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Asymmetric Ring-Opening of Epoxides and Aziridines with Carbon Nucleophiles

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Dedicated to the memory of Prof. Luigi Gomez-Paloma

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Three-membered heterocyclic rings offer a powerful combination of reactivity, stability, availability, and atom economy. While heteroatom-based nucleophiles have been successfully employed, the use of carbon-centered nucleophiles is much less developed, yet represents a significant advance since it builds the basic carbon framework. In fact, the asymmetric ring-opening of epoxides and aziridines with carbon-based nucleophiles, as will be discussed in this Microreview, offers the possibility of generating valuable, chiral, nonracemic building blocks in a very simple, stereodefined manner.

1. Introduction

Epoxides and aziridines are widely utilized as versatile synthetic intermediates and are considered as "spring-loaded" rings for nucleophilic ring-opening.[1] Their reactions are dominated by the electrophilic nature of these heterocycles, generally involve cleavage of the strained three-membered ring, and include a wide range of nucleophilic ring-openings to give β-substituted alcohols and amines.[2–5] In particular, the asymmetric ring-opening (ARO) of *meso* epoxides and aziridines is a very rational and effective way to obtain the formation of two contiguous stereogenic centers, and can be performed using stoichiometric or catalytic amounts of chiral, nonracemic reagents or catalysts.[6–8]

The asymmetric ring-opening of epoxides, and to a lesser extent of aziridines, by means of catalytic processes has increased considerably in the last few years because it is an efficient means to convert readily available, inexpensive (bulk) chemicals into chiral, nonracemic products.[9] A large variety of nucleophiles have been employed successfully in ARO reactions, with the majority of these being heteroatom-based such as N_3^-,[10–12] ROH,[13,14] RSH,[15,16] amines,[17,18] and halides;[19,20] whereas the use of carbon-based nucleophiles remains quite limited.

The nucleophilic ring-opening of epoxides by carbon-based nucleophiles is a useful method for the generation of new carbon–carbon σ bonds in a very simple and stereodefined fashion. In this regard, cyanide is a particularly interesting carbon-based nucleophile because of its low cost and the synthetic versatility of the nitrile ring-opened products. Different organometallic reagents are also useful nucleophiles for the alkylation of epoxides and aziridines; amongst these, organocopper ones are known to be some of the most efficient for accomplishing the nucleophilic substitution of an epoxide in a highly chemo- and stereoselective manner.[21] In the field of the synthesis of natural products, there are plenty of examples in which an organocopper reagent (often generated in situ) alkylates an enantiomerically enriched terminal epoxide (obtained by enantioselec-

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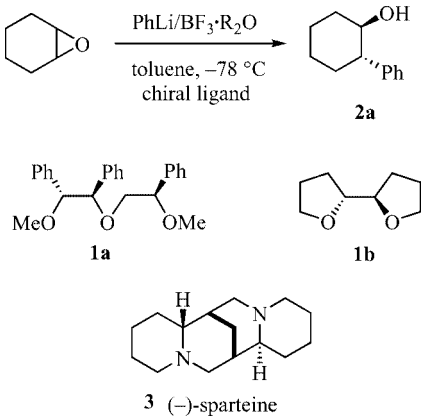
Mauro Pineschi was born in Certaldo (Firenze) in 1964. In 1993 he received his PhD from the University of Pisa under the guidance of P. Crotti on the development of new synthetic methodologies making use of epoxides and aziridines. After a postdoctoral position in the group of B. L. Feringa with a Marie Curie Fellowship of the European Community working on asymmetric catalysis, in 1998 he became researcher of organic chemistry at the University of Pisa. In 2002 he was appointed Associate Professor of organic chemistry at the same University. In 2000 he was the recipient of the Ciamician Medal, a prestigious award for young scientists from the organic division of the Italian Chemical Society. His research interests include enantioselective catalysis and the development of new synthetic methodologies involving small or medium ring heterocycles.

tive epoxidation or Jacobsen hydrolytic kinetic resolution) to give synthetically useful alcohols.[21–28] In fact, especially with nonconjugated terminal epoxides and aziridines, it is more convenient to start from the enantiomerically enriched compound and allow it to react with the necessary carbon nucleophile in a regioselective way.

This Microreview will summarize the intermolecular ARO of epoxides and aziridines with carbon nucleophiles up to 2005, with a particular emphasis on desymmetrization of *meso* substrates rather than on kinetic resolution procedures.



Scheme 1. Enantioselective ring-opening of cyclohexene oxide with an organolithium reagent mediated by stoichiometric amounts of external chiral ligands.

2. Organometallic Reagents

2.1. Hard Alkyl Metal Reagents

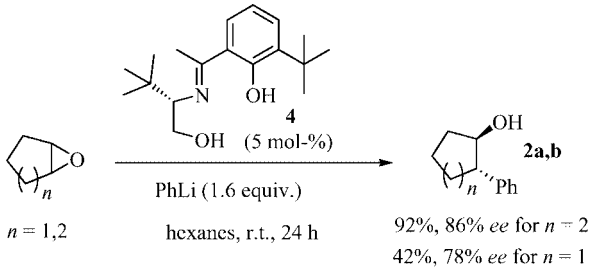
Epoxides can be successfully alkylated by several organometallic reagents, such as organolithium,[29,30] organomagnesium,[31–33] organocopper,[21] organozinc,[34] organoaluminum,[35] and organolanthanide compounds.[36] The corresponding aziridine ring-opening chemistry is complicated by the inherently low reactivity of the unactivated heterocycle and by the ambidentate nature of some activated species such as aziridine carbamates and *N*-acylaziridines. In view of their high chemoselectivity, organocopper compounds are also the organometallic reagent of choice for the ring-opening of aziridines.[37–41] Both organolithium and Grignard reagents have also been used, but this requires robust *N*-sulfonyl protection.[42–44]

In a seminal paper, Davies and Wollowitz reported the reaction of cyclohexene oxide with organocuprates and Grignard reagents in the presence of external chiral ligands such as amino alcohols.[45] Although the corresponding chiral β-substituted alcohols were obtained with very low enantioselectivities (≤3% *ee*), the concept of the combination of an organometallic reagent with a chiral Lewis base for the enantioselective alkylation of epoxides was demonstrated.

It is known that the nucleophilic ring-opening of relatively unreactive cyclohexene oxide is a very slow reaction in the absence of Lewis acids, and activation by coordination of a Lewis acid, such as $BF_3{\cdot}Et_2O$, to the oxygen atom of the epoxide is required. Without the Lewis acid, the utility of the alkylation reaction can be curtailed owing to competing reactions arising from the Lewis acidity or basicity of the organometallic reagent.[2,6,46–50] An external chiral-ligand-controlled enantioselective ring-opening of cyclohexene oxide was achieved in 1996 by Tomioka et al. by the use of a combination of PhLi (2.0 equiv.) and *stoichiometric* amounts of homochiral ethers in the presence of $BF_3{\cdot}Bu_2O$ (1.5 equiv.) at –78 °C (Scheme 1).[51,52] The corresponding 2-phenyl-1-cyclohexanol (**2a**) was obtained with a high yield (99%), and the best enantioselectivity (47%) was reached with 2.1 equivalents of the tridentate ligand **1a** in toluene.

In a related approach, Alexakis et al. have recently used nonracemic, chiral bis-THF **1b** derived from mannitol with very low asymmetric induction (12% *ee*).[53] On the basis that (–)-sparteine (**3**) is amongst the most popular chiral ligands for organolithium reagents, Alexakis et al. also considered the compatibility of this strong Lewis base donor with a strong Lewis acid such as $BF_3{\cdot}Et_2O$.[54] Although incongruous at first sight because competition of the Lewis acid should be in favor of the diamine moiety instead of the oxirane oxygen, this combination was successful, especially when using 1-naphthyllithium as the organometallic reagent (up to 85% *ee*).[55]

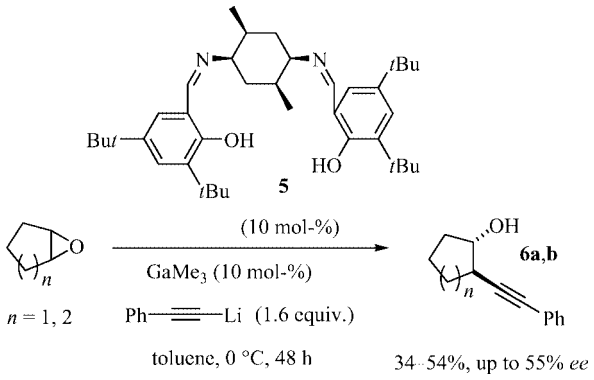
A significant advance towards a *catalytic* enantioselective arylation of symmetrical epoxides was described by Oguni et al.[56] Cyclohexene and cyclopentene oxide reacted at room temperature with phenyllithium in the presence of catalytic amounts (5 mol-%) of chiral Schiff bases to give the corresponding ring-opened products **2a**,**b** with a high enantioselectivity (up to 86% *ee*; Scheme 2). In this case the lithium alkoxides formed in situ by the addition of phenyllithium to chiral Schiff bases, such as **4** derived from (L)-*tert*-leucinol, are probably the real active catalysts.



Scheme 2. Catalytic enantioselective arylation of symmetrical epoxides with chiral Schiff bases.

It should be noted that in all these examples using organolithium reagents, only aryllithium reagents showed significant *ee* values; the use of alkyl-, alkenyl-, or alkynyllithium species gave the corresponding ring-opened products with no selectivity. More recently, an enantioselective alkynylation of *meso* epoxides catalyzed by chiral gal-

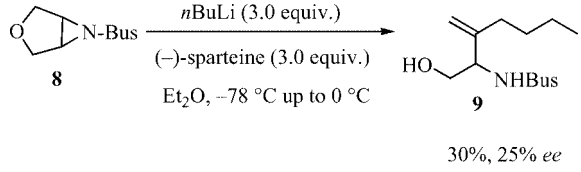
lium complexes was reported by Zhu et al.[57] Given that trimethylgallium is an effective catalyst for the ring-opening of oxiranes with alkynyllithiums, the authors used chiral gallium complexes of salen-based ligands of type **5** derived from a C_2 symmetric 1,4-diaminocyclohexane framework (Scheme 3). Treatment of the ligands with a stoichiometric amount of trimethylgallium gave the catalyst, which was not isolated but directly used in combination with phenylethynyllithium in the asymmetric ring-opening reactions of cyclic *meso* epoxides. The expected β-phenylethynyl alcohols **6a**,**b** were obtained with moderate yields and enantioselectivities. Interestingly, salen ligands derived from the more popular 1,2-diamino motifs provided a lower selectivity in the alkynylation reaction.



Scheme 3. Catalytic asymmetric alkynylation of *meso* epoxides.

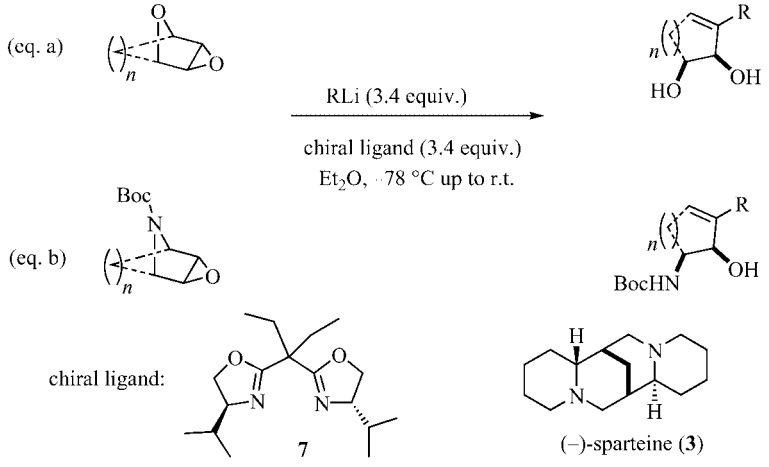
The direct metalation of the oxirane ring produces a carbenoid species, which can undergo several reactions.[46–50] For example, Hodgson et al. have reported an alkylative double ring-opening of dihydrofuran and dihydropyran epoxides with organolithium to give substituted alkenediols,[58] and this reaction was also applied to dihydropyrroles and tetrahydropyridines to give substituted amino alcohols.[59] When the reaction was performed in the presence of stoichiometric amounts of external chiral ligands, such as (–)-sparteine (**3**) or bisoxazoline **7**, the corresponding double ring-opened products were obtained with moderate enantioselectivities [24–43% *ee*; Equation (a) in Scheme 4].[60]

With epoxides derived from oxa- and azabicyclic alkenes, the reaction was more enantioselective (up to 85% *ee* with *i*PrLi) and particularly interesting because it comprised an intermolecular C–C bond-forming reaction with cogeneration of unsaturation and reorganization of two functional groups. It should be noted that the incorporation of the organometallic reagent occurs at a vinylic position, whereas the enantioselective ring-opening of oxa- and azabicyclic compounds usually results in cycloalkenes bearing the nucleophile in an allylic position.[61] This method is particularly valuable with tropane-type *meso* epoxides because it provides a new and enantioselective access to substituted aminocycloheptenols [*n* = 3; Equation (b) in Scheme 4].[60,62] More recently, in a related approach, Hodgson et al. have described an organolithium-induced ring-opening of *N*-*tert*-butylsulfonyl (Bus)-protected aziridines **8** in the presence of (–)-sparteine (**3**) to give amino alcohol **9**, albeit with low yields and enantioselectivity (Scheme 5).[63]



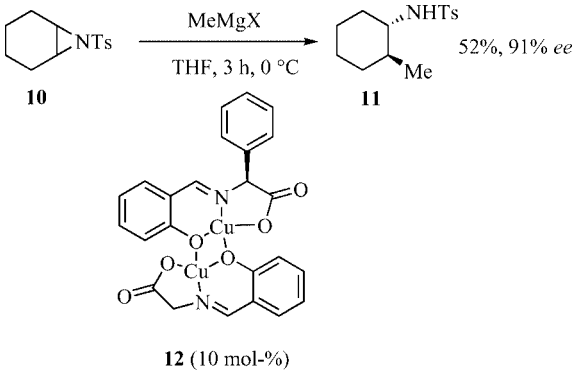
Scheme 5. Organolithium/(–)-sparteine-induced desymmetrization of dihydrofuran *meso*-aziridine **8**.

One of the very few examples of the asymmetric ring-opening of *meso*-aziridine with a hard alkyl metal reagent was reported by Nury and Muller.[64] Whereas the reaction of aziridine **10** with MeMgBr in THF gave almost exclusively the corresponding *trans*-2-bromo derivative, ring-opening occurred readily and compound **11** was formed with 85% yield when the reaction was carried out in the presence of 10% of [Cu(acac)$_2$] (Scheme 6). After the screening of several chiral copper catalysts in order to per-

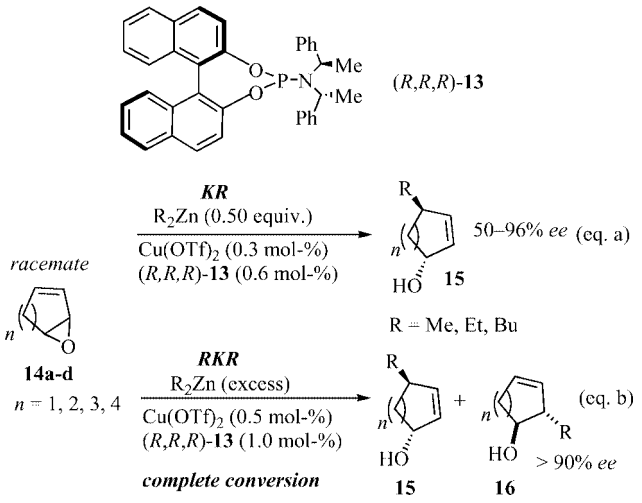


Scheme 4. Enantioselective alkylative double ring-opening of epoxides derived from oxa- and azabicyclic alkenes with organolithiums.

form the reaction in an enantioselective fashion, the copper complexes with Schiff base **12**, obtained upon condensation of salicylaldehyde with phenylglycine, gave the best results.



Scheme 6. Copper-catalyzed desymmetrization of a *meso*-*N*-sulfonylaziridine with methylmagnesium halides.



Scheme 7. Copper/phosphoramidite-catalyzed kinetic and regiodivergent kinetic resolution with dialkylzinc reagents.

Optimization of the reaction conditions by the slow addition of MeMgBr made it possible to obtain compound **11** with 91% *ee*, albeit with only a moderate yield. However, it should be noted that the reaction gives acceptable levels of enantioselectivity with very particular experimental conditions and Grignard reagents, thus revealing the complex nature of this catalytic system.

After a long and frustrating search for a catalytic system to open saturated *meso* epoxides with hard alkyl metals in the presence of diverse chiral ligands enantioselectively, Pineschi et al. envisioned that flanking a double bond to an oxirane ring could give rise to more possibilities of asymmetric nucleophilic ring-opening of the epoxide ring by an organometallic reagent. Allylic epoxides, also called vinyl oxiranes, can be considered as a special class of allylic substrates because they combine the reactivity of epoxides and that of allylic substrates, thus allowing a wide range of synthetically useful transformations.[65] As dialkylzincs are hard alkyl nucleophiles, but usually too weak to react with these conjugate systems, it was tempting to consider the possibility of generating a cuprate in situ by a transmetalation reaction leading to more reactive and selective species.[66] To our delight, we found a remarkable ligand-accelerated catalysis effect in the presence of a catalytic amount of copper complexes with Binol-based phosphoramidites such as **13** (Scheme 7).[67]

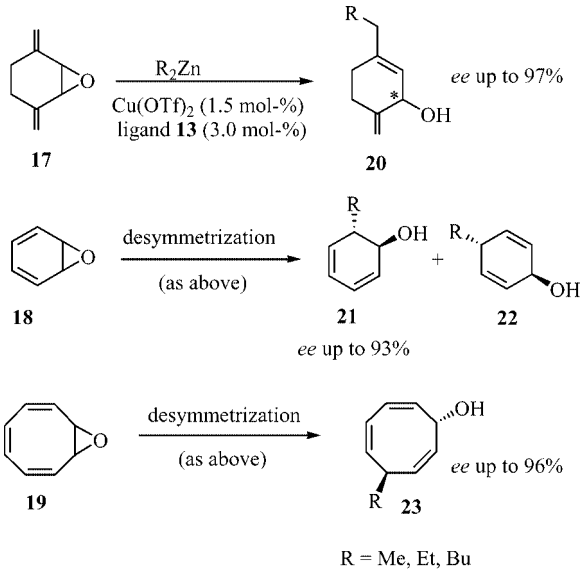
When the reactions were performed in accordance with a classic kinetic resolution (KR) protocol [Equation (a) in Scheme 7], it was possible to obtain the corresponding allylic alcohol (S_N2' pathway) with a high regio- and enantioselectivity and to recover the unreacted allylic epoxide with high optical purity.[68] Very interestingly, the complete conversion of a racemic allylic epoxide into constitutionally different enantiomerically enriched ring-opened products, namely regioisomeric allylic and homoallylic alcohols of type **15** and **16**, was obtained simply by using an excess of the dialkylzinc reagent and a longer reaction time [Equation (b) in Scheme 7].[69] This is one of the very rare examples of a regiodivergent kinetic resolution (RKR) by the use of a hard organometallic reagent and a chiral catalyst in a carbon–carbon bond-forming reaction.[70] More recently, we have shown that the RKR can be successfully applied to a variety of cyclic semi-rigid allylic epoxides and, in some specific cases, also to conformationally mobile allylic epoxides.[71]

On the other hand, Pineschi et al. have shown that this RKR process is not operative with cyclic allylic aziridines: with these substrates it is only possible to obtain a classic kinetic resolution that gives new allylic amines with moderate to good enantioselectivity.[72]

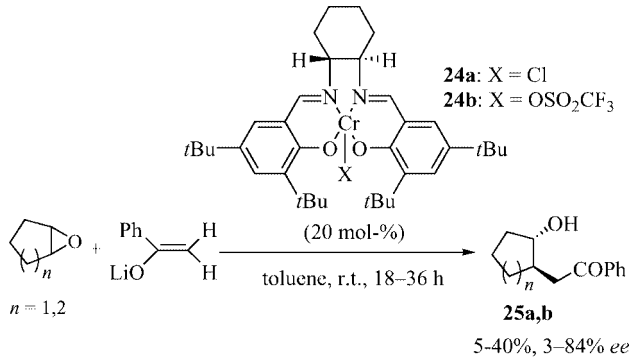
Quite recently, Alexakis and Equey have shown that cyclic allylic epoxides can also be alkylated by organoaluminum reagents in combination with copper salts and chiral phosphoramidites.[73] Under these experimental conditions, the reaction must be carried out in THF as the use of less coordinating solvents such as toluene and CH_2Cl_2 gave only the formation of oligomeric products.

To avoid the inherent limitations of resolution processes, Pineschi et al. have studied the reactions of several symmetrical bis-allylic epoxides with dialkylzinc reagents in combinations of chiral copper phosphoramidite complexes (Scheme 8). For example, *meso*-methylidene cycloalkane epoxide **17** afforded the corresponding bis-allylic alcohols of type **20** with a good yield and a high regio- and enantioselectivity using phosphoramidite **13**.[74]

The effective chiral recognition of two enantiotopic faces is also possible with the same chiral catalyst with very reactive arene oxides. For example, the unprecedented catalytic enantioselective trapping of benzene oxide (**18**) with dialkylzincs gave a crude reaction mixture consisting of the not previously synthesized regioisomeric dienols **21** (*anti*-α adduct) and **22** (achiral γ adduct; Scheme 8).[75] The monoepoxide **19** derived from 1,3,5,7-cyclooctatetraene (COT) is also a symmetrical molecule and it has several distinctive features with respect to the other symmetrical vinyl oxirane



Scheme 8. Catalytic and enantioselective desymmetrization of symmetrical allylic epoxides **17**–**19**.



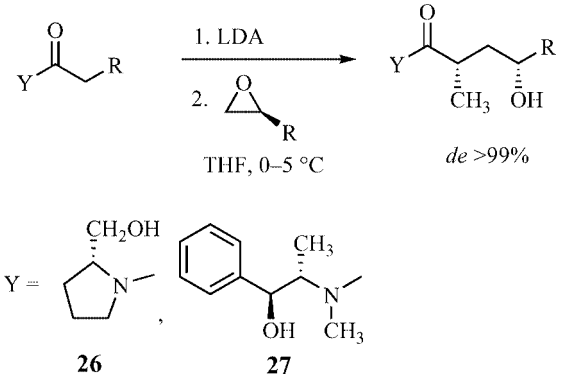
Scheme 9. ARO of epoxides with the lithium enolate of acetophenone in the presence of chiral Lewis acids.

substrates examined. In fact, COT-monoepoxide has a special structure imposed by three consecutive double bonds where the double bonds and the epoxide ring are not in the same plane (ca. 60° of deviation). Moreover, ring-contraction isomerization to the seven-membered trienyl carboxaldehyde, which, in turn, adds to the organometallic reagents to give substituted cycloheptatrienyl alcohols, is the most common reaction observed when organometallic reagents are employed with this substrate.[76] Our catalytic system allowed a highly enantioselective desymmetrization of COT-monoepoxide with dialkylzinc reagents and the corresponding trienyl alcohol addition product **23** was obtained with a high yield, complete conjugated regioselectivity, and high enantioselectivities.[77,78]

2.2. Unstabilized Metal Enolates

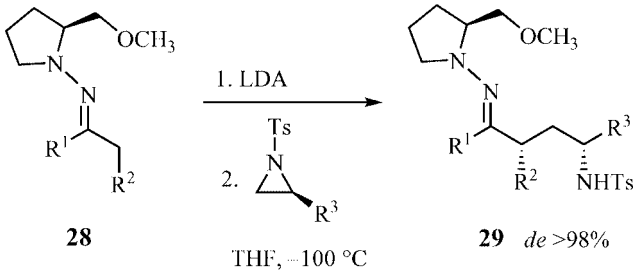
Although enolates, their silyl equivalents, and otherwise stabilized carbanions would be interesting candidates for ARO of *meso* epoxides, no efficient catalytic method has been developed so far. Despite their high reactivity, epoxides typically do not react with lithium enolates of simple monoketones and monoesters without activating the epoxide by addition of a Lewis acid.[79] In an isolated example, Crotti et al. have reported that some chiral Lewis acids are able to promote the asymmetric addition of the lithium enolate of acetophenone to cyclohexene and cyclopentene oxide to give enantiomerically enriched γ-hydroxy ketones **25a**,**b** (Scheme 9).[80] The best results in terms of enantioselectivity were obtained with 20 mol-% of chiral, nonracemic Cr^{III}–salen derivatives **24a**,**b**, although the yield was generally very low as the chromium complex and the lithium enolate are probably incompatible, which results in an inefficient catalyst turnover.

Successful enolate-epoxide bond constructions typically employ a double asymmetric induction approach starting from chiral, nonracemic enolates and enantiomerically enriched epoxides. In this regard, chiral auxiliaries derived from prolinol propionamide (Scheme 10, Y = **26**)[81] and pseudoephedrine amide (Scheme 10, Y = **27**) have proved to be particularly successful.[82]



Scheme 10. Double asymmetric alkylation of enantiomerically enriched epoxides with chiral amide enolates.

It was found that the inherent π-facial selectivity of these chiral amide enolates is the overriding feature in determining the stereochemical outcome of the reaction with monosubstituted epoxides, and it was possible to obtain high *syn*-diastereoselectivities (≥99%) when the stereochemically matched epoxide was used (Scheme 10). However, 1,2-disubstituted epoxides proved to be unreactive under a variety of conditions and an attempted kinetic resolution with

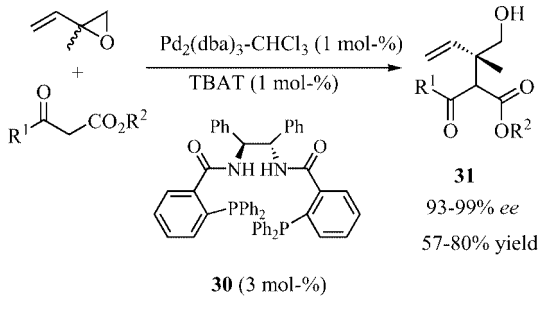


Scheme 11. Double asymmetric ring-opening of enantiomerically enriched aziridines by the SAMP-hydrazone method.

racemic monosubstituted epoxides was not satisfactory.[82] In a related approach, chiral enolates derived from (*S*,*S*)-(+)-pseudoephedrine amides also proved to be particularly useful for the ring-opening of enantiomerically enriched aziridines.[83] A nucleophilic ring-opening of tosylaziridines with chiral aza-enolates **28** derived from the SAMP-hydrazone method was described by Enders and co-workers (Scheme 11).[84] In this case the corresponding α-alkyl-β-amino hydrazones **29** were also obtained with a good *syn*-diastereoselectivity.

2.3. Stabilized Enolates

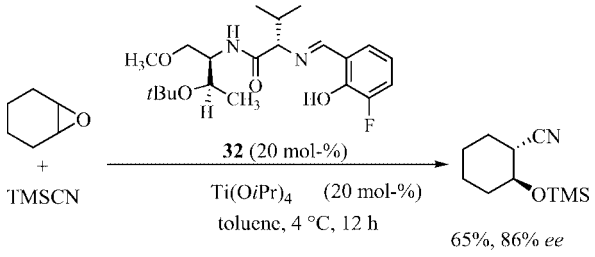
Although the addition of stabilized enolates to epoxides[85] or aziridines[86] is a well-established synthetic transformation, asymmetric versions of this reaction have received little consideration. The palladium-catalyzed allylic alkylation of vinyl oxiranes with soft carbon nucleophiles is known to proceed under neutral conditions with a high 1,4-regioselectivity.[87,88] In order to achieve asymmetric induction in these cases, the palladium must occupy a single prochiral face of the initially formed π-allyl complex. Therefore, the ability to induce asymmetry into this palladium-catalyzed allylic alkylation of racemic acyclic systems stems from enantiofacial exchange of the metal by a σ–π–σ equilibration.[89] Trost and Jiang have described a striking asymmetric addition of ethyl acetoacetate to isoprene monoepoxide catalyzed by 1 mol-% of $[Pd_2(dba)_3]$·$CHCl_3$ and 3 mol-% of chiral ligand (*S*,*S*)-**30** (Scheme 12).[90] As achiral ligands give 1,4-adducts (S_N2' pathway), these reactions demonstrate the unique property of the chiral ligand to control regio- and enantioselectivity, favoring the formation of the desired branched 1,2-product **31** (S_N2 pathway). The addition of 1 mol-% of TBAT (tetra-*n*-butylammonium triphenyldifluorosilicate) to increase the rate of interconversion of diastereoisomeric π-allylpalladium complexes gave a higher 1,2-regioselectivity. Good yields of the desired 1,2-adducts can be obtained with a diverse array of β-keto esters, and nitromethane also provided the corresponding adduct with a 51% yield and 97% *ee*. It should be noted that this asymmetric reaction creates a chiral quaternary center with three of the groups being quite different functional groups, thus furnishing a very useful chiral building block.



Scheme 12. Regio- and enantioselective reactions of β-keto esters with isoprene monoepoxide.

3. Cyanide

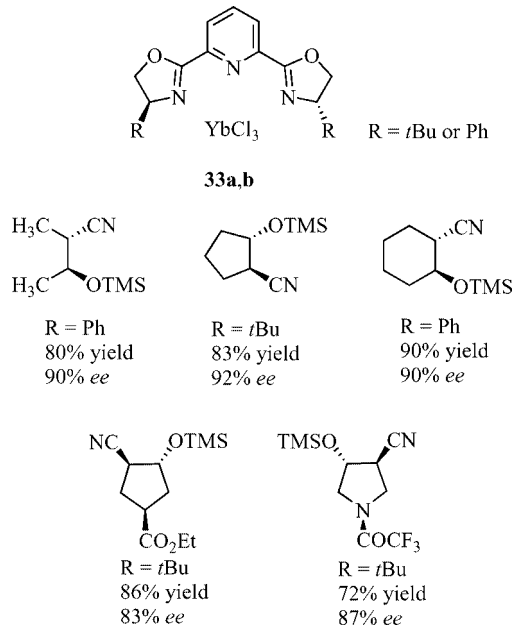
Cyanide is a particularly interesting carbon-based nucleophile for asymmetric ring-opening reactions of epoxides because of its low cost and the synthetic versatility of the nitrile ring-opened products. The most common cyanide source is trimethylsilyl cyanide (TMSCN) and this usually leads to formation of β-trimethylsilyloxy nitriles. However, under certain reaction conditions, most commonly those associated with the use of soft Lewis acids, β-trimethylsilyloxy isocyanide can also be obtained due to the ambidentate character of TMSCN.[91] Oguni and co-workers have found that the addition of trimethylsilyl cyanide to epoxides to give β-trimethylsilyloxy nitriles can be efficiently catalyzed by a combination of titanium tetraisopropoxide and achiral Schiff-base ligands.[92] Inspired by this observation, Snapper and Hoveyda used a combinatorial approach and solid-phase assembly to identify an effective chiral catalyst for this transformation.[93] For example, the desymmetrization reaction of cyclohexene oxide with TMSCN in the presence of the titanium complex of **32** as the chiral catalyst gave the corresponding ring-opened product with good yields and enantioselectivity (Scheme 13).



Scheme 13. Ti-catalyzed enantioselective addition of TMSCN to *meso* epoxides.

As peptide-derived ligands of type **32** possess a modular structure in which the asymmetry can easily be varied by the use of different amino acid building blocks, the same authors, by a careful ligand screening on the solid phase, found the most appropriate chiral ligand for other particular *meso* substrates.[94]

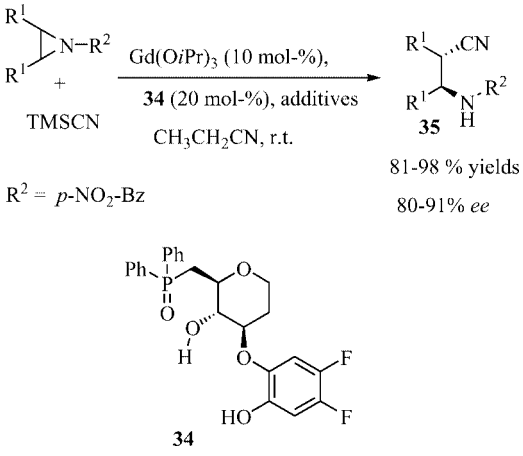
Following the seminal contributions by Kagan[95] and Utimoto[96] on the regioselective ring-opening of terminal epoxides with TMSCN accompanied by minimal production of isomeric isocyanide, Jacobsen et al. envisaged that the multiple coordination sites available to lanthanide salts might allow their coordination with appropriate chiral ligands. A series of different chiral ligands were evaluated in association with some lanthanide chlorides in order to identify the optimal chiral catalyst. The ring-opened products were obtained with the highest enantioselectivities by the use of 12 mol-% of [(pybox)$YbCl_3$] complexes **33a**,**b**, as shown in Scheme 14. Unfortunately, the practical utility of this method is limited because low temperatures must be maintained for very long reaction times (up to seven days) in order to obtain high yields and enantioselectivities.[97]



Scheme 14. Asymmetric ring-opening of *meso* epoxides with TMSCN catalyzed by (pybox)lanthanide complexes.

More recently, an enantioselective ring-opening of a phospholene *meso* epoxide with TMSCN in combination with a (salen)Al^{III} catalyst was reported by Pietrusiewicz et al. The best results (56% yield and 72% *ee*) were obtained with TBME as the reaction solvent; the use of CH_2Cl_2 and THF depressed the yields markedly.[98] Despite these significant efforts, a truly practical, general, and highly enantioselective addition of cyanide to *meso* epoxides has not been discovered so far.

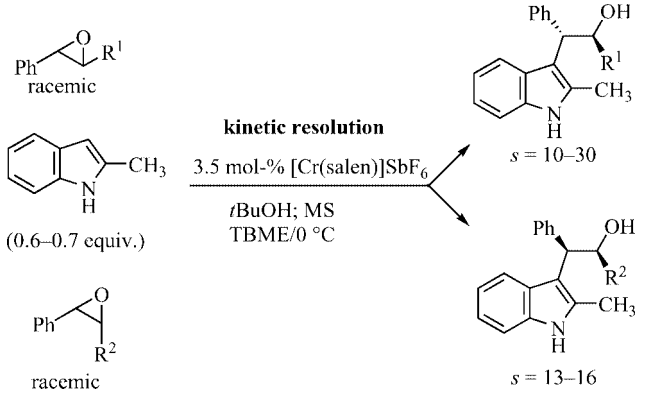
The enantioselective addition of carbon nucleophiles to *meso*-aziridines has been even less studied and represents a formidable challenge due to both the low reactivity of aziridines and the general difficulty in differentiation of enantiotopic centers. Very recently, a catalytic enantioselective desymmetrization of *meso*-*N*-acylaziridines with TMSCN has been described by Shibasaki and Kanai.[99] The Gd^{III} complex with ligand **34** is quite versatile because it has been found to catalyze other asymmetric cyanation reactions (Scheme 15). The use of an *N*-*p*-nitrobenzoyl protecting group on the aziridine nitrogen proved to be crucial for high yields and *ee*'s of the corresponding ring-opened products. The beneficial use of trifluoroacetic acid (TFA) as an additive is believed to effect the bridging of the two Gd^{III} atoms, which rigidifies the complex and allows for more efficient transfer of stereochemical information. The β-amino nitrile products of this reaction, which can be recrystallized to give enantiomerically pure material, are very versatile synthetic intermediates. For example, acid hydrolysis of the adducts and subsequent purification deliver cyclic β-amino acids, which are currently of great interest in the study of protein folding and peptidomimetics.



Scheme 15. Catalytic enantioselective desymmetrization of *meso*-(*p*-nitrobenzoyl)aziridines with TMSCN.

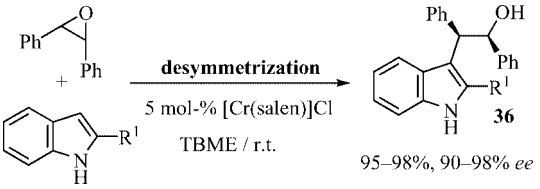
4. Miscellaneous Methods

Although the Friedel–Crafts alkylation is one of the oldest and most intensively studied organic reactions, epoxides have rarely been used as the electrophilic partner.[100] For example, intermolecular Friedel–Crafts alkylations of aromatics with epoxides have only sparingly been reported, and these reactions are often accompanied by various side-reactions.[101] Only electron-rich nitrogen-based heterocycles, such as indoles, are able to react with epoxides in the presence of metal catalysts in a regioselective fashion.[102–105] Given the striking ability of [Cr(salen)Cl], developed by Jacobsen,[9] to generate a suitable chiral environment in the ring-opening of epoxides, Cozzi and Umani-Ronchi developed the first kinetic resolution of racemic *cis* and *trans* aromatic epoxides. The best results in ring-opening reactions were obtained with 3.5 mol-% of cationic [Cr(salen)]SbF_6 in the presence of 4-Å molecular sieves and *t*BuOH in TBME with stereoselectivity factors (*s*) ranging from 10 to 30 (Scheme 16).[106] Interestingly, in the kinetic resolution of racemic styrene oxide, the absolute configuration of the isolated, unreacted epoxide turned out to be the opposite of that in other kinetic resolutions carried out with other nucleophiles in combination with chiral salen catalysts, thus pointing to a different reaction mechanism.



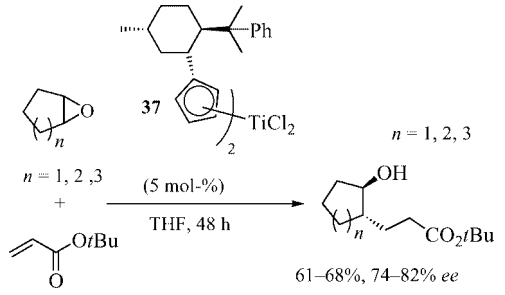
Scheme 16. Kinetic resolution of *cis*- and *trans*-aryl epoxides with 2-methyl indoles.

The [Cr(salen)Cl]-catalyzed addition of indoles to epoxides has also been applied to the ARO of *meso*-stilbene oxide (Scheme 17). In this case, the commercially available [Cr(salen)Cl] (5 mol-%) proved to be effective, and the corresponding indolyl derivatives **36** were isolated with an excellent yield and high enantioselectivity (Scheme 17).



Scheme 17. Catalytic enantioselective desymmetrization of *meso*-stilbene oxide with 2-substituted indoles.

A conceptually different approach from the enantioselective opening of *meso*-epoxides by an S_N2 reaction, where the path of the incoming nucleophile has to be controlled, is the catalytic electron-transfer reaction. In this case, to achieve a high enantioselectivity, the catalyst should allow for distinctly differing interactions of the ligand with the enantiotopic reaction sites of the epoxide. In this respect, Gansäuer and co-workers have reported a high enantio- and diastereoselective C–C bond forming reaction by the addition of a β-titanoxy radical, obtained by treatment of a cyclic epoxide with a chiral, nonracemic titanocene species, to *tert*-butyl acrylate.[107] The use of 5 mol-% of titanocene complex **37** gave satisfactory results in the optimized conditions for the enantioselective openings of some bicyclic *meso* epoxides (Scheme 18).



Scheme 18. Enantioselective C–C bond forming reactions by the addition of β-titanoxy radical to *tert*-butyl acrylate.

The enantioselectivity of the epoxide opening increased with ring size, reaching synthetically useful levels for the six- and seven-membered rings (n = 2, 3). This reasonably indicates a better fit of the larger substrates into the chiral pocket of the catalyst.

5. Conclusions

Whereas the vast majority of asymmetric carbon–carbon bond-forming reactions involve addition to prochiral π-systems (e.g. alkenes, carbonyl, imines etc.), there are far fewer examples dealing with the enantioselective substitution of C–O σ-bonds of epoxides and aziridines with carbon nucleophiles. This lack of successful examples is particularly evident when the alkylation of *meso*-epoxides and aziridines with sp^2-hybridized organometallics such as metallic enolates, their synthetic equivalents such as enol silanes, and allylic metals is considered. The so-called privileged chiral ligands,[108] such as salen-based catalysts, which are well-suited for the ARO of epoxides with heteronucleophiles, are often not suitable when carbon nucleophiles are used. This is particularly evident when organometallic reagents are considered because they are often incompatible with these ligands. Despite some isolated examples of the successful asymmetric arylation of epoxides with hard alkyl metal reagents such as PhLi, an enantioselective addition of milder arylating agents (such as arylboronic acids and derivatives) to epoxides and aziridines would be of particular value for increasing the scope and the functional group tolerance of this potentially versatile arylation reaction.

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