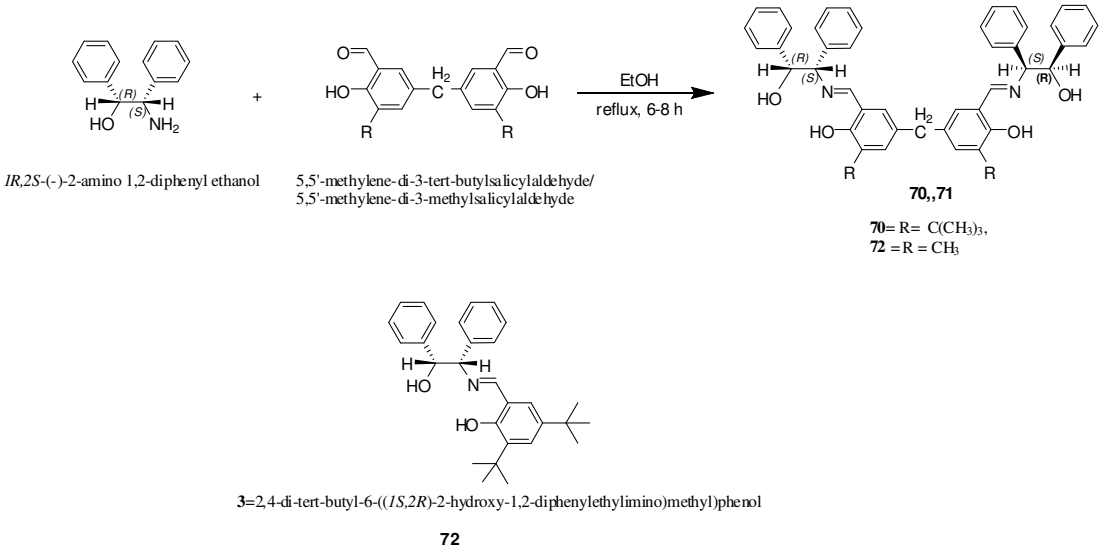
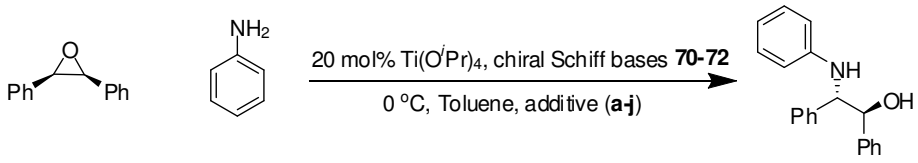
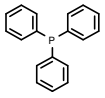
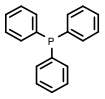
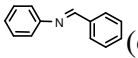
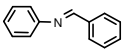
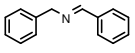
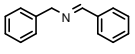
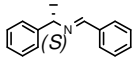
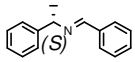
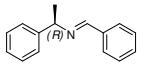
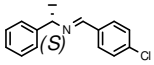
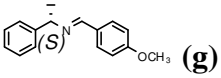
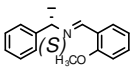
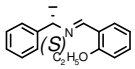
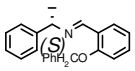
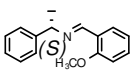
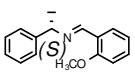


Figure 23 Synthesis of Chiral aminoalcohol ligands **70-72**

Table 10 Products Yield and ee's of asymmetric ring opening reaction *of meso*-stilbene oxide with aniline using complexes 70-72



Catalyst	Additive	Time (h)	Yield [%][g]	Ee [%]	Confign. of β-aminoalcohol
70	None	10	79	60	1*S*,2*S*
71	None	10	66	50	1*S*,2*S*
70	 **(a)**	10	89	65	1*S*,2*S*
71	 **(a)**	10	82	55	1*S*,2*S*
70	 **(b)**	10	90	68	1*S*,2*S*
71	 **(b)**	10	80	59	1*S*,2*S*
70	 **(c)**	10	94	70	1*S*,2*S*
71	 **(c)**	10	88	59	1*S*,2*S*
70	 **(d)**	10	92	69	1*S*,2*S*
71	 **(d)**	10	87	58	1*S*,2*S*
70	 **(e)**	10	99	94	1*S*,2*S*
71	 **(e)**	10	92	78	1*S*,2*S*
70	 **(e')**	10	80	65	1*S*,2*S*
71	 **(f)**	10	84	88	1*S*,2*S*
70	 **(g)**	10	94	86	1*S*,2*S*
70	 **(h)**	10	99	>99	1*S*,2*S*
70	 **(i)**	10	70	62	1*S*,2*S*
70	 **(j)**	10	74	55	1*S*,2*S*
70	 **(h)**	24	75	64	1*S*,2*S*
72	 **(h)**	24	86	76	1*S*,2*S*

70 (2nd cycle)	**(h)**	10	97	>99	1*S*,2*S*
70 (3rd cycle)	**(h)**	10	95	>99	1*S*,2*S*
70 (4th cycle)	**(h)**	10	95	>99	1*S*,2*S*

The literature on KR of epoxides in the synthesis of chirally pure 1,2-amino alcohols is dominated by salen based chiral catalysts. Another important class of ligand used in various asymmetric organic transformations is BINOL. However, its use in ARO of epoxides is limited and under homogeneous condition with no catalyst recycling data available [30-32,88,89]. In a one off study, Kureshy et al. [99] reported (*S*)-(–)-BINOL-Ti complexes **73-76** as recyclable catalysts in enantioselective ring-opening reaction of *meso*stilbene oxide and cyclohexene oxide with anilines to obtain β-amino alcohols in high yield (95%) and enantioselectivity (*ee*, 78%) at ambient temperature [Table 11]. The catalyst was recovered after first use and was recycled four times with retention in its performance.

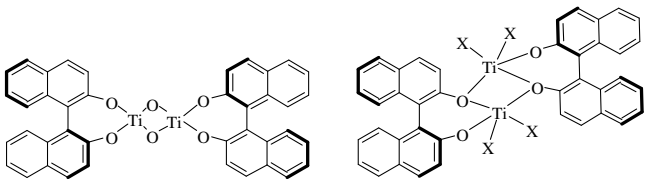
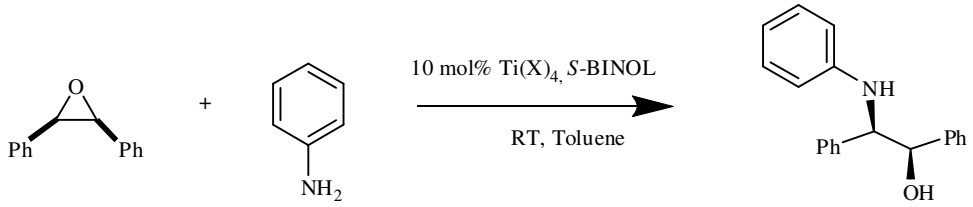


Figure 24 Structure of the (*S*)- BINOL catalysts **73-76**

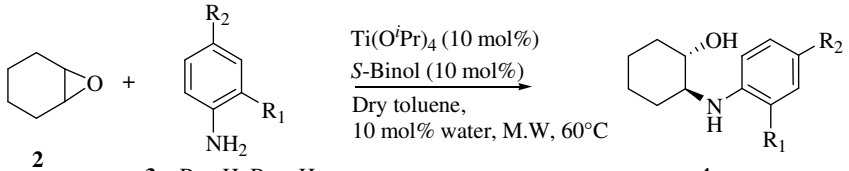
Table 11 Asymmetric catalytic ring opening of *meso* stilbene oxide with aniline using complexes 73-76



Catalyst	Time (h)	Yield of 3a [%]	*ee* [%]
73	7	90	67
74	8	85	63
75	5	20[c]	35
76	5	40[c]	51
73 (2nd cycle)	7	75	65
73 (3rd cycle)	7	70	64
67 (4th cycle)	7	60	64

The same catalyst **73** also worked efficiently for catalytic asymmetric ring opening of cyclohexene oxide and meso-stilbene oxide [34] with anilines under microwave irradiation to afford β-amino alcohols in high yield (up to 95%) and good enantioselectivities (ee up to 55%). The reaction under microwave was found to be 10 times faster than traditional oil-bath heating without compromising enantioselectivity. Also the ee for the product β-amino alcohols was comparable with the values obtained at room temperature (Table 12).

Table 12 Asymmetric ring opening of cyclohexene oxide with anilines catalyzed by complex 73 under microwave irradiation.



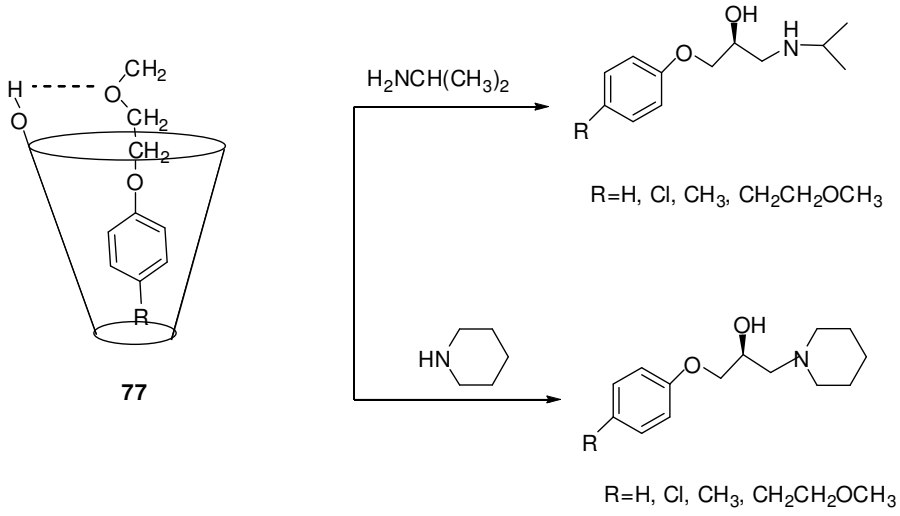
2

3a; R_1= H, R_2 = H
3b; R_2 = H, R_2 = OMe
3c; R_1 = OMe, R_2 = H
3d; R_1 = H, R_2 = Me
3e; R_1 = H, R_2 = Cl

4a-e

Amine	Additive	Temperature	Reaction time	Isolated Yield **4a-e** [%]	*ee* [%]	TON	TOF
3a	TPP	27	2h	92	39	9.2	4.6
3a	TPP	40	30s	80	50	8.0	960
3a	TPP	60	30s	90	49	9.0	1080
3a	-	60	30s	85	17	8.5	1020
3a	TPP	60	6m	93	54	9.3	93
3a	TPP	70	30s	95	26	9.5	1140
3a	TPP	70	5m	94	55	9.4	112
3b	TPP	60	30s	90	46	9.0	1080
3c	TPP	60	30s	92	50	9.2	1104
3d	TPP	60	30s	95	47	9.5	1140
3e	TPP	60	30s	94	48	9.4	1128

Rao et al. [100] for the first time report the biomimetic approach for the synthesis of a single enantiomer of β-aminoalcohol. In this approach β-cyclodextrin formed by the inclusion of complex **77** with racemic aryloxyepoxide which reacted enantioselectively with amines under solid state condition to give the product in 100% ee and 70-79% isolated yield. The yield which was above 50% was explained in terms of continuous racemization of the epoxide by β-cyclodextrin, hence termed as dynamic kinetic resolution. Ironically, no data on recycling of the catalyst was reported.



77

Scheme 32 Dynamic kinetic resolution of racemic aryloxy epoxides with amine using the catalysts **77**

Conclusion and out look

The primary goal for heterogenization of chiral catalyst is to make it recoverable and reusable for economic and environmental reasons. The present chapter provides an up to date literature on this aspect for epoxide ring opening reaction which has great potential in industry and academia. Among various epoxide ring opening reactions presented in this chapter, HKR of racemic epoxide is one of the most studied reactions and some of the strategies for this transformation have already been practiced in industry at multi-ton level. There may be historical reason for that as HKR of racemic epoxides was one of the earliest epoxide ring opening reaction for achieving desired epoxide and diols in a very high optical purity and yield. What surprises authors that one of the very important epoxide ring opening reaction (ARO) of racemic and meso epoxide with amine has been neglected for heterogenization. Nevertheless Kureshy et al. have reported complexes of recyclable catalysts for this organic transformation under homogeneous system. There remain lot of scope to take up this very exciting organic transformation to the process level where it can be economically viable at process level in industry. Some of the potential candidates for heterogenization are BINOL/SALEN and Bipyridyl complexes for ARO of racemic, terminal and meso epoxides with amines.

Acknowledgements

RIK is thankful to DST and CSIR Network project on Catalysis for financial assistance and also thankful to Dr. P. K. Ghosh, the Director, of the Institute for providing instrumentation facilities.

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