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Asymmetric Catalytic Routes to Dialkyl Peroxides and Oxaziridines

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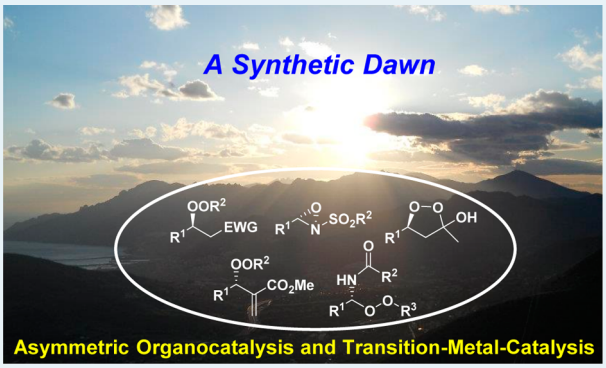
ABSTRACT: Enantioenriched dialkyl peroxides and oxaziridines are two classes of compounds showing important biological activities, being useful synthetic intermediates and reagents for asymmetric oxidations and cycloaddition reactions. Chiral substrate-controlled diastereoselective preparations of these compounds have been developed almost exclusively in the last decades. The aim of this perspective article is to provide the reader with recent efforts devoted to addressing the challenging task of their synthesis via either enantioselective organo- and transition metal-catalyzed oxidations or via alternative nonoxidative approaches.



KEYWORDS: *asymmetric synthesis, dialkyl peroxides, oxaziridines, organocatalysis, transition metal catalysis, kinetic resolution, desymmetrization*

1. INTRODUCTION

Catalytic asymmetric oxidations are of utmost importance in synthetic organic chemistry, often representing the key step in the preparation of biologically relevant compounds or intermediates.[1] Several optically pure dialkyl peroxides exhibit anticancer and antibacterial activity;[2] moreover, they can be valuable synthetic building blocks.[3] Chiral nonracemic oxaziridines serve as an important class of stereoselective oxidants,[4] reagents for cycloaddition reactions,[5] or a precursor of rearrangement products.[6] A certain number of procedures for the diastereoselective oxidation of unsaturated compounds have been developed during recent decades; however, general and efficient methods for the preparation of dialkyl peroxides and oxaziridines via asymmetric catalytic oxidation are highly limited.

Direct catalytic enantioselective oxidation of alkenes and imines is a straightforward process to obtain dialkyl peroxides and oxaziridines in an enantiomerically enriched form; however, the transformation is highly challenging, and successful approaches to oxaziridines, reported until recently, have relied upon diastereoselective oxidations of commercially available enantiopure reagents. An obvious limitation of this approach concerns the restricted structural diversity of the final potentially achievable products. A well-known and remarkable example is the work illustrated by Davis and coauthors, based on the diastereoselective oxidation of camphor-derived *N*-sulfonylimines and application of the corresponding oxaziridines **1** and **2** as effective oxidants in the enantioselective α-hydroxylation of enolates[4b,7] and oxidation of prochiral sulfides to sulfoxides,[8] respectively (Chart 1). In the context of chiral nonracemic dialkyl peroxides, most of the examples reported in the literature exploit a diastereoselective oxidative step necessary to install the hydroperoxide group into a chiral precursor.[9] The hydroperoxide is then transformed into a dialkyl peroxide moiety, often incorporated onto a cyclic structure to afford endoperoxides as potentially bioactive compounds. Among the several natural endoperoxides, isolated in terrestrial or marine sources, artemisinin A represents a remarkable lead drug, showing potent antimalarial activity; plakinic acid A is the first member of 5-membered cyclic peroxides showing antibiotic, antifungal, and anticancer activity; whereas verruculogen is a mycotoxin able to inhibit mammalian cell lines and to alter GABA receptor binding (Chart 1).[10] Radical species are suggested to be involved in the therapeutic action displayed by artemisinin A and related molecules bearing the labile peroxide unit. Indeed, the peroxide bond reduction by intraerythrocitic parasite Fe(II) ions would generate reacting O-centered radicals responsible for the antiproliferation activity.[11]

The synthesis of enantiomerically enriched dialkyl peroxides and oxaziridines has recently been a subject of intensive investigation. In this Perspective, we highlight the significant progress achieved in the development of the first successful general methods for their preparation through catalytic enantioselective oxidation of simple alkenes and imines. An overview of previously developed diastereocontrolled oxidations to access the target compounds is included. Peroxo-type alkylation, kinetic resolution, or desymmetrization strategies have also been found useful to achieve the goal. Most of these processes have been catalyzed by primary, secondary, or tertiary amines readily derived from the chiral pool, with *meta*-chloroperbenzoic acid (MCPBA), *tert*-butyl hydroperoxide

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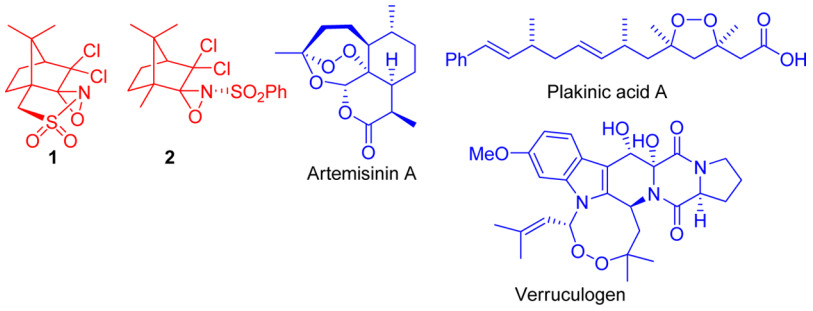
Chart 1. Structures of Camphor-Derived Oxaziridines and Peroxide-Containing Natural Products

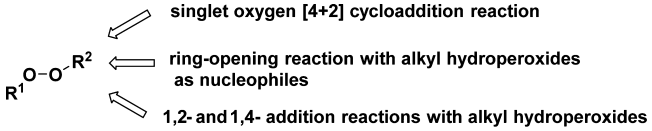


(TBHP), hydrogen peroxide, and oxone as the oxidants. In addition, successful examples of catalysis mediated by chiral phosphoric acids and metal complexes have been reported. Asymmetric oxidations leading to the preparation of alkyl hydroperoxides and their further elaboration to dialkyl peroxides are beyond the purpose of this article and will not be included.

2. ASYMMETRIC SYNTHESIS OF DIALKYL PEROXIDES

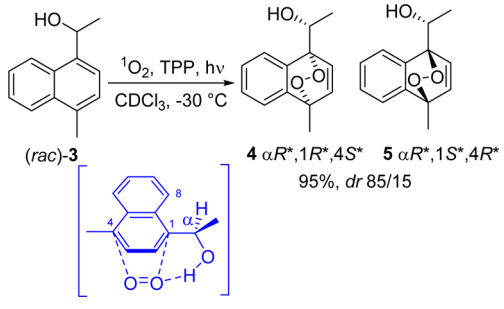
The major stereoselective approaches used thus far to prepare dialkyl peroxides can be recognized in (i) singlet oxygen [4 + 2] cycloaddition reaction with dienes or ene reaction with alkenes; (ii) ring-opening reactions with alkyl hydroperoxides serving as the nucleophiles; or (iii) 1,2- or 1,4-addition of alkyl hydroperoxides to imine derivatives and electron-poor alkenes, respectively (Chart 2).

Chart 2. Major Synthetic Routes to Dialkyl Peroxides



One of the most studied reactions for the synthesis of endoperoxides has been the diastereocontrolled [4 + 2] cycloaddition of chiral racemic or nonracemic alkenes with singlet oxygen.[12] In 1995, the Adam group demonstrated that photooxygenation of chiral racemic naphthyl alcohols of type **3** with tetraphenylporphine (TPP) proceeded with good diastereo-stereoselectivity to give the corresponding endoperoxides **4** and **5** (Scheme 1).[13] The presence of the free OH group in the

Scheme 1. Diastereoselective [4 + 2] Cycloaddition Reaction of Naphthyl Alcohol with Singlet Oxygen

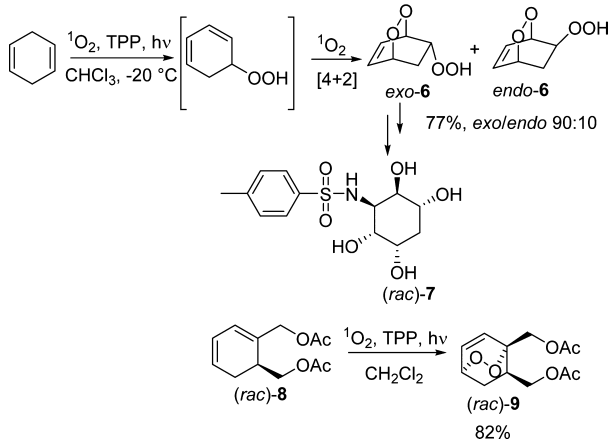


reagent and the concomitant use of nonpolar solvents guaranteed the highest π-facial selectivity. A transition state has been suggested to justify the preferential formation of diastereoisomer **4**, in which hydrogen bonding interaction between the hydroxyl moiety and singlet oxygen dienophile would lead to a reduced peri strain between the methyl group and the 8-H. The diastereoselectivity dropped to a 1:1 mixture of the products when the OH group was protected either as an acetate or a trimethyl silyl moiety.

Similarly, Dussault and co-workers investigated the photooxygenation of acyclic dienolethers of different geometries, incorporating optically pure alcohol moieties.[14] However, in these examples, conformational freedom of the reagents enabled achievement of only modest levels of diastereoselectivity (dr up to 2.9:1) for the alkoxyendoperoxide products.

In 2000, Balci and co-workers reported the TPP-sensitized photooxygenation of 1,4-hexadiene at −20 °C in chloroform (Scheme 2).[15] The hydroperoxy endoperoxides *exo*-**6** and

Scheme 2. Diastereoselective Photooxygenation on 1,4-Hexadienes



endo-**6** were formed in good yield and 90/10 diastereoisomeric ratio. Mechanistically, an ene reaction of singlet oxygen to give the monohydroperoxide, followed by a diastereoselective [4 + 2] cycloaddition of singlet oxygen on the intermediate, was proposed. Traces of *bis*-hydroperoxides derived by a double ene reaction on the starting diene with singlet oxygen were additionally detected. Unexpectedly, the *exo*-**6** peroxide was highly prevalent, suggesting that hydrogen-bonding interactions would not be operative in this case.

Compound *exo*-**6** has been used as the starting material for the synthesis of a new aminoquercitol derivative **7** with potential activity against glycosidases.[16] In addition, the same group developed a completely diastereoselective and high-yielding [4 + 2] cycloaddition of singlet oxygen on racemic cyclohexadiene

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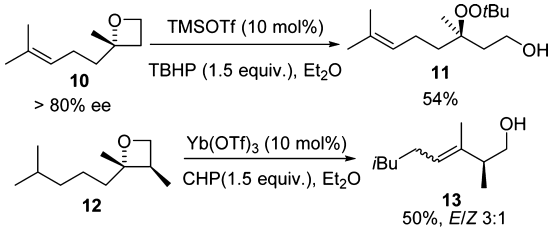
8 to endoperoxide **9** (Scheme 2).[17] The exclusive formation of *anti*-peroxide **9**, confirmed by X-ray analysis, was rationalized in terms of a repulsive interaction between the axial acetoxymethylene group and the approaching singlet oxygen. Endoperoxide **9** was elaborated, via peroxide reduction/epoxidation/epoxide ring-opening sequences, to a small library of carbasugars tested against α-glycosidase.

Triplet oxygen was recently utilized as a reagent in the radical autoxidation of an enantiomerically pure tetracyclic lactam, providing an optically pure, symmetrically substituted peroxide with complete control of the diastereoselectivity.[18]

Inspired by some literature reports on acid-catalyzed opening of epoxides with alkyl hydroperoxides,[19] Dussault and co-workers reported a straightforward route for the synthesis of enantioenriched acyclic peroxides such as 3-alkylperoxy alkanols. Given the ability of the oxetane ring to undertake alcoholysis,[20] a Lewis acid-catalyzed ring-opening reaction of chiral nonracemic oxetanes, previously prepared via a three-step sequence, by alkyl hydroperoxides was envisaged.[21] Tertiary oxetane **10**, when treated with TBHP and catalytic loading of trimethylsilyltriflate, afforded 3-peroxyalkanol **11**, bearing a quaternary stereocenter, in satisfactory yield. The ring-opening step was demonstrated to occur with ~90% inversion (Scheme 3).

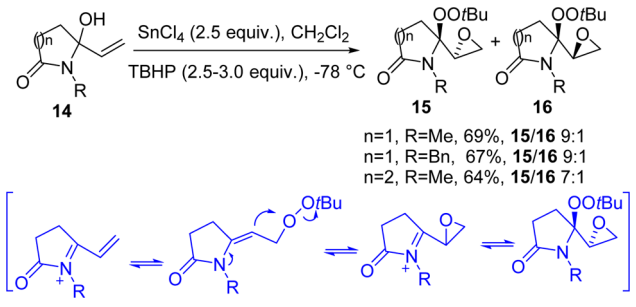
Scheme 3. Lewis-Acid Catalyzed Ring-Opening Reaction of Enantioenriched Oxetanes with Alkyl Hydroperoxides



Other alkyl hydroperoxides, including hydrogen peroxide, could be used as the nucleophiles, although elimination appeared to be the predominant pathway when reacting more sterically demanding oxetanes, such as compound **12** with cumyl hydroperoxide (CHP).

Marson and co-workers illustrated a formal S_N2 replacement of a hydroxyl group with a *tert*-butyl peroxy moiety and a concurrent epoxidation of allylic alcohols **14** incorporating a lactam ring (Scheme 4).[22] The transformation proceeded with

Scheme 4. Diastereoselective $SnCl_4$-Promoted Oxidation of Allylic Alcohols Incorporating a Lactam Ring

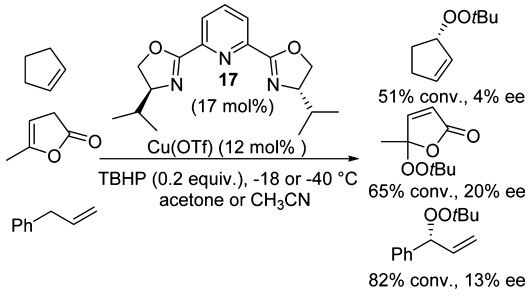


high anti diastereoselectivity and good conversions in the presence of overstoichiometric amounts of tin(IV) chloride and TBHP as the oxidant.

The stereochemical outcome and the nature of the products of this reaction differ from the $VO(acac)_2$/TBHP-catalyzed epoxidation of the analogous carbocycles, in which the sole *syn*-epoxy alcohols were the preferentially observed diastereoisomers.[23] Hence, epoxidation via hydroxyl coordination to the tin metal would not appear a likely route. Although the mechanism was not investigated, a Lewis acid-catalyzed acyl iminium ion formation was hypothesized, followed by a Weitz–Scheffer nucleophilic epoxidation.[24] A stereoselective 1,2-addition of the TBHP onto an epoxy acyl iminium ion intermediate would afford the final product.

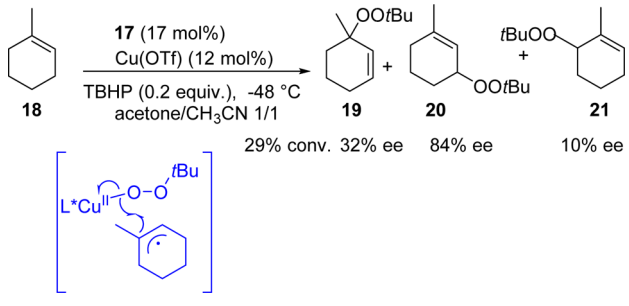
In 1998, the Schulz group reported[25] the first example of an enantioselective copper-catalyzed allylic peroxidation, that is, the Kharasch reaction.[26] Prochiral allylic and benzylic compounds treated with TBHP under catalytic loadings of Cu(I)-triflate and chiral bisoxazoline ligand **17** gave the corresponding peroxides in satisfactory yield but low ee values (Scheme 5).

Scheme 5. Enantioselective Copper-Catalyzed Allylic Peroxidation



Although the peroxidation of methyl cyclohexene **18** proceeded with poor regioselectivity, isomer **20** was obtained with 84% ee (Scheme 6). The structure of alkene as well as the

Scheme 6. Enantioselective Copper-Catalyzed Peroxidation of Methylcyclohexene



reaction conditions strongy influenced the regio- and stereochemical outcome of the peroxidation. Presumably, these findings made particularly difficult the full exploitation and discouraged further investigations of this highly attractive oxidation. Indeed, in principle, it would allow a straitghforward enantioselective peroxidation of a large number of easily accessible alkenes under mild reaction conditions.

Mechanistically, allylic radicals, likely formed under the reaction conditions, would react with an in situ generated alkylperoxy Cu(II) complex or with an alkylperoxy radical coordinated to the Cu(II) center to afford the products.

More recently, organocatalysis has become a powerful synthetic tool to access either simple or complex molecular scaffolds.[27]

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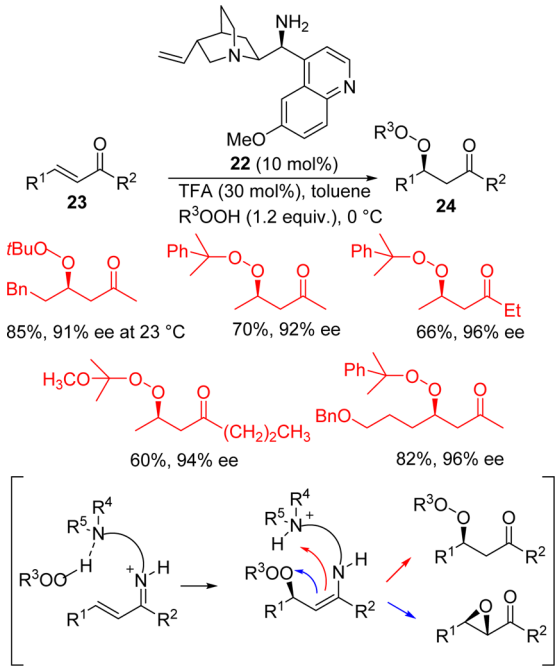
Optically pure organic molecules served as effective promoters in a variety of asymmetric catalytic oxidations, such as epoxidation, sulfoxidation, the Baeyer–Villiger reaction, and hydroxylation, to cite the most relevant.[28]

In 2008, the Deng group reported the first example of a catalytic enantioselective peroxidation of acyclic aliphatic enones by using 10 mol % of readily accessible 9-amino-9-deoxyepiquinine **22** and different alkyl hydroperoxides with TFA (30 mol %) as an additive (Scheme 7).[29] The oxidation proceeded at 0 °C with

Scheme 7. Cinchona Alkloid-Derived Primary Amine Catalyzed Enantioselective Peroxidation of Enones with Alkyl Hydroperoxides



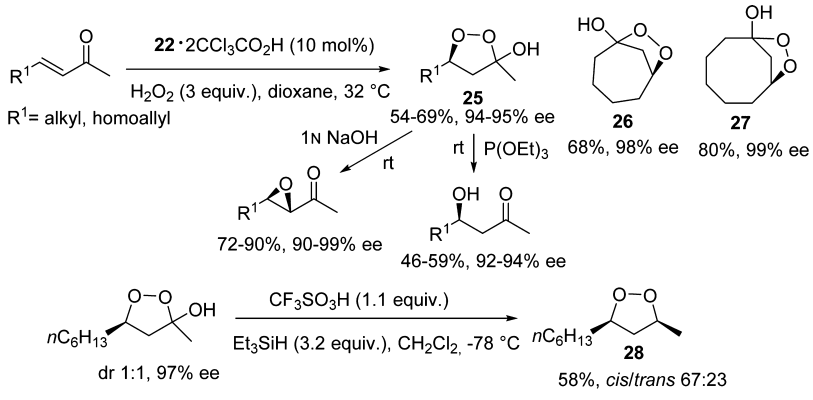
preferential formation of dialkyl peroxides **24**, whereas only low amounts (<20%) of epoxide byproducts were detected. The process proved to have good applicability because compounds **24** were isolated in good yield and up to 97% ee, regardless the alkyl hydroperoxide used or the substitution pattern of enones. Peroxides **24** of opposite absolute configuration could be isolated by employing the pseudoenantiomeric primary amine derived from quinidine. Interestingly, increasing the reaction temperature up to 25 or to 50 °C enabled switching the reaction pathway toward the epoxides, obtained with comparable level of enantioselectivity. From a mechanistic point of view, after the formation of an iminium ion between the enone and primary amine of the catalyst **22**, the alkyl hydroperoxide would be steered through hydrogen-bonding interaction with the tertiary quinuclidine amine to preferentially attack one face of the C–C double bond of the chiral iminium ion. Enantioenriched peroxyenamine would then evolve to peroxide **24**, through protonation by the closely located ammonium site or to the epoxide through intramolecular nucleophilic substitution, in agreement with a Weitz–Scheffer type mechanism.

The List group independently reported the oxidation of aliphatic enones with 50% aqueous hydrogen peroxide in the presence of amine salt catalyst **22**·2CCl_3CO_2H (10 mol %) (Scheme 8).[30] Isolable cyclic linear or branched substituted peroxyhemiketals **25** were directly obtained as a comparable mixture of diastereoisomers in good yield and high enantioselectivity. Peroxyhemiketals **25** proved to be versatile intermediates to obtain, under slightly modified conditions followed by a basic work up, highly enantiomerically enriched epoxides. A one-pot enantioselective hydroperoxidation–reduction sequence to prepare challenging β-hydroxy ketones was also developed.

Although aromatic and trisubstituted enones were not suitable substrates for the reaction, medium sized cyclic enones, such as 2-cycloheptenone and 2-cyclooctenone led to first observed bicyclic endoperoxides **26** and **27** in good yield and excellent ee values. Nevertheless, this outcome was not general because smaller or bigger cyclic enones provided the epoxide under the same reaction conditions. The formation of products **26** and **27** has been rationalized in terms of conformational constraints of the corresponding peroxyenamine intermediates (Scheme 7) hampering the antiperiplanar alignment of the π system with the peroxidic bond required for the ring-closure.

It is worth noting that this represents the first asymmetric methodology that allows installation of the 1,2-dioxolane subunit, the key structural motif of plakinic acid A, a member of an important family of bioactive marine compounds (Chart 1).[31] Toward this end, List and co-workers demonstrated a useful application of the methodology to obtain the *cis*-1,2-dioxolane motif, via the first direct reduction of an enantioenriched diastereoisomeric mixture of a peroxyhemiketal to dioxolane **28**. Remarkably, the use of the same catalyst **22**, in the procedures developed by the groups of Deng and List, opened a facile asymmetric route to either acyclic peroxides,

Scheme 8. Cinchona Alkaloid-Derived Primary Amine Salt Catalyzed Enantioselective Hydroperoxidation of Enones with H_2O_2



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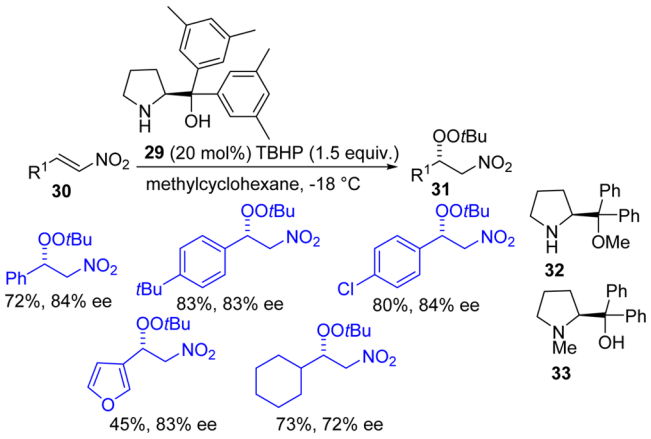
1,2-dioxolane products and bicyclic peroxides by simply changing the nature of the oxidant. These methodologies should find wide synthetic applications.

In the same year, Russo and Lattanzi, after screening a variety of secondary amines derived from L-proline, disclosed that commercially available diaryl-(*S*)-prolinol **29** is a well-suited catalyst for the first enantioselective *β*-peroxidation of aromatic substituted nitroalkenes **30** (Scheme 9).[32]

Scheme 9. Diaryl Prolinol-Catalyzed Enantioselective Peroxidation of Nitroalkenes



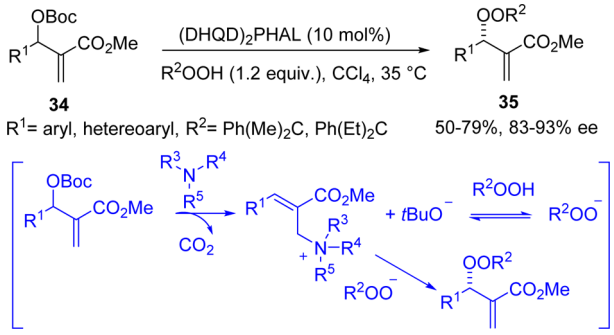
Peroxides **31**, which could be one-pot reduced to highly valuable chiral 1,2-amino alcohols, were generally obtained in good yield and enantioselectivity when using TBHP as the oxidant. Applicability of the reaction to less reactive aliphatic nitroalkenes appeared somewhat limited and substrate-dependent. Both enantiomerically enriched products **31** can be obtained using the commercially available *R*-configured prolinol **29**. It has been proposed that the enantioselectivity is controlled by hydrogen-bonding interactions provided by the basic and acidic moieties of the bifunctional organocatalyst with TBHP and nitroalkene, respectively. The key role displayed by both free OH and NH groups in the oxa-Michael addition was ascertained in the model reaction performed on *trans*-nitrostyrene using catalysts **32** or **33**. Indeed, a dramatic drop of the enantioselectivity was observed as the corresponding nitro peroxide was isolated with at best 7% ee value.

In 2009, Chen and co-workers presented an original route to acyclic peroxides based on an asymmetric peroxo-allylic alkylation of Morita–Baylis–Hillman (MBH) carbonates with alkyl hydroperoxides, catalyzed by the commercially available tertiary base *bis*-cinchona alkaloid $(DHQD)_2PHAL$.[33] The reactions were carried out under mild conditions, employing 10 mol % of the organocatalyst in CCl_4 at 35 °C (Scheme 10).

A variety of aromatic and heteroaromatic substituted MBH carbonates were converted into the corresponding highly functionalized peroxides **35** in good yield and high enantioselectivity. The reaction was postulated to proceed via a selective S_N2'-type displacement by the peroxide anion attack on the in-situ-generated chiral allylic ammonium ion intermediate.

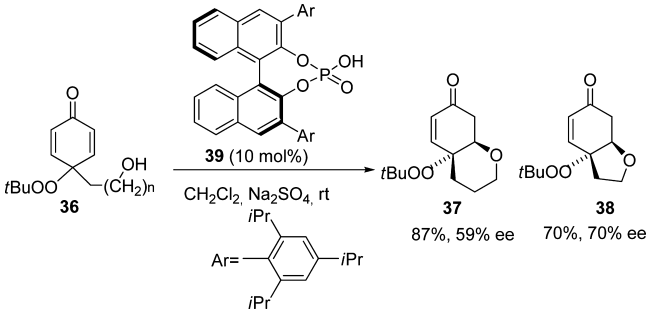
Recently, the Doyle group illustrated a preliminary investigation on an alternative appealing strategy based on an oxa-Michael addition reaction to construct bicyclic peroxy-containing scaffolds as synthetic useful intermediates. Indeed, 4-*t*-butylperoxy-2,5-dienones **36**, bearing tethered nucleophiles and a preexisting alkyl peroxide group, could be desymmetrized

Scheme 10. $(DHQD)_2PHAL$-Catalyzed Enantioselective Peroxo-Allylic Alkylation of MBH Carbonates



via an intramolecular oxa-Michael addition. Cyclic derivatives **37** and **38** could be easily obtained using 10 mol % of a commercially available chiral phosphoric acid **39** as the organocatalyst (Scheme 11).[34] Products **37** and **38**, bearing

Scheme 11. Desymmetrization of 4-*t*-Butyl Peroxy-2,5-Dienones with Phosphoric Acids



contiguous quaternary and tertiary stereogenic centers, were isolated in good yield as single diastereoisomers with up to 70% ee. Extension of substrate scope for this acid-catalyzed desymmetrization to other tethered nucleophiles to construct a variety of bicyclic peroxy derivatives of different ring sizes as well as improvements of the enantioselectivity would be likely expected, given the broad availability of structurally modified chiral phosphoric acids as suitable catalysts.[35]

Some representative bioactive natural peroxides contain an *α*-amino peroxide unit, as in verruculogen illustrated in Chart 1. A few examples of the stereoselective synthesis of *α*-acylaminoperoxides and hydroperoxides have been reported, mainly with the aim of developing novel optically pure reagents for asymmetric oxidations.[36] Liebscher and co-workers attempted a diastereoselective synthesis of *α*-acylaminoperoxides by reacting at low temperature *R*-menthyl chloroformate with isoquinolines (Scheme 12).[37]

The in-situ-formed *N*-acyliminium salt was trapped by TBHP, giving the desired product **40**. However, the ^1H NMR analysis revelead the presence of labile peroxide **40** as a 1:1 diastereoisomeric mixture, which hampered further characterization of the product.

In this respect, the Antilla group disclosed a direct and simple access to the *α*-amino peroxide moiety. In 2010, they reported the first asymmetric 1,2-addition reaction of alkyl hydroperoxides to aromatic imines **41** (Scheme 13).[38]

The oxidation smoothly proceeded in the presence of 5 mol % of sterically demanding phosphoric acid **43** in isopropyl acetate as solvent by using TBHP or CHP as the oxidant

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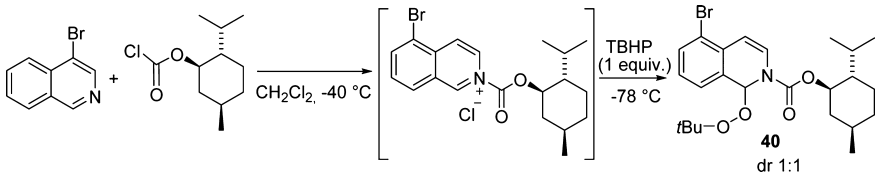
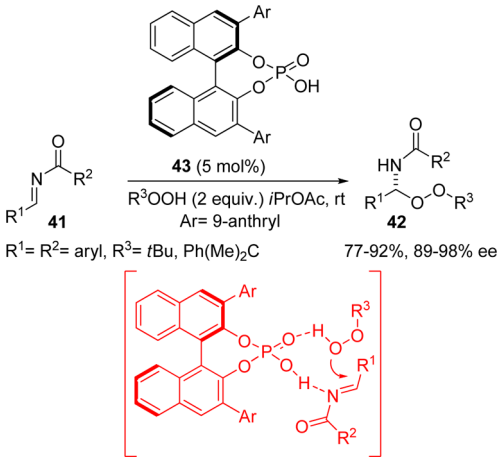
Scheme 12. Chiral Substrate-Controlled Approach to α-Acylaminoperoxides



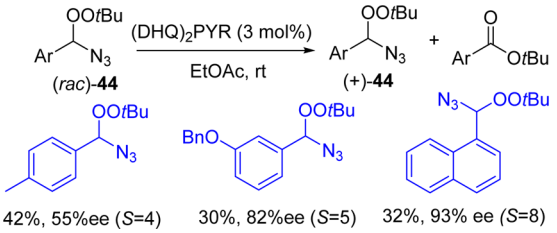
Scheme 13. Chiral Phosphoric Acid-Catalyzed Peroxidation of Imines



at room temperature. High yields and excellent ee values were achieved for differently aryl-substituted α-amino peroxides **42**. The enantioselectivity was retained throughout the oxidation, indicating the absence of a racemization pathway via potential retro-addition reaction. Activation of the reagents was hypothesized to occur through hydrogen-bonding interactions provided by the bifunctional Brønsted acid–base nature of the organocatalyst. This type of activation has been often invoked when using phosphoric acids; however, the generation of a chiral ion-pair through protonation of the imine by the acid cannot be ruled out.[35] Despite the methodology appears limited to aromatic imines, overall, the simplicity of the reaction conditions, the relatively low catalyst loading combined with the notable level of enantioselectivity, makes this transformation highly attractive and worthy of further investigation focused on widening the substrate scope.

Interestingly, Ghorai and coauthors very recently demonstrated the kinetic resolution of racemic peroxides to be a feasible process to enantioenriched peroxides. Commercially available *bis*-cinchona alkaloid $(DHQ)_2PYR$ catalyzed, at only 3 mol % loading, the kinetic resolution of some racemic α-azido peroxides **44** (Scheme 14).[39] The latter were previously

Scheme 14. $(DHQ)_2PYR$-Catalyzed Kinetic Resolution of Racemic α-Azido Peroxides



obtained through $FeCl_3$-catalyzed TBHP addition of $TMSN_3$ to aromatic aldehydes.

One of the two enantiomers of the secondary α-azido peroxide was preferentially transformed into *tert*-butyl ester via base-catalyzed *tert*-butyloxide anion transfer in a Kornblum DeLaMare type rearrangement.[40] Encouraging levels of enantioselectivity for unreacted peroxides **44** were achieved, as attested by the stereoselectivity factors, highlighting this approach as an interesting synthetic option to prepare enantioenriched peroxides.

3. ASYMMETRIC SYNTHESIS OF OXAZIRIDINES

Since their early discovery,[41] oxaziridines progressively have become widely employed oxidants in organic synthesis, behaving as oxygen or nitrogen donors, depending on their structural electronic features and the nature of the nucleophile.[42,43] However, although *N*-alkyl and *N*-aryloxaziridines are only weak oxidants, the analogues bearing an electron-withdrawing group, such as *N*-sulfonyl and *N*-phosphinoyl oxaziridines, react with a broad array of nucleophiles, including enolates, silyl enol ethers, organometallic compounds, alkenes, arenes, tertiary amines, thiols, thioethers, and selenides.[42] A remarkably useful property of these heterocyclic compounds is the configurational stability of the nitrogen atom, due to the combined effects of the ring strain and the presence of the electron-withdrawing oxygen atom, so that it is possible to synthesize enantioenriched oxaziridines.[44] During the past 30 years, chiral oxaziridines, especially the *N*-sulfonyl derivatives, commonly known as Davis reagents, have been successfully employed in several enantioselective oxidations, such as α-hydroxylation of enolates, oxidation of sulfides, selenides, alkenes, and sulfenimines.[4,45−47] In addition, the stereoselective photochemical rearrangement of various chiral oxaziridines affords chiral lactams,[6] and dipolar cycloaddition to unsaturated compounds leads to chiral heterocyclic products.[5]

The most exploited strategy to access chiral oxaziridines consists of the oxidation of chiral imines with MCPBA or peroxymonosulfate (oxone). Acyclic imines usually afford mixtures of diastereoisomers that could be separated by fractional crystallization or chromatography,[5,45,48−53] as reported in Scheme 15.[45a] The best diastereoselectivities have been generally achieved with cyclic substrates, even though, in most instances, recrystallization is required to obtain optically pure products.[46,54−57]

However, diastereomerically pure oxaziridines could be obtained in the oxidation of some specific substrates,[7,8,47,58−61] as illustrated in Chart 1.[44] A typical example is the oxidation of camphor-derived cyclic sulfonylimines.[7,8,58−61] The oxidation of compound **45**, for instance, occurred exclusively on the exo face, leading to oxaziridine **46** (Scheme 16).[58]

On the other hand, the enantioselective synthesis of oxaziridines based on the use of a chiral oxidizing agent proved to be an unsuccessful approach. The few oxidations performed with monoperoxycamphoric acid yielded the desired products in low ee values,[62,63] as reported in the example of Scheme 17.[62]

An original method of enantioselective synthesis involved the photocyclization of nitrones in a crystalline inclusion complex with chiral 2,4-diyne-2,6-diol. However, the performances were

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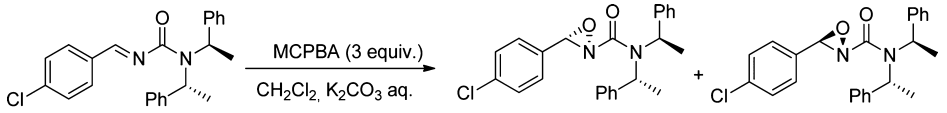
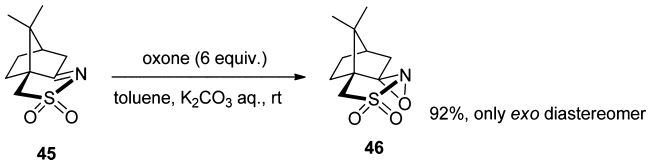
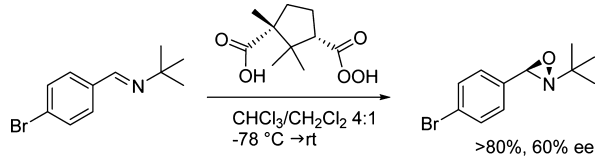
Scheme 15. Diastereoselective Oxidation of an Acyclic Chiral Imine



Scheme 16. Stereoselective Oxidation of Camphor-Derived Imine



Scheme 17. Oxidation of an Acyclic Achiral Imine with Monoperoxycamphoric Acid



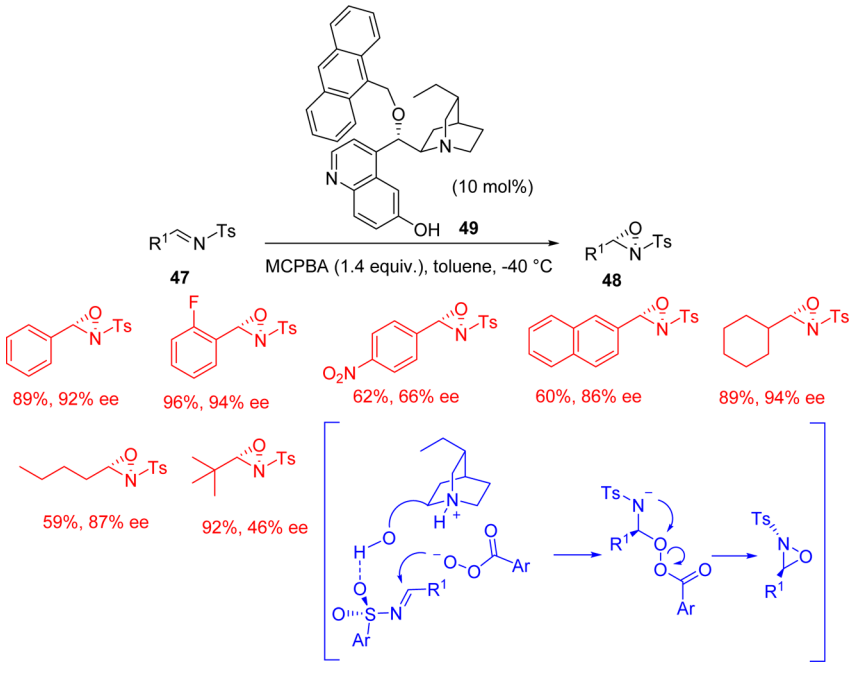
strongly substrate-sensitive, spreading out in the 10−100% ee range.[64]

As stated above, highly stereoselective synthesis of oxaziridines could be performed starting from some specific scaffold of the chiral pool. Conversely, general methods, applicable to a large array of starting materials, would be highly desirable. Until recently, no method based on the asymmetric catalysis starting from achiral imines was available. In the past three years, some efficient catalytic methods have been described, although all of them are limited to the synthesis of *N*-sulfonyl oxaziridines.

In 2011, the Jørgensen group disclosed the first catalytic enantioselective oxidation of acyclic sulfonyl aldimines **47** to *N*-sulfonyl oxaziridines **48**.[65] The working approach of this pioneering study entailed the employment of a chiral base catalyst to activate the nucleophilic attack of a peracid. Dihydro derivatives of cinchona alkaloids were evaluated for this purpose. Alternative oxidants were not suitable for this process. The presence of a hydrogen-bonding donor group in the catalyst structure proved to be an essential requisite to obtain high enantioselectivity. This result was explained assuming the reaction to proceed through a highly organized transition state, wherein the catalyst is also able to activate the imine through coordination with the sulfonyl group. The anthracenylmethyl-modified catalyst **49** led to the best results (Scheme 18). A wide range of aromatic *trans*-*N*-tosyl oxaziridines were obtained by oxidation of the corresponding *N*-tosyl aldimines, with MCPBA achieving good to excellent enantioselectivity. This method was successfully applied to aliphatic *N*-tosyl aldimines, provided that a bulky tertiary alkyl group was not present (Scheme 18). However, the authors did not detail whether the quasi-enantiomeric *O*-anthracenyl hydrocupreine-derived catalyst could afford efficiently the (*R*,*R*)-tosyl oxaziridines.

Mechanistic study on concentration dependence effects and on the kinetics of differently substituted imines were not supportive of a concerted nucleophilic attack on the peroxidic oxygen, typical of metal-catalyzed epoxidations. Indeed, a stepwise mechanism with the former nucleophilic attack of the oxygen atom of the peracid to the imine, followed by ring-closure favored by the heterolytic cleavage of the O−O bond

Scheme 18. Cinchona Alkaloids-Catalyzed Oxidation of *N*-Tosyl Aldimines with MCPBA



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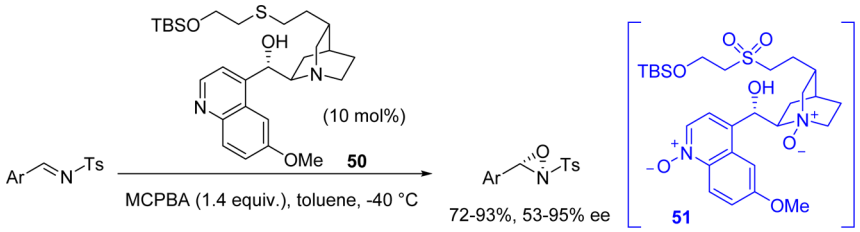
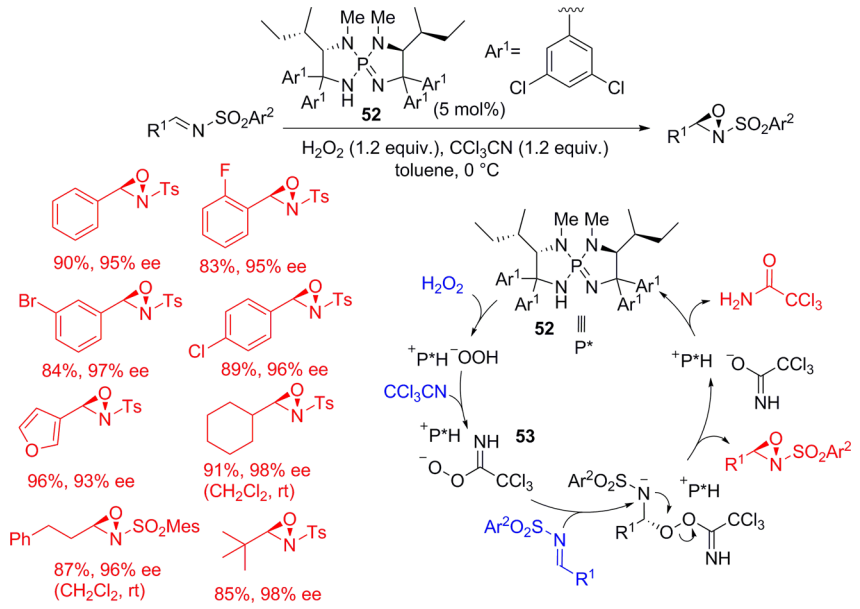
Scheme 19. Cinchona Alkaloid-Catalyzed Oxidation of Aromatic *N*-Tosyl Aldimines with MCPBA



Scheme 20. Chiral Triaminoiminophosphorane Catalyzed Oxidation of *N*-Sulfonyl Aldimines with H_2O_2/CCl_3CN



was suggested. In the rate-determining step, both the imine and the peracid would be activated by the bifunctional catalyst through hydrogen-bonding and ion-pairing, respectively. Undoubtedly, the method developed by Jørgensen is attractive in terms of broad substrate scope and excellent level of enantioselectivity, although a modest performance remains with hindered *N*-sulfonyl imine substrates.

Jin and coauthors recently reinvestigated this process screening a variety of catalysts elaborated at 9-OH, 6′-OH and terminal vinyl groups of quinidine and quinine compounds.[66] Quinidine derivative **50**, bearing the free 9-OH group and a sulfur-containing chain linked to the quinuclidine core, catalyzed the oxidation, achieving the products with high yield and moderate to excellent enantioselectivity, albeit generally lower than those obtained with compound **49** (Scheme 19). The 9-OH group apparently played a crucial role in the bifunctional mechanism, in place of the phenolic 6′OH group, but they proved the results were also positively affected by the presence of the sulfur-containing chain. An important drawback of this method is the inability to obtain both enantiomers. Although the *trans*-(*R*,*R*)-oxaziridine is efficiently formed in the reaction catalyzed by compound **50**, its quasi enantiomer, derived from quinine, produced a racemic mixture.

From a mechanistic point of view, the involvement of *N*-oxide species cannot be ruled out because the authors identified in the reaction mixture the fully oxidized catalyst **51** after a few minutes, whereas only a small amount of the oxaziridine had been formed. However, when aldimine was reacted in the presence of compound **51**, previously obtained by premixing MCPBA with catalyst **50**, both yield and ee values were observed to fall down.

Recently, the Ooi group delevoped an impressive organocatalytic oxidation of *N*-sulfonyl aldimines, proceeding with an excellent level of enantioselectivity.[67] A P-spiro chiral triaminoiminophosphorane **52** was employed as a strong basic catalyst, and a mixture of hydrogen peroxide and trichloroacetonitrile served as the oxidizing system. Under such conditions, known as Payne modification,[68] the base-activated hydrogen peroxide reacted with trichloroacetonitrile, generating a chiral aminophosphonium peroxyimidate **53** as the active oxidant (Scheme 20). Species **53** could be considered an analogue of the ammonium peroxycarboxylate nucleophilic oxidant operating in the mechanism proposed by Jørgensen. Its attack on the C═N *Re* face of the imine would selectively occur, favored by the high stereocontrol exerted by the chiral aminophosphonium counterion. The chiral peroxyhemiaminal intermediate formed would undergo smooth cyclization to the chiral oxaziridine, releasing the good leaving group amidate ion. Finally, proton shift, with formation of the neutral trichloroacetamide side-product and regeneration of the catalyst, would complete the catalytic cycle.

This method proved to be outstandingly high-performing, providing equally excellent yield and enantioselectivity in the oxidation of a broad range of aromatic, heteroaromatic, and aliphatic *N*-sulfonyl aldimines, regardless of the substituent bulkiness (Scheme 20). The reactions with aromatic, heteroaromatic and tertiary aliphatic *N*-tosyl aldimines were successfully conducted in toluene at 0 °C. Optimized conditions for the

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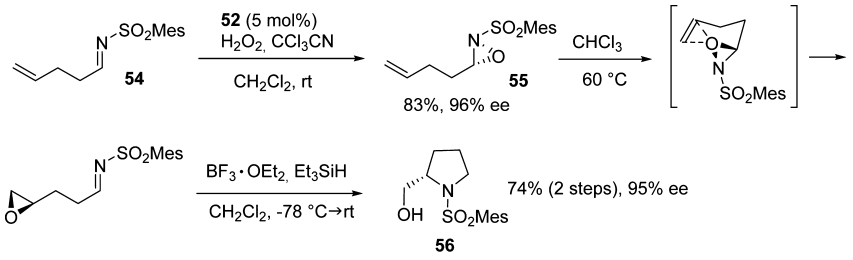
Scheme 21. Enantioselective Synthesis of a Prolinol Derivative via Oxaziridination of an Unsaturated Imine

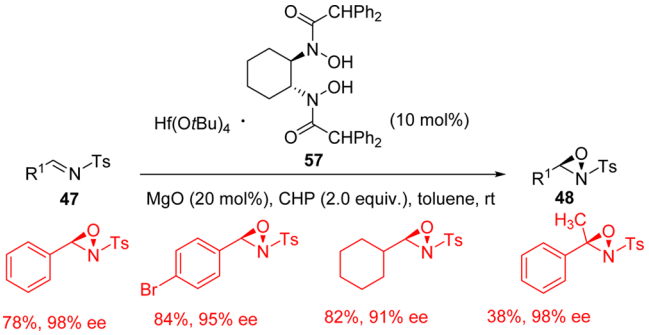


other aliphatic substrates required CH_2Cl_2 as solvent working at room temperature. Primary aliphatic aldimines were oxidized in high yield if *N*-mesitylenesulfonyl was installed as the protecting group instead of a *N*-tosyl moiety. Further significant advantages of the Payne-type conditions are the highest convenience and atom-economy of H_2O_2 as the oxygen source over the use of peracids and the chemoselectivity of the process when potentially oxidizable groups are present.

As a synthetically useful proof, unsaturated imine **54** was enantioselectively and chemoselectively converted into oxaziridine **55**, which under heating underwent intramolecular epoxidation, yielding a chiral intermediate to access prolinol derivative **56** (Scheme 21).[67] The overall synthesis occurred with complete preservation of the optical purity.

In 2012, the Yamamoto group described the only method so far available of asymmetric metal-catalyzed oxaziridination of *N*-tosyl imines **47** (Scheme 22).[69]

Scheme 22. Enantioselective Hafnium-Catalyzed Oxaziridination of *N*-Tosyl Imines



The oxidation of aromatic and aliphatic *N*-tosyl aldimines with CHP, catalyzed by an in-situ-formed hafnium complex with C_2-symmetric chiral bishydroxamic acid **57**, furnished *trans*-oxaziridines **48** in good yield and excellent enantioselectivity, although only a few substrates were tested.

Interestingly, less reactive *N*-tosyl methylketimine was oxidized to the corresponding oxaziridine in excellent ee value, albeit in low conversion. The work of Yamamoto appears to be unique to address the challenging task of synthesizing oxaziridines via enantioselective oxidation of the corresponding ketoimines. This finding highlights the great potential of metal catalysis over organocatalysis.

An alternative enantioselective nonoxidative catalytic approach explored was the kinetic resolution of racemic oxaziridines.

In 2010, Ye and coauthors reported an asymmetric formal Lewis base catalyzed [3 + 2]-cycloaddition of racemic *N*-tosyloxaziridine **58** to a variety of disubstituted ketenes **59**.[70] The use of *N*-heterocyclic carbene obtained from imidazolium salt **60** allowed the isolation of *cis*-oxazolin-4-ones **61** in high enantioselectivity. Likewise, enantioenriched oxaziridine (−)-**58** was recovered in good to excellent enantioselectivity, depending on the ketene employed (Scheme 23). Reaction conditions were preferentially optimized to achieve the highest yield of compounds **61**, affording compound (−)-**58** in low yield. However, whereas the scope of ketenes was fully explored, only oxaziridine **58** was tested in the process. The other enantiomer, (+)-**58** was obtained in distinct decreased ee values by employing an O-silylated precatalyst **62**, derived from L-pyroglutamic acid.

Yoon and co-workers, during their study of an analogous formal asymmetric [3 + 2]-cycloaddition of racemic *N*-nosyl oxaziridines with styrenes to oxaziridines catalyzed by a chiral iron complex, noticed unreacted oxaziridines to be highly enantioenriched (80% ee);[71] however, only one example was reported, and the process was not developed for the synthesis of chiral oxaziridines.

The principle of kinetic resolution was fully exploited for preparative purposes by the Feng group in the recently developed reaction of racemic azlactones **63** with racemic *N*-sulfonyl oxaziridines **64**, catalyzed by chiral bisguanidinium salt **65** (Scheme 24).[72]

In this process, the authors took advantage of the ambiphilic nature of azlactones which, after enolization, could act as a nucleophile at the α-carbon and as an electrophile at the carbonyl group. The combination with oxaziridines resulted in a formal [3 + 2] cycloaddition, generating intermediate **66**. A subsequent ring-opening reaction afforded enantioenriched oxazolin-4-ones **67**. During the reaction, one enantiomeric oxaziridine was preferentially consumed, giving rise to an efficient process of kinetic resolution.

In contrast, despite the high stereoselectivity of the process, both enantiomers of compound **63** were consumed at an equal rate because of the concomitant fast racemization under the reaction conditions. The scope of both azlactones and oxaziridines was broadly explored with generally excellent results. Oxazolin-4-ones were obtained in high diastereo- and enantioselectivity, except when a *N*-nosyl oxaziridine was used. Aryl, heteroaryl, and alkyl *N*-sulfonyl oxaziridines could be recovered in good to excellent enantioselectivity.

A hint about the mechanism was given by the observation that only hemisalt **65**, obtained after treatment of an equimolar mixture of bisguanidine and its bivalent hydrogen chloride salt with 2 equiv of $NaB[3,5\text{-}(CF_3)_2C_6H_3]_4$, efficiently catalyzed the process. Conversely, the bivalent $HB[3,5\text{-}(CF_3)_2C_6H_3]_4$ salt did not catalyze the reaction, but the neutral guanidine afforded racemic products. These findings suggested a bifunctional mechanism in which the guanidinium moiety would serve to recognize and activate the (*S*,*S*)-oxaziridine, whereas the guanidine might function as a Brønsted base in the activation of the azlactone.

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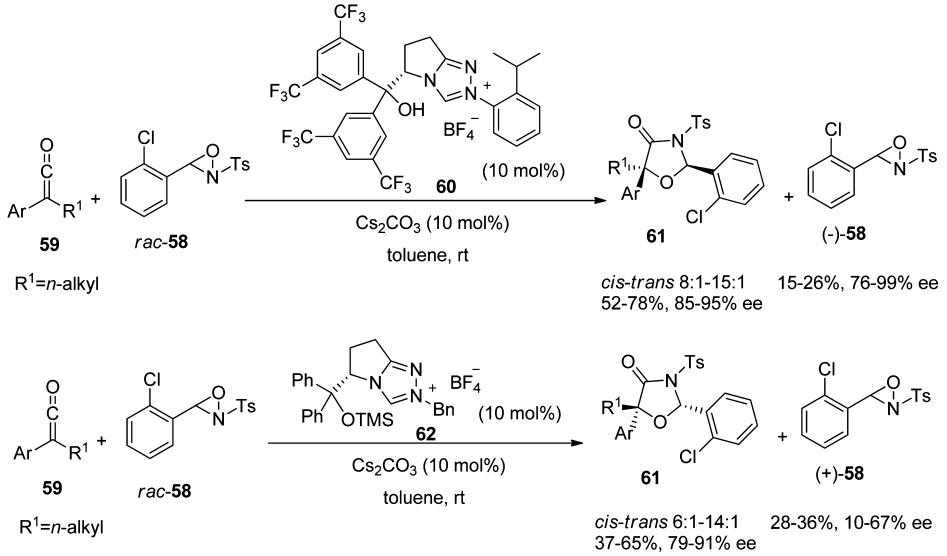
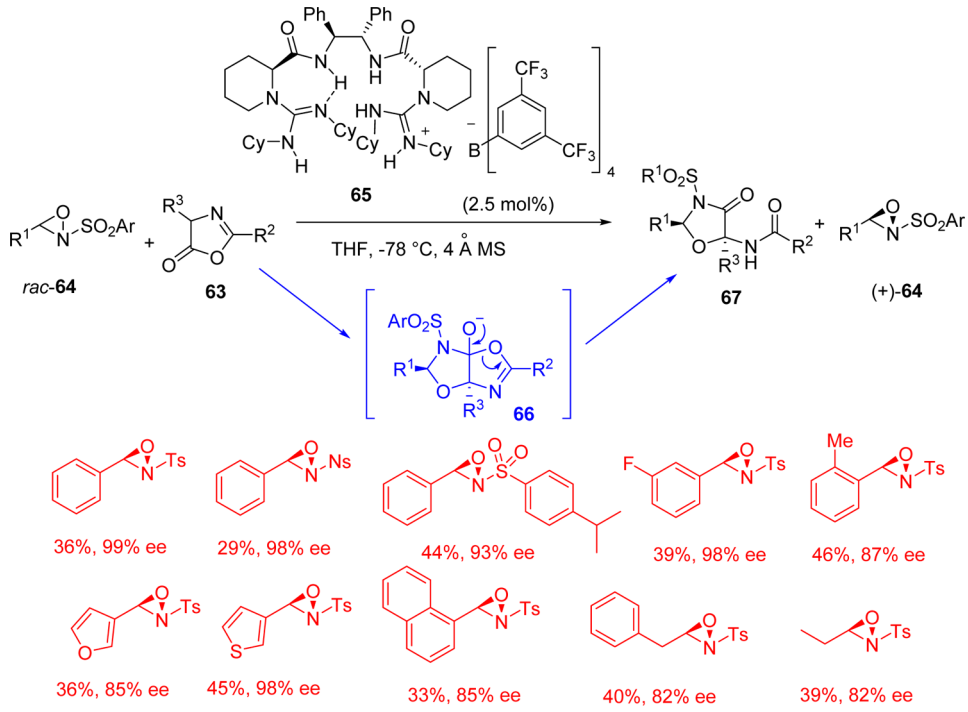
Scheme 23. Kinetic Resolution of *N*-Tosyl Oxaziridine 58 by Formal [3 + 2] Cycloaddition to Ketenes Catalyzed by *N*-Heterocyclic Carbenes



Scheme 24. Guanidinium Salt-Catalyzed Kinetic Resolution of *N*-Sulfonyl Oxaziridines by Formal [3 + 2] Cycloaddition to Azlactones



4. CONCLUSION

Significant progress has been achieved, but more properly, in less than a decade, a gap has started to be filled in the development of catalytic general enantioselective methods for the preparation of optically enriched dialkyl peroxides and oxaziridines. As a testimony of this fact, literature precedents almost entirely relied on a classical stoichiometric chiral substrate/auxiliary-controlled approach. The availability of different types of readily accessible organocatalysts has opened a way to explore well-established or novel routes to access these compounds by taking advantage of covalent or noncovalent activation strategies of the reagents.

Catalytic asymmetric oxidations of electron-poor alkenes and imines with alkyl hydroperoxides or peroxy acids promoted by chiral bases; phosphoric acids; and, to a lesser extent, by transition-metal-complexes have been the most investigated, turning out to be particularly effective processes. Interestingly, nonoxidative desymmetrization and kinetic resolution strategies deserve attention as appealing routes for the synthesis of these challenging but versatile synthetic compounds.

Overall, the organocatalytic methods display good synthetic potential and appear to be more successful than metal-catalyzed reactions because they predominantly enabled the synthesis of a variety of compounds. Further discoveries are to be expected in the years to come, and improvements are also required because

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this area is in its infancy. Forthcoming work in this field should aim to broaden the still limited substrate scope, design more powerful bifunctional or multifunctional catalytic systems to reduce the catalyst loading, and probe unexplored activation strategies (for example, combining metal- and organocatalysis).

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Notes

The authors declare no competing financial interest.

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