

Asymmetric Ring Opening of Epoxides

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Abstract: This review deals with the metal promoted asymmetric ring opening of achiral epoxides using achiral carbon-, nitrogen-, oxygen-, sulphur- and halogen-containing nucleophiles. The use of chiral bases in the asymmetric deprotonation of achiral epoxides yields chiral allylic alcohols. Finally, kinetic resolution of racemic epoxides can be achieved using chiral metal complexes.

1. INTRODUCTION

Enantiomerically pure or enriched product synthesis represents an important and challenging task to both academic and industrial chemists. Asymmetric synthesis can be done by generation of a stereocentre from a prochiral precursor (generally having a sp^2 -hybridized structure) or by a stereospecific substitution, as well as by desymmetrisation of *meso* starting materials or kinetic resolution of racemic substrates. This last stereospecific transformation is an effective, attractive and powerful tool in asymmetric synthesis.

The importance of a synthetic procedure lies not only in the generated product, but also in the availability of the starting materials. Generally, epoxides are very easily prepared from the corresponding alkenes by an oxidation process, achiral and racemic epoxides being readily available products from simple alkenes precursors [1,2], so the ring opening of epoxides becomes an interesting synthetic process.

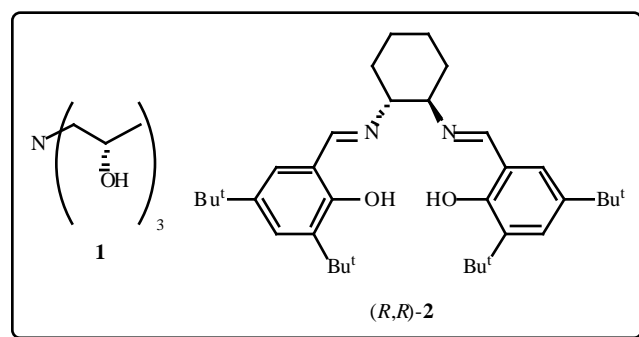
Due to their strain ring (having a high thermodynamic driving force, usually greater than 20 kcal/mol [3]), the usual reactivity of the epoxides by ring-opening can be enhanced by using a Lewis acid coordinating the oxygen atom. In the framework of asymmetric synthesis, the use of chiral Lewis acids raises as an interesting chance of performing asymmetric ring opening (ARO) of epoxides. There are two main groups of epoxides to perform ARO with: (a) *meso*-epoxides which generate a product with two new neighbouring stereocentres; (b) racemic mixtures of epoxides which can undergo kinetic resolution, the latest case being valuable either for the enantioselective formation of the ring opening product and/or for the isolation of the non-reacting epoxide enantiomer which is difficult to be obtained by another enantioselective route.

The asymmetric opening of epoxides via catalytic processes has grown in the last decade [4]. Herein, recent advances in ARO of epoxides covering literature from 1996 to 2003 will be revised. Due to the length of this review, enzymatic ring opening of epoxides will not be considered.

2. DESYMMETRISATION OF MESO-EPOXIDES

2.1. Nitrogen Containing Nucleophiles

After the pioneering work by Nugent on catalytic desymmetrisation of *meso*-epoxides with azidotrimethylsilane as nucleophile and by using a complex of zirconium or titanium with the ligand (+)-(*S,S,S*)-triisopropanolamine (**1**) as chiral Lewis acid [5], azido compounds have been the most used among the possible nitrogen nucleophiles [6].

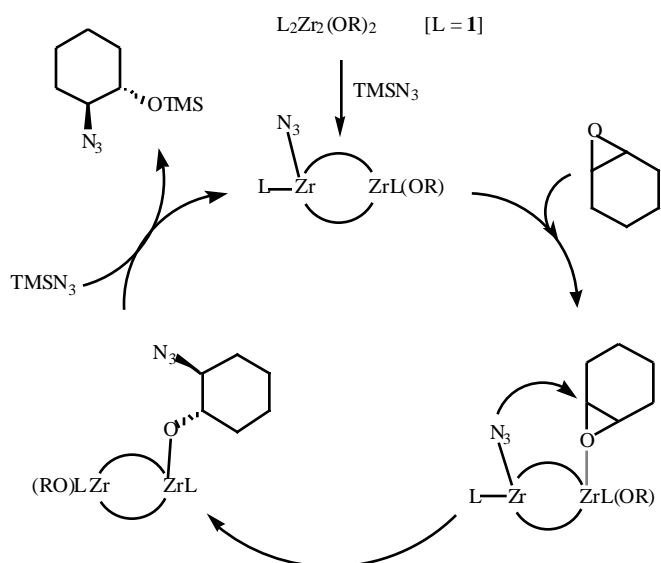


Mechanistic studies on the catalytic activity of zirconium-**1** complex in the enantioselective addition of the azide group to epoxides were investigated [7]. The reaction required a bimetallic system, so the dimeric precatalyst could be activated by exchange of an alkoxide by azide, which could also coordinate the epoxide at the other metal centre, so intramolecular delivery of azide gave the product after exchange by a new $TMSN_3$ molecule (Scheme 1).

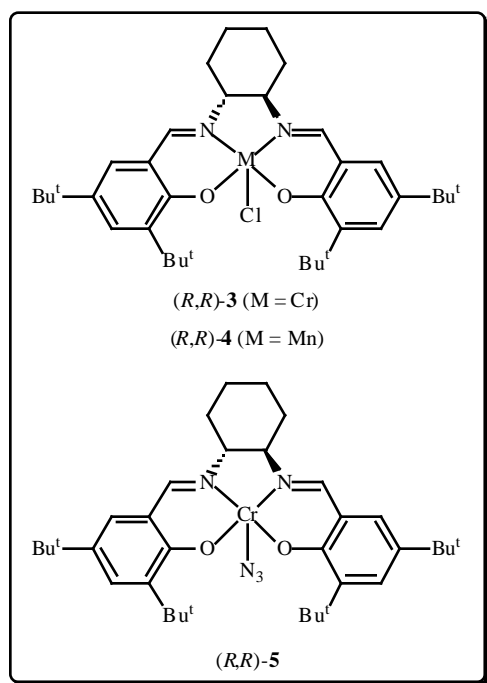
Salen-type ligand **2** can be easily prepared [8] starting from a diamine and an aromatic aldehyde, so different metals can be coordinated by the salen ligands, the corresponding complexes being useful for different catalytic processes.

In 1995, Jacobsen and *et al.* [9] found that the same salen ligands used for asymmetric epoxidation, but changing the metal (chromium, complex **3**, instead of manganese, complex **4**), could be used as chiral Lewis acid for ARO. In this first approach, the catalytic reaction was done in solution (ethereal solvent) and with a low catalyst loading (2 mol %), thus *meso*-epoxides underwent ring opening with azidotrimethylsilane as nucleophile, yielding the corresponding 1,2-azido silylether with good to high enantioselectivity (over 94% ee for cyclopentene oxide derivatives). Later on [10], the same group improved the mentioned

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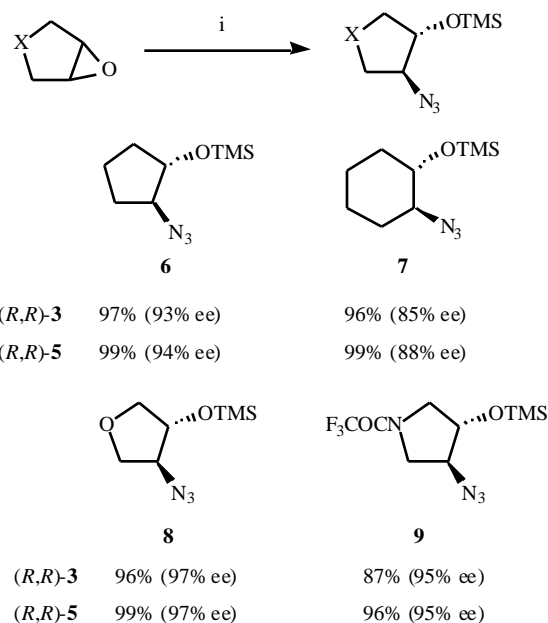


Scheme 1. Proposed catalytic cycle for the ARO of epoxides using the Zr-1 complex.



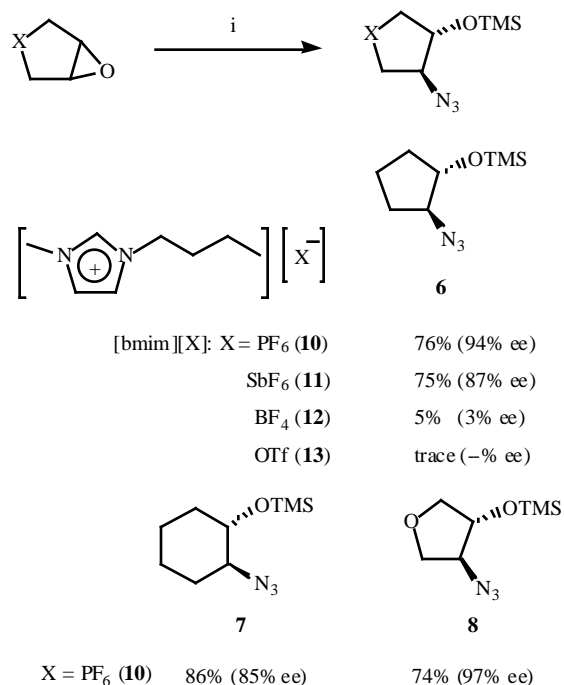
methodology by performing the reaction in the absence of solvent (with similar enantioselectivity and yield), and the products were conveniently isolated by vacuum distillation from the reaction mixture, and then converted into the corresponding 1,2-amino alcohols. Moreover, the residue after distillation was characterised as the azide complex **5**, which can be re-used for catalytic ARO without loss of activity and/or enantioselectivity. Even 10 times re-used catalyst (at 1 mol % level) showed no loss of activity. There is a slightly difference in yield by using complex (*R,R*)-3 or (*R,R*)-5 (see, for instance, compounds **6-9**, Scheme 2), a small amount of the corresponding product resulting from a ring opening by chloride being detected when using the catalyst **3**.

The use of air and moisture stable ionic liquids based on 1-butyl-3-methylimidazolium salts (**10-13**, [bmim][X]) as

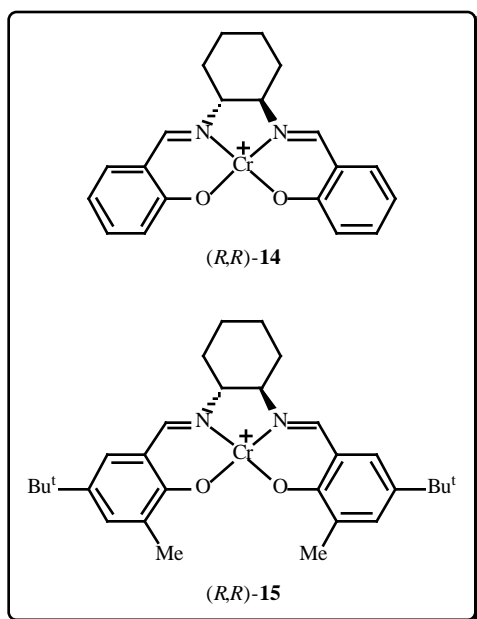


Scheme 2. Reagents: i, (*R,R*)-3 or (*R,R*)-5 (2 mol %), TMSN₃, rt.

media to perform the ARO by using chromium salen complexes was reported [11]. Performing the ring opening reaction at room temperature, with 3 mol % of the catalyst, and azidotrimethylsilane in the hydrophobic ionic liquid [bmim][PF₆] (**10**), the corresponding azido silyl ethers (**6-8**) were obtained with comparable yield and enantiomeric excess as in homogenous conditions (Scheme 3) [9]. After the reaction was finished, the product was extracted from the ionic media with hexane, in those conditions the complex remaining in the ionic liquid as a suspension and being able to be re-used several times without losing neither activity nor enantioselectivity. In the study, they showed an



Scheme 3. Reagents: i, (*R,R*)-5 (3 mol %), TMSN₃, ionic liquid (**10-13**), rt.



important counter ion effect, thus carrying out the reaction in a more hydrophilic ionic liquid [i.e. [bmim][BF₄] (**12**) or [bmim][OTf] (**13**)], the ring opening hardly occurred.

In the field of the heterogeneous catalysis, the influence of encapsulation on the enantioselectivity of chiral Cr(salen) complexes was studied [12]. Cationic complexes (R,R)-**14** and (R,R)-**15** were immobilized into the cavities of zeolites (Y and EMT) and into the interlamellar region of

montmorillonite (K-10) by a stepwise synthesis, where ligand formation was done in the presence of templating Cr(III) ions, already resident in pre-exchanged zeolite or montmorillonite. The supported complexes showed a variable activity as catalyst for ARO of cyclopentene and cyclohexene oxides with TMSN₃ to afford the corresponding azido silyl ether and minor amounts of azido alcohols. The heterogeneous catalysis was less effective than the corresponding homogeneous ones in terms of reactivity and enantioselectivity. The authors pointed out both, the presence of adventitious acid sites and possible different operating mechanism, as main reasons for the unhelpful assistance of the inorganic support.

The high stability of chromium salen complexes under the reaction conditions allowed to perform mechanism studies in the ARO with an azido reagent [13]. Actually, the azide complex **5** is the true active catalyst for the reaction and when using the chlorinated precatalyst **3**, the first step is the generation of the catalyst **5** in the reaction media. Taking this into account, the azide is delivered from the catalyst to the epoxide in the course of the reaction, what was confirmed by stoichiometric delivery from complex **5** in absence of TMSN₃ as nucleophile source. However, this fact does not exclude a participation of the Cr(III) complex (with or without azide ligand associated) activating the epoxide as a Lewis acid. Zero-order dependence on the concentration of the nucleophile and second-order dependence on the concentration of the catalyst were observed in kinetic studies performed on the catalytic reaction of HN₃ as nucleophile with an excess of epoxide in the presence of the complex **5**.

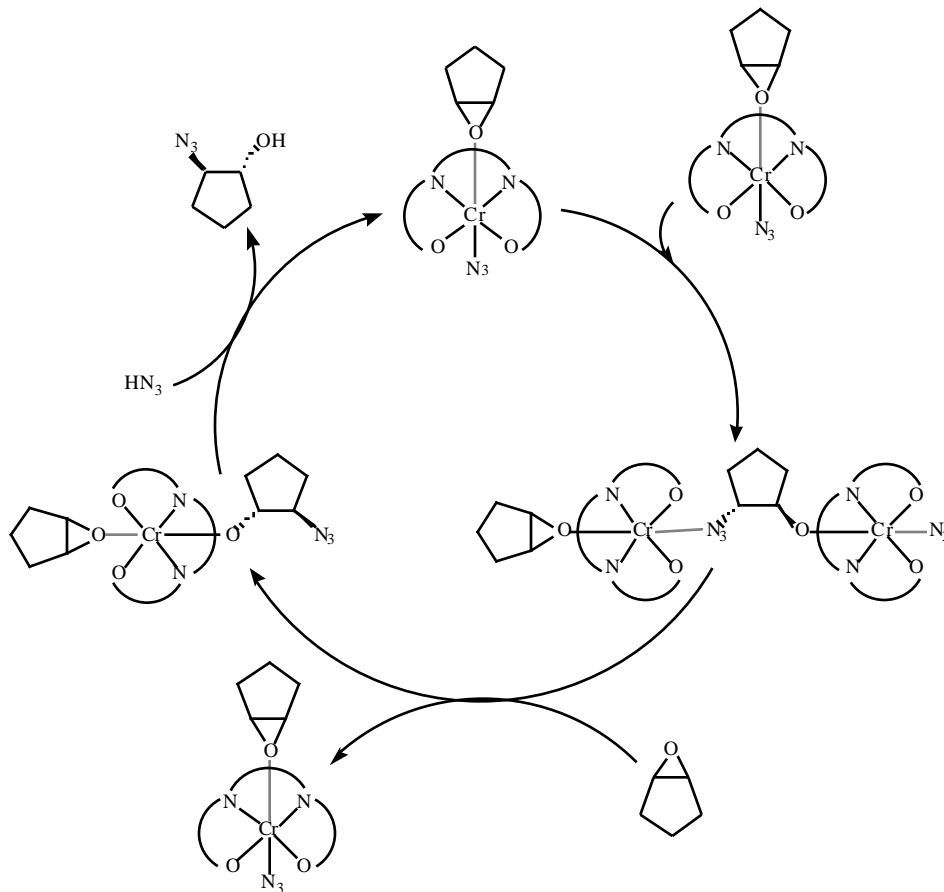
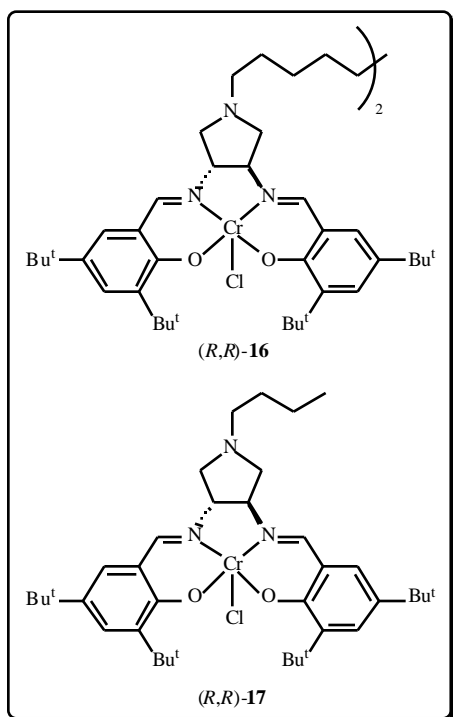


Fig. (1). Proposed mechanism for ARO of cyclopentene oxide by salen complexes involving bimetallic species.



Thus, a mechanism involving a bimetallic intermediate in the rate-determining step was suggested, where both nucleophile and electrophile undergo catalyst activation (Figure 1). The non-linear effects of enantiomeric composition of the catalyst showed in the ARO by the Cr(salen) complex, were consistent with the proposed mechanism.

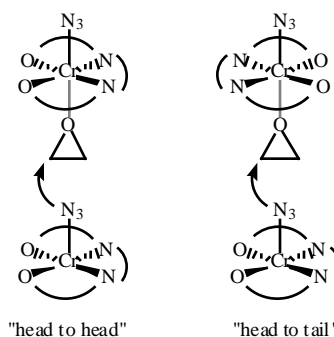
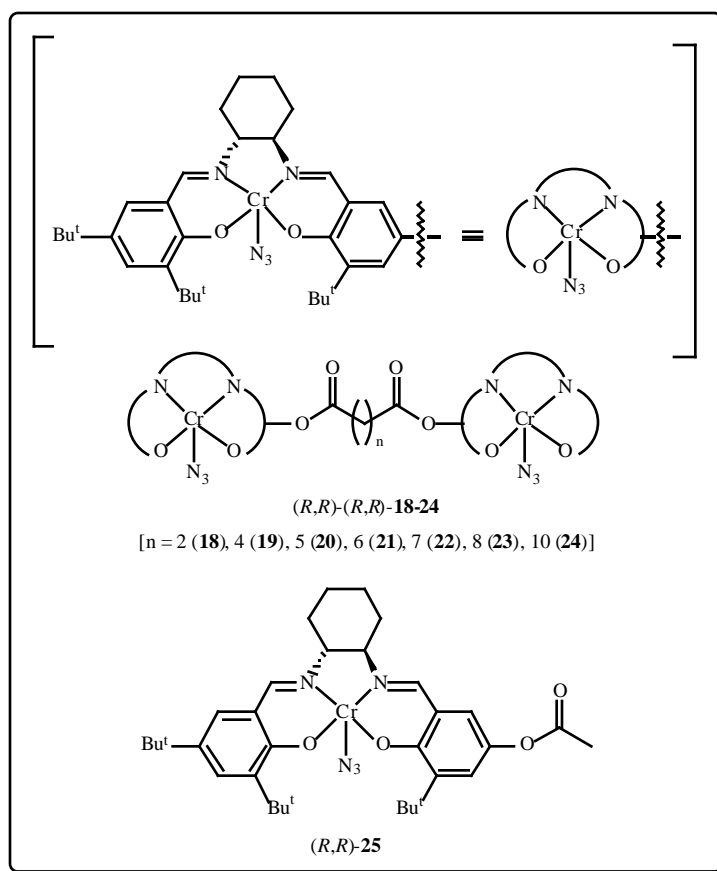


Fig. (2). Two limiting geometries for the bimetallic transition state.

The above mentioned mechanistic observations opened up the design of catalysts that enforce the bimetallic cooperation, so, construction of covalently linked dimeric complexes was taken into consideration [14]. In that way, dimeric complex **16** and its monomeric analogue **17** were prepared and tested in the catalytic ARO of cyclopentene oxide with TMSN_3 . Chromium salen complex **17** showed comparable effectiveness than complex **3** (93% ee) giving the corresponding azido silylether with 90% ee. However, the dimer **16** was not so effective, the opened product being isolated with only 8% ee. Despite that, kinetic studies indicated that, at the complex concentration used, dimer **16** catalyzed the ARO mainly through a first-order pathway, showing thus a cooperative transition state. The authors postulated two limiting geometries for the bimetallic transition state: (a) head to head and (b) head to tail (Figure 2), and they claimed that complex **16** gave the non-favourable piling up (head to head) transition state.

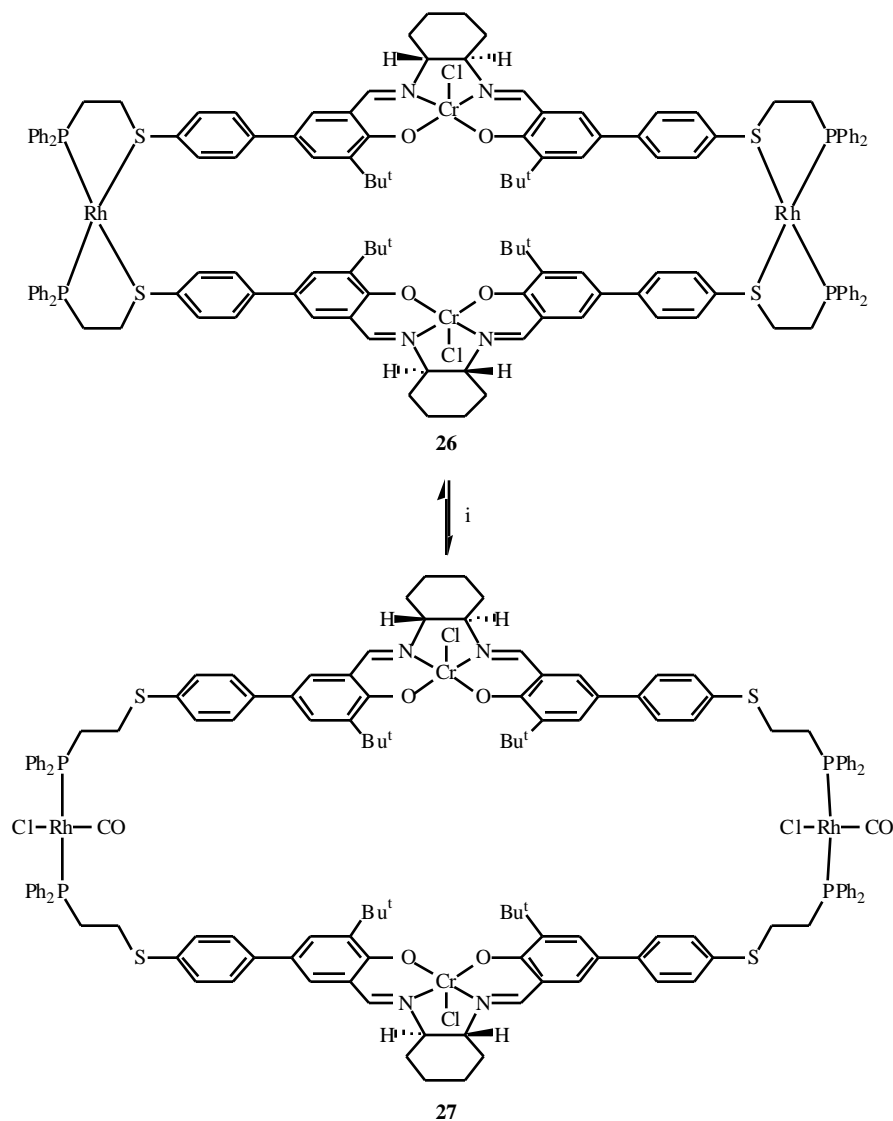


Other dimeric ligands **18-24** were also prepared [14], so a wider range of geometries in the transition state were allowed, the monomeric analogue acetate **25** being also prepared. Complexes **18-25** catalyzed the ARO of cyclopentene oxide with TMSN_3 yielding the opened product in the same level of enantiopurity as for complex **5**. Under kinetic studies, in the rate equation factors for both components "intramolecular" and "intermolecular" were evaluated. In general, all the dimeric catalyst gave a faster ARO reaction compared to the monomeric **5** or **25**. The length of the linker in complex **20** was the one giving the fastest catalytic reaction and showing the highest value for the "intramolecular" factor.

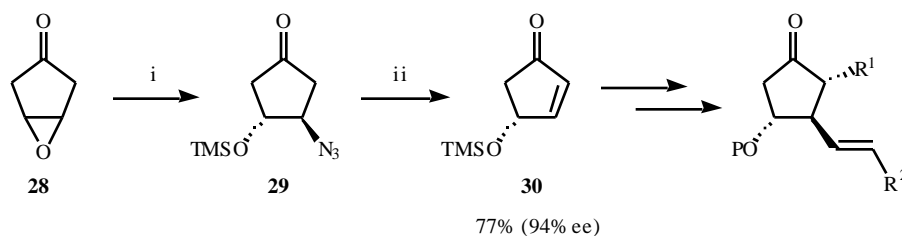
Concerning bimetallic cooperative complexes, a supra-molecular catalyst was designed (Scheme 4) [15], which presents an allosteric control between both the close (**26**) and the open (**27**) forms. The allosteric effect was achieved via a modification of the catalytic activity changing the ligands around each Rh(I) centre, so the reversible binding of Cl^- [by using bis(triphenylphosphor-anylidene)ammonium chloride, PPNCl] and CO would result in changes in the activity of the functional Cr(III) metal centres, due to the dramatic

difference in shape between **26** and **27**. Catalytic properties of these complexes were tested in the ring opening of cyclohexene oxide by TMSN_3 in benzonitrile as solvent (necessary to dissolve the complex), giving 1-azido-2-(trimethylsiloxy)cyclohexane in 68% ee. In contrast, complex **3** gave the product with only 12% ee under these reaction conditions. Moreover, a significant 20-fold increase in rate was obtained for complex **26**, in the presence of allosteric activators a double reaction rate being observed. Unfortunately, the lack of solubility of complexes **26** and **27** in solvents where ARO of epoxides with salen complexes used to give higher enantioselectivities [4b], made difficult the study under other conditions.

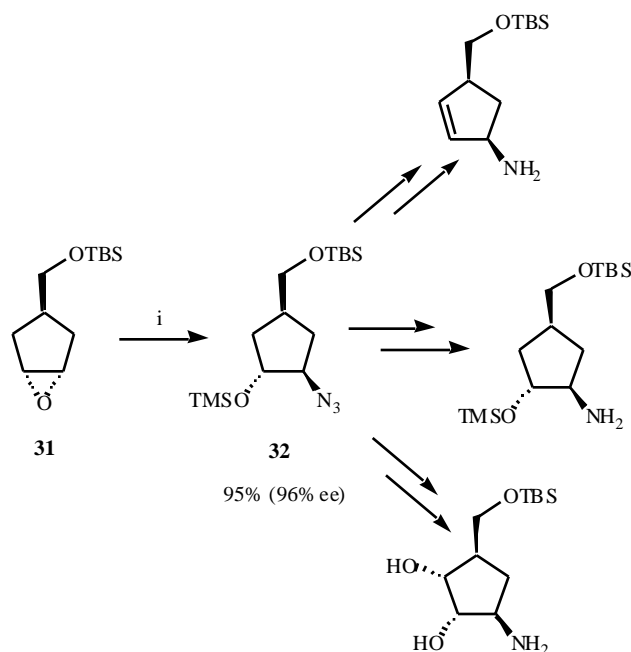
The Cr(salen) complex catalyzed ARO reaction was applied to prepare interesting building blocks for biologically active compounds. By the catalytic ARO of *meso*-epoxide **28** with TMSN_3 at low temperature (-10°C) using complex (*S,S*)-**5**, gave the corresponding azido silyl ether **29**, which was treated with basic alumina to promote the azide elimination generating the *O*-protected (*R*)-4-hydroxy-2-cyclopentenone (**30**) in 77% overall yield and 94% ee (Scheme 5) [16]. This enone **30** was used in the



Scheme 4. Reagents: i, PPNCl/CO , benzonitrile, rt.



Scheme 5. Reagents: i, TMSN_3 , (*S,S*)-**5** (2 mol %), $-10\text{ }^\circ\text{C}$; ii, Al_2O_3 .



Scheme 6. Reagents: i, TMSN_3 , (*S,S*)-**5** (2 mol %), rt.

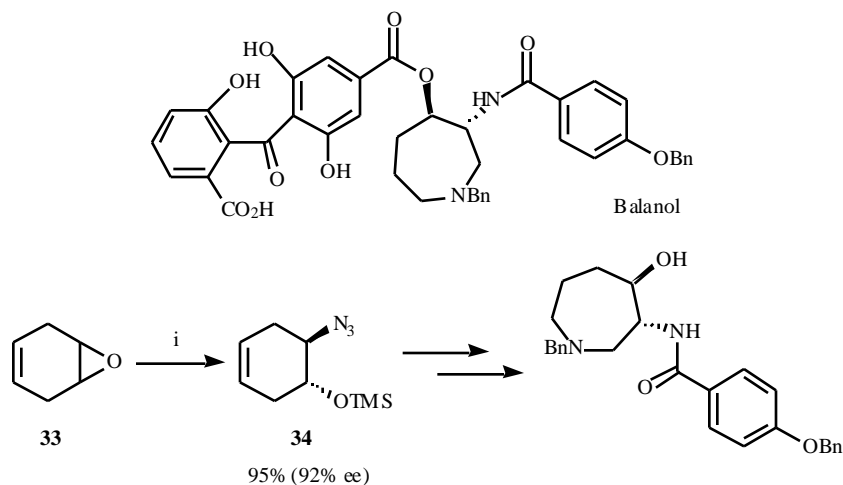
synthesis of prostaglandins by the Noyori's three-component coupling method [17].

Different key intermediates for the preparation of carbocyclic nucleoside analogue structures were prepared from compound **32**, which was obtained by means of ARO of the epoxide **31** (Scheme 6). Thus, enantioselective ring opening of compound **31** with TMSN_3 catalyzed by the complex (*S,S*)-**5** occurred quantitatively, giving the azido silyl ether **32** in 95% yield and 96% ee [18].

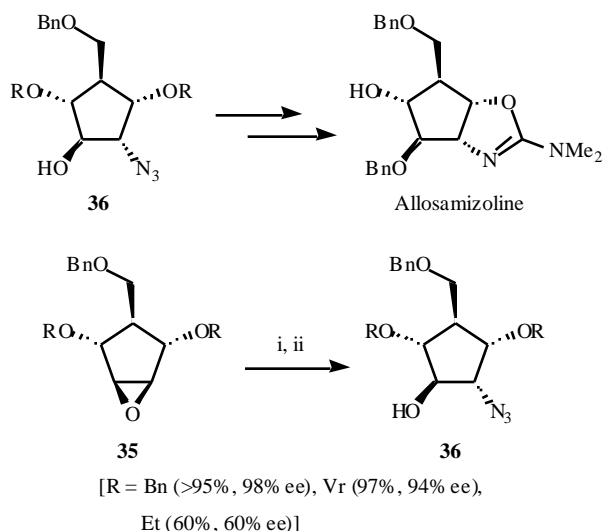
The ARO protocol by using salen complex **5** permitted the generation of both stereogenic centres of balanol in a single catalytic step [19]. Therefore, under solvent-free conditions and with catalyst (*S,S*)-**5** (7.5 mol %), 1,4-cyclohexadiene monoepoxide (**33**) underwent ring opening with TMSN_3 to afford the azido silyl ether **34** in 95% yield and 92% ee (Scheme 7). This compound was used for the preparation of the balanol heterocyclic amino alcohol core (in 12 steps with 31% overall yield).

The synthesis of allosamizoline, a chitinase inhibitor allosamidin derivative, was carried out by using Cr(salen)-catalyzed ARO reaction with trimethylsilyl azide [20]. Highly functionalised epoxide **35** showed different reactivity in the ARO depending on the adjacent ether substituents. Thus, non protected alcohols ($\text{R} = \text{H}$), acetyl ($\text{R} = \text{Ac}$) or silyl ether ($\text{R} = \text{TMS}$, TBDMS) derivatives gave no reaction, whereas benzyl ($\text{R} = \text{Bn}$) or veratryl ($\text{R} = \text{Vr}$) ether derivatives produced the corresponding azido alcohols **36** in good yield and high enantioselectivity (Scheme 8). Alkyl ether ($\text{R} = \text{Et}$) derivatives gave moderate results in both yield and enantiopurity. On the other hand, in order to make this reaction to proceed with a useful rate, a higher amount of the catalyst was needed (20 mol %).

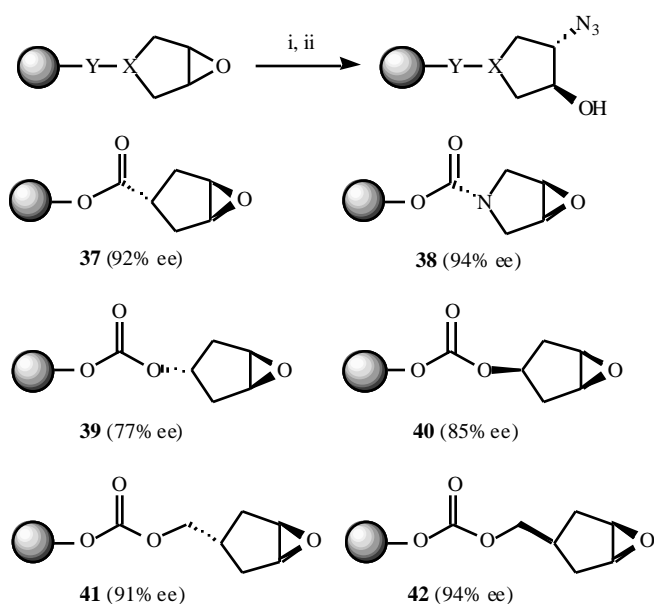
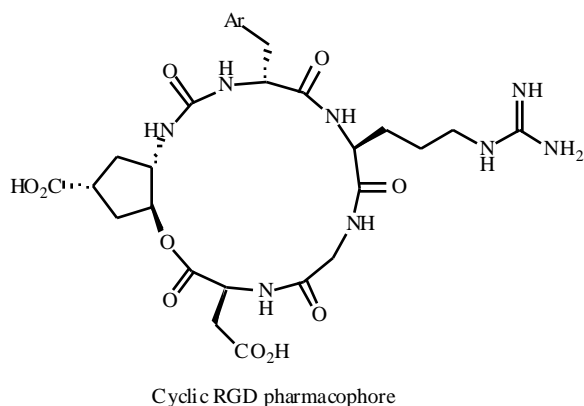
Diverse templates for the preparation of cyclic compounds with the amino acid sequence Arg-Gly-Asp (RGD) of pharmacological interest were prepared by asymmetric catalytic ring opening of *meso*-epoxides with TMSN_3 [21]. The catalytic ARO reaction was performed on polymer supported epoxides, hence TentaGel S PHB-supported epoxides were treated with an excess of TMSN_3 in the presence of (*R,R*)-**5**, following desilylation gave the polymer-bound azido alcohol. Afterwards, compounds **37-42** were used as conformationally constrained templates for the synthesis of RGD-containing products (Scheme 9).



Scheme 7. Reagents: i, TMSN_3 , (*S,S*)-**5** (7.5 mol %), $-10\text{ }^\circ\text{C}$.



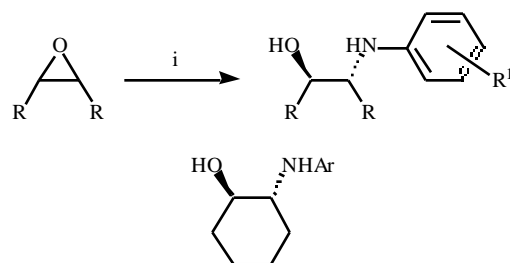
Scheme 8. Reagents: i, TMSN₃, (*R,R*)-**5** (20 mol %), TBME, rt; ii, CSA, MeOH, 0 °C.



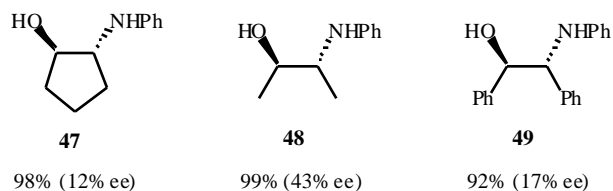
Scheme 9. Reagents: i, TMSN₃ (20 eq.), (*R,R*)-**5** (10 mol %), Et₂O; ii, TFA/MeOH (1/100).

The use of amines as nucleophile source in the asymmetric ring opening of epoxides has an inherent problem due to possible deactivation of the chiral Lewis acid catalyst by

stable complex formation with the amine used as nucleophile and/or with the generated α -amino alcohol. Nevertheless, lanthanide complexes prepared from (*R*)-BINOL and a LnCl₃ salt were tested as catalysts in the ARO of cyclohexene oxide with aniline [22]. Among them, the best catalyst was the corresponding optical active α -amino alcohol in good yield but in moderate enantioselectivity (30% ee). In addition, ytterbium triflate in combination with (*R*)-BINOL showed



- 43: R¹ = H 90% (80% ee)
44: R¹ = *o*-Et 92% (86% ee)
45: R¹ = *p*-Cl 98% (76% ee)
46: R¹ = *p*-MeO 64% (37% ee)

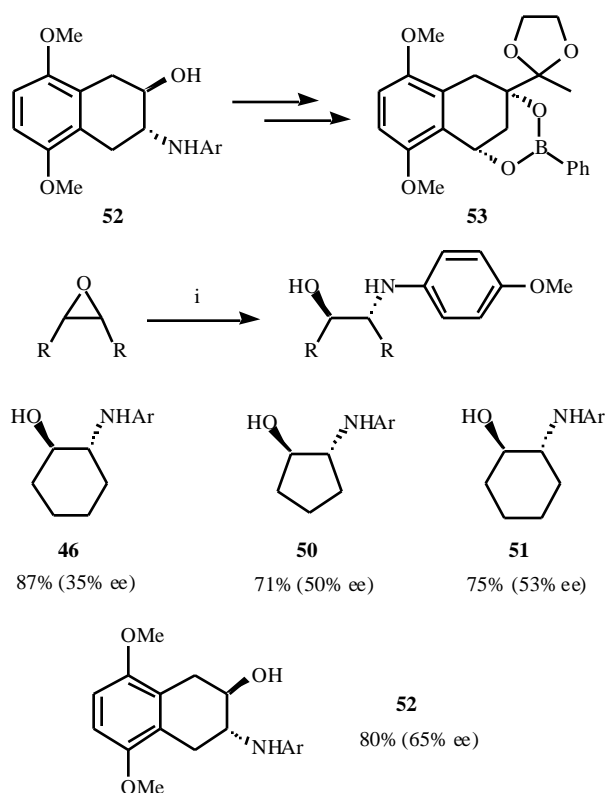


Scheme 10. Reagents: i, ArNH₂ (1.2 eq.), Yb(OTf)₃ (10 mol %), (*R*)-BINOL (12 mol %), 4 Å MS, toluene, -78 °C.

better influence in the asymmetric ring opening of epoxides with aniline derivatives (Scheme 10) [23].

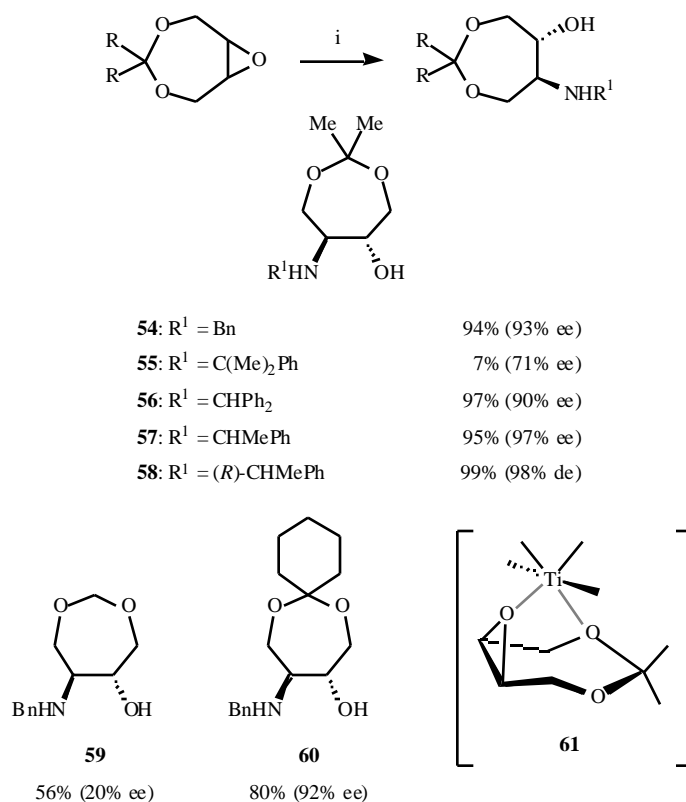
On the former topic, Shibasaki and co-workers studied the use of lanthanide salts in combination with BINOL to perform asymmetric opening of epoxides by *p*-anisidine as nucleophile [24]. After taking into account different factors, the authors employed the BINOL-Pr(OPr^t)₃ (2:1) combination as the best catalytic mixture in the presence of triphenylphosphine oxide as additive in order to obtain the corresponding α -amino alcohols in good yields and moderate enantioselectivities (Scheme 11). Compound **52** has been used to prepare the benzenboronate **53**, which is an intermediate of a clinically important anthracycline antibiotics class [25]. Despite compound **52** was obtained with only 65% optical purity, 95% ee could be achieved by recrystallisation.

Benzylamines were reported to give desymmetrisation of 3,5,8-trioxabicyclo[5.1.0]octane derivatives by means of titanium-BINOL catalysis [26], the reaction providing enantiomerically enriched 2-amino-1,3,4-butanetriol equivalents **54-60**, which are versatile chiral C4 building blocks (Scheme 12). Other epoxides such as cycloheptene oxide gave no reaction, so the authors proposed intermediate **61**, derived from a dioxacycloheptene oxide to take part where one of the two ketal oxygen atoms and the oxygen of the epoxide fitted well in the geometry of chelating the



Scheme 11. Reagents: i, *p*-MeOC₆H₄NH₂ (1.2 eq.), Pr(OPrⁱ)₃ (10 mol %), (*R*)-BINOL (20 mol %), Ph₃PO (30 mol %), toluene, 50 °C.

titanium atom, which should assume a typical tetragonal bipyramidal structure.



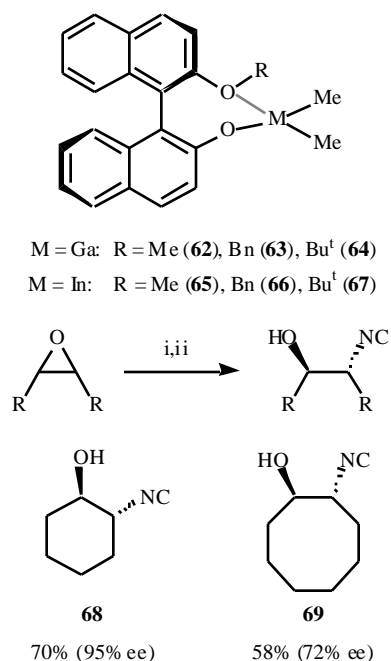
Scheme 12. Reagents: i, R¹NH₂ (1 eq.), Ti(OPrⁱ)₄-(*S*)-BINOL (0.5-1 mol %), 40 °C.

The reaction of an epoxide with the ambidentate nucleophile trimethylsilyl cyanide (TMSCN) leads to the formation of either β -trimethylsiloxy nitrile (carbon nucleophile, see the next section 2.2.) or α -trimethylsiloxy isocyanide (nitrogen nucleophile) depending on the type of the catalyst. Thus, asymmetric isocyanosilylation could be done by using soft chiral Lewis acid as catalyst, gallium and indium complexes being employed in this reaction [27]. In general, gallium complexes **62-64** gave lower yields than the corresponding indium complexes **65-67** (ca. 10-15% difference), gallium complexes giving better results in terms of selectivity. Performing the reaction with the best gallium catalyst (**63**) and after desilylation, the corresponding α -isocyanohydrins were obtained (Scheme 13).

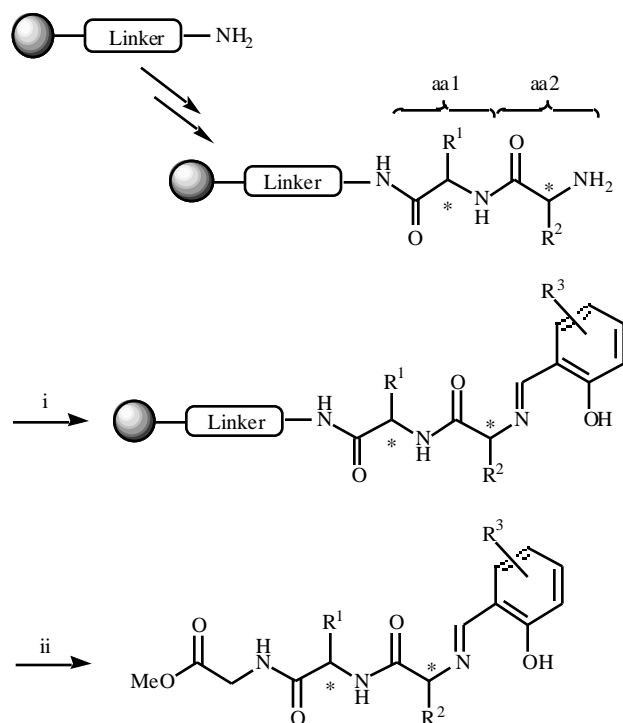
2.2. Carbon Containing Nucleophiles

Cyanide is a particularly interesting carbon-containing nucleophile for epoxide ring opening reactions due to its low cost and the transformation versatility of the α -cyanohydrins obtained. In this context, ring opening epoxides reactions with TMSCN catalyzed by titanium alkoxide-Schiff base complexes were reported [28].

Hoveyda *et al.* [29] made an important breakthrough in this area by applying a novel solid-phase optimisation approach to the discovery of titanium-based catalysts for the ARO of *meso*-epoxides with TMSCN. Ligands **70-72** were prepared easily and efficiently from two amino acids and a salicylaldehyde derivative on a solid support by standard methods, a glycine (Gly) unit being used as linker because ligands with Gly as terminal amino acid showed higher selectivity (Scheme 14).



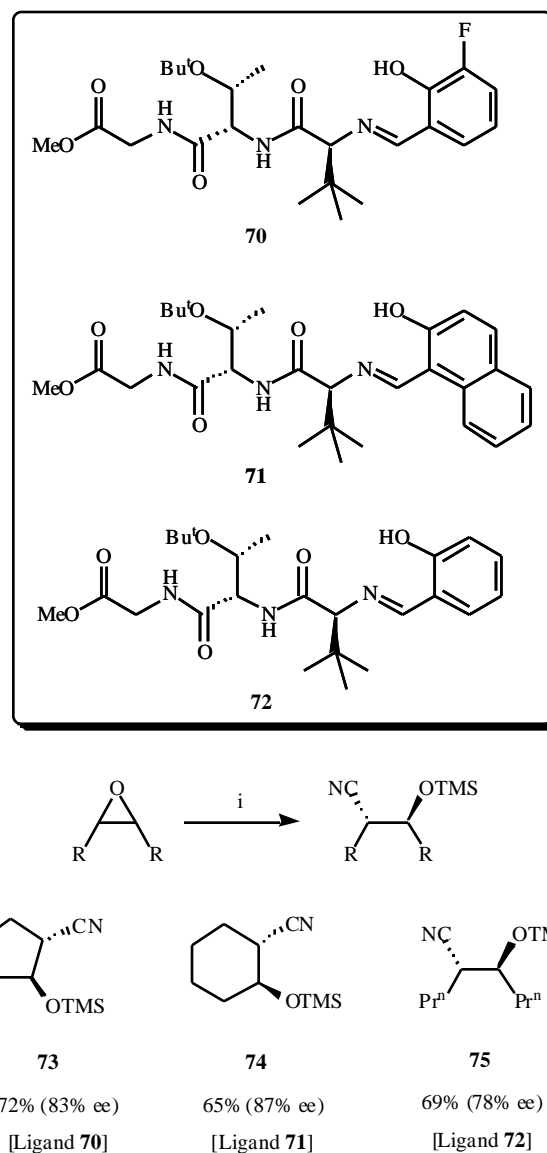
Scheme 13. Reagents: i, TMSCN (1.2 eq.), **63** (10 mol %), 4 Å MS, CH₂Cl₂, -78°C; ii, KF/MeOH, rt.



Scheme 14. Reagents: i, Salicylaldehyde, DMF, 2 h; ii, MeOH, Et₃N, DMF, 60 h.

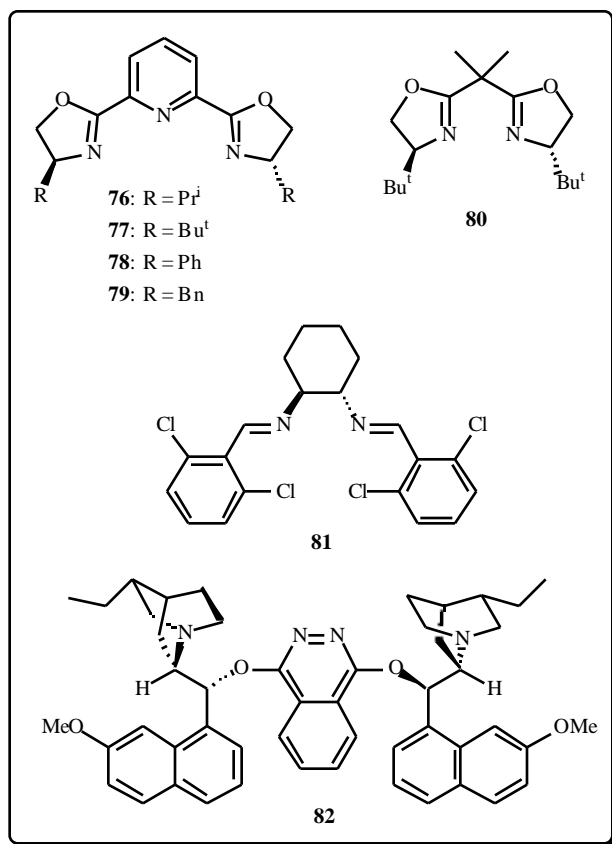
Generally, the catalyzed reaction with the ligand attached on the solid-phase gave lower enantioselectivity than the catalyzed reaction with the ligand in solution, a correlation being observed: the best ligand in solution was the best ligand on the solid support catalysis, what could be applied for searching the best ligand without cleavage of the ligands from the solid support [30]. A substrate specificity in the

asymmetric induction as a function of the ligand structure was found when testing the ligands in the titanium(IV) catalyzed ARO of different epoxides, so ligand optimisation could be carried out for each particular substrate (see, for example, compounds **73-75**, Scheme **15**).

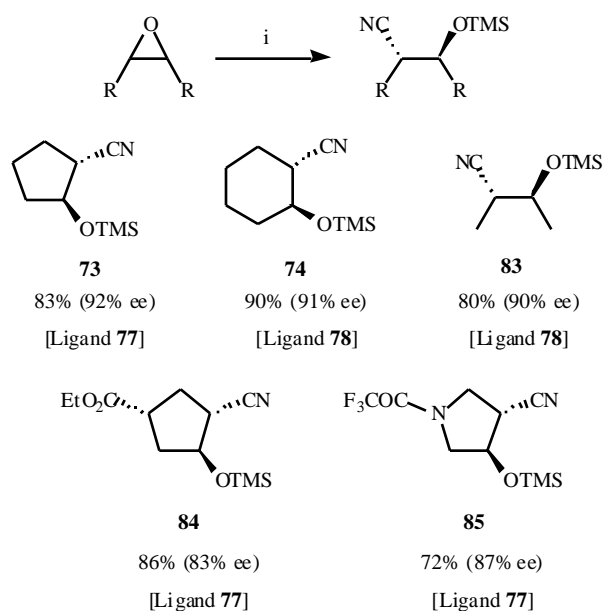


Scheme 15. Reagents: i, Ti(OPrⁱ)₄ (20 mol %), **70-72** (20 mol %), 4 °C, toluene, 6-20 h.

It is known that lanthanide salts promote efficiently the epoxide ring opening with nucleophiles such as TMSCN [31]. In the asymmetric catalytic version, Jacobsen *et al.* [32] evaluated different chiral ligands **76-82** with YbCl₃ finding that albeit all ligands carried out the reaction in the same rate, only the pybox ligands (**76-79**) gave an enantiomeric enriched product (i.e. 45% ee at room temperature using ligand **76**). Other different lanthanide (Ce, Pr, Nd, Eu, Dy, Lu) than ytterbium were studied and a correlation was observed: the smaller the ionic radius (higher atomic number) the higher the enantiomeric excess (from 0% ee for cerium to 51% ee for lutetium using ligand **76** at room temperature).

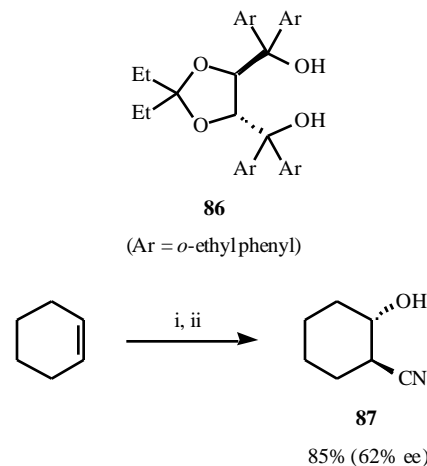


Several epoxides underwent ARO with good enantioselectivity and yield by employing the Yb(pybox) catalyst combination, although the optimal ligand and reaction temperature proved to be highly dependent on the substrate (see, for instance, compounds **73**, **74** and **83-85** Scheme 16). In contrast to the results obtained using alkyl substituted ligands, aryl substituted ligand **78** gave the corresponding product with the opposite absolute configuration. From a mechanistic point of view, kinetic studies illustrated a



Scheme 16. Reagents: i, TMSCN (1.2 eq.), YbCl₃ (10 mol %), pybox ligand (12 mol %), CHCl₃, 4-7 d.

second-order dependence on the catalyst, thus a bimetallic rate-limiting step seemed to be involved, as it was above mentioned for Cr(salen) complexes in the addition of azide to epoxides.



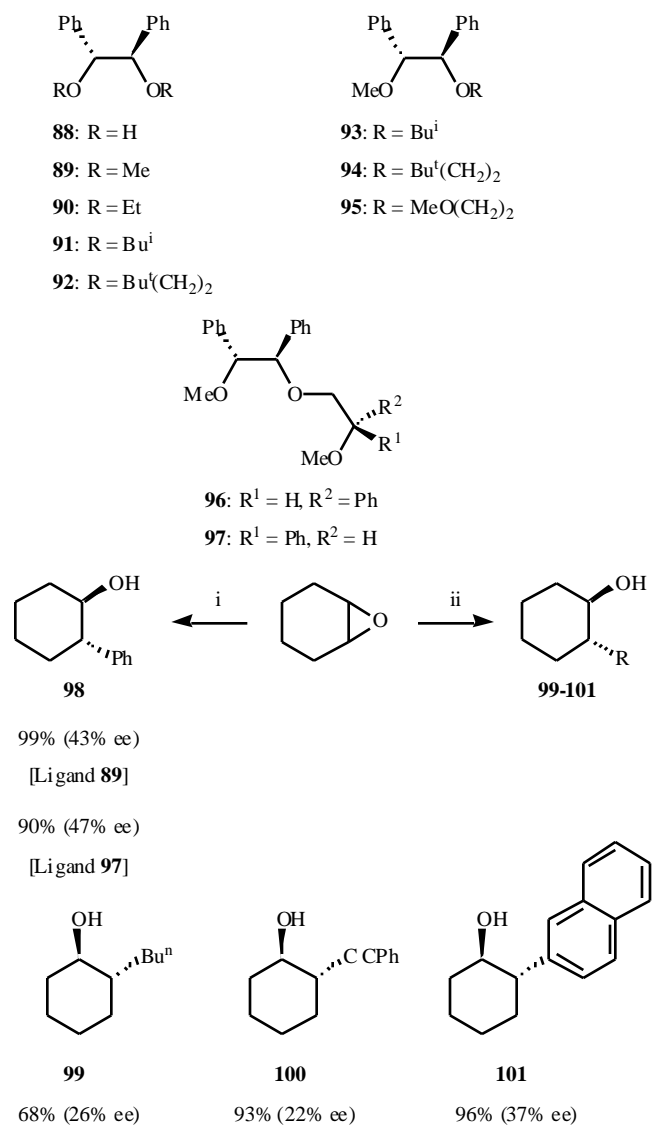
Scheme 17. Reagents: i, Zr(OBu^t)₄ (20 mol %), **86** (20 mol %), H₂O (20 mol %), bis(trimethylsilyl) peroxide (2 eq.), TMSCN (2 eq.), ClCH₂CH₂Cl, 50 °C, 48 h; ii, KF, MeOH.

Shibasaki and co-workers developed a one-pot preparation of *trans*-cyanohydrins directly from an alkene by using a zirconium catalyst for both steps: oxidation of the double bond to the corresponding epoxide and then ring opening with TMSCN [33]. By using the TADDOL derivative **86** as chiral ligand, the expected product **87** was obtained with a moderate enantioselectivity (Scheme 17).

In the framework of organometallics as nucleophiles, Tomioka *et al.* prepared a collection of bi- and tridentate ether-derived ligands **88-97** [34], which were tried in the catalytic addition of phenyllithium to cyclohexene oxide in the presence of a Lewis acid, such as boron trifluoride, necessary in order to get turnover in the reaction. After studying different reaction conditions, such as solvents, additives or Lewis acids, only moderate enantioselectivities were achieved, also for other organolithium reagents under the same reaction conditions (see, for instance, compounds **98-101** Scheme 18).

Oguni *et al.* presented the use of chiral Schiff-based ligands (such as compounds **102-106**) in the ARO reaction of epoxides by phenyllithium, only 5 mol % of the ligand being necessary to achieve good enantioselectivities and no Lewis acid was needed to get the reaction to work [35]. Thus, in the addition to cyclohexene oxide using the ligand **102**, the corresponding 2-phenylcyclohexanol was obtained quantitatively in 90% ee. Other epoxides gave moderate to high enantioselectivities in the ring-opening reaction by using ligand **103** (Scheme 19). Besides, salen-type ligand (**107**) was prepared and tried under the same conditions showing similar enantioselectivity. Concerning possible reaction intermediates, the authors suggested lithium alkoxides and/or *N*-lithium amides as the real active catalysts.

In situ generated organocopper reagents, starting from dialkylzinc compounds and chiral copper complexes, were used to perform enantioselective addition to cyclooctatetraene (COT) monoepoxide [36]. Dialkylzinc reagents underwent S_N2' addition to afford products **110-112** in good



Scheme 18. Reagents: i, PhLi (2 eq.), **89** or **97** (2.1 eq.), BF₃·OEt₂ (1.5 eq.), -78 °C; ii, RLi (2 eq.), **97** (2.1 eq.), BF₃·OBuⁿ₂ (1.5 eq.), -78 °C.

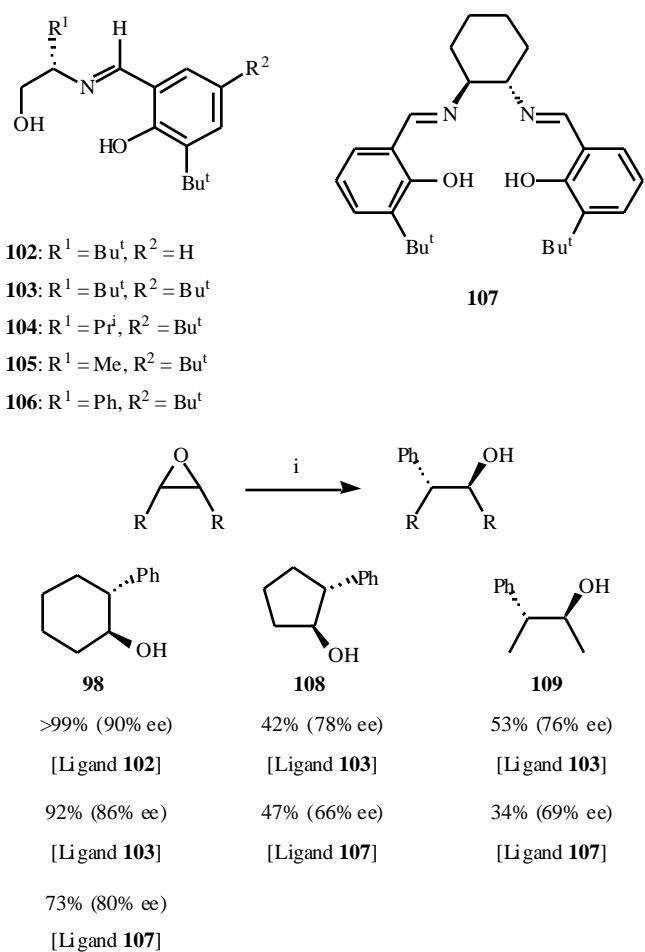
yield and enantiomeric excess in the presence of a catalytic amount of copper triflate together with Feringa's phosphoramidite (*S,R,R*)-**113** [37] (Scheme **20**). This reaction was the first enantioselective alkylation of cyclohexene oxide giving no ring-contraction-isomerisation.

Phosphoramidite **114** (12 mol %) catalyzed the addition of MeMgBr to cyclohexene oxide in the presence of copper triflate (6 mol %) to produce (*S,S*)-2-methyl-1-cyclohexanol, but with low enantioselectivity (15% ee) and moderate yield (45%) [38].

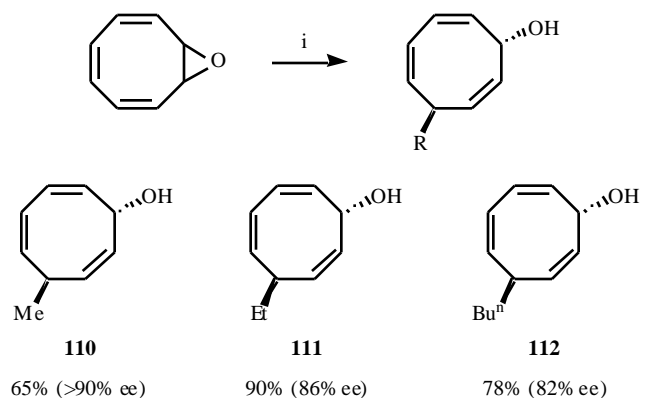
2.3. Oxygen Containing Nucleophiles

Oxygen containing nucleophiles are interesting candidates since their reaction with achiral epoxides provides an effective route to valuable chiral building blocks such as 1,2-diol derivatives, thus nucleophiles such as carboxylic acid derivatives, alcohols or phenols, would produce different monoprotected 1,2-diols.

Salen ligand (*S,S*)-**2** in combination with transition metals catalyzed the ARO of *meso*-epoxides using benzoic

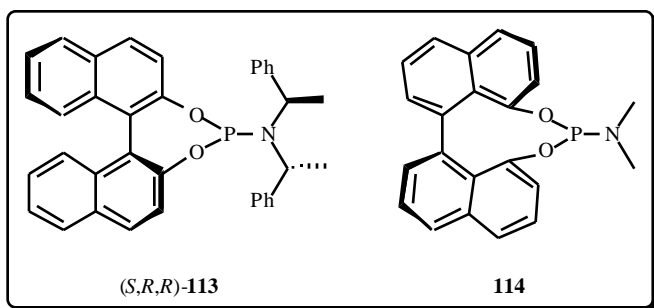


Scheme 19. Reagents: i, PhLi (1.5 eq.), **102**, **103** or **107** (5 mol %), rt.

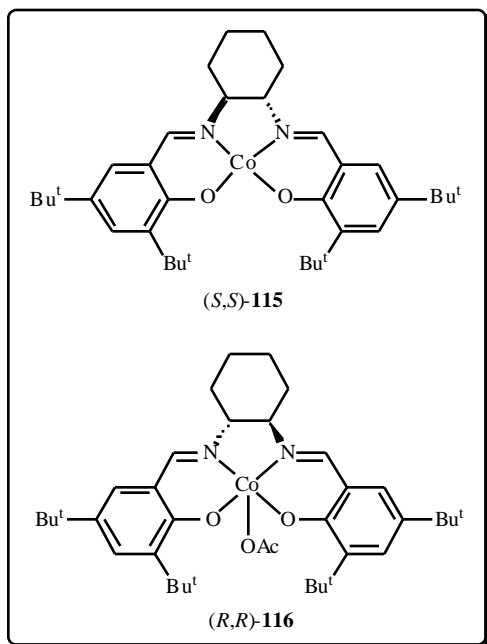


Scheme 20. Reagents: i, R₂Zn (1.5 eq.), Cu(OTf)₂ (1.5 mol %), (*S,R,R*)-**113** (3 mol %), toluene, -78 °C to 0 °C.

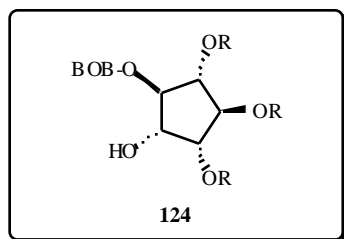
acid as nucleophile to yield products **117-123** (Scheme **21**) [39]. Among the metals assayed, only chromium and cobalt mediated a clean transformation into the corresponding 1,2-diol mono ester, Co(II) complex (*S,S*)-**115** giving better enantioselectivity than Cr(III) complex (*S,S*)-**3** (68% ee vs. 43% ee). Moreover, the addition of tertiary amines to the reaction mixture improved the rate, yield and enantioselectivity of the process. From a mechanistic point of view, the authors suggested that Co(III) species appeared



to be the reactive catalyst, although Co(II) complexes could be used to carry out the reaction.

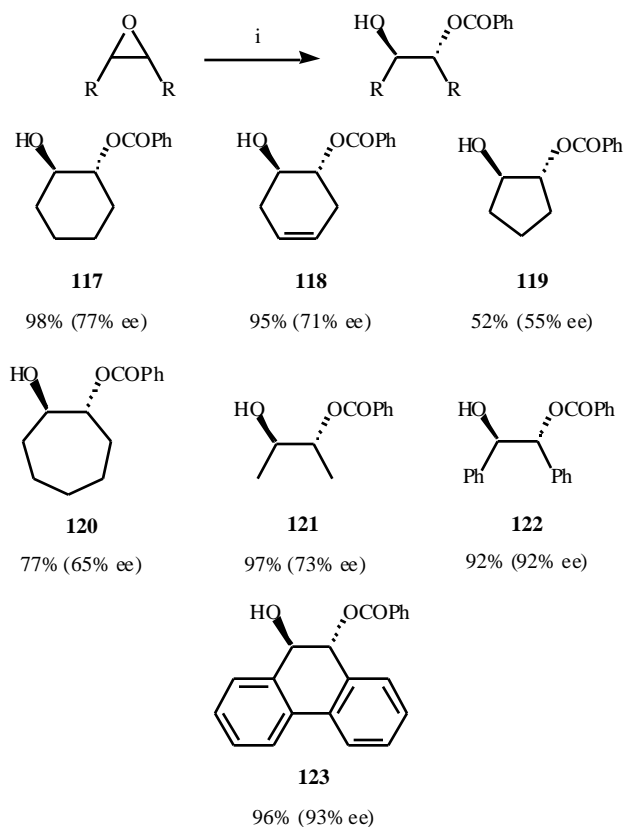


The former methodology was used for the preparation of an intermediate (**124**) in the synthesis of naturally-occurring glycolipid mimics produced by marine sponges [40]. In that case, 4-benzyloxybutyric acid (BOB-OH) opened the epoxide to generate the diol mono-BOB ester.



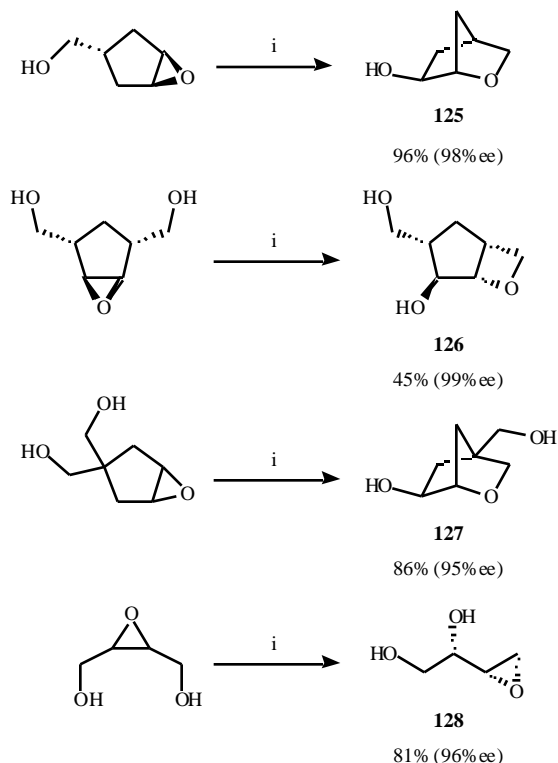
An intramolecular ARO reaction catalyzed by a Co(III) salen complex with alcohols as nucleophiles was described by Jacobsen *et al.* [41], some transformations being depicted in (Scheme 22) (formation of compounds **125-128**), which were carried out in the presence of a catalytic amount of complex the (R,R)-116.

Shibasaki and *et al.* presented the first catalytic ARO of epoxides with phenols by using Ga-Li-bis(BINOL) (GaLB, **129** and **130**) complexes as catalysts in combination with 4Å molecular sieves [42].

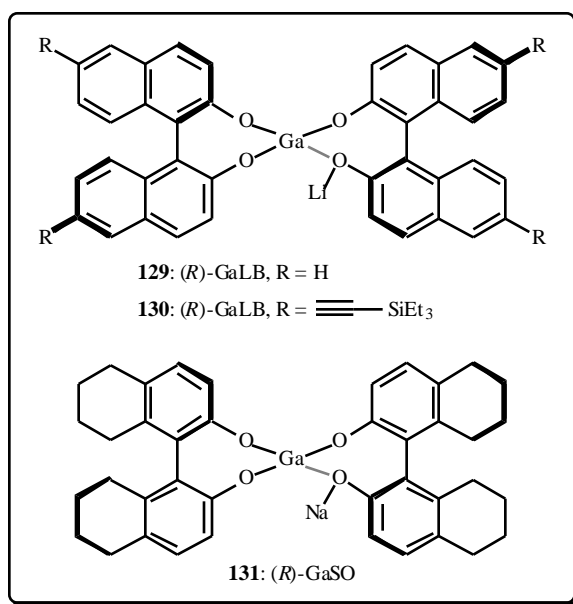


Scheme 21. Reagents: i, PhCO₂H (1.1 eq.), (S,S)-115 (1 mol %), Pr^t₂NEt (1.1 eq.).

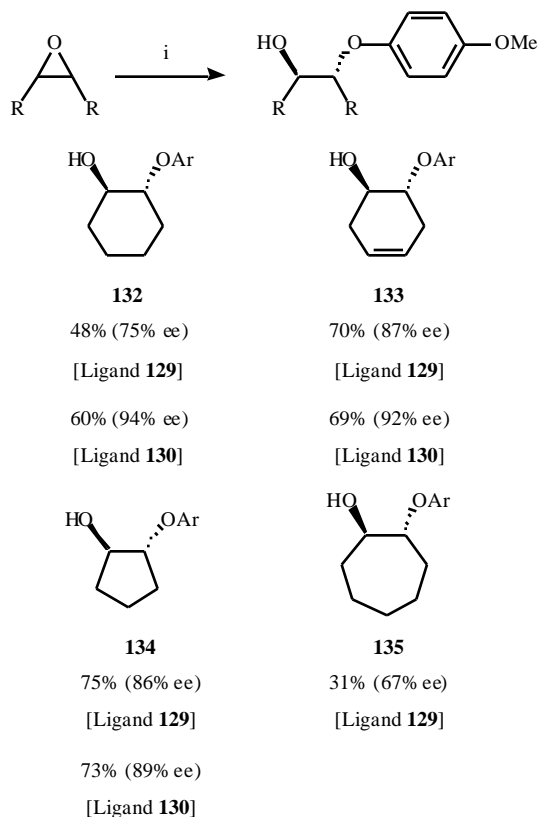
The reaction of a wide range of epoxides with 4-methoxyphenol catalyzed by GaLB **129** afforded versatile



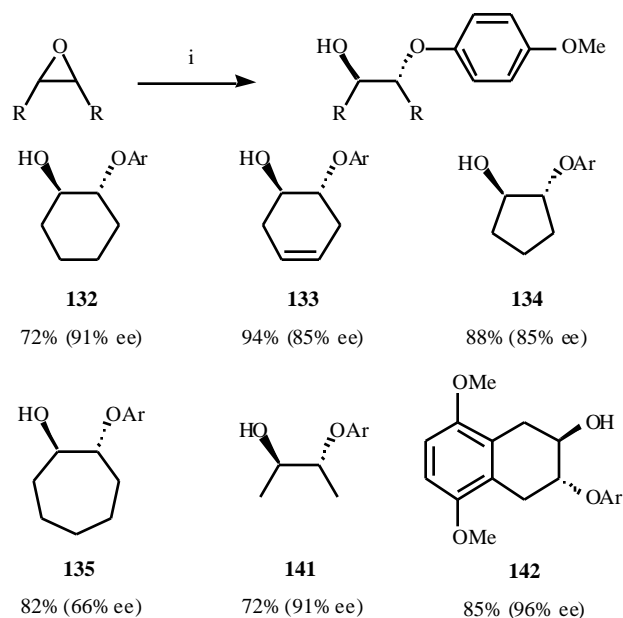
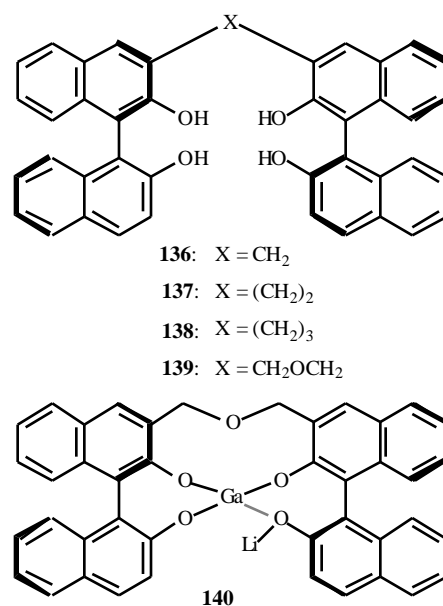
Scheme 22. Reagents: i, (R,R)-116 (2 mol %), TBME.



1,2-diol monoethers [43] in excellent enantiomeric excess and moderate yields (Scheme 23). Using the complex GaLB **130** improvement both in yields and enantioselectivity were achieved, the main drawbacks of this catalytic system being the high catalyst loading needed (20 mol %) and the long reaction times (3-7 days at 50 °C). In order to find a more effective catalyst, different heterobimetallic gallium complexes were tried, among those, complex (*R*)-GaSO (**131**) showed higher catalytic activity, albeit with modest enantioselectivity.



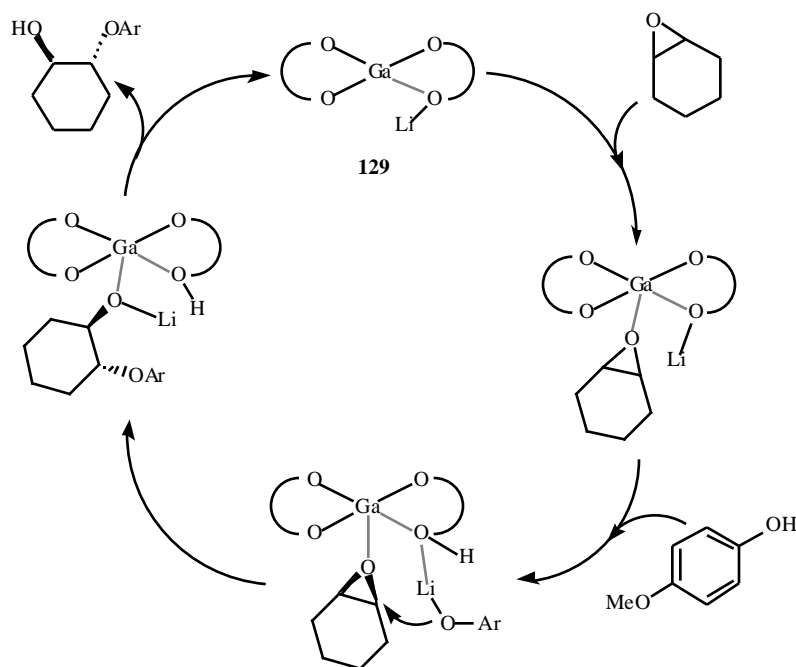
Scheme 23. Reagents: i, *p*-HOC₆H₄OMe (1.2 eq.), **129** or **130** (20 mol %), MS 4Å, toluene, 50 °C.



Scheme 24. Reagents: i, *p*-HOC₆H₄OMe (2 eq.), **140** (10 mol %), MS 4Å, toluene.

Looking for a better complex in terms of activity and selectivity, Shibasaki *et al.* prepared ligands **136-139** by linking two BINOL molecules [44]. Gallium complexes derived from ligands **136-138** were ineffective in the enantioselective opening of cyclohexene oxide with *p*-methoxyphenol (low yield and very poor ee), probably due to the formation of undesired oligomeric structures of these linked-BINOL complexes. However, in the case of the ligand **139**, the oxygen atom in the linker might coordinate to gallium during the complex formation helping the generation of the desired monomeric Ga-complex (**140**). By using complex **140**, the catalyst amount could be reduced to 10 mol % giving the desired products with similar enantioselectivities as with complex **130** but in much higher chemical yield (Scheme 24) [45].

The proposed catalytic cycle for the ARO of epoxides shown in (Scheme 24) is depicted in (Scheme 25). Thus, the



Scheme 25. Catalytic cycle for the ring opening of epoxide with 4-methoxyphenol catalyzed by GaLB.

bimetallic GaLB complex has a lithium binaphthoxide moiety acting as a Brønsted base, activating and controlling the orientation of the phenol, a gallium centre acting as a Lewis acid controlling the orientation of the epoxide [44].

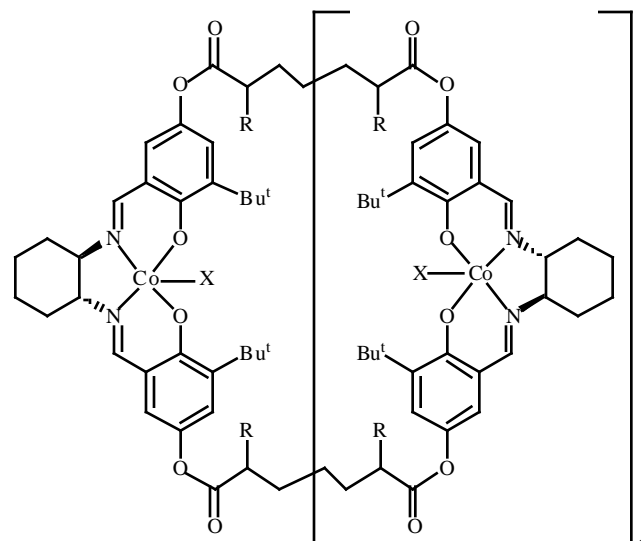
Cyclic oligomeric Co(salen) catalysts **143-145** were synthesised and tested in the asymmetric hydrolysis of epoxides [46]. Oligomeric complexes, used as a mixture of different ring sizes, catalyzed the ring opening of cyclohexene oxide by water with better reactivity and enantioselectivity than the corresponding monomeric analogues, which gave around 70% yield and 71% ee in the best cases (Scheme 26).

In the case of the oligomeric complex **144**, all three different isomers (i.e. dimer, trimer and tetramer) were prepared. Trimer showed higher enantioselectivity (95% ee) and reactivity in the asymmetric hydrolysis of cyclohexene oxide than both the dimer and the tetramer, the activity and selectivity of the mixture being an average of the mixture components, as expected [46b].

2.4. Sulphur Containing Nucleophiles

Regarding sulphur nucleophiles, gallium catalyst GaLB **129** reported by Shibasaki *et al.* gave excellent results in the ARO of *meso*-epoxides with thiols [47]. In fact, the use of 10 mol % of the GaLB catalyst and 4 Å molecular sieves was found to effect the addition of *tert*-butyl thiol to different epoxides at room temperature (Scheme 27), this methodology being applied for the preparation of a prostaglandin precursor (compound **30** shown in Scheme 5). Molecular sieves enhanced the reaction rate, although its role in the catalytic cycle is unclear, and the working model suggested is the same depicted in Scheme 25, but with a thiol as nucleophile instead of phenol.

Another sulphur nucleophile, such as benzyl thiol, was also tried under the previous reaction conditions in order to open cyclohexene oxide, but only moderate enantioselectivity was achieved (40% ee) on the catalytic version

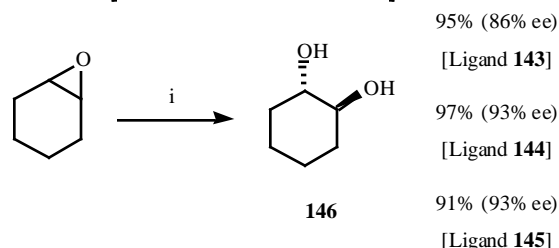


143: X = OTs, R = Cl, n = 1-5

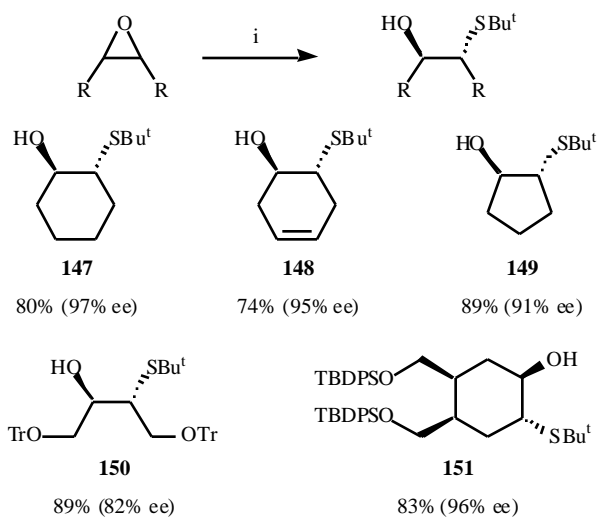
144: X = csa, R = H, n = 1-3

145: X = nbs, R = H, n = 1-3

[csa = 10-camphorsulfonate,
nbs = 3-nitrobenzenosulfonate]



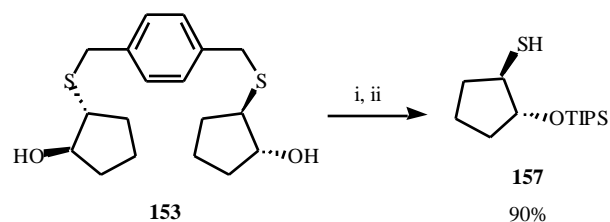
Scheme 26. Reagents: i, H₂O, **143-145** (1.5 mol %), CH₃CN/CH₂Cl₂, 4 h.



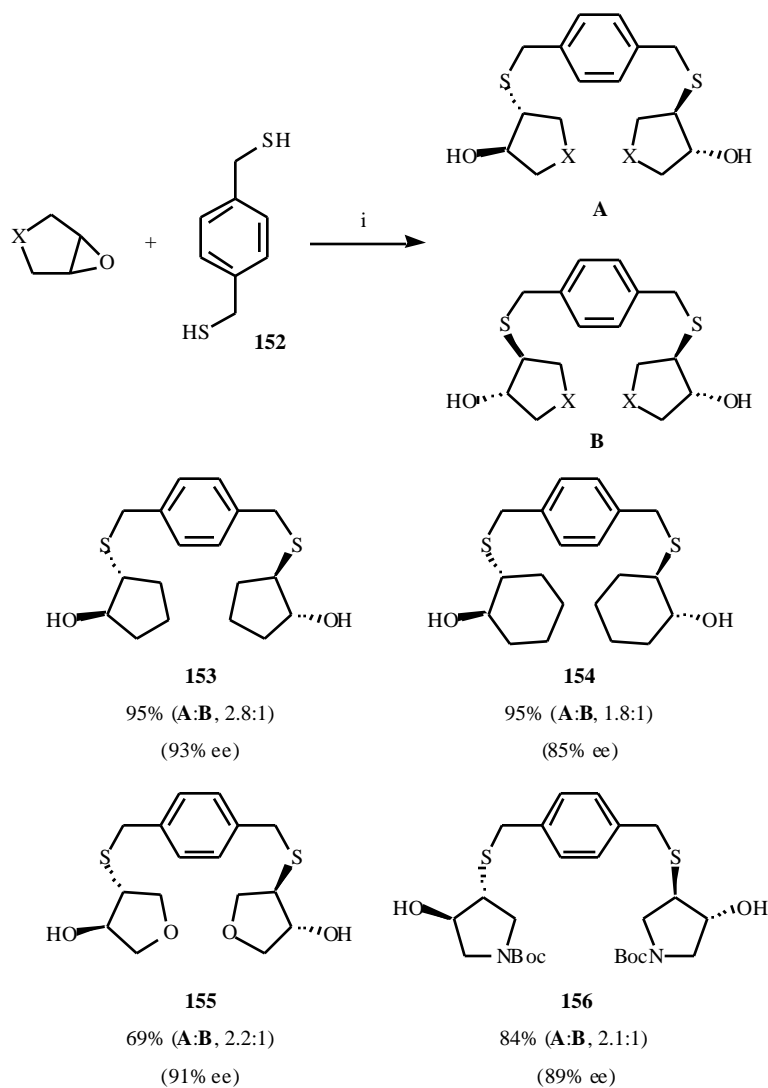
Scheme 27. Reagents: i, Bu^tSH (1.2 eq.), **129** (10 mol %), 4 Å MS, toluene, rt.

whereas using stoichiometric amount of complex **129**, 2-(benzylthio)cyclohexanol was obtained in 88% ee. Jacobsen

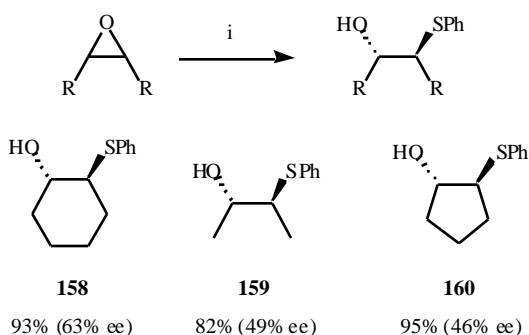
et al. reported the use of the complex (*S,S*)-**3** (used for ARO with TMSN₃ very successfully) giving the expected product with good yield but in moderate optical purity (59% ee) [48]. Improvement in terms of selectivity was achieved by using the dithiol **152**, which in the catalyzed ring-opening reaction afforded a mixture of bishydroxy sulphides (**A** and **B**, Scheme **28**), the chiral one **A** (which resulted significantly enantiomerically enriched) being separated from the *meso* form **B**. Afterwards, chiral products **153-156** could be transformed into the corresponding -silyloxy thiols, as it is exemplified in the transformation of compound **153** into **157** in good yield shown in Scheme **29**.



Scheme 29. Reagents: i, TIPSCl, imidazole, CH₂Cl₂, rt; ii, Na/NH₃, THF, -78 °C.



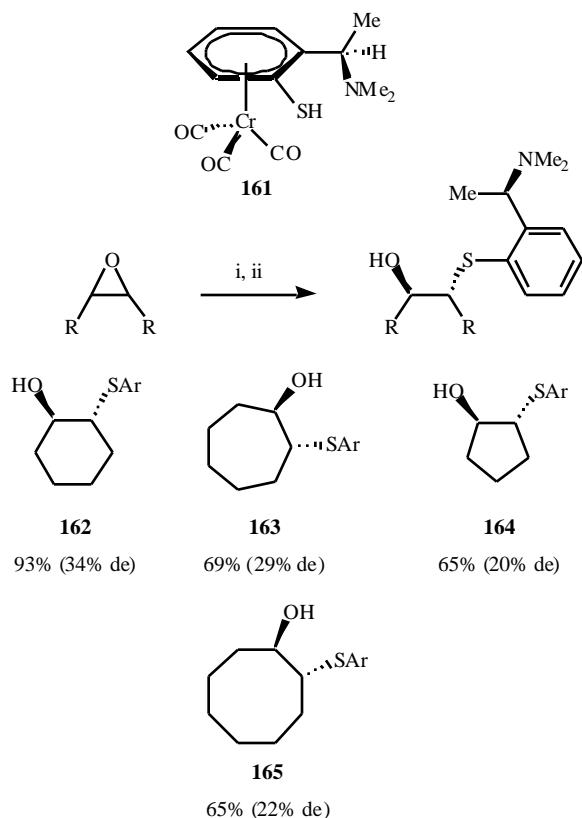
Scheme 28. Reagents: i, (*S,S*)-**3** (2 mol %), TBME, rt.



Scheme 30. Reagents: i, PhSH (1 eq.), $\text{Ti}(\text{OPr}^i)_4$ (5 mol %), (*R,R*)-**2** (5.5 mol %), hexane, -40°C .

Salen-type ligands were also used in combination with $\text{Ti}(\text{OPr}^i)_4$ to catalyze the asymmetric ring opening of *meso*-epoxides with thiols [49]. In fact, the in situ formed Ti(IV)-(*R,R*)-**2** complex promoted the opening of different epoxides with thiophenol to give the corresponding β -hydroxy sulphides in good yield but moderate ee (Scheme 30), other *para* substituted thiophenols giving similar yields and enantioselectivities in the ring opening of cyclohexene oxide. On the other hand, benzyl thiol yielded 2-(benzylthio)cyclohexanol only in 36% yield and with 42% ee.

Chiral benzenethiolchromium complex **161** reacted with achiral epoxides to give enantioenriched products [50]. The ring opening of various epoxides was carried out with chiral **161** at room temperature without any additional additive giving, after oxidative removal of the chromium moiety, the



Scheme 31. Reagents: i, **161** (0.85 eq.), CH_2Cl_2 , rt, 65 h; ii, CAN, K_2CO_3 , MeOH, rt, 1 h.

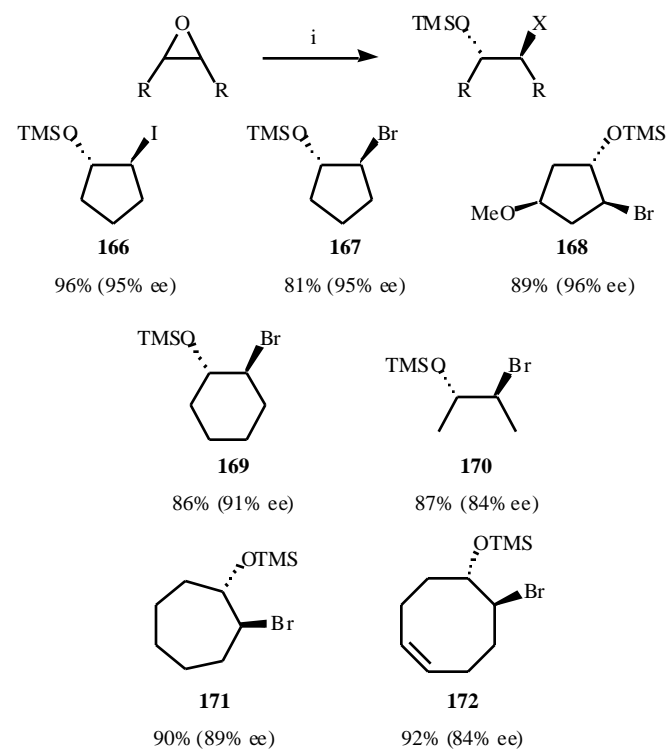
corresponding products **162-165** with moderate chemical yield and low optical yield (Scheme 31).

2.5. Halogen Containing Nucleophiles

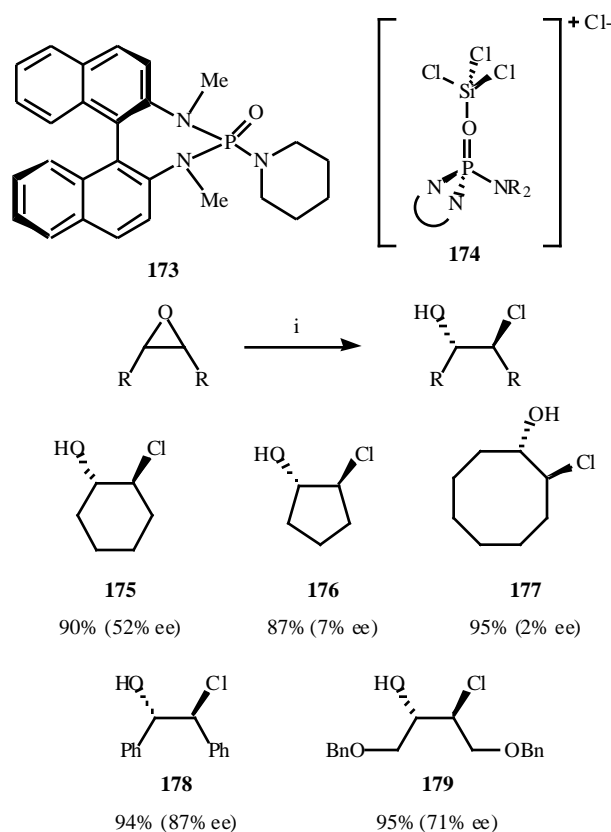
Nugent applied the zirconium-**1** complex (already reported for addition of TMSN_3) to the ring-opening epoxides by halogens [51]. Using allyl halide as a halogen source, TMSN_3 was also needed to form an active catalyst (where by azido-halogen exchange at the metal centre proceeded) in the ARO of different epoxides to give the corresponding β -halohydrins **166-172** with high both chemical and optical yields (Scheme 32). Excess of allyl halide was necessary to suppress the formation of the corresponding β -azido silyl ether.

Denmark *et al.* reported a procedure for the preparation of enantioenriched β -chlorohydrins from epoxides with SiCl_4 and a catalytic amount of phosphoramidate **173** as chiral Lewis base involved in the process [52]. The authors suggested initial formation of a complex between SiCl_4 and the phosphoramidate, which evolved via ionization to highly reactive silicon cation and a chloride ion (intermediate **174**). Chlorohydrins **175-179** were cleanly obtained in excellent yields, although the enantioselectivity of the reaction was highly substrate dependent (Scheme 33).

Planar chiral complexes **180-182** were prepared and examined as catalysts in the desymmetrization of acyclic *meso*-epoxides with SiCl_4 [53]. The more increase in the steric bulkiness of the R group in the complex, the better enantioselectivity results in the ARO reaction, thus complex **182** was the best of the complex family. This complex (5 mol %) catalyzed the ring opening of a number of epoxides with SiCl_4 at low temperature giving the corresponding



Scheme 32. Reagents: i, TMSN_3 (1.2 eq.), allyl-Hal (2 eq. for Hal = I, 20 eq. for Hal = Br), $\text{Zr}(\text{O}i\text{Bu})_4$ -**1** (5 mol %), PhCl, rt, 48 h.



Scheme 33. Reagents: i, SiCl_4 (1.1 eq.), **173** (10 mol %), CH_2Cl_2 , -78°C .

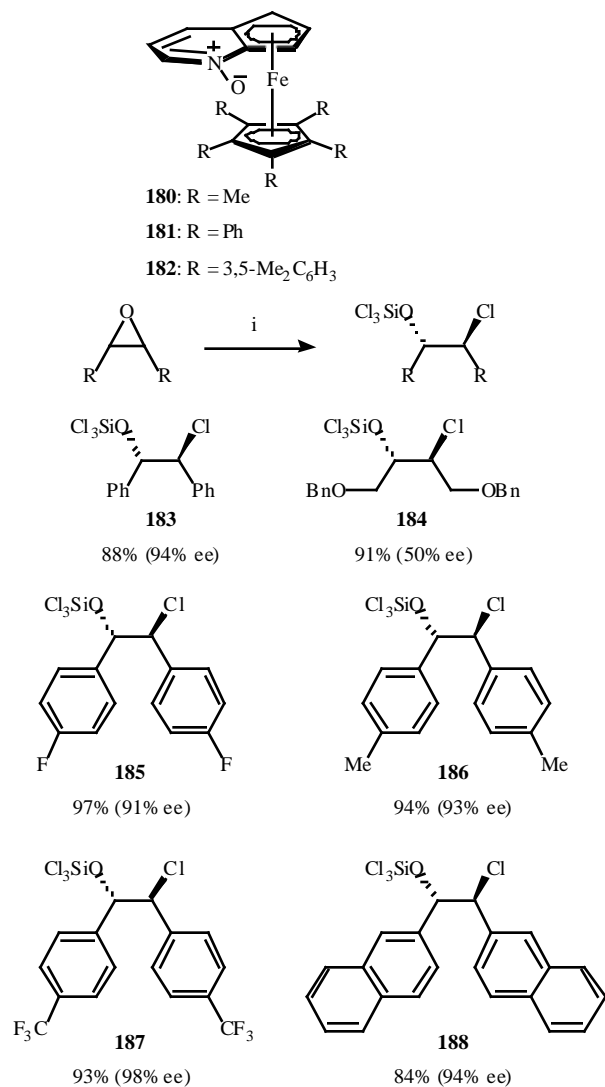
products **183-188** in very good yield and high stereo-selection (Scheme 34).

Based on the former results with *N*-oxide catalyst, Nakajima *et al.* tried chiral *N,N'*-dioxide catalysts **189** and **190** in the epoxide opening with SiCl_4 [54], the catalyst **190** giving the best results, and as in Fu's system, good chemical and optical yields were obtained for acyclic epoxides (Scheme 35).

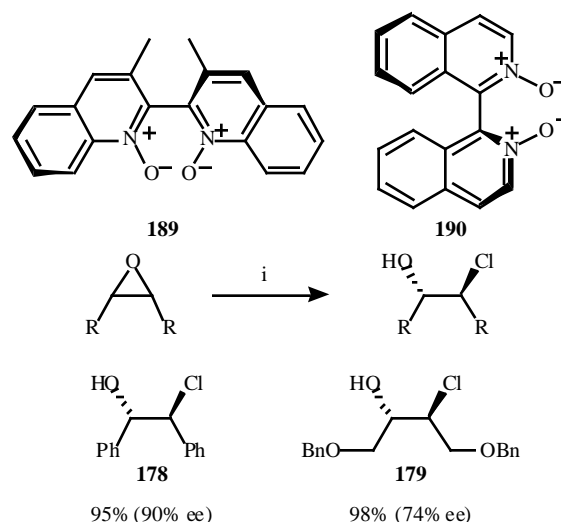
The ferrocene complex **191** was also tried in the former reaction but almost racemic mixtures were obtained regardless type of substrates or temperature [55].

Ring opening of epoxides using the (*R,R*)-tartrate-based titanium complex **192** or the titanium (*R*)-BINOL catalyst **193**, in combination with dilithium tetrachlorocuprate (Li_2CuCl_4) or TMSCl as chloride donors, were also tried [56], good chemical yields of vicinal chlorohydrins or their silyl ethers being obtained in both cases, but with very poor selectivities.

Owing to the growing interest in fluorine substituted organic compounds, recent studies were done in the enantioselective introduction of fluoride by ring opening of epoxides using hydrofluorinating reagents. The chromium salen complex **3** seemed to be the choice in terms of catalyst, albeit stoichiometric or slightly sub-stoichiometric (80 mol %) amounts of the complex were needed to get moderate to good enantioselectivities. The first asymmetric ring opening of cyclohexene oxide was performed using KHF_2 /18-crown-6 as fluorinating agent in the presence of one equivalent of the complex (*S,S*)-**3** in DMF, so (*R,R*)-2-fluorocyclohexanol (**194**) was obtained in 82% yield and 55% ee, 2-

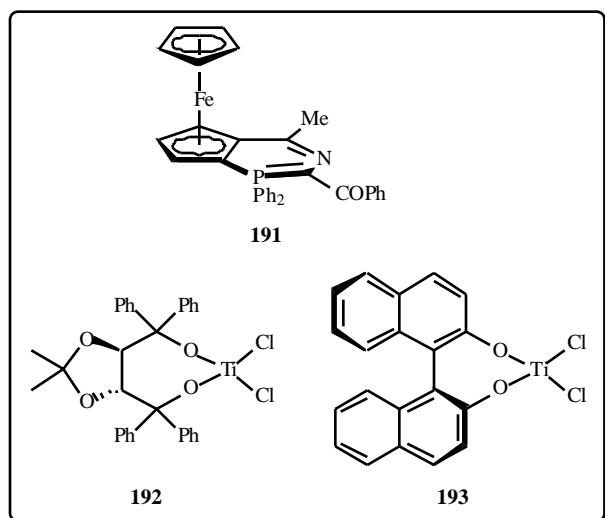


Scheme 34. Reagents: i, SiCl_4 (1.2 eq.), **182** (5 mol %), $\text{EtN}(\text{Pr}^i)_2$ (1 eq.), CH_2Cl_2 , -78°C .

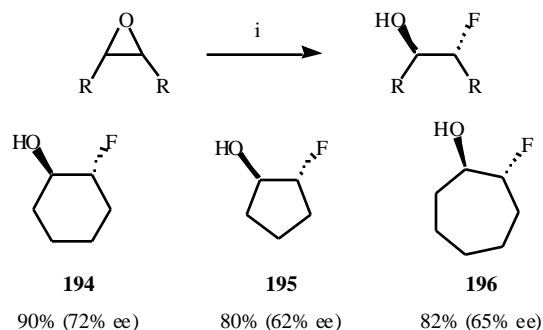


Scheme 35. Reagents: i, SiCl_4 (2 eq.), **190** (10 mol %), $\text{EtN}(\text{Pr}^i)_2$ (1.5 eq.), CH_2Cl_2 , -78°C .

chlorocyclohexanol (**175**) being the main by-product (17%), which came from the chloride delivery from the complex



[57]. Changing the fluoride source for silver fluoride led to improvement of yield and enantioselectivity, hence compound **194** was isolated in 90% yield and 72% ee [58], and, what was more interesting, the chlorinated by-product was completely suppressed under the new reaction conditions. Different *meso*-epoxides were subjected to the reaction with AgF catalyzed by (*S,S*)-**3** giving the corresponding vicinal fluorohydrins with high yields and moderate to good selectivities (Scheme 36) [59].



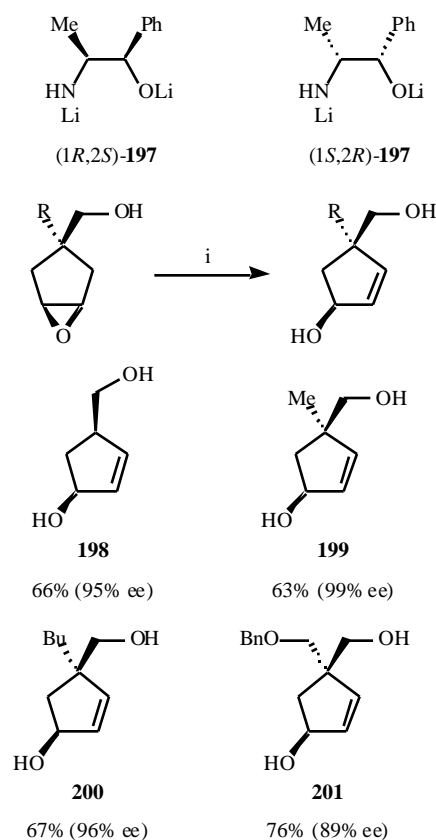
Scheme 36. Reagents: i, AgF (1.5 eq.), (*S,S*)-**3** (100 mol %), CH₃CN, 50 °C.

2.6. Desymmetrization by Deprotonation

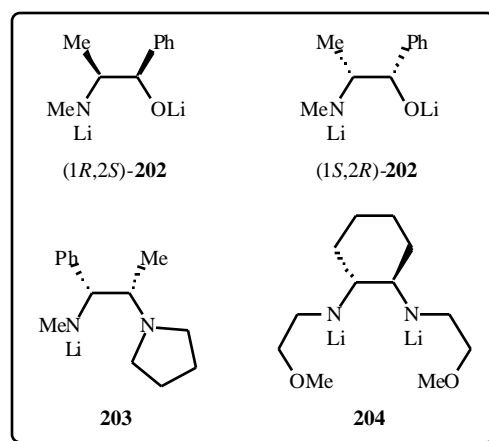
Hodgson *et al.* used excess of in situ prepared dilithium salts of (*1R,2S*)-norephedrine [(*1R,2S*)-**197**] to effect enantioselective deprotonation of functionalised cyclopentene oxides with excellent enantiomeric excesses of the resulting allylic alcohols **198-201** (Scheme 37) [60].

Both enantiomers of dilithiated norephedrine (**197**) and ephedrine (**202**) were compared for particular cases, albeit ephedrine base offered better levels of substrate conversion, better enantioselectivities were achieved with norephedrine base [61]. Bis-lithium norephedrine-based amide **203** was independently developed by O'Brien *et al.* [62] and Ahlberg *et al.* [63], and used in excess to open cyclohexene oxide derivatives in high yield and enantioselectivity.

Bis-lithium amide base **204** was prepared by Alexakis *et al.* and gave the ring-opening of cyclohexene and cyclooctene oxides within good yields and selectivities when it was used in more than stoichiometric quantity (Scheme 38) [64], base

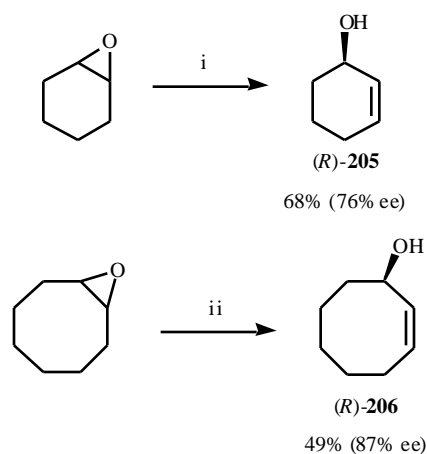


Scheme 37. Reagents: i, (*1R,2S*)-norephedrine (3 eq.), BuⁿLi (6 eq.), benzene/THF (3:2), 0 °C to rt.

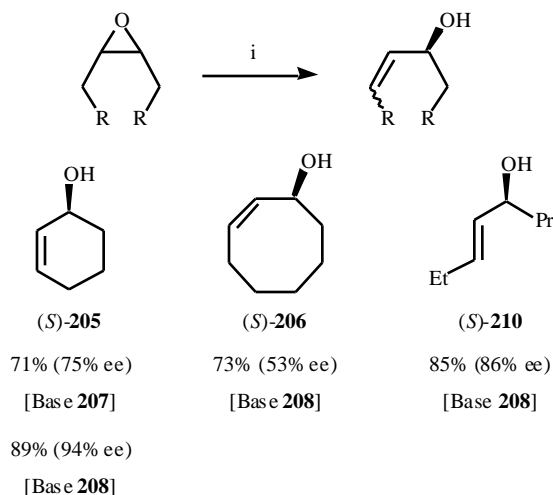
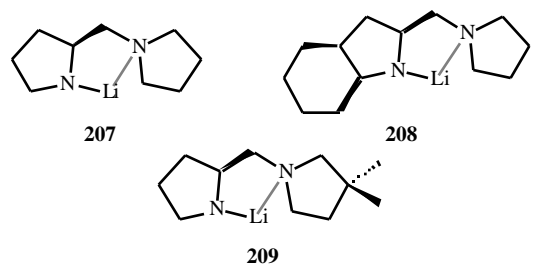


lacking methoxy groups proceeding with a drop in both chemical and optical yield.

An interesting breakthrough in the former reaction was to use a sub-stoichiometric amount of the chiral base together with an excess of another base [such as lithium diisopropylamide (LDA)] to regenerate the chiral base. Asami *et al.* used the proline-derived base **207** and the octahydroindole-derived base **208** in 20 mol % in combination with LDA (1.8 eq.) to afford the corresponding allylic alcohols from *meso*-epoxides (Scheme 39) [65]. Another proline-derived base **209** was also used, giving the same level of activity and enantioselectivity in the mentioned deprotonation reaction [66].

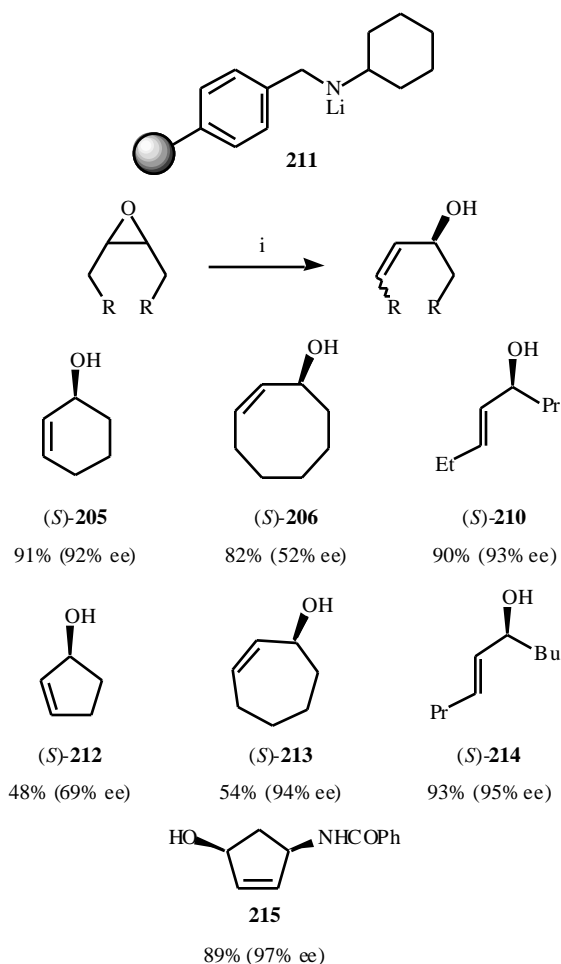


Scheme 38. Reagents: i, **204** (1.5 eq.), THF, 0°C to rt; ii, **204** (1.5 eq.), benzene, 5 °C to rt.



Scheme 39. Reagents: i, **207** or **208** (20 mol %), LDA (1.5 eq.), THF, 0°C.

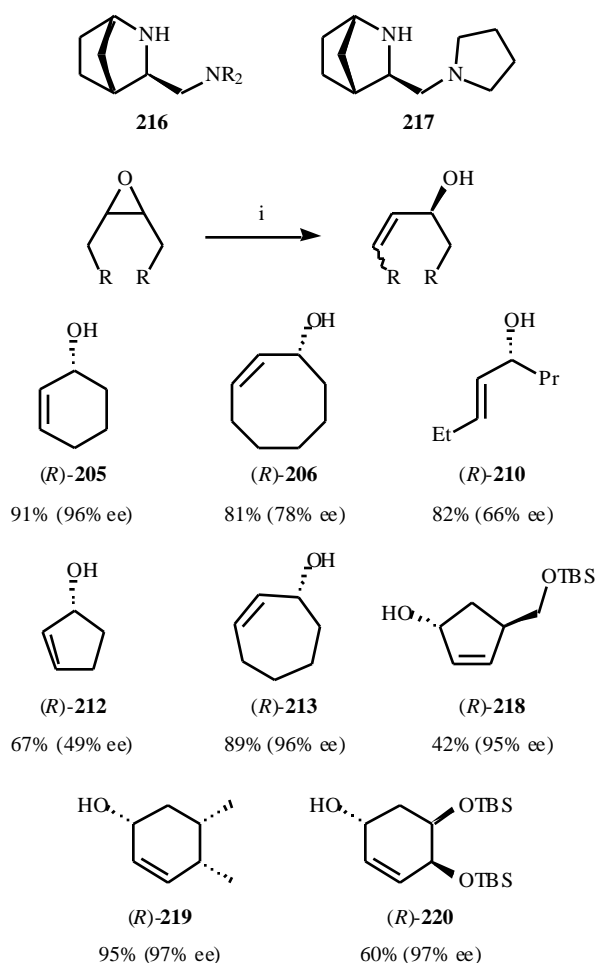
Cross-linked polymer-bound lithium amide (**211**) was employed as reagent to regenerate in situ a chiral lithium amide in the catalytic enantioselective deprotonations of *meso*-epoxides [67]. As a result, the catalytic system was improved, and chiral allylic alcohol derivatives were obtained in high enantiomeric excesses by using an excess of polymer-bound amide reagents and a sub-stoichiometric amount of the chiral lithium amide **208**, the loading level being possible to be reduced to 5 mol % (Scheme 40). This protocol, using 20 mol % of the chiral base, was applied to the preparation, in good yield and excellent optical purity, of compound **215**, a useful chiral synthetic intermediate for carbocyclic nucleosides and their analogues.



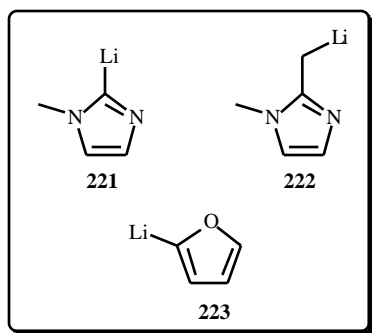
Scheme 40. Reagents: i, **208** (5 mol %), **211** (1.45 eq.), THF, rt.

Another system based on a bicyclic amine was developed by Andersson *et al.* [68]. Thus, different chiral amides with the general structure **216** have been tried for the catalytic asymmetric LDA-mediated isomerization of epoxides to allylic alcohols. The best results were obtained for compound **217** (5 mol %) and an excess of LDA, the use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as cosolvent inhibiting the formation of aggregates, consequently less than 5 eq. of DBU led to a detriment in chemical and optical yields (Scheme 41).

For the former catalytic system, other achiral bases different than LDA were assayed, but no significant improvement was achieved. Even though, by slow addition of the achiral base (in order to keep the concentration low during the reaction) revealed a slight improvement in the results [69]. In this context, Ahlberg *et al.* stated that achiral bulk bases with lower kinetic basicity than LDA, but comparable thermodynamic basicity, would improve the degree of enantioselectivity [70]. Accordingly, imidazole-derived bases **221** and **222** and furan-derived base **223** were found to be strong enough to regenerate the chiral lithium amide without competing with the deprotonation of the epoxide. Excess of bases **221-223** were used together with 20 mol % of the chiral base **203** in THF at room temperature to open cyclohexene oxide producing allylic alcohol (S)-**205** in high enantiomeric excess (93% ee) and yield (91-96%). As a



Scheme 41. Reagents: i, **217** (5 mol %), LDA (2 eq.), DBU (5 eq.), THF, 0 °C.

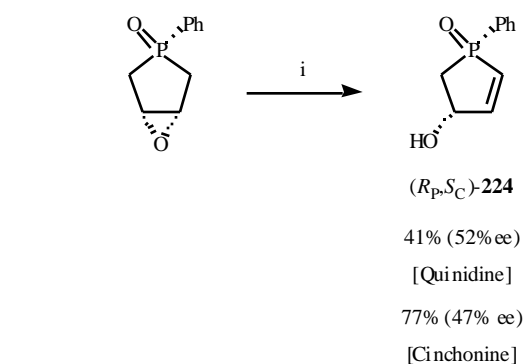


reference, LDA produces (*S*)-**205** in 90% yield (20% ee) under the same conditions.

Tertiary amines are known to efficiently rearrange phospholene epoxides to the corresponding allylic alcohols (Scheme 42). Cinchona alkaloids were effective as chiral bases for the enantioselective rearrangement generating the expected products with moderate enantiomeric excess [71]. The best alkaloids were quinidine and cinchonine, which produced product **224** in 52% ee and 47% ee respectively.

3. RACEMIC EPOXIDES: KINETIC RESOLUTION

There are some kinds of enantiopure epoxides which are not easily to obtain by asymmetric catalysis (i.e. terminal epoxides and *trans*-epoxides), despite recent advances in the asymmetric catalytic epoxidation [72]. Those epoxides are

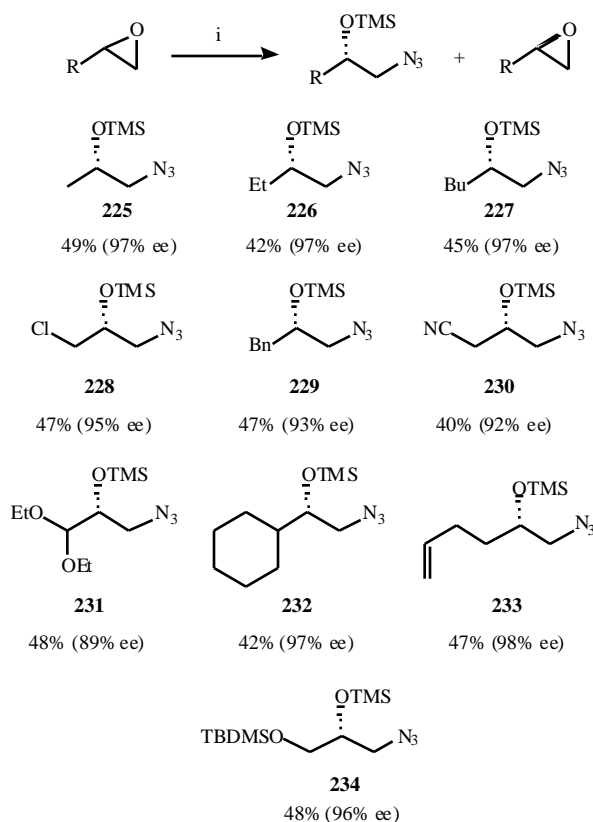


Scheme 42. Reagents: i, Quinidine (0.5 eq.) or cinchonine (1 eq.), CH₂Cl₂, rt, 90 d.

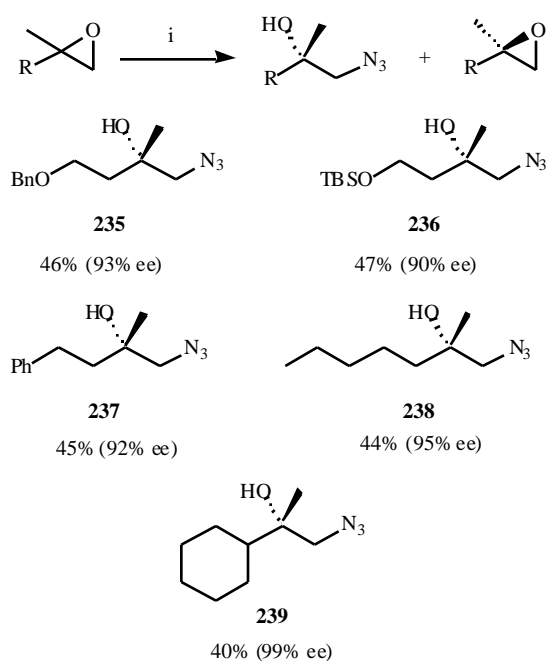
readily available as racemic mixtures, so by using kinetic resolution [73] enantiomerically pure materials can be obtained. When applying this strategy, both the unreacted enantioenriched epoxide and/or the corresponding optical active ring-opening product might be potentially of synthetic value.

3.1. Kinetic Resolution with Nitrogen Containing Nucleophiles

Jacobsen *et al.* extended the use of Cr(salen)-complex **5** to the ARO of racemic terminal epoxides with TMSN₃ [74]. Thus, the reaction of different terminal epoxides with half-equivalent of TMSN₃ gave, via kinetic resolution, the corresponding 1-azido-2-trimethylsiloxyalkanes **225-234** in good yield (based on a maximum theoretical yield of 50%) and very high enantiopurity (Scheme 43).



Scheme 43. Reagents: i, (*R,R*)-**5** (1-5 mol %), TMSN₃ (0.5 eq.), 0 °C, 18-50 h.



Scheme 44. Reagents: *i*, (*R,R*)-**5** (2 mol %), TMSN_3 (0.5 eq.), Pr^iOH (0.5 eq.), TBME, 0 °C.

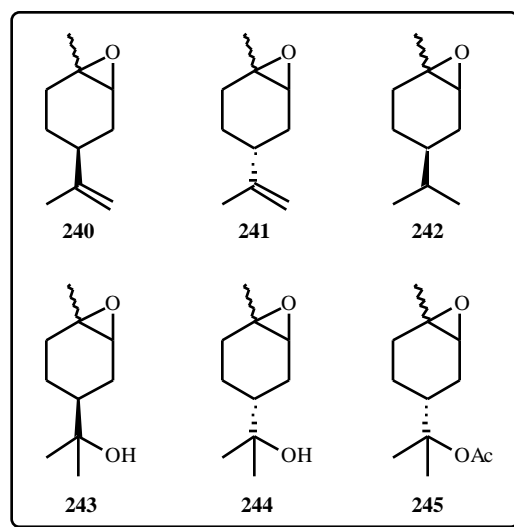
In the case of epichlorohydrin, it was found that racemization could occur under the reaction conditions. So, under the appropriate conditions it may be possible to effect the dynamic kinetic resolution of epichlorohydrin to give product **228** in highly enantiomerically enriched form and with yields over 50%. Indeed, the controlled addition of nucleophile (TMSN_3) allowed the system to undergo racemization, and compound **228** was obtained in 76% yield (based on the racemic epoxide) and with high enantioselectivity (97% ee) [75].

Impregnation of Cr(salen)-complexes on silica was used by Jacobs *et al.* to perform asymmetric ring opening of epoxides via heterogeneous catalysis [76]. Similar levels of selectivity, compared with the homogeneous reaction, were achieved when performing kinetic resolution of 1,2-epoxyalkanes. After the ARO reaction, the catalyst was recovered (80 %) and could be re-impregnated on a fresh support to be re-used.

The same homogeneous methodology, using Cr(salen) complexes, allowed the kinetic resolution of 2,2-disubstituted epoxides, giving excellent results in terms of selectivity when substituents have significantly different steric properties [77]. Treatment of those epoxides with HN_3 (0.55 eq., generated by combining equimolar amounts of TMSN_3 and 2-propanol) in the presence of the catalyst (*R,R*)-**5** (2 mol%) produced the corresponding azidoalcohols **235**-**239** with high enantioselectivity (Scheme 44). Also of synthetic interest are the non-reacting enantiomer of the epoxide, which could be transformed to enantiomerically enriched tertiary alcohols, that are difficult to be prepared by other asymmetric methods. For example, the corresponding enantioenriched epoxide resulted from a kinetic resolution afforded compound **236** was used in the synthesis of taurospongins A [78].

A range of trisubstituted epoxides (**240**-**245**), particularly derived from monocyclic terpenes, underwent ARO with

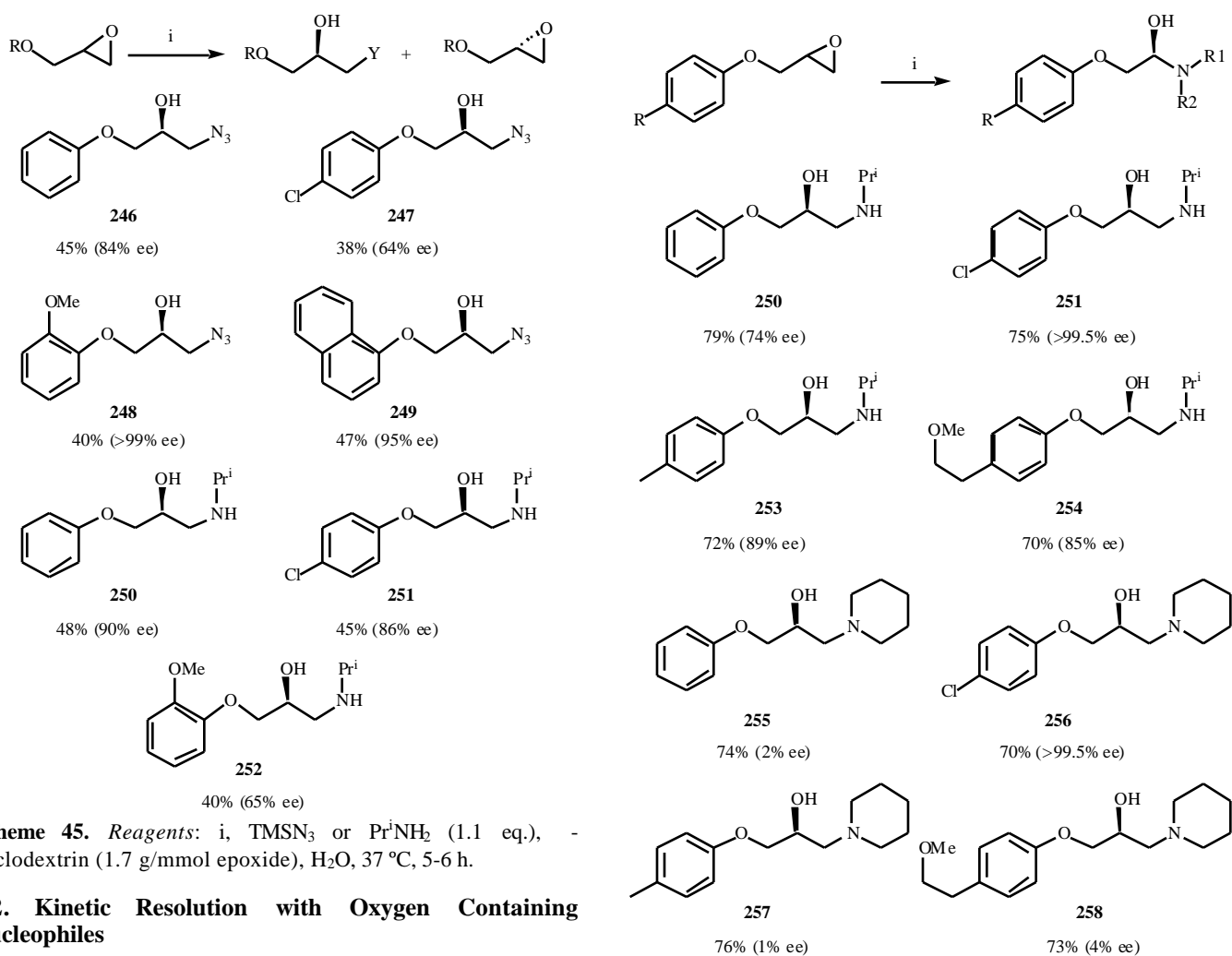
TMSN_3 using Cr(salen) complex **5** (5 mol%) to produce the corresponding opened products with high diastereomeric excess (85-96%). Curiously, formation of the same diastereomer independently of the catalyst enantiomer used was observed. Therefore, the selectivity was not due to the chiral properties of the Cr(salen) catalyst, but it was caused by the presence of the substituent in C-4, which forced the substrate molecule to adopt the most stable conformation blocking the approach of the Cr- N_3 specie from one side. Hence, racemic catalyst mixtures can be used to obtain the same levels of selectivity [79].



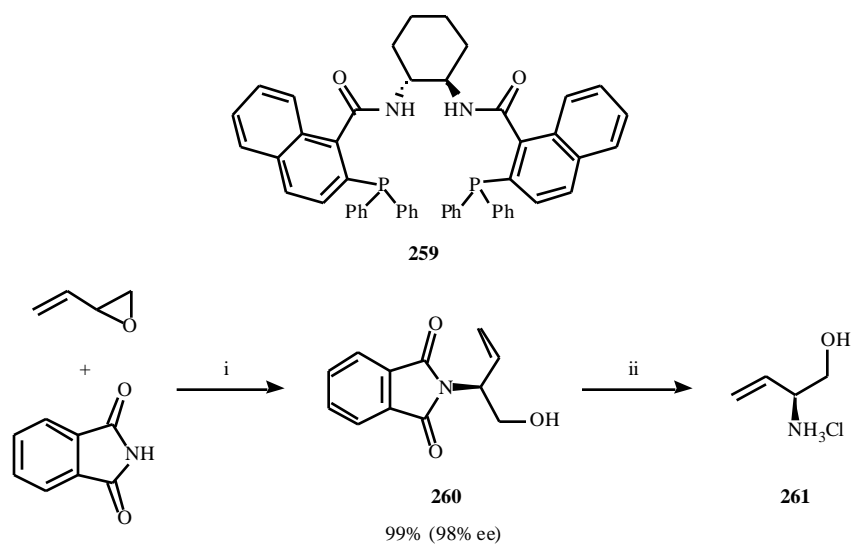
-Cyclodextrin was also reported to catalyze the ARO of epoxides by nitrogen nucleophiles [80]. The reaction of different 3-aryloxy-1,2-epoxypropanes with TMSN_3 in the presence of β -cyclodextrin (1.7 g/mmol of epoxide) in water gave a mixture of the ring-opened azido alcohol (**246**-**249**) and the non-reacting enantiomer of the epoxide (Scheme 45). Following the same procedure kinetic resolution of different epoxides were also performed by using isopropylamine as nucleophile, thus the corresponding amino alcohols (**250**-**252**) were obtained (Scheme 45).

Rama Rao *et al.* reported the racemization of the 3-aryloxy-1,2-epoxypropanes when performing the reaction in presence of cyclodextrin but in absence of solvent (solid state conditions) [81]. The corresponding β -amino alcohols (**250**, **251**, **253**-**258**) were prepared by a dynamic kinetic resolution by mixing in a mortar equimolar amounts of the racemic epoxide, β -cyclodextrin and the amine. Good yields were obtained in all cases and good to excellent selectivities were achieved when using isopropyl amine (Scheme 46).

Trost *et al.* showed the Pd-catalyzed dynamic kinetic asymmetric transformation of butadiene monoepoxide into vinylglycinol (**261**) by using phthalimide as nucleophile [82]. After testing different phosphine-derived ligands, ligand **259** gave the best results (Scheme 47). In this case, the formation of a π -allyl palladium complex was responsible for the epoxide ring opening and then the oxygen would help delivering the nucleophile to the adjacent carbon, the stereochemistry being controlled by the palladium ligand (Figure 3). This methodology was employed for the asymmetric syntheses of different biological active compounds, such as vigabatrin and ethambutol.



the hydrolytic kinetic resolution of terminal epoxides by using chiral Co(salen) complexes [83]. Thus, the solvent free



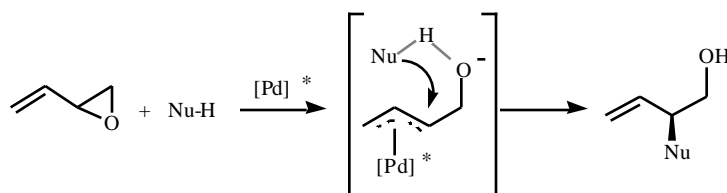
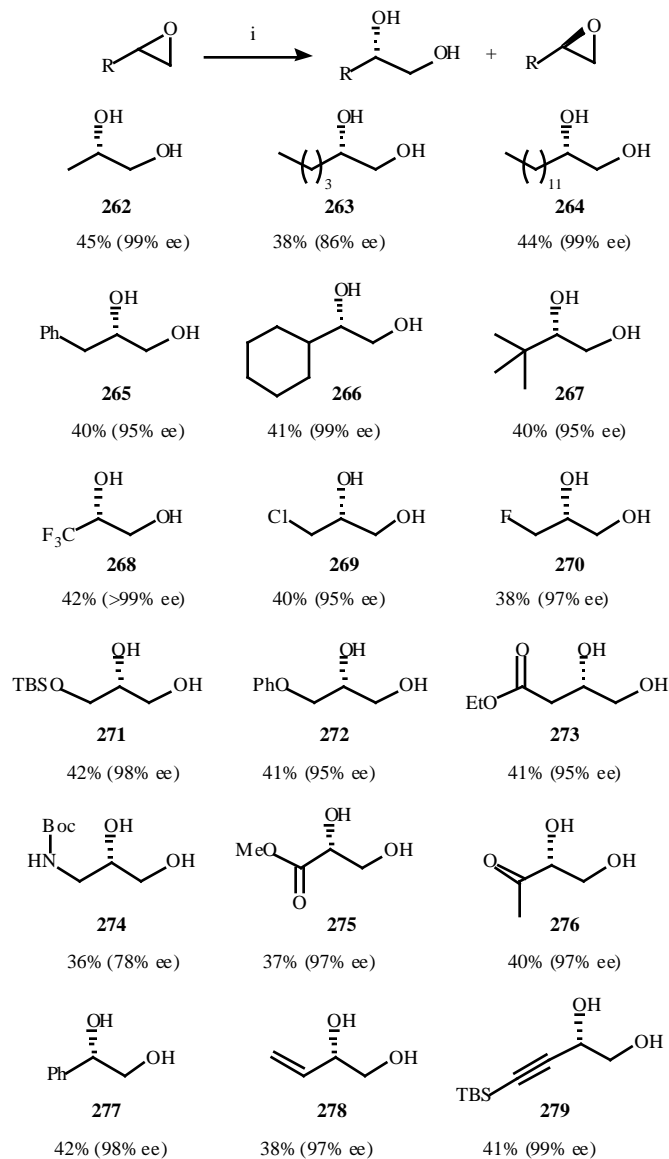
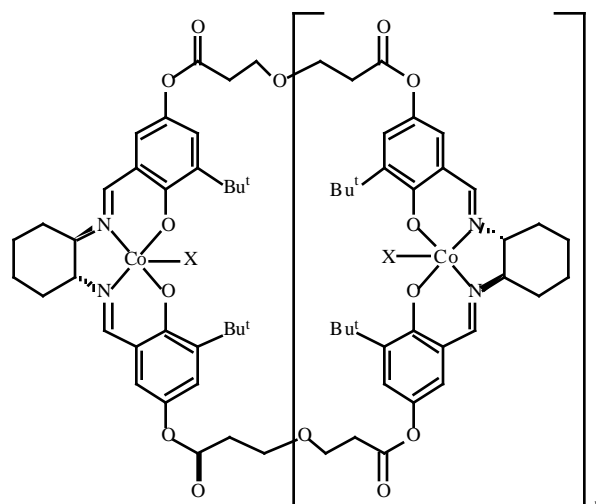


Fig. (3). Proposed mechanism for asymmetric ring opening of butadiene monoepoxide by a nucleophile promoted by palladium complexes.



Scheme 48. Reagents: i, (*R,R*)-**116** (0.2-2 mol %), H₂O (0.45 eq.), rt.

reaction of a racemic epoxide with water in the presence of the Co(III) complex **116** proceeded at room temperature to give a mixture of the corresponding 1,2-diol and the unreacted epoxide, both being separated by fractional distillation with high chemical and optical yields. Moreover, the Co(II) complex **115** was recovered from non-volatile residue and used to regenerate the complex **116**, which was reused without losing activity or selectivity. This HKR of epoxides resulted to be a very general reaction, allowing efficient kinetic resolution of virtually any type of terminal



- 280:** X = OTf, n = 1-3
281: X = OSO₂[C₆H₃(2,4-(NO₂)₂)], n = 1-2
282: X = OSO₂[C₆H₄(3-NO₂)], n = 1-2
283: X = OTs, n = 1-2

Scheme 49. Reagents: i, **280** (0.015-0.0003 Co mol %), H₂O (0.55 eq.), rt.

epoxide, some examples are depicted in (Scheme 48): diols **262-267** from aliphatic epoxides, diols **268-270** from halogenated epoxides, diols **271-276** from epoxides bearing ether or carbonyl moieties and diols **277-279** from aryl, vinyl or alkynyl epoxides [84]. Regarding the possible mechanism, bimetallic species seemed to be involved in the transition state as shown for other ARO of epoxides by using chromium complexes.

Cyclic oligomeric Co(salen) catalysts (**143-145**), tested in the asymmetric hydrolysis of *meso*-epoxides, were also very effective in the HKR of terminal epoxides [46b]. In fact, these catalysts showed a very high activity probably due to the proximity of different reactive centres, which could help

in the formation of the bimetallic transition state. Thus, compound **277** was obtained in 44% (97% ee) from racemic styrene oxide using a very low loading of catalyst **144** (0.08 mol %), and even more impressive was the HKR of propylene oxide using catalyst **145** (loading of 0.0004 mol %) to yield diol **262** (50%, 97% ee). However, these catalysts needed the addition of acetonitrile as solubilising agent what entailed practical limitations during the isolation procedures, so new oligomeric Co(salen) ligands (**280-283**) were designed taking into account the linker unit and the cobalt counterion as crucial elements for the chemical and physical properties of the complexes [85]. Different racemic epoxides underwent HKR with this kind of ligands giving good yields and excellent enantioselectivities with very low catalyst loading and under solvent-free reaction conditions (Scheme 49).

The Co(salen) complex **116** was attached to a solid support, such as polystyrene and silica [86]. These polymer-supported chiral complexes showed to be as efficient and highly enantioselective for the HKR as complex **116**, and the catalyst can be separated from the reaction media by simple filtration and re-used without any loss of reactivity or enantioselectivity. The complex **116** was also immobilised on a siliceous MCM-41 material, the resulting mesoporous material being tested in the HKR of different terminal epoxides under very mild conditions, yielding the corresponding diols with good chemical yields but, within few exceptions, lower selectivities than previous by supported Co(salen) complexes [87].

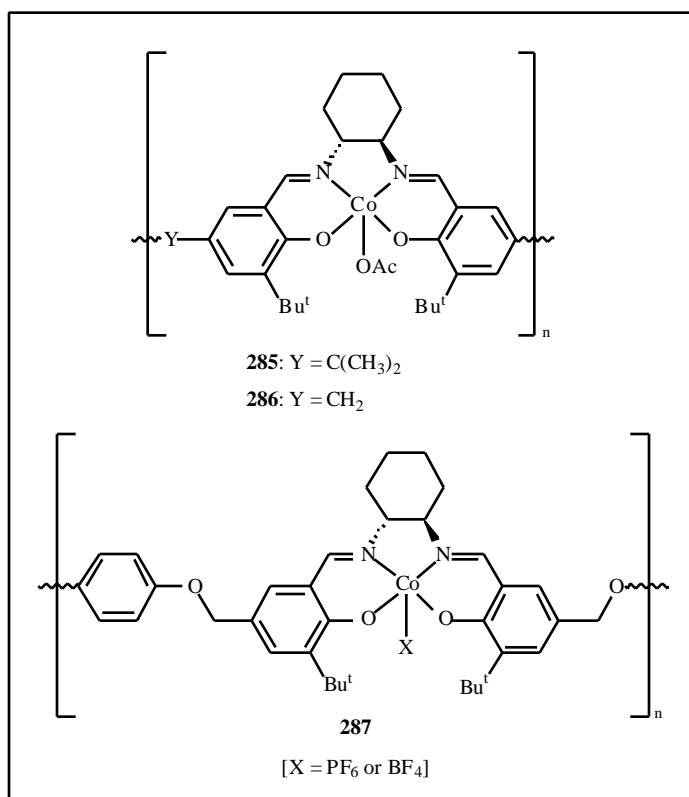
Polymeric catalysts based on the Co(salen) complex (**285** and **286**) were also prepared, by Zheng *et al.* and employed in the HKR of terminal epoxides whereas good results were obtained with the polymeric material **285** producing diols **262**, **269** and **272**, with the poly-salen-Co complex **286**

lower selectivities were in general achieved [88]. On this field, Kim *et al.* prepared polymeric complexes **287-290**, which catalyzed the HKR of terminal epoxides with good to excellent yields and selectivities, regardless the linker between salen complexes and the cobalt counterion [89]. Catalysts **290** were reused without further treatment after simple filtration in 7 catalytic reactions without losing both reactivity or selectivity.

The synthesis of dendrimer-bound Co(salen) complexes based on polyamidoamine (PAMAM) were also reported [90]. The dendritic framework enforced the cooperative interactions between catalyst units in the bimetallic transition state (Figure 4). Indeed, dendritic catalysts 4-Co(salen)-PAMAM and 8-Co(salen)-PAMAM enhanced the reactivity of the Co(salen) complexes.

Pozzi *et al.* reported the preparation of Co(salen) complexes containing perfluoroalkyl substituents, so cobalt (II) complexes **291-293** were oxidized by air in the presence of perfluorononanoic acid prior used to afford the corresponding Co(III)(salen) complex having also a fluorinated counterion ($C_8F_{17}COO^-$) which enhanced their activities and selectivities [91]. Performing the HKR of terminal epoxides (such as, propylene oxide, 1-hexene oxide, 1-octene oxide, styrene oxide and epichlorohydrin) under solvent-free conditions and in the presence of small amounts (0.002 mol %) of these fluorous chiral Co(salen) complexes, similar catalytic activities and enantioselectivities compare to similar non-fluorous catalytic systems were achieved. The best results were obtained using the complexes **292** and **293**, both containing less fluorous substituents.

As it has been mentioned before, enantioenriched terminal epoxides or 1,2-diols are often important building blocks in the synthesis of natural or biological active products. A retrosynthetic analysis of Muconin suggested



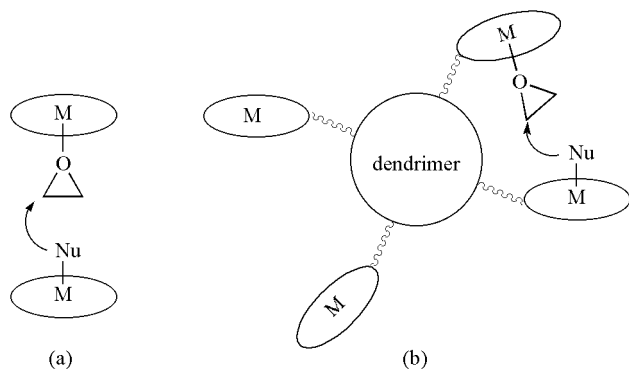
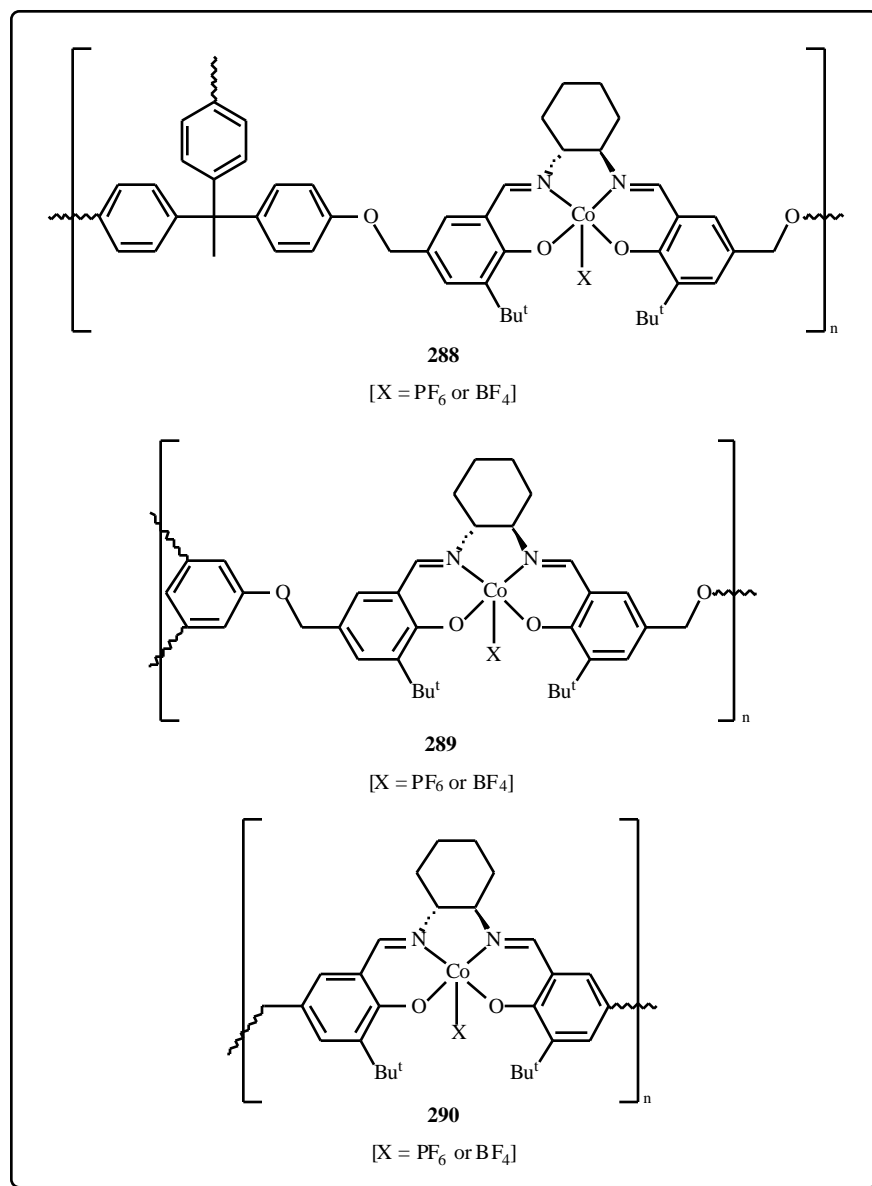


Fig. (4). (a) Proposed mechanism for cooperative catalysis in ARO of epoxides. (b) Cooperative catalytic ARO within a dendrimeric framework.

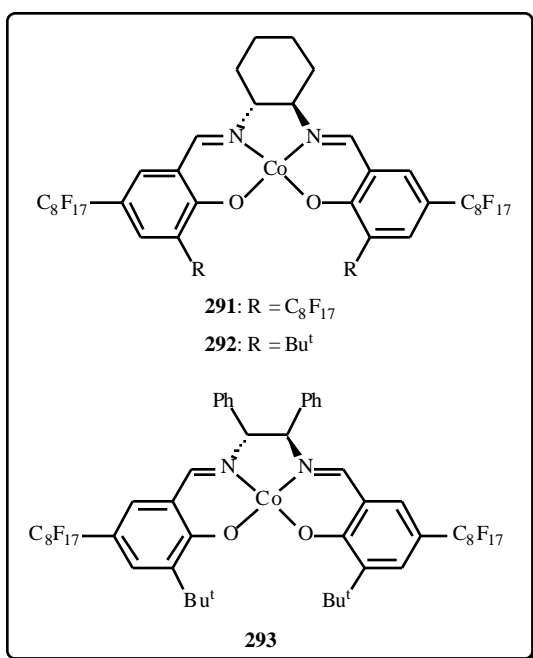
diol **294**, and epoxides **295** and **296** as three of the four starting materials. Compound **294** was obtained (45%, >99% ee) by HKR from racemic tetradecene oxide using

(*S,S*)-**116** (0.5 mol %). Chiral epoxide **295** was the non-reacting enantiomer (isolated in 41% yield, >99% ee) during the HKR of epichlorohydrin in the presence of (*S,S*)-**116** (0.5 mol %). Finally, compound **296** was the non-reacting enantiomer (48%, 98% ee) during the HKR of propylene oxide with catalyst (*R,R*)-**116** (0.2 mol %) [92].

Tetrahydropyrans are important structural units present in a variety of biologically active compounds (such as antibiotics, marine toxins, pheromones,...). In the preparation of enantiopure tetrahydropyrans the epoxide **297** was used, which was obtained (43%, >99% ee) by kinetic resolution of racemic 4-phenylbutylene oxide using (*R,R*)-**116** [93].

Different α -adrenergic blocking agents, such as (*S*)-propranolol, (*S*)-moprolol and (*S*)-toliprolol, were prepared using the chiral epoxide **298** which remained (40%, >99% ee) after HKR of racemic *N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine in the presence of (*S,S*)-**116** [94].

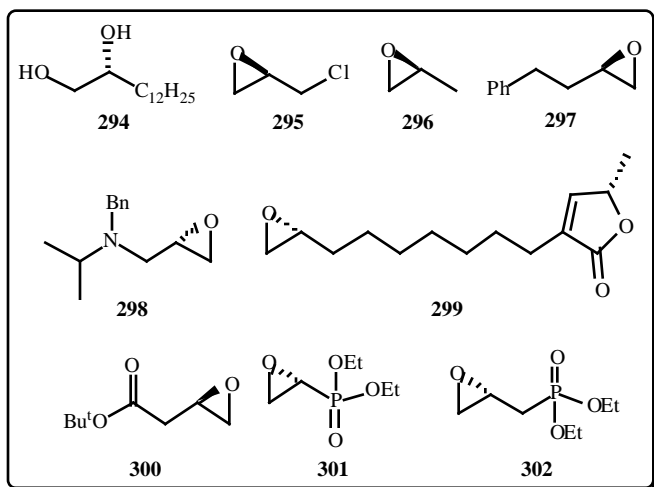
Chiral compound **299** was used as an intermediate in the synthesis of (10*R*)-corossolin, and it was obtained from the



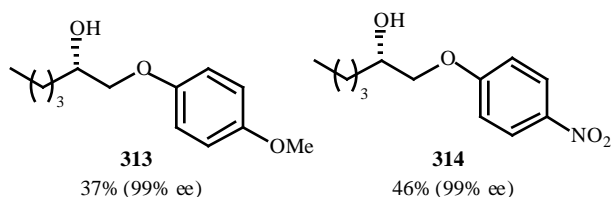
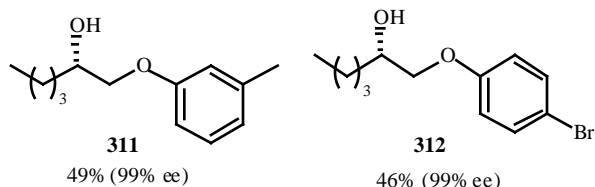
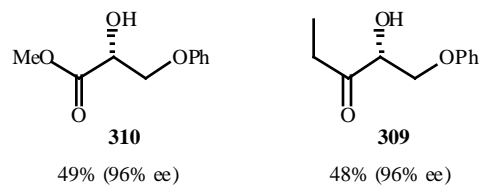
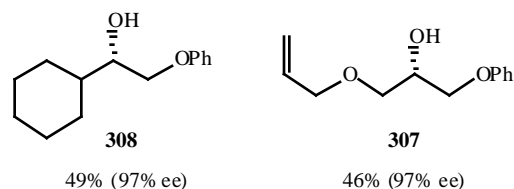
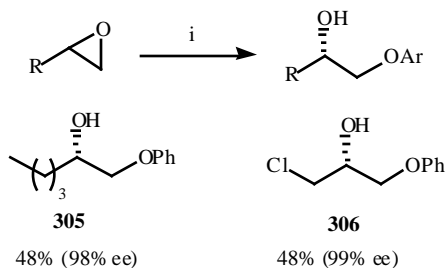
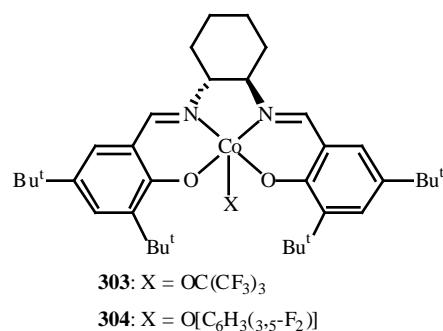
racemic mixture of terminal epoxide by HKR using the (*R,R*)-Co(salen) complex **116** [95].

The total synthesis of (–)-mycalolide A (which showed antifungal activity) started from the epoxide **300**, which was obtained in 47% yield and good enantioselectivity (99% ee) from the racemic terminal epoxide by HKR using the cobalt complex (*R,R*)-**116** [96].

Other interesting intermediates are terminal epoxides bearing a phosphonate moiety which were also treated under HKR conditions with (*R,R*)-**116**. Thus, whereas compound **301** was obtained in good yield and enantioselectivity (39%, >99% ee) and was used in the preparation of (*R*)-2-amino-1-hydroxyethylphosphonic acid (a protozoal plasma membrane component) [97], compound **302** was isolated in 34% (94% ee) and was used in the preparation of (*S*)-phosphocarnitine [98].



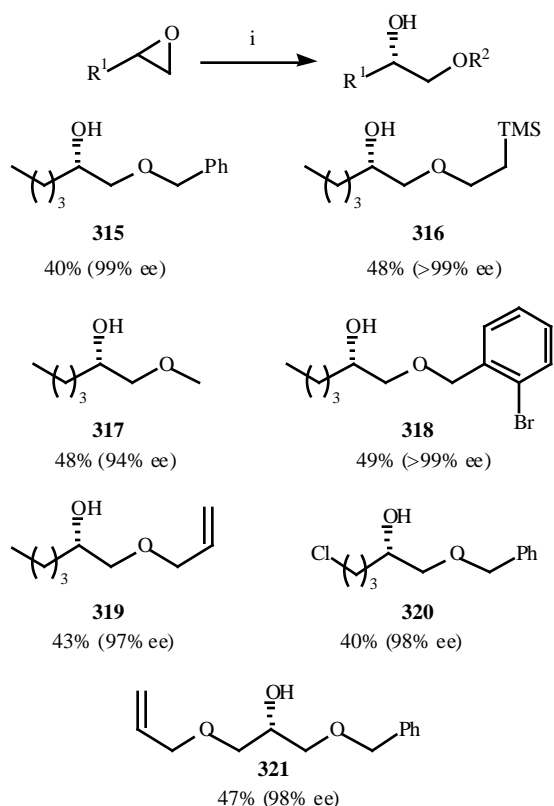
Jacobsen *et al.* reported also the kinetic resolution of terminal epoxides with phenols by means of a Co(salen) catalyst [99]. Complex **116** showed activity and selectivity in this reaction, albeit not good conversion was achieved.



Scheme 50. Reagents: i, **303** (0.088-0.044 mol %), ArOH (0.45 eq.), TBME, MS 3Å, rt.

Certainly, the identity of the counterion for the Co(salen) complex proved to be important in this context, so the perfluoro *tert*-butoxide complex **303** gave the best reactivity and enantioselectivity. This kinetic resolution proved to have a broad substrate scope with respect to both the terminal epoxide and the phenol derivative, thus compounds (**305-314**) were obtained by means of this protocol (Scheme 50).

Polymer-supported Co(salen) complexes were tested in the ARO of terminal epoxides by phenol derivatives [86]. Moreover, this solid-phase catalyst was applied in the

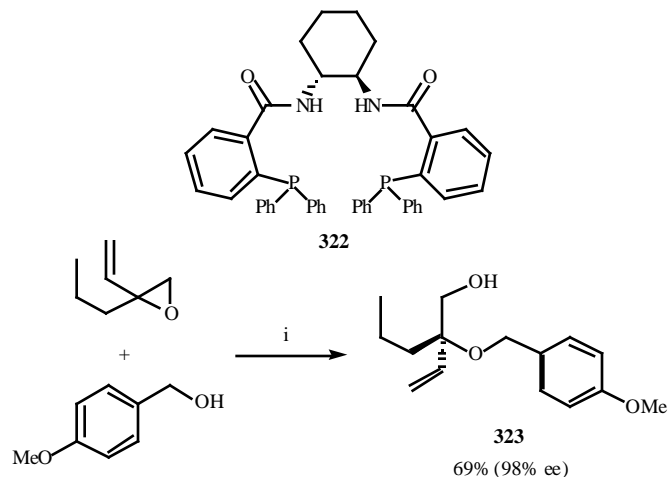


Scheme 51. Reagents: i, **143** (0.1-2 mol %), R²OH (0.45 eq.), CH₃CN, 4 °C.

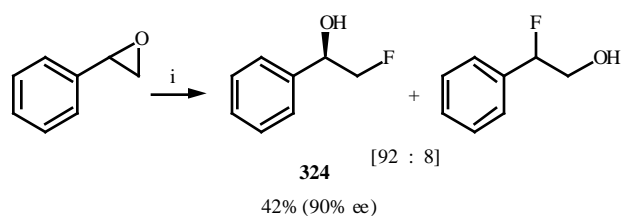
preparation of parallel libraries via enantioselective catalytic synthesis which provided access to important classes of pharmacologically active compounds [100].

Kinetic resolution of terminal epoxides with alcohols was performed in the presence of the oligomeric complex **143** to yield compounds **315-321** (Scheme 51) [46].

Trost *et al.* used a palladium-catalyzed dynamic kinetic asymmetric opening of an epoxide with p-methoxybenzyl alcohol to yield compound **323** in 69% and with good enantioselectivity (98% ee) (Scheme 52) [101]. This compound was an intermediate in the synthesis of tipranavir, a protease inhibitor.



Scheme 52. Reagents: i, **322** (3 mol %), Pd₂(dba)₃ (1 mol %), Et₃B (1 mol %).



Scheme 53. Reagents: i, **3** (50 mol %), KHF₂/18-crown-6, DMF, 60 °C.

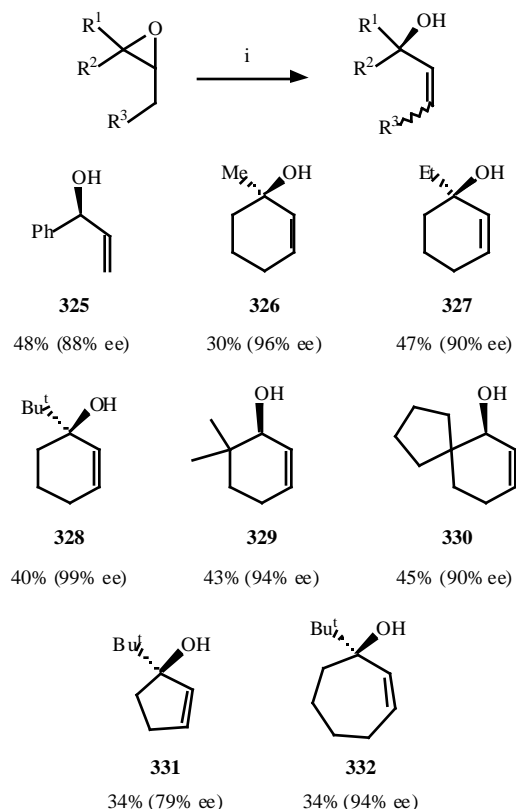
3.3. Kinetic Resolution with Halogen Containing Nucleophiles

Haufe *et al.* reported the use of titanium complexes **192** and **193** in combination with tetrachlorocuprate (Li₂CuCl₄) or TMSCl as chloride donors for asymmetric ring opening of styrene and stilbene oxides with very poor regio- and enantioselectivities [56].

Regarding fluorine as nucleophile, Haufe *et al.* applied the Cr(salen) complex **3** to resolve kinetically styrene epoxide to yield (*R*)-2-fluoro-1-phenylethanol (**324**) with good regioselectivity (92:8) and enantioselectivity (90% ee) (Scheme 53) [57-59]. This methodology was not satisfactory in terms of regio- and enantioselectivity for other racemic epoxides.

3.4. Kinetic Resolution by Deprotonation

Bicyclic amine system developed by Andersson *et al.* was applied for the kinetic resolution of racemic mixtures of epoxides [68]. Using LDA as stoichiometric base and the diamine **217** as catalytic chiral base, different racemic epoxides were asymmetrically deprotonated generating allylic alcohols **325-332** with good enantioselectivities (Scheme 54)



Scheme 54. Reagents: i, **217** (10 mol %), LDA (2 eq.), DBU (5 eq.), THF, 0 °C.

[102]. The non-reacting enantiomeric epoxide was recovered also with good to excellent enantiomeric excess (70-99% ee).

Asami *et al.* reported the use of stoichiometric amount of the chiral base **207** to perform kinetic resolution of different *cis*-3-alkylcyclohexene oxides, the corresponding allylic alcohols being obtained in not more than 60% optical yield [103].

ACKNOWLEDGEMENTS

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REFERENCES

- [1] Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; Vol. 7, pp. 357-387.
- [2] For recent advances in olefin epoxidation using methylrhenium trioxide as catalyst, see: (a) Saladino, R.; Neri, V.; Pelliccia, A. R.; Mincione, E. *Tetrahedron* **2003**, *59*, 7403. (b) Yudin, A. K.; Chiang, J. P.; Adolffson, H.; Coperet, C. *J. Org. Chem.* **2001**, *66*, 4713. (c) Adolffson, H.; Converso, A.; Sharpless, K. B. *Tetrahedron Lett.* **1999**, *40*, 3991. (d) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189. (e) Herrmann, W. A.; Kühn, F. E. *Acc. Chem. Res.* **1997**, *30*, 169.
- [3] Epoxides can be considered as "spring-loaded" ring for nucleophilic opening: Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
- [4] (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.
- [5] Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768.
- [6] For some examples of using azido compounds, see: (a) Adolffson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 2023. (b) Hayashi, M.; Kohmura, K.; Oguni, N. *Synlett* **1991**, 774. (c) Yamashita, H. *Chem. Lett.* **1987**, 525.
- [7] McClelland, B. W.; Nugent, W. A.; Finn, M. G. *J. Org. Chem.* **1998**, *63*, 6656.
- [8] Larrow, J. F.; Jacobsen, E. N. *Org. Synth.* **1997**, *75*, 1.
- [9] Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.
- [10] Scahus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197.
- [11] Song, C. E.; Oh, C. R.; Roh, E. J.; Choo, D. J. *Chem. Commun.* **2000**, 1743.
- [12] Gigante, B.; Corma, A.; García, H.; Sabater, M. J. *Catal. Lett.* **2000**, *68*, 113.
- [13] Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.
- [14] Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780.
- [15] Gianneschi, N. C.; Bertin, P. A.; Nguyen, S. T.; Mirkin, C. A.; Zakharov, L. N.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 10508.
- [16] Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389.
- [17] (a) Noyori, R.; Suzuki, M. *Chemtracts: Org. Chem.* **1990**, *3*, 173. (b) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11689.
- [18] Martínez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963.
- [19] Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997**, *38*, 1693.
- [20] Kassab, D. J.; Ganem, B. *J. Org. Chem.* **1999**, *64*, 1782.
- [21] Annis, D. A.; Helluin, O.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1907.
- [22] Fu, X.-L.; Wu, S.-H. *Synth. Commun.* **1997**, *27*, 1677.
- [23] Hou, X.-L.; Wu, J.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron: Asymmetry* **1998**, *9*, 1747.
- [24] Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 75.
- [25] Anthracycline antibiotics are used most often in antitumor combination chemotherapy: Neidle, S. *Nature* **1977**, *268*, 195.
- [26] Sagawa, S.; Abe, H.; Hase, Y.; Inaba, T. *J. Org. Chem.* **1999**, *64*, 4962.
- [27] Zhu, C.; Yuan, F.; Gu, W.; Pan, Y. *Chem. Commun.* **2003**, 692.
- [28] Hayashi, M.; Tamura, M.; Oguni, N. *Synlett* **1992**, 663.
- [29] Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668.
- [30] Shimazu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704.
- [31] (a) Vougioukas, A. E.; Kagan, H. B. *Tetrahedron Lett.* **1987**, *28*, 5513. (b) Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209.
- [32] Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.
- [33] Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256.
- [34] Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699.
- [35] Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 9023.
- [36] Del Moro, F.; Crotti, P. Di Bussolo, V.; Macchia, F.; Pineschi, M. *Org. Lett.* **2003**, *5*, 1971.
- [37] For a review, see: Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.
- [38] Müller, P.; Nury, P.; Bernardinelli, G. *Helv. Chim. Acta* **2000**, *83*, 843.
- [39] Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.
- [40] Clark, M. A.; Ganem, B. *Tetrahedron Lett.* **2000**, *41*, 9523.
- [41] Wu, M. H.; Karl, B. H.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2012.
- [42] Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2223.
- [43] Diol monoether can be converted into the 1,2-diol by treatment with ammonium cerium(IV) nitrate (CAN): Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.
- [44] Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252.
- [45] For a review on linked-BINOL applications, see: Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3.
- [46] (a) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687. (b) Ready, J. M.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 1374.
- [47] Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783.
- [48] Wu, M. H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252.
- [49] Wu, J.; Hou, X.-L.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron: Asymmetry* **1998**, *9*, 3431.
- [50] Fukuzawa, S.-I.; Kato, H.; Ohtaguchi, M.; Hayashi, Y.; Yamazaki, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3059.
- [51] Nugent, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 7139.
- [52] Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428.
- [53] Tao, B.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353.
- [54] Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 8827.
- [55] Paek, S. H.; Shim, S. C.; Cho, C. S.; Kim, T.-J. *Synlett* **2003**, 849.
- [56] Bruns, S.; Haufe, G. *Tetrahedron: Asymmetry* **1999**, *10*, 1563.
- [57] Bruns, S.; Haufe, G. *J. Fluorine Chem.* **2000**, *104*, 247.
- [58] Haufe, G.; Bruns, S.; Runge, M. *J. Fluorine Chem.* **2001**, *112*, 55.
- [59] Haufe, G.; Bruns, S. *Adv. Synth. Catal.* **2002**, *344*, 165.
- [60] Hodgson, D. M.; Gibbs, A. R. *Tetrahedron: Asymmetry* **1996**, *7*,

- 407.
- [61] Brookes, P. C.; Milne, D. J.; Murphy, P. J.; Spolaore, B. *Tetrahedron* **2002**, *58*, 4675.
- [62] (a) de Sousa, S. E.; O'Brien, P.; Steffens, H. C. *Tetrahedron Lett.* **1999**, *40*, 8423.
(b) Colman, B.; de Sousa, S. E.; O'Brien, P.; Towers, T. D.; Watson, W. *Tetrahedron: Asymmetry* **1999**, *10*, 4175.
- [63] Pettersen, D.; Amedjkouh, M.; Nilsson Lill, S. O.; Dahlén, K.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 2*, **2001**, 1654.
- [64] Tierney, J. P.; Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1019.
- [65] Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **1997**, *38*, 6425.
- [66] (a) Khan, A. Z.-Q.; Arvidsson, P. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1996**, *7*, 399.
(b) Khan, A. Z.-Q.; de Groot, R. W.; Arvidsson, P. I.; Davidsson, Ö. *Tetrahedron: Asymmetry* **1998**, *8*, 1223.
- [67] (a) Asami, M.; Seki, A. *Chem. Lett.* **2002**, 160. (b) Seki, A.; Asami, M. *Tetrahedron* **2002**, *58*, 4655.
- [68] (a) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760.
(b) Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610.
- [69] Bertilsson, S. K.; Andersson, P. G. *Tetrahedron* **2002**, *58*, 4665.
- [70] (a) Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *Tetrahedron* **2002**, *58*, 4669.
(b) Amedjkouh, M.; Pettersen, D.; Nilsson Lill, S. O.; Davidsson, Ö.; Ahlberg, P. *Chem. Eur. J.* **2001**, *7*, 4368.
- [71] Pakulski, Z.; Koprowski, M.; Pietrusiewicz, K. M. *Tetrahedron* **2003**, *59*, 8219.
- [72] Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457.
- [73] Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.
- [74] Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.
- [75] Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937.
- [76] Dooos, B. M. L.; Jacobs, P. A. *Tetrahedron Lett.* **2003**, *44*, 8815.
- [77] Lebel, H.; Jacobsen, E. N. *Tetrahedron Lett.* **1999**, *40*, 7303.
- [78] Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624.
- [79] Dooos, B. M. L.; Jacobs, P. A. *Tetrahedron Lett.* **2003**, *44*, 4715.
- [80] Kamal, A.; Arifuddin, M.; Rao, M. V. *Tetrahedron: Asymmetry* **1999**, *10*, 4261.
- [81] Rajender Reddy, L.; Bhanumathi, N.; Rama Rao, K. *Chem. Commun.* **2000**, 2321.
- [82] Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968.
- [83] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.
- [84] (a) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776.
(b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
(c) Gurjar, M. K.; Sarma, B. V. N. B. S.; Sadalpure, K.; Adhikari, S. *Synthesis* **1998**, 1424.
(d) Savle, P. S.; Lamoreaux, M. J.; Berry, J. F.; Gandour, R. D. *Tetrahedron: Asymmetry* **1998**, *9*, 1843.
- [85] White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633.
- [86] Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147.
- [87] Kim, G.-J.; Park, D.-W. *Catal. Today* **2000**, *63*, 537.
- [88] Song, Y.; Yao, X.; Chen, H.; Bai, C.; Hu, X.; Zheng, Z. *Tetrahedron Lett.* **2002**, *43*, 6625.
- [89] Kwon, M.; Kim, G.-J. *Catal. Today* **2003**, *87*, 145.
- [90] Breinbauer, R.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 3604.
- [91] Cavazzini, M.; Quici, S.; Pozzi, G. *Tetrahedron* **2002**, *58*, 3943.
- [92] Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876.
- [93] Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092.
- [94] Hou, X.-L.; Li, B.-F.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 2319.
- [95] Yu, Q.; Wu, Y.; Xia, L.-J.; Tang, M.-H.; Wu, Y.-L. *Chem. Commun.* **1999**, 129.
- [96] Liu, P.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 1235.
- [97] Wyatt, P. B.; Blakskjær, P. *Tetrahedron Lett.* **1999**, *40*, 6481.
- [98] (a) Wróblewski, A. E.; Hałajewska-Wosik, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2053.
(b) Wróblewski, A. E.; Hałajewska-Wosik, A. *Eur. J. Org. Chem.* **2002**, 2758.
- [99] Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086.
- [100] Peukert, S.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1245.
- [101] Trost, B. M.; Andersen, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320.
- [102] Gayet, A.; Bertilsson, S.; Andersson, P. G. *Org. Lett.* **2002**, *4*, 3777.
- [103] Asami, M.; Sato, S.; Honda, K.; Inoue, S. *Heterocycles* **2000**, *52*, 1029.