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Organocatalytic Asymmetric Ring-Opening Reactions of Epoxides: Recent Progress

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Abstract: In this Minireview recent advances in the asymmetric ring-opening reaction (ARO) of *meso* and racemic epoxides promoted by organocatalysts is reviewed. A variety of organic promoters such as chiral phosphoric acids, amino- and peptidyl thioureas, sulfinamides was successfully used in ring-opening reaction of epoxides under catalytic conditions to give enantioenriched 1,2-bifunctional alcohols, carbonyl compounds and nitroepoxides. Dual activation of the reagents provided by the organocatalysts appears to be an effective strategy useful to face other unmet challenges in ARO reactions of epoxides.

Introduction

Ring-opening reactions represent an important tool in organic synthesis to obtain in a single-step functionalized linear or cyclic molecules bearing multiple chiral centers at contiguous or distal carbon atoms.[1]

Although stereospecific substitution of σ-bonds is not a predominant strategy in asymmetric synthesis, over the last decades, notable results have been achieved in the ring-opening reactions of epoxides.[2] Undoubtedly, they are highly versatile synthons and among the most important compounds able to undergo S_N2-type ring-openings, largely by heteroatom based nucleophiles, due to the significant strain of the three-membered ring. Moreover, a variety of differently substituted non racemic epoxides, accessible via oxidative or alternative methods,[3] facilitates their employment to obtain highly valuable products in stereodefined manner such as 1,2-amino alcohols, 1,2-diols, 2-hydroxy sulfides, 1,2-halohydrins, 1,2-cyanohydrins, allylic alcohols. However, structural features of the epoxides and reaction conditions affect the regio- and stereocontrol of the ring cleavage, thus showing some limitations in the application of this tool.

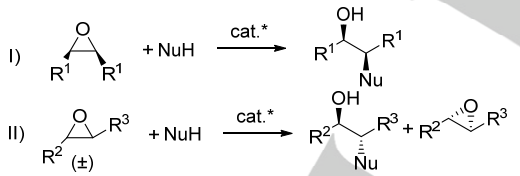

Figure 1. Schematic approaches of catalytic asymmetric ring-opening reaction of I) *meso*-epoxides and II) racemic epoxides.

Asymmetric ring opening (ARO) reactions of epoxides circumvent the availability of chiral non racemic epoxides as source, being a synthetic alternative to produce 2-functionalised alcohols and enantioenriched epoxides difficult to access by classical methods. Indeed, ready available achiral and racemic epoxides are used as the starting material in ARO reactions promoted by non racemic catalysts (Figure 1). These processes can be grouped into: I) desymmetrization of *meso*-epoxides and II) kinetic resolution of racemic epoxides.

The desymmetrization of *meso*-epoxides (I) is the most investigated approach to obtain enantioenriched 2-functionalised alcohols.[4] The two enantiotopic carbons of the oxirane are differentiated by the presence of chiral non racemic Lewis acid, which through coordination with the epoxide oxygen facilitates the nucleophile attack. This approach is particularly attractive as achiral compounds can be manipulated to enantioenriched products in up to quantitative yields. Several chiral ligand metal systems based on Zr(IV)-trialkanolamines,[5] Cr(III)-[6] and Co(III)-salen,[7] Yb(III)-, Ti(IV)- and Mg(II)- BINOL,[8] Sc(III)-bipyridine,[9] Li-Ga$(BINOL)_2$[10]have been developed for this scope with azide, amines, alcohols, water, carboxylic acids, thiols, selenols, cyanide as the nucleophiles. For the synthesis of halohydrins, chiral non racemic Lewis bases in the presence of $SiCl_4$, developed by Denmark, showed to be a first conceptually different system to apply for this challenging example of ARO reaction.[11] Likewise, few examples were reported for the ARO reaction of *meso*-epoxides with hard or soft carbon based nucleophiles.[2b,12] A particularly useful application of ARO reaction exploits strong chiral lithium amides. They demonstrated the ability to catalyze the rearrangement of *meso*-epoxides to enantioenriched allylic alcohols via intramolecular elimination, an area which experienced significant improvement over the years.[13]

Kinetic resolution of racemic epoxides (II) is a strategy of primary importance especially when chiral non racemic epoxides cannot be achieved through classical asymmetric methods. To serve as an efficient process, reaction rates of the two enantiomers have to differ significantly in the selectivity-determined step, involving diastereoisomeric transition states, as measured by the stereolectivity factor ($S=k_{rel}=k_{fast}/k_{slow}$).[14] Taking into account that in an ideal kinetic resolution the theoretical maximum of 50% yield of unreactive epoxide is attainable, the control of the regioselectivity is a crucial point for the successful application of this tool. Unsurprisingly, ARO reaction of racemic terminal epoxides came out as the first impressive example, considering either the high regiocontrol experienced in their ring-opening reactions and the lack of general asymmetric methods to produce them.

Jacobsen and coworkers first demonstrated that Cr(III)-[15] and Co(III)-salen[16] complexes serve as highly efficient catalyst for the kinetic resolution of a broad range of terminal epoxides obtained together with 2-functionalised alcohols in practically useful yields and excellent level of enantioselectivity. These catalytic systems showed stereoselectivity factor S values higher than 100, typical of enzymatic catalysis. In this respect, different hydrolases have been also successfully used in ARO reactions of either *meso*- and racemic epoxides.[4b,17]

This Minireview focuses on the recent debut of popular bifunctional organic promoters in the area of ARO reaction of *meso*- and racemic epoxides, namely chiral phosphoric acids, amino- and peptidyl thioureas, sulfinamides. Organocatalysed ARO reactions of epoxides are divided into three sections: I) the desymmetrization of *meso*-epoxides; II) kinetic resolution of

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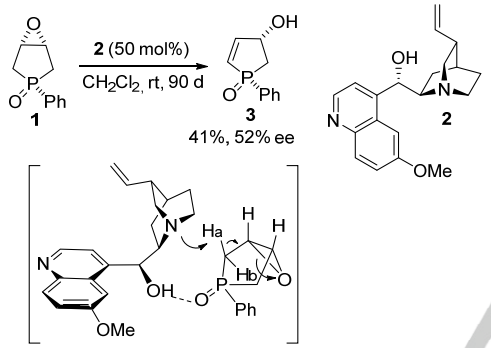
racemic epoxides. Rearrangements involving 1,2-migration of a substituent from one carbon atom of the epoxide ring to the other via either a Meinwald or semi-pinacol rearrangement process will be treated in a separate section. ARO reactions catalyzed by either strong chiral lithium amides and Lewis bases/$SiCl_4$ systems have been previously reviewed and will not be considered here.[2a,18]

Desymmetrization of *meso*-epoxides

Intramolecular elimination to allylic alcohols

In 2002, inspired by the activation strategy reported in strong chiral organolithium bases mediated rearrangement of *meso*-epoxides to allylic alcohols,[13] Pietrusiewicz and co-authors illustrated the first example where a bifunctional organocatalyst was used in the desymmetrization of *meso*-1-phenyl-3-phospholene oxide **1** (Scheme 1).[19]

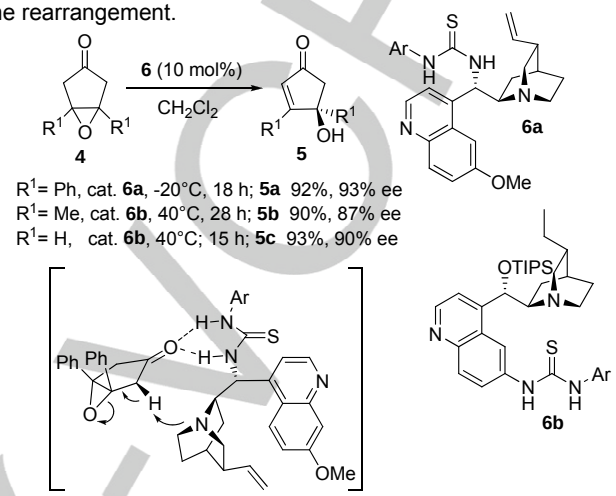


Scheme 1. Quinidine catalysed desymmetrization of phospholene epoxide **1**.

The allylic alcohol **3**, bearing also a stereogenic phosphorous center, was obtained in 41% yield and 52% ee. The best performing catalyst quinidine **2**, among the cinchona alkaloids tested, was suggested to preferentially deprotonate the H_a hydrogen atom *anti* to the epoxide oxygen. In the H-bonded binary epoxide-quinidine complex, the interaction of the catalyst OH group with the phosphoryl oxygen of the reagent was important to selectively direct the deprotonation. The opposite enantiomer of the product was recovered when using pseudoenantiomeric quinine catalyst. The role of the hydroxyl moiety proved to be critical as the *O*-acetyl quinidine was found to be completely inactive. Although a substoichiometric loading of quinidine and long reaction time were necessary to achieve modest conversion, this process paved the way to the employment of readily available bifunctional organocatalysts in base catalysed rearrangements of *meso*-epoxides.

More recently, Jørgensen and coworkers illustrated an elegant rearrangement of *meso*-epoxycyclopentanones **4** to 4-hydroxycyclopent-2-enones **5** catalysed by thiourea-derived cinchona alkaloids (Scheme 2).[20] The transformation is particularly interesting in view of the usefulness of enantioenriched compounds **5** as starting reagents for the synthesis of prostaglandins.[21]

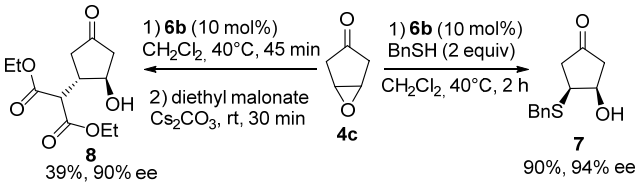
The outcome of the ARO reaction of epoxides **4** was found to be dependent on epoxide substitution and high enantioselectivity was achieved with organocatalysts **6a-b**, bearing the thiourea and the quinuclidine nitrogen placed at different distance. In the case of compound **5c**, the absolute configuration was confirmed by X-ray analysis which helped to formulate a transition state for the rearrangement.



Scheme 2. Thiourea-derived cinchona alkaloids catalysed desymmetrization of *meso*-epoxycyclopentanones (Ar = 3,5-$(CF_3)_2C_6H_3$, TIPS = triisopropylsilyl).

The authors suggested that hydrogen bonding of the thiourea group with the carbonyl moiety enhances acidity of the α-protons, thus easily and selectively deprotonated by the quinuclidine nitrogen according to a E1cb-like mechanism.

Interestingly, one-pot desymmetrization/Michael addition sequences were reported by using *meso*-epoxycyclopentanone **4c** and catalyst **6b** to obtain functionalised 4-hydroxycyclopentanone scaffolds in high stereocontrol (Scheme 3).



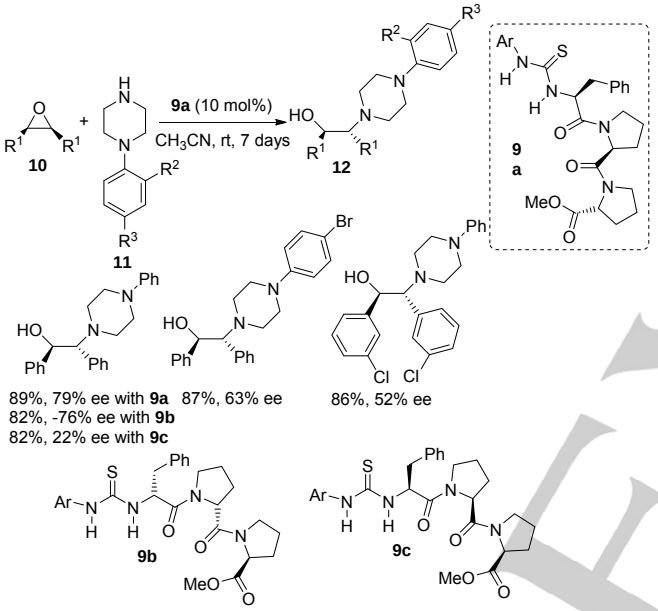
Scheme 3. One-pot desymmetrization/Michael sequence to functionalised 4-hydroxycyclopentanones.

Nucleophilic ring-opening to 2-amino alcohols, 2-hydroxy sulfides, *O*-protected 2-hydroxythiols and 1,2-diols

Peptides are becoming attractive catalysts in asymmetric synthesis thanks to their facile access and more importantly, the great variety of structural diversity achievable in the final scaffold.[22] However, the high level of functionalization coupled with their conformational complexity in solution make hard either the catalyst design and to get an insight into the origin of enantioselectivity when compared to simpler bifunctional organocatalysts. Hence, it is not surprising that we have not

assisted to a rapid growth in the application of peptides in asymmetric catalysis over the last years.

In 2014, Chimni and coauthors designed a chiral combined thiourea peptidyl scaffold for the desymmetrization of *meso*-epoxides with amines. The idea was to exploit a dual activation of the epoxide, provided by the thiourea moiety and the nucleophile by a generic site in the chiral peptidyl moiety. According to the literature,[23] a peptide linker incorporating β-turn conformations, introduced with L-Pro-D-Pro and D-Pro-Gly dipeptides, would have expected to be the most effective. After a preliminary screening of peptidyl thiourea catalysts and reaction conditions on model reaction of *cis*-stilbene oxide and *N*-phenyl piperazine, catalyst **9a**, used at 10 mol% loading, was selected to explore the scope of the ARO reaction in CH_3CN as solvent at room temperature (Scheme 4).



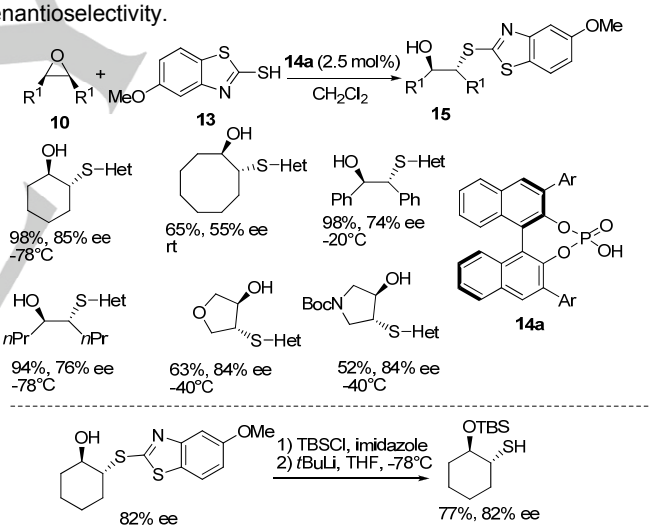
Scheme 4. Peptidyl thiourea organocatalysed ARO reaction of *cis*-stilbene oxides with *N*-aryl piperazines (Ar = 3,5-$(CF_3)_2C_6H_3$).

The 1,2-amino alcohols **12** were isolated in high yield and and up to 79% ee, *meta* and *para* halogen substitution on the aromatic ring of either the piperazine and the epoxide. *ortho*-Halogen and nitro-substituted epoxides were not ring-opened by the amine, likely due to steric reasons and deleterious competitive H-bonding ability of nitro group with respect to the oxirane oxygen with the thiourea moiety of the catalyst. Simple *N*-alkyl substituted piperazine, piperidine and primary or secondary alkyl amines afforded racemic products. By further screening, it was established that the absolute configuration of the *N*-terminal residue controlled the enantioselectivity of the product. Predictably, the opposite enantiomer of compounds **12** are obtainable when using enantiomeric catalyst **9b** and a significant impact on the enantiocontrol was observed when using diastereoisomeric catalyst **9c**, bearing opposite absolute configuration of the *C*-terminal residue (Scheme 4). It will be necessary to enhance the catalytic efficiency and to extend the scope of this rather challenging ARO reaction, possibly developing new hybrid thiourea peptidyl organocatalysts.

The catalytic activity of a large number of transformations mediated by BINOL-derived phosphoric acids has been explained invoking a Lewis base-Brønsted acid catalysis.[24] DFT studies supported concerted mechanisms, where the organocatalyst establishes simultaneous H-bonding interactions with the electrophile and the nucleophile.[24a,b] Being this type of bifunctional activation well-suited for a ring-opening reaction, it has been successfully applied in the BINOL-derived phosphoric acid mediated nucleophilic ARO reaction of *meso*-epoxides.

In 2013, Sun and co-authors reported the first example by using mercaptobenzothiazoles.[25] A variety of potential nucleophiles such as alcohols, phenols, amines and thiols were checked in the model ARO reaction of cyclohexene oxide in the presence of a phosphoric acid without success. Only when using highly nucleophilic 5-methoxymercaptobenzothiazole **13** the desired alcohol derivative was obtained. (*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP) **14a** was found to be the most effective catalyst in CH_2Cl_2 as the solvent (Scheme 5).

The process was affected by the nature of the starting epoxide and accordingly it was performed at low or at room temperature using 2.5 mol% of the organocatalyst. Cyclic and acyclic products **15** were recovered in moderate to good yield and enantioselectivity.



Scheme 5. TRIP-BINOL-derived phosphoric acid catalysed ARO reaction of *meso*-epoxides with mercaptobenzothiazoles (Ar = 2,4,6-(iPr)$_3C_6H_2$), TBS = *t*butyldimethyl silyl.

The authors proposed the activation of epoxide through hydrogen-bonding by the acidic group of the TRIP-BINOL-derived phosphoric acid, whereas the tautomeric form of the nucleophile would be involved in H-bonding interaction with the basic phosphoryl oxygen (Figure 2).

Although this process appears to be restricted to mercaptobenzothiazoles as the nucleophiles, cleavage of the heteroaromatic moiety of product **15**, to give the corresponding 2-mercapto alcohols without erosion of the enantioselectivity,

demonstrated to be a synthetically useful derivatization (Scheme 5).

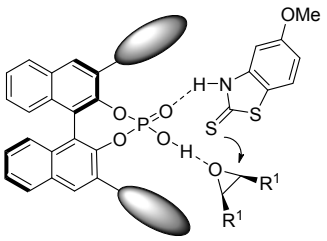
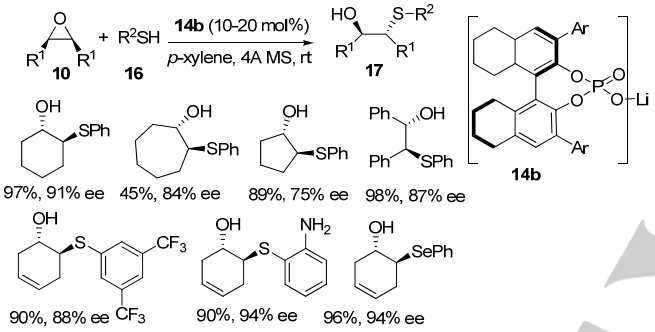


Figure 2. Activation of the reagents by TRIP-BINOL-derived phosphoric acid in the ARO reaction of *meso*-epoxides with mercaptobenzothiazoles.

Recently, Antilla and coauthors developed a protocol for the thiolysis of *meso*-epoxides based on the usage of a lithium complex of H_8-TRIP-BINOL-derived phosphate **14b** and aromatic thiols (Scheme 6).[26]



Scheme 6. Lithium H_8-TRIP-BINOL-derived phosphate catalysed ARO reaction of *meso*-epoxides with aromatic thiols (Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$).

The reaction proceeded at room temperature with a variety of cyclic epoxides and thiophenol to give the product in good yield and enantioslectivity. A remarkable result was achieved in the ARO reaction of more challenging stilbene epoxide by using Zn[(*R*)-BINOL-phospate]$_2$ complex as the organocatalyst. Functionalised aromatic thiols bearing either electron-donating or withdrawing groups afforded 2-hydroxy sulfides **17** in good to high yield and enantioselectivity. Phenyl selenol could be an additional useful nucleophile in the ARO reaction, although aliphatic thiols proved to be unreactive.

The activation of the epoxide was supposed to be provided by the phosphate-bound Lewis acidic metal center, whereas the phosphoryl oxygen would behave as Brønsted base activating the thiol (Figure 3). Unreactivity of the alkyl thiols would be justified by their lower acidity with respect to aromatic thiols.

Kureshi and coworkers reported the ARO reaction of *meso*-epoxides with anilines catalyzed by an easily available enantiomerically pure sulfinamide **18** (Scheme 7).[26] Cinchona alkaloids such as cinchonidine and quinidine did not catalyze the reaction, whereas commercially available (*S*)- and (*R*)-*tert*-butylsulfinamides led to both enantiomerically enriched products **20** with modest yield but encouraging level of enantioselectivity. Improvements were achieved when modifying catalyst structure by introducing a chiral amide portion with a view to enhance either the H-bonding ability and exploit matching effects.

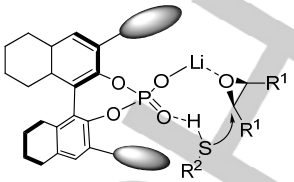
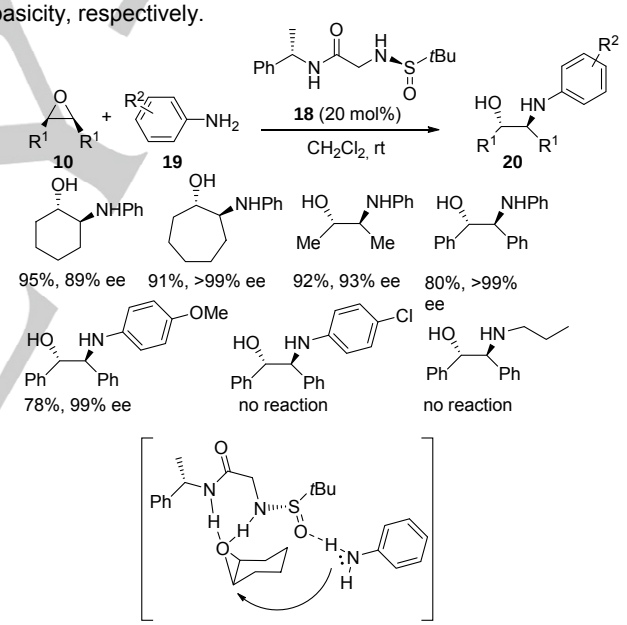


Figure 3. Activation of the reagents by lithium H_8-TRIP-BINOL-derived phosphate in the ARO reaction of *meso*-epoxides with aromatic thiols.

Replacement of the sulfinamido group with a chiral secondary amine moiety drastically decreased the level of enantioselectivity, showing the preferential role of sulfinamide chirality in directing the absolute configuration of the final product. Cyclic and linear *meso*-epoxides were smoothly transformed into 1,2-amino alcohols in high yield and enantioselectivity when using aniline as the nucleophile. Electron-withdrawing *para*-substituted anilines proved to be unreactive as well as aliphatic amines, which was ascribed to their low nucleophilicity and strong basicity, respectively.

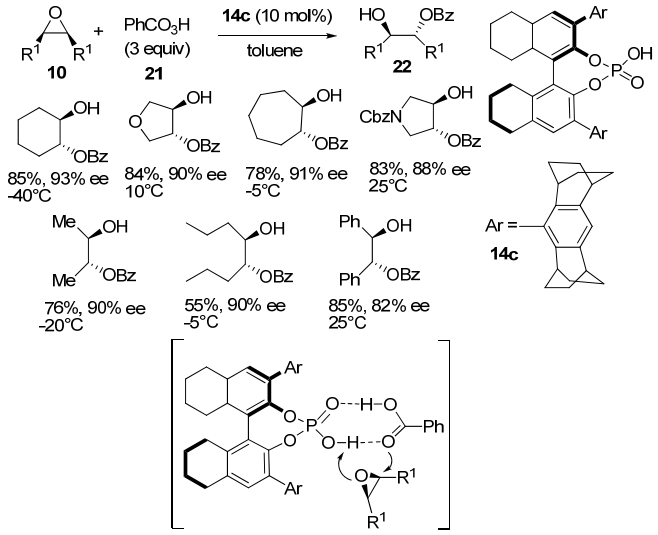


Scheme 7. Sulfinamide catalysed ARO reaction of *meso*-epoxides with anilines.

These results showed that electronic effects are critical in regulating the activation of the reagents by sulfinamide **18**. NMR experiments would support the formation of a H-bonding network among catalyst, epoxide and aniline in the transition state of the process (Scheme 7).

A conceptually new approach for ARO reactions, has been recently devised by List and coworkers in the hydrolysis of *meso*-epoxides catalyzed by BINOL-derived phosphoric acids.[28] Inspired by the mechanism of action of epoxide hydrolases,[17] a class of enzymes which do not depend upon metal cofactors, they envisaged the organocatalyst could activate a carboxylic

acid in a supramolecular assembly, which is responsible of nucleophilicity enhancement of the carboxylic acid as well as the acidity of the assembled heterodimer species (Scheme 8).[29]

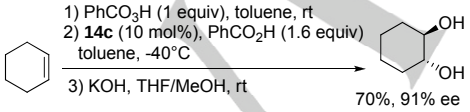


Scheme 8. H_8-BINOL-derived phosphoric acid catalysed ARO reaction of *meso*-epoxides with benzoic acid.

To achieve this goal new H_8-BINOL-derived phosphoric acids, bearing sterically demanding groups at the 3,3'-position of the BINOL-derived backbone, were designed. The compact structure of this modified class of BINOL-derived phosphoric acids, named "confined catalysts", was conceived to impart higher substrate selectivity by decreasing the size of the active site.

Under optimized conditions a variety of cyclic epoxides, also bearing heteroatoms in the ring, reacted with benzoic acid in the presence of 10 mol % of catalyst **14c** at variable temperatures, to give the mono-protected *trans*-1,2-diols in high yield and enantioselectivity. Interestingly, the ARO reaction catalysed by compound **14c** showed to have a broad substrate scope including challenging acyclic small epoxides and stilbene oxide.

A convenient one-pot sequential approach to enantiomerically enriched *trans*-diols was developed starting from the corresponding *Z*-alkenes. Benzoic acid, by-product, generated from the epoxidation of the alkene, was partially consumed as reagent of the following ARO reaction (Scheme 9).

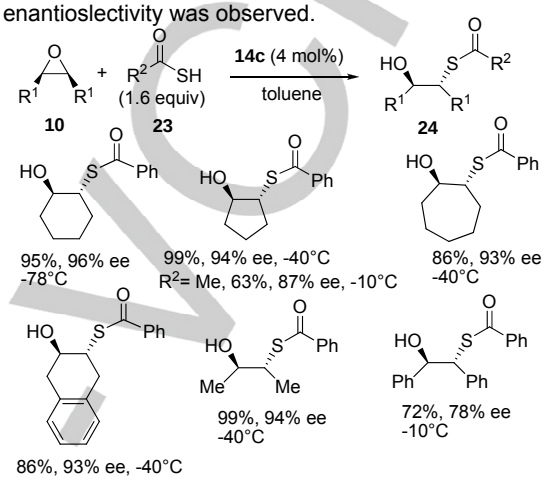


Scheme 9. One-pot sequential asymmetric synthesis of *trans*-diols from *Z*-alkenes.

The sequence illustrated in Scheme 9 can be considered a first complementary chemical protocol to the well-known Sharpless asymmetric *syn*-dihydroxylation of alkenes.[30]

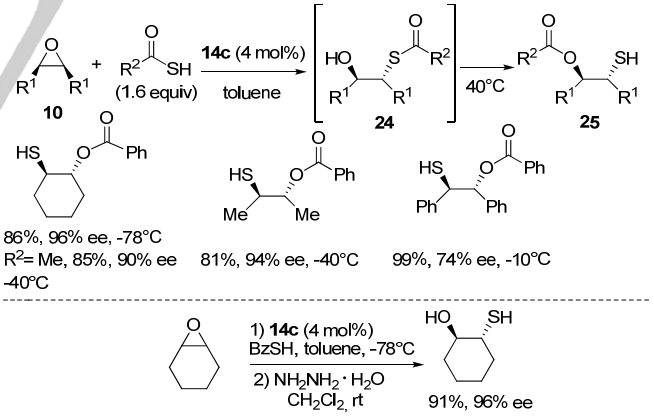
The same group reported a valuable extension of the activation strategy illustrated in Scheme 8 using thiocarboxylic acids **23** to obtain the corresponding 2-hydroxythioesters **24** (Scheme 10).[31]

This transformation enabled a facile entry to the synthesis of a variety of 2-hydroxy thioesters with excellent level of enantioselectivity when employing thiobenzoic acid. The usage of thioacetic acid was also feasible, although a slight decrease of the enantioslectivity was observed.



Scheme 10. H_8-BINOL-derived phosphoric acid catalysed ARO reaction of *meso*-epoxides with thiobenzoic acid.

By modifying the reaction parameters, a cascade process has been developed encompassing a Brønsted acid-catalyzed intramolecular transesterification reaction to the corresponding esters bearing a free thiol group (Scheme 11).



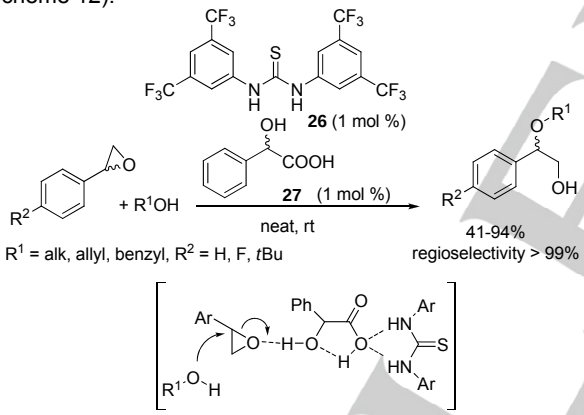
Scheme 11. H_8-BINOL-derived phosphoric acid catalysed ARO reaction of *meso*-epoxides with thiobenzoic acid.

Moreover, products **24** could be easily in situ deprotected by hydrazine to give almost enantiopure 1,2-hydroxy thiols as exemplified in Scheme 11. The entire sequence stands for a first example of formal asymmetric sulfhydrolysis reaction of epoxides. It is interesting to point out that the ARO reaction of *meso*-epoxides catalysed by Brønsted acid **14c** is the key-step

to obtain by choice, thio-protected alcohols **24** or *O*-protected thiols **25** of the same absolute configuration.

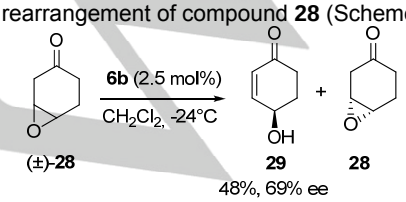
Kinetic resolution

As already mentioned, the majority of kinetic resolution examples focused on terminal epoxides for two equally important reasons: i) the nucleophilic attack in ARO reaction occurs with high regioselectivity to the sterically less hindered position and ii) racemic terminal epoxides are easily obtainable from inexpensive and broadly available terminal olefins. For the catalytic kinetic resolutions of racemic epoxides, mainly heteroatom-centered (nitrogen and oxygen) and, in a far lesser extent, carbon-centered nucleophiles have been used.[2a]
Besides water,[16a] azide,[15] anilines,[32] alkyl amines,[33] *N*-Boc protected sulfonamides[34] and unprotected *tert*-butyl, Cbz, Fmoc carbamates[16] have been employed in the catalytic kinetic resolution.
In the field of organocatalysis, cornerstone research showed that achiral ureas[35] and thioureas[36] are able to promote the regioselective ring opening reaction of epoxides.
In 2008, Schreiner and coauthors developed a regioselective alcoholysis of styrene oxides assisted by an organocatalytic system composed of two Brønsted acids, *N*,*N*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea **26** and mandelic acid **27** (Scheme 12).[36a]



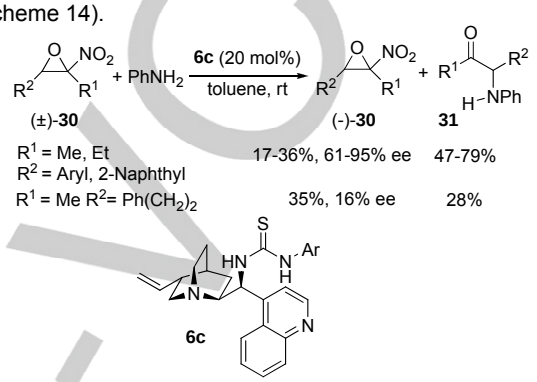
Scheme 12. Alcoholysis of styrene oxides promoted by two cooperative hydrogen-bonding organocatalysts.

The authors suggested a cooperative Brønsted acid catalysis, where the thiourea coordinates to the acid **27** through double H-bonding interaction enhancing its acidity.
The first example of ARO reaction via kinetic resolution of a racemic epoxide has been illustrated by Jørgensen and coworkers in the thiourea-derived cinchona alkaloid **6b** catalyzed rearrangement of compound **28** (Scheme 13).[20]



Scheme 13. Amino thiourea **6b** catalysed ARO reaction of racemic epoxide **28**.

Synthetically useful compound **29** was isolated in good yield and 69% ee.
We have recently disclosed the first example of an asymmetric aminolytic kinetic resolution (AKR) of racemic β-aryl-substituted α-nitroepoxides with aniline.[37] The process, catalyzed by thiourea-derived cinchona alkaloid **6c**, allowed the first enantioselective synthesis of β-aryl-substituted α-nitroepoxides **30** (Scheme 14).



Scheme 14. Amino thiourea organocatalyzed aminolytic kinetic resolution of α-nitroepoxides (Ar = 3,5-$(CF_3)_2C_6H_3$).

Racemic β-aryl-substituted α-nitroepoxides are well suited substrates to undergo a process of catalytic kinetic resolution. Indeed, in the 70s, it was first demonstrated they could be ring-opened with complete regioselectivity by different nucleophiles to give α-substituted ketones or heterocyclic compounds.[38]
The substrate scope of AKR was satisfying for variously substituted aromatic nitroepoxides **30**, bearing either electron-donating and withdrawing groups and the epoxides were recovered in acceptable yield and good to high enantioselectivity. Unfortunately, the kinetic resolution of aliphatic α-nitroepoxides proved to be inefficient. Modest values of selectivity factors (3<S<7) were determined, although underestimated by the contribution of background ring-opening pathway, partially taking place in absence of catalyst **6c**. It has been tentatively suggested that the bifunctional organocatalyst would activate the reagents by general acid-base catalysis leading to the preferred regioselective opening of one enantiomer of the epoxide (Figure 4).

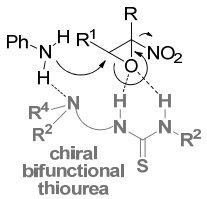
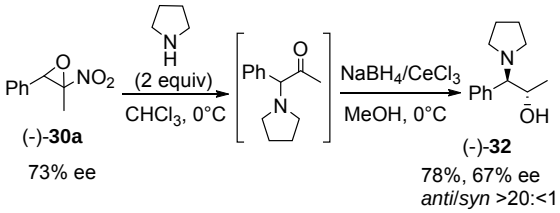


Figure 4. Hypothetical activation mode of α-nitroepoxides and aniline by an amino thiourea.

The synthetic utility of enantioenriched α-nitroepoxides was also demonstrated, developing a convenient one-pot stereoselective

approach to highly valuable *anti*-1,2-amino alcohols (Scheme 15).

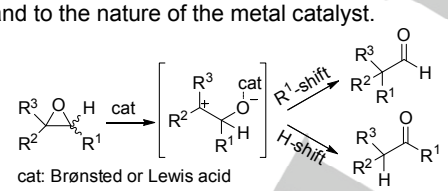
Further investigations will be necessary to clarify the activation mode and improve the AKR of readily accessible α-nitroepoxides to be of practical value for the asymmetric synthesis of either the epoxides and the α-amino ketones.



Scheme 15. Synthetic elaboration of enantioenriched α-nitroepoxide *to anti*-1,2-amino alcohol.

Rearrangements

Ring-opening reactions of epoxides in the presence of Brønsted or Lewis acids include 1,2-rearrangements, i.e. the migration of a substituent from one carbon of the epoxide ring to the other via either a Meinwald or semipinacol rearrangement process (Scheme 16) to give a carbonyl compound.[39] Selective 1,2-rearrangements, mainly rely on epoxide structure and the possibility to form either stable tertiary or benzylic carbocations. With 1,1-disubstituted epoxides (R^1 = H), the regiospecific generation of cation intermediate occurs, without competition between H-shift and alkyl-shift, leading to aldehydes formation. On the other hand, this competition takes place with trisubstituted epoxides that are consequently more challenging substrates. In this case, the selectivity for the alkyl versus hydrogen shift is highly sensitive to the substitution pattern of the epoxide and to the nature of the metal catalyst.



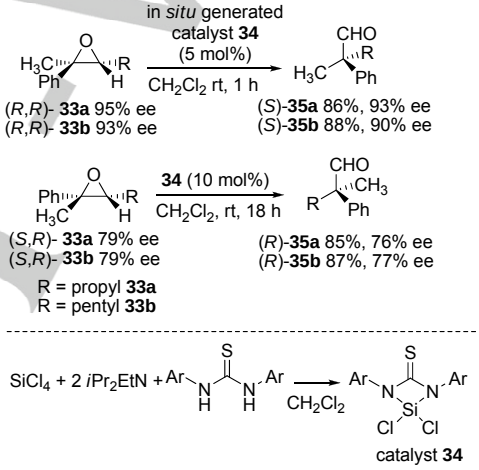
Scheme 16. Acid-catalyzed rearrangement of epoxides to aldehydes or ketones.

The asymmetric ring-opening reactions can be performed on chiral non-racemic epoxides exploiting a substrate-controlled asymmetric rearrangement promoted by achiral acid catalysts. More conveniently, but less investigated, an enantioselective rearrangement of *meso* and racemic epoxides can be promoted by chiral Lewis or, more rarely, Brønsted acids. A series of Lewis acids have been widely described to promote the asymmetric 1,2-rearrangement of chiral non racemic epoxides.[40]

In contrast, chiral catalyst controlled enantioselective 1,2-rearrangement of *meso* and racemic epoxides has been less frequently accomplished using Lewis or Brønsted acids. For instance, titanium-BINOL complexes promoted the kinetic resolution of racemic epoxides via 1,2-rearrangement.[41]

In 2011, Schreiner and coauthors developed an interesting organocatalytic example of stereospecific rearrangement of enantioenriched trisubstituted epoxides to quaternary carbaldehydes catalyzed by a silicon-thiourea catalyst obtained by combination of a thiourea and a weak silicon Lewis acid ($SiCl_4$) (Scheme 17).[42]

After having developed an efficient methodology for the catalytic rearrangement of trisubstituted racemic epoxides, the authors studied the stereospecificity of the rearrangement using enantioenriched *trans* and *cis*-epoxides **33a,b**. The in *situ* generated catalyst **34** provided the aldehydes **35a,b** in good yield and with a negligible loss of enantiopurity. The *trans* alkyl shift to the aryl moiety was markedly faster than that observed for the *cis*-configured epoxide. The latter needed several hours to achieve a good conversion to aldehyde and a partial hydrogen shift (3-5% ketone) was also observed.



Scheme 17. Chiral non racemic epoxide rearrangement catalysed by silicon-thiourea Lewis acid (Ar = 3,5-$(CF_3)_2C_6H_3$).

The authors noticed that the enantiopurity of both product (*R*)-**35a** and the starting epoxide (*S,R*)-**33a** increased over the time. They rationalized these data proposing the mechanism illustrated in Figure 5. Complexation between catalyst **34** and starting material would occur to give diastereomeric matched and mismatched transition structures. This would generate an increase in ee values during the reaction, in a similar way to a kinetic resolution of non-racemic starting material.[14]

An example of semipinacol rearrangement has been reported by Tu and Cao, who developed an one-pot procedure for the synthesis of various trioxygenated-spirocycloalkanedione derivatives, bearing a tertiary and quaternary contiguous centers.[43] The entire process is based on an asymmetric epoxidation, catalyzed by primary amine **36**, followed by a semipinacol rearrangement (Scheme 18). Water as co-solvent was found to be essential for the rearrangement to proceed. A series of vinylogous α-ketol substrates were checked in the asymmetric epoxidation with H_2O_2 followed by in situ acidification.

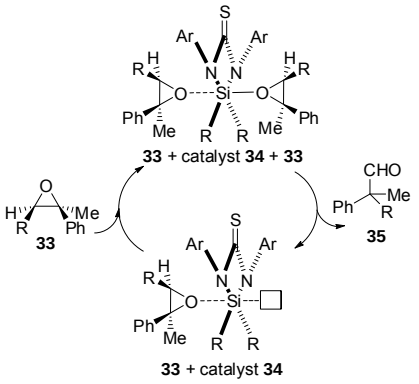
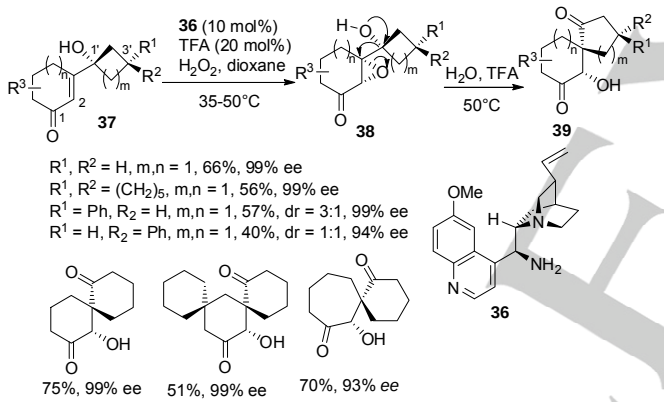


Figure 5. Mechanistic hypothesis for the epoxide rearrangement catalysed by silicon-thiourea Lewis acid.

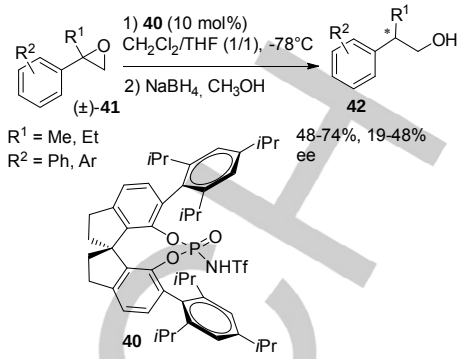
This protocol proved to be highly efficient in terms of stereocontrol when using different substituents at the C-3' position of the cyclobutanol moiety, including cyclic portions. The one-pot reaction worked with the same efficiency also with a larger C3-cyclopentanol moiety. The rearrangement proceeded via a concerted S_N2-type process, as attested by the isolation of a single spiro-isomer.



Scheme 18. One-pot synthesis of spiro-cycloalkanediones by an organocatalytic asymmetric epoxidation/semipinacol rearrangement.

The examples illustrated in Schemes 17-18 are substrate-controlled asymmetric rearrangements of chiral non racemic epoxides which allowed to produce optically active carbonyl compounds.

A first study on an asymmetric 1,2-rearrangement of racemic epoxides controlled by a chiral organocatalyst, has been recently reported by Du and coauthors.[44] SPINOL-derived *N*-triflyl phosphoramide **40**, was employed as more effective catalyst with respect to less acidic BINOL-derived phosphoric acids, in the deracemization of terminal epoxides **41**, proceeding via 1,2-rearrangement to chiral non racemic aldehydes (Scheme 19).



Scheme 19. 1,2-Rearrangement of racemic terminal epoxides catalysed by a SPINOL-derived *N*-triflyl phosphoramide.

The latter were in *situ* reduced to afford more stable alcohols **42**, isolated in satisfactory yield and up to 50% ee. The postulated reaction mechanism, would involve activation of the epoxide by the Brønsted acid with consequent ring-opening, as depicted in Figure 6. The carbocation formed would undergo an asymmetric 1,2-hydride shift, generating the chiral non racemic aldehyde.

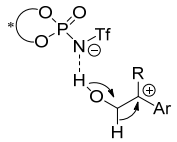


Figure 6. Hypothetical transition state for the Brønsted acid catalysed 1,2-rearrangement of terminal racemic epoxides.

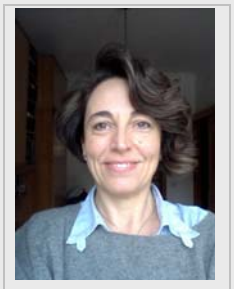
It is likely to expect an improvement of this process by using confined BINOL-derived phosphoric acids.

Summary and Outlook

Studies in ARO reaction of epoxides, previously established with chiral metal-based systems, strong lithium amides and hydrolases, have recently stimulated the employment of some of the most effective bifunctional organocatalysts as players in the ARO reaction of *meso*- and racemic epoxides with a variety of nucleophiles. Notable and more general results have been achieved in the desymmetrization of *meso*-epoxides with BINOL-derived phosphoric acids when using thiols, anilines, benzoic and thioacids. These catalysts displayed also potential application in asymmetric 1,2-rearrangements of epoxides. Hybrid peptidyl thioureas showed to be promising promoters in the challenging ARO reaction of *cis*-stilbene oxides with amines. Cinchona derived thioureas served as catalysts in the desymmetrization of *meso*-epoxides proceeding through intramolecular elimination to give allylic alcohols and in the kinetic resolution of α-nitroepoxides. As a general remark, simultaneous activation of the epoxide and the nucleophile provided by the organocatalysts has been proposed to be the leitmotif. The purpose of this Minireview was to highlight the

underexplored potential of organocatalysed ARO reaction of epoxides and inspired researchers for further improvements. At present, the organocatalyzed ARO reactions of epoxides are limited to highly nucleophilic heteroatom centered reagents. The design of more sophisticated organocatalysts suitable to extend the arena of nucleophiles, including softer carbon centered ones, will significantly expand application of this tool for the asymmetric synthesis of functionalized scaffolds.

Sara Meninno was born in Ariano Irpino (Italy). She received her MSc in Chemistry from the University of Salerno in 2011. In 2015, she earned her PhD in Chemistry at University of Salerno under the supervision of Professor A. Lattanzi working on asymmetric oxyfunctionalizations and tandem reactions. At present, she is working as a postdoctoral fellow on the development of new organocatalytic asymmetric methodologies for the construction of heterocyclic compounds.



Alessandra Lattanzi was born in Rome (Italy). She graduated and received her PhD from "Sapienza" University of Rome. She has been visiting scientist in the groups of Prof. V. K. Aggarwal (Sheffield, 1999-2000) and Dr. N. E. Leadbeater (London, 2001). Since 2005 she has been Associate Professor at University of Salerno. Her research interests include asymmetric organocatalysis, stereoselective metal-catalysed oxidations, description of chiral structures through algebraic and geometrical methods.

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.**Keywords:** organocatalysis • epoxides • ring-opening • desymmetrization • kinetic resolution

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MINIREVIEW

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Organocatalytic Asymmetric Ring-Opening Reaction of Epoxides: Recent Progress

At the starting blocks: this Minireview highlights recent studies on asymmetric ring opening reactions of *meso* and racemic epoxides by hetereoatom centered nucleophiles using some of the most popular bifunctional organocatalysts. BINOL-derived phosphoric acids appear to be a step ahead as promoters of general use in ARO reactions. A mechanistic picture of dual activation of the reagents provided by the organocatalysts has been proposed.