Review

#-Substituted #-Lithiated Oxiranes: Useful Reactive Intermediates

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α-Substituted α-Lithiated Oxiranes: Useful Reactive Intermediates

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1. Introduction

Epoxides, strained three-membered ring heterocycles, are among the most versatile intermediates in organic chemistry. The paramount interest for this type of heterocyclic system is amply justified by the great number of biologically significant molecules that contain this motif within their structures and its large use as synthetic building block. A number of important advances have been achieved in the chemistry of epoxides over the last years. Reviews and books have been published to summarize such achievements.[1] Undoubtedly, one of the most fascinating aspects of the chemistry of epoxides is concerned with their behavior toward bases or nucleophilic reagents.

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Saverio Florio received his "Laurea" in Chemistry at the University of Bari (Italy) and started his academic career there, first as Assistant Professor (1969) and then as Associate Professor of Organic Chemistry (1982). In 1986, he was appointed Full Professor of Organic Chemistry at the University of Lecce. In 1990 he moved to the University of Bari on the chair of organic chemistry. He has been the Director of Dipartimento Farmaco Chimico of the University of Bari from 1993 to 1997 and, at present, is Director of "Consorzio Interuniversitario sulle Metodologie e Processi Innovativi di Sintesi" (CINMPIS) since its institution in 1994. He has been member and vice president of the Division of Organic Chemistry of the Italian Chemical Society from 1993 to 1997. Since 1997 to 2001 he acted as the President of the same division and from December 2007 he is vice president of the Italian Chemical Society. He has been component of national committees for the evaluation of associate and full professors of organic chemistry in national competitions. At present, Prof. Florio is a member of the Board of consulting editors of *Tetrahedron* and *Tetrahedron Letters*, a member of the Scientific Advisory Board of the Ischia IASOC School, and a member of the "Academy of Science and Arts of Salsburg". His research interests are concerned with the synthesis and reactivity of heterocyclic compounds, in particular metallated epoxides and aziridines, asymmetric synthesis, organometallic chemistry, spectroscopic and computational investigation of organic lithiated species. Prof. Florio has supervised many dozens of undergraduate and PhD students and published more than 180 papers on important international scientific journals and acts as referee for international journals. He has been awarded with "Ziegler-Natta Lecture" (Deutscher Chemiker) in 2005 and with the "Angelo Mangini Gold Medal" of the Division of Organic Chemistry of the Italian Chemical Society in 2007.

Depending on the ring substituents, treatment of an epoxide with a base/nucleophile may cause mainly three different events: (a) cleavage of the strained heterocyclic ring (*path a*); (b) abstraction of a β-proton to give an allylic alcohol in a process that is called β-elimination (*path b*); (c) removal of an α-proton to generate an α-metallated epoxide (oxiranyl anion) (*path c*) (Scheme 1).

This review will focus on generation, reactivity, and synthetic applications of α-metallated oxiranes with special attention addressed to α-lithiated oxiranes.

α-Lithiated oxiranes (LO) and their chemistry have driven the interest of several research groups after the pioneering

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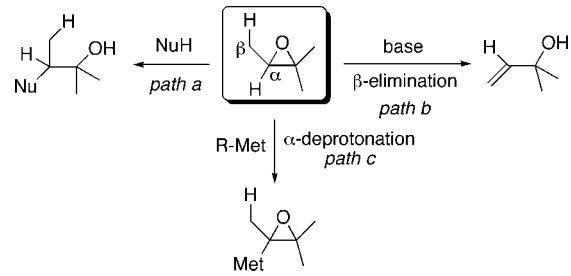
Vito Capriati was born in Bari, Italy, in 1965. He received his degree in Chemistry and Pharmaceutical Technology (with honors) at the University of Bari in 1990 with a two-year experimental thesis in the field of synthetic organic chemistry. In January 1992, after his national service in the "Centro Carabinieri Investigazioni Scientifiche" in Rome, now known as "Reparto Investigazioni Scientifiche (R.I.S.)", he returned to the University of Bari where he worked as a fellow in the Centre on "Metodologie Innovative di Sintesi Organiche", now merged into "Istituto di Chimica dei Composti Organometallici", under the supervision of Prof. Francesco Naso, until December 1993. In 1994, he became Assistant Professor and joined Prof. Saverio Florio's research group at the Dipartimento Farmaco-Chimico of the University of Bari working in the field of organometallic chemistry, and, in 2002, he was appointed Associate Professor of Organic Chemistry at the same university. In 2001, he was visiting scientist at the Ohio State University (Columbus, Ohio, USA) and, in 2003, at the Göteborg University (Sweden) working in the field of $^{6}Li/^{13}C$ NMR spectroscopy applied to the study of anionic species in solution. His current research interests revolve around organolithium chemistry, mechanistic studies, asymmetric synthesis of small-ring functionalized heterocycles and stereochemical determination of their relative and absolute configurations, multinuclear NMR investigations on highly reactive organic intermediates, such as oxiranyllithiums, their structures and dynamics behavior. He is coauthor of more than 60 papers in specialized international peer-reviewed journals. Besides chemistry, he is a member and volunteer translator for EURORDIS (The European Organization for Rare Deseases) to empower rare disease organizations, patients, and families throughout Europe to contribute to building a rare disease community across national and linguistic lines.

Renzo Luisi was born in Luxembourg (EU) in 1971. After graduation from high school in 1990, he worked as an analytical chemist for a wine company until 1994. In 1996, he received his degree (with honors) in Chemistry and Pharmaceutical Technology at the University of Bari and, in 2000, he got his PhD in Chemical Sciences at the University of Bari under the supervision of Prof. Saverio Florio. In 1999, he was Visiting Scholar at the University of Illinois in Prof. Peter Beak's group. In 2001, after a seven month fellowship at the "Consorzio Interuniversitario sulle Metodologie e Processi Innovativi di Sintesi" of the University of Bari, he became Assistant Professor at the same University and joined the permanent staff of Prof. Saverio Florio's research group. In January 2005, he was appointed Associate Professor of Organic Chemistry at the University of Bari. His current research interests are focused on organolithium chemistry, asymmetric synthesis, reactivity and synthetic applications of metalated small heterocycles, dynamics of aziridines in solution and multinuclear NMR techniques aimed at solving mechanistic and stereochemical problems. He is co-author of more than 50 papers in specialized international journals and has attended several national and international conferences.

work by Cope et al. who first proposed the involvement of an α-lithiated oxirane **2** to explain the rearrangement of cyclooctatetraene oxide **1** to cycloocta-1,3,5-trien-7-one (**3**) on treatment with lithium diethylamide[2] and in the base-induced stereospecific isomerization reaction of both *cis*- and *trans*-cyclooctene oxides **4** and **5** to bicyclic alcohols **6** and **7**, respectively (Scheme 2).[3] House and Ro[4] presented the first experimental evidence for the existence of metallated epoxides in the reaction of *cis*- and *trans*-α-methyl-*β*-benzoylstyrene oxide **8** with NaOEt followed by deuteration to give adduct **9** (Scheme 2), while Eisch and Galle[5] studied the lithiation reaction of aryloxiranes and silyloxiranes as well as the synthetic utility of the trapping of the resulting lithiated species with electrophiles.

Most of the work on this topic has been done over the past 15−20 years. The field has been comprehensively reviewed by Satoh[6] in 1996, by Mori,[7] and, more recently, by Hodgson,[8] Chemla,[9] and Florio.[10] However, efforts are still carried out in order to elucidate aspects concerned with generation, structural features, reactivity [carbanions or carbenoids (as a noun), meant, according to Closs and Moss definition,[11] as "intermediates capable to exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species", thermal as well as configurational stability and stereochemistry of their reactions.

Scheme 1

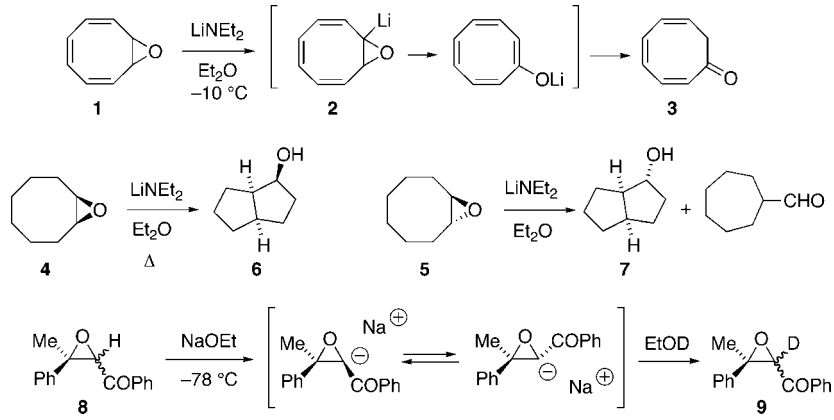


2. Generation of α-Lithiated-α-Substituted Oxiranes

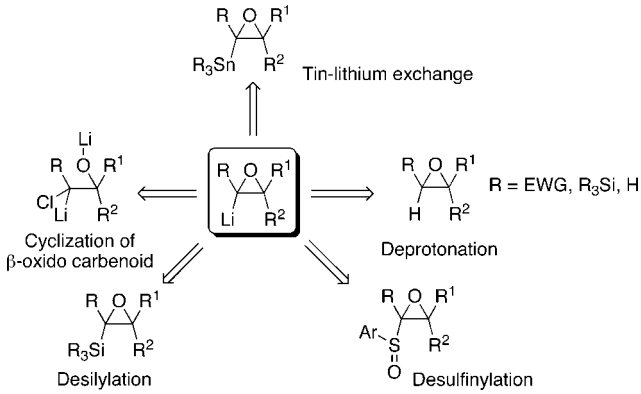
After the first difficulties related to the experimental conditions (temperature, solvent, cosolvent, ligand, lithiating agent) encountered for years, the generation of LOs is no longer a problem. Nowadays, almost any kind of LO can be generated and trapped using various procedures such as tin−lithium exchange, desilylation of epoxysilanes, desulfinylation of epoxysulfoxides, and cyclization of *β*-oxido carbenoids. By far, the most convenient and used procedure is deprotonation with strong bases such as lithium amides and organolithiums eventually in the presence of ligands. It works well not only when an electron-withdrawing group (EWG) or a trialkyl(triaryl)silyl group is present on the oxirane ring carbon to be deprotonated but also with some cycloalkene oxides and terminal epoxides, as recently demonstrated (Scheme 3).[12]

LOs enjoy a very rich chemistry substantially resulting from their carbenoidic character, which is determined by their structural features and tuned by experimental conditions.[13] Indeed, once generated, as nucleophiles, they can be captured

Scheme 2



Scheme 3



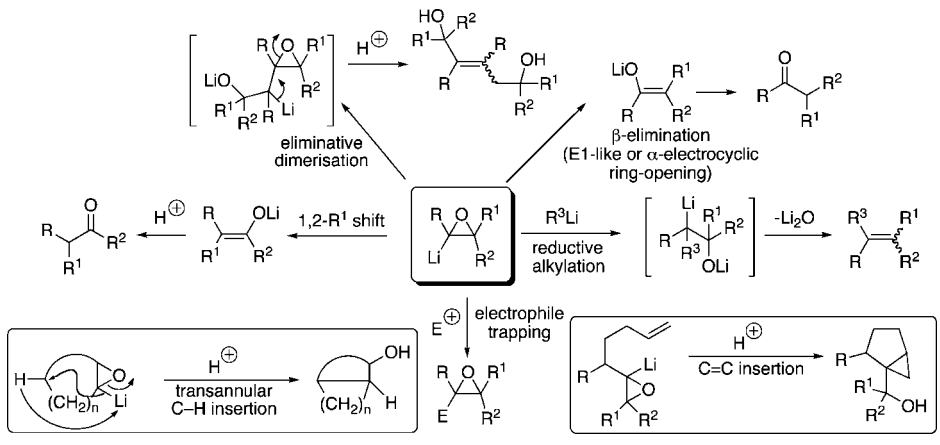
by electrophiles to give more functionalized oxiranes and products derived from (Scheme 4), while all the other reactions illustrated in Scheme 4 have to be ascribed to the carbenoidic character, such as 1,2-R shifts to give enolates, eliminative dimerization (in which the same α-lithiated species acts simultaneously as a nucleophile and an electrophile), β-elimination via an E_1-like mechanism or electrocyclic α-ring-opening process, intramolecular cyclopropanation onto a double bond (C=C insertion), transannular C−H insertion concerning, in particular, medium-sized oxiranes, and reductive alkylation. All these reactions proved to be very useful resulting in some interesting synthetic applications such as dimerization, desymmetrization of meso epoxides and other C−H insertion.

The reaction of an α-lithiated epoxide with an electrophile is a potentially attractive route to a more substituted epoxide. Eisch and Galle were the first to utilize this concept in the middle of 1970s reporting that an α-lithiated styrene oxide or an α-lithiated silyl epoxide **10** could be trapped with an electrophile to generate a more substituted epoxide **11** (Scheme 5).

Since then and for long time, α-lithiated epoxides have been considered highly labile assuming necessary that an electron-withdrawing or a trialkyl(triaryl)silyl group, able to increase the anion lifetime, be present on the epoxide ring. This could create problems to the synthetic chemist as not only must the anion "activating group" be introduced into the starting epoxide but, if this group is not required in the final target, then it must be removed in subsequent transformations. However, it must be pointed out that some "activating groups" not only can be easily introduced and smoothly removed, but their presence can be exploited for synthetic elaborations. In any case, it might be useful to classify α-lithiated oxiranes as "activated", when an electron-withdrawing (aryl, vinyl, alkynyl, cyano, sulfonyl, amido, heterocyclic, trifluoromethyl, ester, phosphinyl, halogen) or a trialkyl(triaryl)silyl group is present on the lithiated oxirane ring carbon atom and "unactivated" in the absence of such groups.

This review is concerned with the chemistry of *activated α-lithiated oxiranes*, their generation and synthetic applications, mainly because the *lithiation of unactivated oxiranes* (that is, unsubstituted at the lithiation site) has been recently reviewed.[8] Let us say right away that the role of the α-substituent, such as those cited above, is to facilitate deprotonation and prolong the lifetime of these otherwise very fleeting intermediates in order to allow manipulation

Scheme 4



Scheme 5

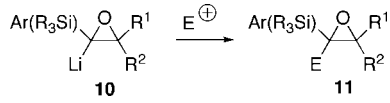
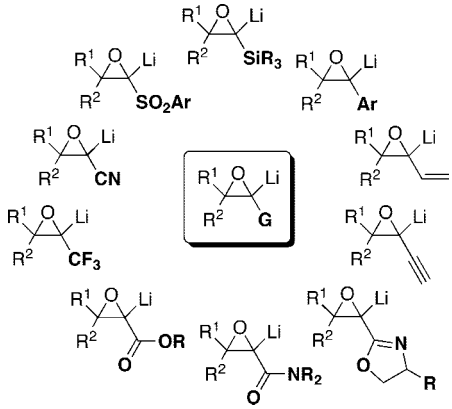


Chart 1. α-Substituted-α-lithiated Oxiranes



and to exploit their *nucleophilic character* (over their *carbene-type reactivity*) in the trapping reaction with electrophiles. It is worth noting that a given group may "stabilize" a lithiated oxirane also from a remote position through an intramolecular chelation.[14] In Chart 1 a collection of α-substituted-α-lithiated oxiranes is presented. Some of them, depending upon the geometry of the starting epoxide, exhibit a *kinetic configurational stability*, that is, retain their stereochemistry also in the absence of an external stereogenic influence (e.g., α-lithiated trifluoromethyloxiranes). Additionally, α-lithiated styrene oxides, which are also kinetically configurationally stable, do exhibit a switch of reactivity on going from a carbanion to a carbenoid character (see ahead) when generated in absence of an external ligand such as TMEDA. Other anions (e.g., α-lithiated oxazolinyloxiranes) tend instead to lose their stereochemical integrity undergoing a quick interconversion at the lithiated carbon also at low temperature; therefore, they can be considered configurationally unstable. Moreover, for the latter, the presence of an external ligand such as TMEDA is needed to minimize their isomerization with the time. Throughout this review, we shall use simply the term "stability" or "thermal stability" with reference to α-lithiated oxiranes that are *structurally robust on the macroscopic time scale at a certain temperature,* in the sense they can be easily generated (usually at a temperature below −78 °C), kept in solution for long time (minutes or hours), and sometimes also warmed to room temperature with a minimum of decomposition. These types of intermediates are, therefore, particularly useful from the synthetic point of view.

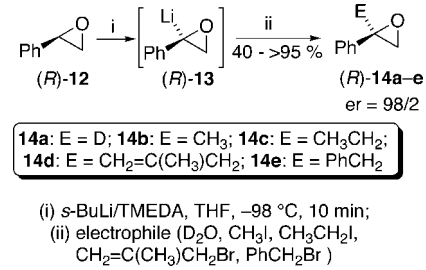
3. α-Lithiated Aryloxiranes

3.1. Generation and Reactivity

Optically active styrene oxide derivatives are useful chiral building blocks for the synthesis of natural products and biologically active compounds.[15] Therefore, the development of efficient methods for their synthesis is amply justified. Among the existing methods, the oxiranyl anion-based methodology had not been investigated till recently. Some evidence reported by Eisch[5c] (see also Introduction) on racemic *cis*-disubstituted β-phenylepoxysilanes, *cis*- and *trans*-diphenyloxiranes and by our group[16] on β-aryl-substituted oxazolinyloxiranes have proved the configurational stability of aryl-substituted lithiated oxiranes. The first successful use of the oxiranyl anion-based methodology for the stereoselective synthesis of styrene oxide derivatives has been recently developed.[17]

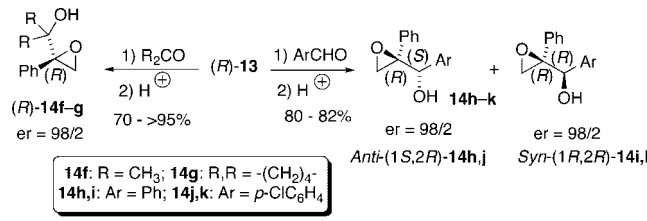
Treatment of a precooled mixture (−98 °C) of styrene oxide (*R*)-**12** (1 equiv) and TMEDA (3 equiv) with *s*-BuLi (1.2 equiv) (*n*-BuLi and LDA were ineffective) in THF for 10 min led to regioselective generation of oxiranyllithium (*R*)-**13**, which was subsequently allowed to react with a series of electrophiles to give stereospecifically the corresponding α,α-disubstituted epoxides (*R*)-**14a**−**e** in good to excellent yields and very high enantiomeric ratios (er = 98/2 in all cases) (Scheme 6); this shows that the reactions proceeded with retention of configuration at the stereogenic center.

Scheme 6



Lithiated styrene oxide (*R*)-**13** also reacted smoothly with ketones (acetone and cyclopentanone) to give products **14f**,**g** in good yields and with aldehydes (benzaldehyde and *p*-chlorobenzaldehyde) leading to good yields of products **14h**−**k**, although with poor diastereoselectivity at the newly created stereogenic center (*anti*/*syn* ratio = 66/34) (Scheme 7). The enantiomers could be similarly prepared, starting from (*S*)-**13**.

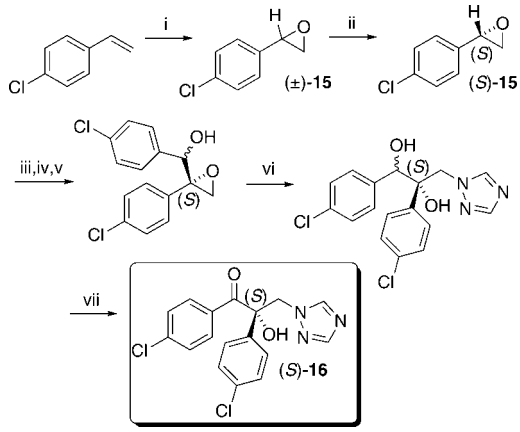
Scheme 7



A short, highly efficient synthesis of the industrially relevant triazole antifungal agent (*S*)-**16**[18] illustrates the value of this methodology starting from optically active (*S*)-4-chlorostyrene oxide **15**, prepared from *p*-chlorostyrene upon epoxidation followed by hydrolytic kinetic resolution according to the Jacobsen method (Scheme 8). Lithiation of (*S*)-**15** followed by the trapping with *p*-chlorobenzaldehyde and ring-opening with triazole resulted in the formation of a diastereomeric mixture of diols; subsequent Swern oxidation furnished a quantitative yield of almost optically pure (*S*)-**16**.

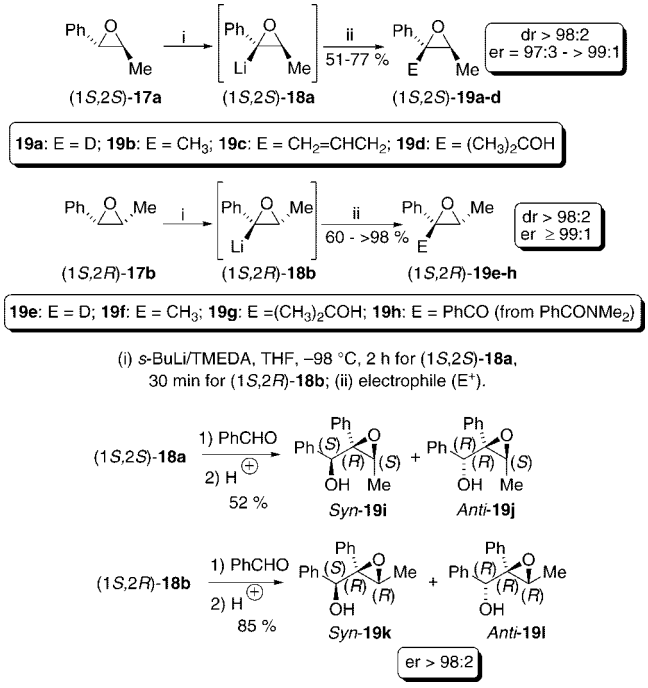
The substituent effect in the α-lithiation of *cis*- and *trans*-phenylpropylene oxides has been evaluated.[19] Treatment of a precooled mixture (−98 °C) of (1*S*,2*S*)-(−)-1-phenylpropylene oxide **17a** and TMEDA (3 equiv) in THF with *s*-BuLi (3 equiv) (*n*-BuLi and LDA were ineffective) gave a cherry-red solution, likely to be ascribed to the lithiooxirane **18a**, which proved to be stable at low temperature (−98 °C) for at least 2 h. The trapping of **18a** with D_2O furnished the

Scheme 8



corresponding α-deuterated phenylpropylene oxide **19a** in a good yield after distillation (77%, > 98% D): the reaction took place with complete retention of configuration at the α-carbon (dr >98:2, er ≥97:3) (Scheme 9). The reaction of

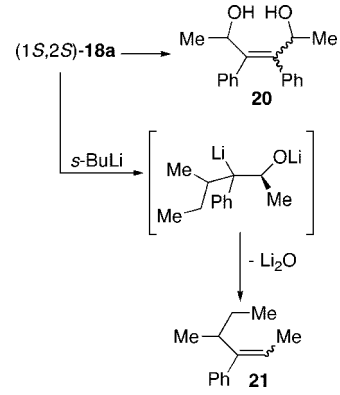
Scheme 9



(1*S*,2*S*)-**18a** with other electrophiles (CH_3I, allyl bromide, and acetone) again occurred stereospecifically providing the corresponding α-substituted phenylpropylene oxides **19b**−**d** in good yields and high dr and er values (Scheme 9). Lithiated epoxides (1*S*,2*S*)-**18a** and (1*S*,2*R*)-**18b** also reacted smoothly with PhCHO leading in good yields to products **19i,j** and **19k,l** (Scheme 9), respectively, although with poor diastereoselectivity at the newly created stereogenic center: dr *anti*/*syn* **19i,j** = 70/30, dr *anti*/*syn* **19k,l** = 60/40. However, stereoisomers could be separated by preparative HPLC and spectroscopically characterized.

The use of a nondonor solvent (hexane), the absence of TMEDA, and a higher temperature (> −98 °C) favored the carbenoid nature of **18a**, thus leading to the formation of enediols **20** ("eliminative dimerization")[13a,20] and alkenes **21** which are the result of a "reductive alkylation" process promoted by *s*-BuLi on **18a** with concomitant elimination of Li_2O (Scheme 10).[21]

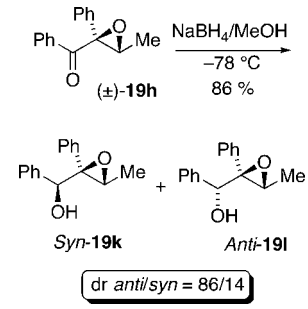
Scheme 10



The observed configurational stability of (1*S*,2*R*)-**18b** is worth noting as, in contrast to what was found for lithiated *cis*-disubstituted oxazolinyloxiranes[22] and by Molander[23] for silicon-stabilized *cis*-*t*-butyl-substituted oxiranyllithiums, the strain created in forcing the methyl and the phenyl groups both on the same side of the oxirane ring of **18b** did not promote any interconversion between (1*S*,2*R*)-**18b** and (1*S*,2*S*)-**18a**.

For the stereoselective synthesis of α,β-epoxy alcohols, which are excellent starting materials for the preparation of stereodefined polyols, natural products or biologically active compounds,[24] the carbonyl reduction of the α,β-epoxy ketone (±)-**19 h** with $NaBH_4$ was employed (Scheme 11), where a

Scheme 11

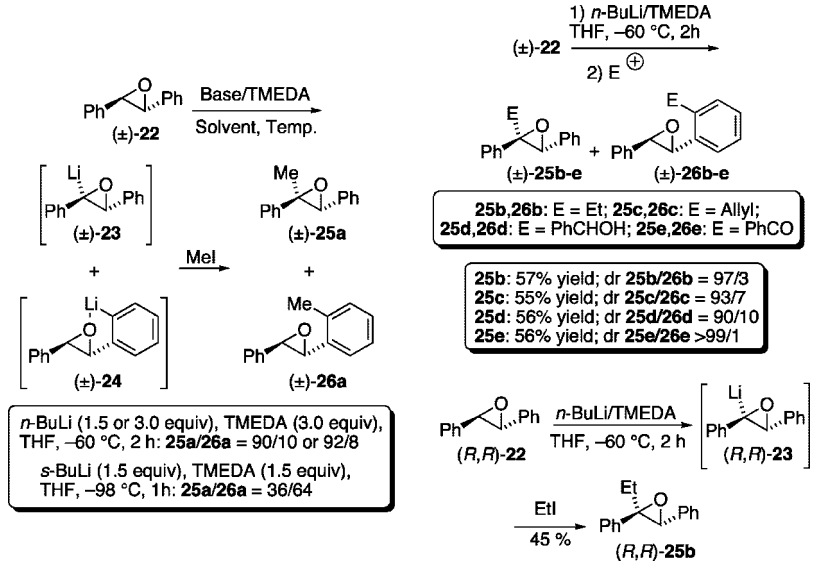


Felkin-Ahn model was proposed for the observed antistereoselectivity (*anti*-**19l** vs *syn*-**19k**).

Lithiation of (±)-**22** followed by quenching with MeI gave a mixture of the expected epoxide *trans*-**25a** and the *ortho*-methylated epoxide **26a**, the **25a**:**26a** ratio being dependent upon the experimental conditions (Scheme 12).[25] The use of *n*-BuLi (1.5 or 3.0 equiv) in THF in the presence of TMEDA at −60 °C and 2 h as the reaction time favored the α-lithiation (α/*ortho* ratio = 90:10 or 92:8, respectively), while *s*-BuLi (1.5 equiv), TMEDA (1.5 equiv), THF, −98 °C and 1 h as the reaction time represented the best conditions for the formation of epoxide **26a** (**25a:26a** ratio = 36:64). Looking for even better experimental conditions for the *ortho*-lithiation it was discovered that this happens when α,α′-dideuterated *trans*-stilbene oxide was treated with *s*-BuLi and TMEDA at −98 °C (α/*ortho* ratio of about 90/10). To account for the formation of **26a** it has been proposed that there is coordinative assistance of the epoxide oxygen to the H−Li exchange on the phenyl ring (intermediate **24**). In other words, the epoxide is acting as an *ortho*-directing group (D*o*M methodology).[26]

Lithiation of **22** with either 3 equiv or 1.5 equiv of *n*-BuLi and 3 equiv of TMEDA in THF at −60 °C for 2 h gave the

Scheme 12

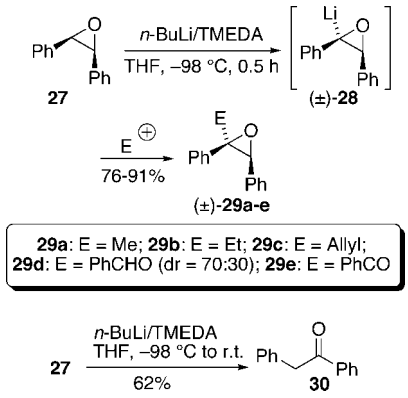


best conversion of **22** to **23** with high regioselectivity. Quenching under these conditions with MeI, EtI, AllylBr, PhCHO, and $PhCONMe_2$ gave mainly or almost exclusively the α-substituted products **25b**−**e** over the *ortho*-substituted adducts **26b**−**e** (Scheme 12).

The lithiation of enantioenriched (*R*,*R*)-*trans*-stilbene oxide **22** (ee = 98%) with *n*-BuLi at −60 °C gave the lithiated derivative (*R*,*R*)-**23** which, similarly, proved to be quite stable and could be kept for at least 2 h at this temperature. Quenching with EtI furnished (*R*,*R*)-*trans*-stilbene oxide (+)-**25b** ($[\alpha]_D$ = +22, 45% yield) together with the starting epoxide (*R*,*R*)-**22** (27%) (Scheme 12).

The lithiation of *cis*-stilbene oxide **27** has been also investigated. When MeI was added to the lithiated *cis*-stilbene oxide **28** (generated by deprotonation of **27** with *n*-BuLi (1.5 equiv)/TMEDA (3.0 equiv) in THF at −98 °C for 30 min), α-methylated compound (±)-**29a** formed exclusively (Scheme 13). The absence of *ortho*-lithiation may

Scheme 13



reflect the reduced steric hindrance associated with α-lithiation of *cis*-stilbene oxide compared to the trans isomer. The higher reactivity of *cis*-epoxides toward deprotonation with respect to the *trans* isomers is well documented.[22] Similarly, treatment of (±)-**28** with other electrophiles produced exclusively α-functionalized stilbene oxides (±)-**29b**−**e** again with complete retention of configuration (Scheme 13). Allowing the reaction mixture to reach room temperature, **28** undergoes a rearrangement to give ketone **30** via an electrocyclic α-ring-opening or a 1,2-H shift (Scheme 13).[25]

Therefore, α-lithiated stilbene oxides **23** and **28** proved to be thermally much more stable than lithiated styrene oxide. Indeed, (±)-**23** and (*R*,*R*)-**23** can be kept at −60 °C for at least 2 h and (±)-**28** at −98 °C for 30 min. The reaction of *ortho*-lithiated aryloxiranes with carbonyl compounds[27] and α,β-unsaturated Fischer carbene complexes[28] has been exploited for the synthesis of hydroxyalkyl phthalans and polysubstituted tetrahydronaphthols, respectively.

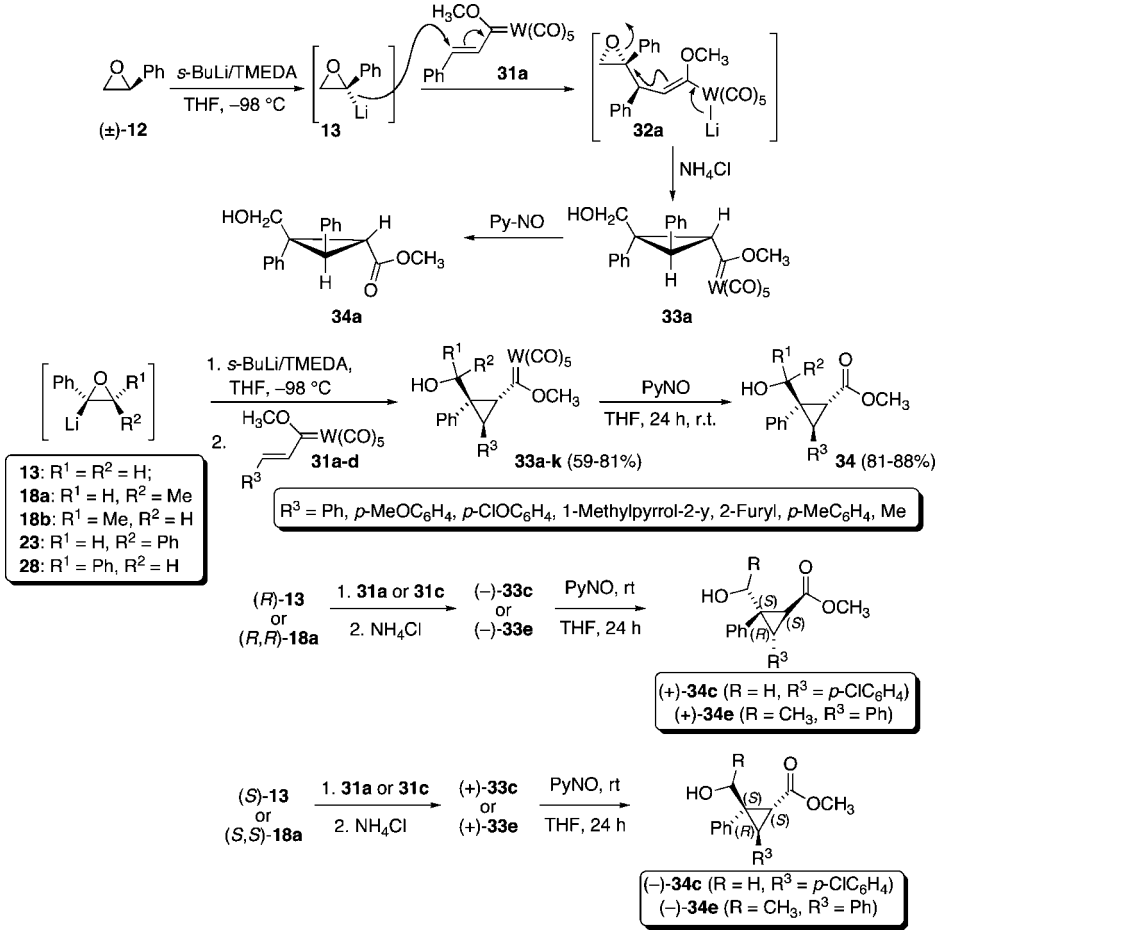
3.2. Stereoselective Synthesis of Cyclopropanes

A highly stereoselective synthesis of polyfunctionalized cyclopropanes, based on the reaction of racemic and optically active α-lithiated aryloxiranes, such as styrene oxides **13**, phenylpropylene oxides **18a**, and stilbene oxides **23** with α,β-unsaturated Fischer carbene complexes, has been developed.[29]

Treatment of (±)-**12** with *s*-BuLi/TMEDA in THF at −98 °C produced α-lithiated styrene oxide **13** (Scheme 14): addition to the α,β-unsaturated tungsten carbene complex **31a** resulted in the formation of cyclopropane derivative **33a** as the sole diastereomer (73%). Oxidation with pyridine *N*-oxide gave the corresponding cyclopropanecarboxylate **34a**.

The stereochemical outcome of the above reaction might reasonably be accounted for with a diastereoselective nucleophilic 1,4-addition of **13** to **31a** leading to the lithium derivative **32a** in which the appropriate orbital alignment allows the overlap of the carbanion lone pair on the β-carbon (with respect to the oxirane ring) with the antibonding orbital of the oxirane C−O bond, thus promoting cyclopropanation simultaneously with the oxirane ring-opening. Comparable results were obtained when **13** was reacted with other unsaturated Fischer carbene complexes such as **31b** (R^3 = *p*-$MeOC_6H_4$), **31c** (R^3 = *p*-$ClOC_6H_4$), and **31d** (R^3 = Me) (74−81%) (Scheme 14). Lithiated phenylpropylene oxides (*R**,*R**)-**18a** (R^1 = H, R^2 = Me) and (*R**,*S**)-**18b** (R^1 = Me, R^2 = H) reacted with carbenes **31a** and **31e** (R^3 = *p*-MeC_6H_4) to give the corresponding cyclopropanecarbenes **33e,f** (68−71% from **18a**) and **33g** (70% from **18b**) (Scheme 14). Moreover, the addition of lithiated stilbene oxides

Scheme 14



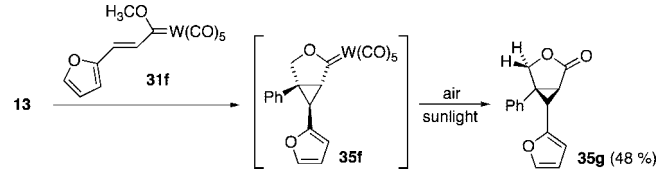
(*R**,*R**)-**23** (R^1 = H, R^2 = Ph) and (*R**,*S**)-**28** (R^1 = Ph, R^2 = H) to **31a** resulted in the formation of carbenes **33h** (73%) and **33j** (77%) (for both R^3 = Ph), respectively (dr > 98:2). This was a clear confirmation that the lithiated aryloxirane retains the configuration in the Michael addition step but inverts at the α-carbon in the oxirane ring-opening. All the above cyclopropanecarbenes could be easily oxidized to the corresponding cyclopropanecarboxylates **34** with pyridine *N*-oxide (PyNO) in THF (rt, 24 h) (Scheme 14).

The addition of (*R*)-**13** to the complex **31c** resulted in the formation of tetrasubstituted arylcyclopropane (1*S*,2*S*,3*R*)-(−)-**33c** (79% yield, dr > 98/2), whereas the addition of (*S*)-**13** furnished the enantiomeric arylcyclopropane (1*R*,2*R*,3*S*)-(+)-**33c** (81% yield, dr > 98/2) (Scheme 14). A cascade process involving the stereospecific Michael addition (retention of configuration at the α-carbon) of (*R*)- or (*S*)-**13** to **31c** (according to that described in Scheme 14), followed by the oxirane ring-opening-promoted cyclopropanation (inversion of configuration at the α-carbon), might likely explain the formation of (−)- and (+)-**33c**.

Similarly, (*R,R*)-**18a** and (*S,S*)-**18a** (Scheme 14), generated by deprotonation of (*R,R*)-**17a** and (*S,S*)-**17a**, reacted smoothly with **31a** to furnish cyclopropanecarbenes (1′*S*,1*R*,2*R*,3*S*)-(−)-**33e** and (1′*R*,1*S*,2*S*,3*R*)-(+)-**33e**, respectively, in both cases highly enantiomerically enriched [er > 98:2, via (*S*)-MTPA chloride]. Compounds (−)- or (+)-**33c** and (−)- or (+)-**33e** could be easily oxidized with PyNO to give the corresponding cyclopropanecarboxylates (+)-/(−)-**34c**, (87% yield) and (+)-**34e** (85% yield) and (−)-**34e** (88% yield), respectively (Scheme 14), which have to be considered as potential precursors of conformationally constrained γ-amino acids. The configuration remained unaffected. These are the first examples to be reported of optically active lithiated aryloxiranes capable of inducing asymmetry in the coupling reaction with prochiral substrates.

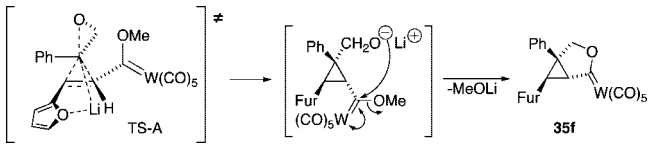
The furyl carbene complex **31f** reacted with **13**, through its precursor **35f** (not isolated), leading, as a single diastereomer, to the cyclopropane-γ-butyrolactone **35g** (48% yield) (Scheme 15).

Scheme 15

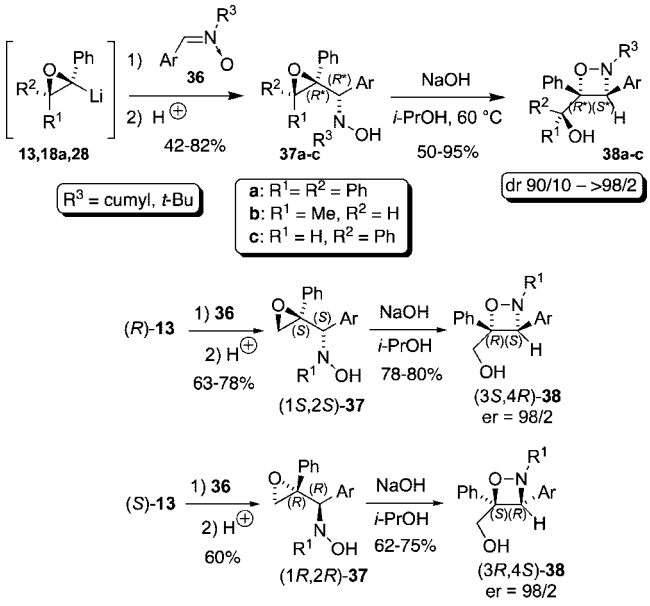


The formation of **35g** through **35f** was quite intriguing. A tentative mechanistic explanation might reside in the *electrophilic* character of the lithiated styrene oxide even at low temperature (!) A mechanism has been proposed in which the π bond of the Fischer carbene attacks, as a nucleophile, the lithiated styrene oxide, after a preliminary coordination of lithium on the furyl oxygen (TS-A, Scheme 16), with a stereochemistry which puts the alkoxy group and the metal fragment *cis* to each other on the cyclopropane ring. It is worth pointing out that (*R**,*R**)-**18a**, in contrast to **13**, reacted with **31f** to give the corresponding cyclopropanecarbene **33k** (75%) (Scheme 14).

Scheme 16



Scheme 17



3.3. Stereoselective Synthesis of β,γ-Epoxyhydroxylamines and 4-Hydroxyalkyl-1,2-oxazetidines

A highly stereoselective preparation of novel β,γ-epoxyhydroxylamines and 4-hydroxyalkyl-1,2-oxazetidines based on the addition of α-lithiated aryloxiranes to nitrones has been developed.[30]

Addition of α-lithiated styrene oxide **13** to *N*-cumyl and *N*-*t*-butyl aryl and heteroaryl nitrones **36** furnished, after quenching with aq. NH_4Cl, the epoxyhydroxylamines **37a** with an excellent diastereoselectivity (Scheme 17). The highly diastereoselective formation of these hydroxylamines **37a** is quite intriguing considering that lithiated aryloxiranes have been reported to couple with carbonyl compounds with no or poor diastereoselectivity.[17,19,25]

Subsequent treatment with NaOH/*i*-PrOH led to the stereospecific formation of 4-hydroxymethyl-1,2-oxazetidines **38a** (dr > 98/2), which is the result of an oxirane ring-opening-promoted intramolecular cyclization taking place in a 4-*exo*-tet mode.

Lithiated phenylpropylene oxide **18a** and *cis*-stilbene oxide **28** reacted with the *N*-cumyl-*p*-chlorophenyl nitrone giving the expected hydroxylamines **37b,c** and then oxazetidines **38b,c** in comparable yields and diastereoselectivity after treatment with NaOH/*i*-PrOH. In contrast, no addition occurred when lithiated *trans*-stilbene oxide **23** was treated with the above nitrone, likely because of steric reasons. Concerning the nitrone *N*-substitution, we found that the reaction of **13** with some *N*-*t*-butyl nitrones afforded, as expected, *N*-*tert*-butyl hydroxylamines **37** and subsequently oxazetidines **38**.

Moreover, it was found that either (*R*)-**13** or (*S*)-**13** add to some *N*-cumyl nitrones with an excellent diastereo- and enantioselectivity leading to the formation of hydroxylamines (1*S*,2*S*)-**37** and (1*R*,2*R*)-**37** and then to oxazetidines (3*S*,4*R*)-**38** and (3*R*,4*S*)-**38**, respectively, upon treatment with NaOH/*i*-PrOH (Scheme 17). These novel scaffolds, that are accessible in two steps, and are perfectly stable, seem to be promising for the synthetic elaboration to other substances. The facility with which the cumyl group could be removed is quite remarkable (see ahead).

The observed diastereoselectivity was accounted for with a preliminary coordination of the lithiated oxirane on the nitrone oxygen followed by the addition to the nitrone going through two different 5-membered cyclic transition states: the one leading to the observed (1*R**,2*R**) diastereoisomer (TS-A), subsequent to the addition of **13** to the *re* face of the nitrone, would not experience the steric interaction between the two aryl groups, which instead is important in the transition state TS-B leading to the (1*R**,2*S**) diastereomer (Scheme 18).[31]

4. Lithiated Oxazolinyloxiranes

4.1. α-Lithiated Oxazolinyloxiranes: Generation and Reactivity

An electron-withdrawing group such as the 2-oxazolinyl group, which is a well-known masked form of the carbonyl and carboxylic functionalities, would be an ideal stabilizing group for α-lithiated oxiranes also considering that it is amenable to synthetic elaboration. Moreover, the presence of stereocenters on the heterocyclic ring could induce asymmetry in the reactions of the related lithiated oxirane.

Lithiated oxiranes, that can be generated by deprotonation of oxazolinyloxiranes, are particularly attractive reactive intermediates in synthetic organic chemistry for being susceptible of elaboration, after trapping with electrophiles, to a variety of other substances (Chart 2).

The interest for lithiated oxazolinyloxiranes had origin when it was found that oxiranes of the type of **39** (Scheme 19) could be smoothly deprotonated with strong bases, and the resulting oxiranyllithium **40** proved to be stable[32] at low temperature for hours or even for days without undergoing any transformation. Such a stability may be attributed to the electron-withdrawing effect of the oxazolinyl group as well as to its coordinating ability. Only upon warming to room temperature, isomerization to enolate occurs, likely through an E_1-like mechanism involving the unusual C_β−O bond cleavage in the rate determining step which permits the ideal alignment of the orbitals to be involved in the C−C double bond formation of the enolate.[33] However, the electrocyclic mechanism which has been proposed by several authors for other systems cannot be ruled out, at least at present. Whatever the mechanism, this is a good route to acyl oxazolines **41**, which have potential in medicinal chemistry (indeed, as peptidyl derivatives, have been described as potent inhibitor of human neutrophil elastase)[34] and could be elaborated to other substances (e.g., dihydro-1,4-oxazin-2-ones **42**) as reported for 2-formyloxazolines.[35]

The nucleophilicity of lithiated epoxides of the type of **43** could be proved by their trapping with a variety of electrophiles to give **44** (Scheme 20).

Lithiated oxazolinyloxirane **46**, generated from the *trans* precursor **45**, reacted regio- and stereospecifically with a series of electrophiles with complete retention of configuration at the α-carbon to give **47** (Scheme 20).[22]

Scheme 18

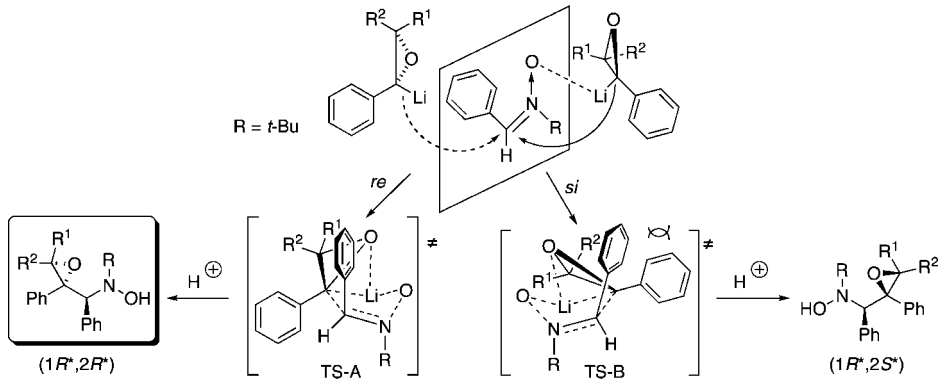
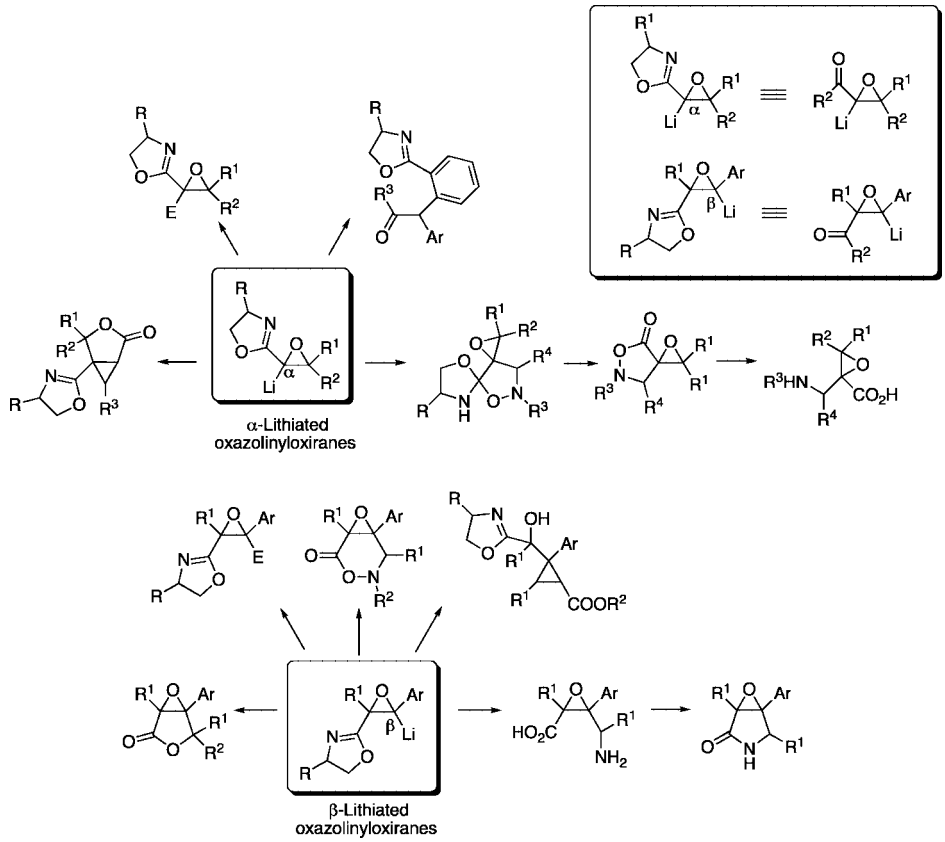
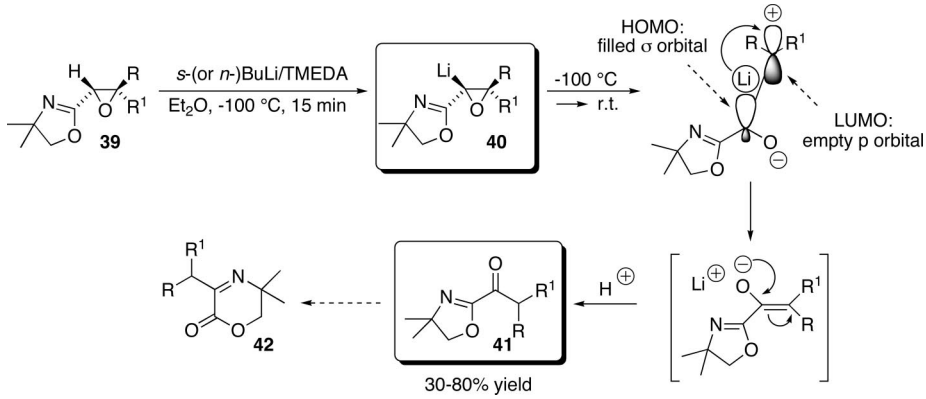


Chart 2

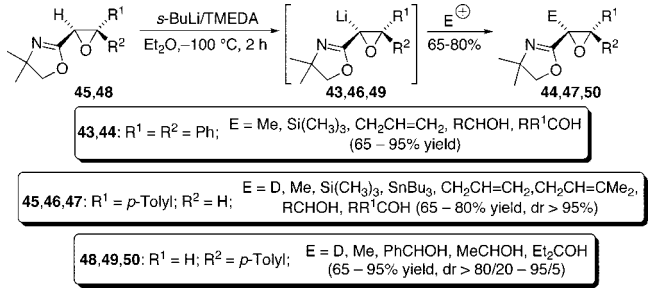


Scheme 19



The reaction of **46** with symmetrical ketones occurred stereospecifically and provided potentially useful hydroxyalkyl oxazolinyloxiranes **47**, whereas the reaction with aldehydes led to diastereomeric mixtures of *syn*/*anti* hydroxyalkyl oxazolinyloxiranes **47**. In contrast, *cis* lithiated oxazolinyloxirane **49**, obtained by deprotonation of **48**,

Scheme 20



proved to be configurationally unstable and reacted with electrophiles to give derivatives **50** with poor diastereoselectivity (Scheme 20). This has to be ascribed to the fact that **49** tends to convert into the more stable *trans* isomer **46** because of the strain which originates in forcing the oxazolinyl and the aryl groups cis to each other on the oxirane ring. An acceptable diastereoselectivity could be achieved only when the reaction was carried out under Barbier's conditions (*in situ* quenching). On the other hand, it has been experimentally proved that the *cis*-**49** isomer is more reactive than the *trans* counterpart **46**. The relative stability of the two isomeric oxiranyllithiums **46** and **49** (which are in a dynamic equilibrium in solution) and their interconversion barrier energy have been investigated by ab initio and semiempirical calculations.[22] Once the *cis*-*trans* equilibrium has been attained, the *trans*-**46** isomer is the most stable species, as ascertained by high-level DFT calculations. Moreover, from PM3 energetics on structure **I** that could act as intermediate, it can be postulated that the interconversion barrier between these two lithiated diastereomers should be as high as a few kcal/mol (ca. 1.5 kcal/mol) (Figure 1).

Equally configurationally unstable proved to be the α-lithiated oxazolinyloxiranes of the type of **52** generated from optically active oxazolinyloxiranes **51**; indeed, they tend to epimerize (Scheme 21).[36]

Treatment of optically pure 2-chloromethyloxazoline **53** with dibutylboron triflate and *N*,*N*-diisopropylethylamine (Bu_2BOTf/*i*-Pr_2NEt) furnished the boron azaenolate **54a**, which, without isolation, was reacted with 4,4′-dimethylbenzophenone to give oxazolinyloxirane **55a** (dr = 93:7).[37] Treatment of **55a** with *s*-BuLi/TMEDA at −100 °C in Et_2O, followed by the addition of D_2O (10 min), gave deuterated oxirane **56a** (dr = 76:24). On the other hand, the deprotonation-methylation of **55a** afforded methylated oxirane **56b** (dr = 80:20). Therefore, the stereochemistry of the major isomer for the two derivatives **56a** and **56b** reflect that of **55a**. In contrast, the deprotonation-deuteration of **55b** (dr = 95:5) (prepared by the reaction of boron azaenolate **54b** with 4,4′-dimethylbenzophenone) provided deuterated oxirane **56a** (dr = 70:30), whereas the deprotonation-methylation sequence afforded oxirane **56b** (dr = 80:20). Therefore, starting from **55b**, the original stereochemistry is substantially lost in the related deuterated and methylated compounds as the major isomer has an opposite stereochemistry with respect to that of **55b** (Scheme 22).

The observed preferential formation of *S*-configured substituted epoxides at Cα, starting from the above optically enriched oxiranes **55a,b**, could be rationalized by assuming that the electrophile could approach the azaenolate either from the top or from the bottom but with a preference from the side opposite to the phenyl group, via a transition state in which the lithium is coordinated by the methoxy group

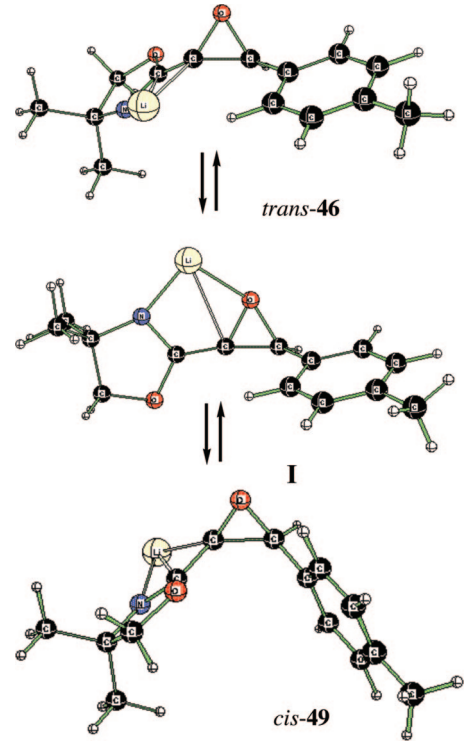


Figure 1. Interconversion process between *trans*-**46** and *cis*-**49** through **I**.

(Scheme 23). This was just a tentative explanation and more convincing evidence is needed.

4.1.1. Synthesis of Oxazolinylaryl Alkanones

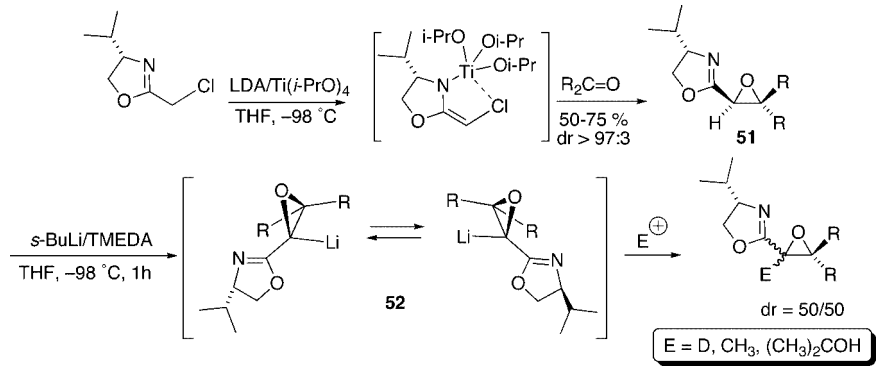
Lithiated oxazolinyloxiranes are useful reactive intermediates that can be used for the preparation of a number of interesting compounds (see Chart 2). Several years ago Meyers had planned to synthesize oxazolinylaryl alkanones of the type of **58** according to the retrosynthetic approach described in Scheme 24 counting on the observation that Grignard reagents and organolithiums replace fluorine or methoxy groups of oxazolinylaryl fluorides or ethers. The failure with enolates was attributed to their soft character.[38]

The preparation of this type of arylalkanones, such as **60** (Scheme 25), has been performed following a strategy which includes steps involving lithiated oxiranes **59**.[39]

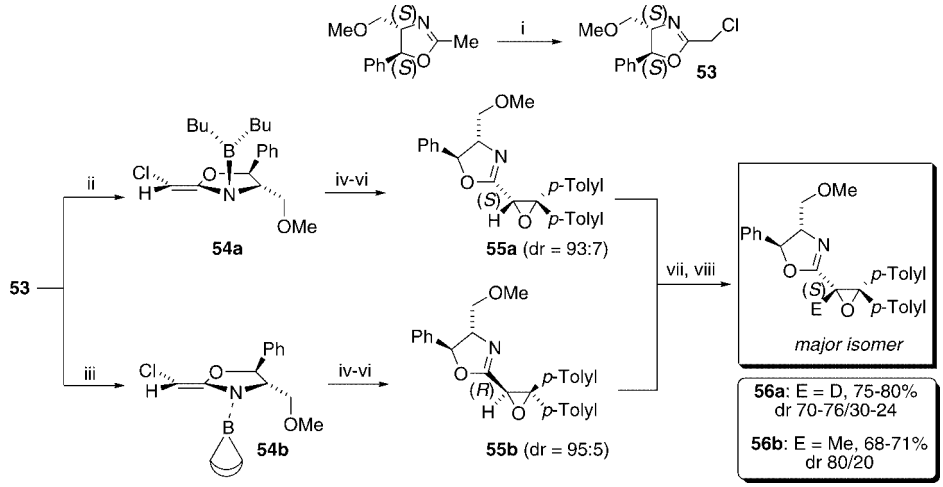
The mechanistic explanation is probably as shown in Scheme 26: *ortho* lithiation takes place in the oxirane phenyl ring cis to the oxazoline moiety to give **61**; then, a cascade reaction initiates involving nucleophilic addition to the C−N double bond of the oxazoline ring, generation of the spirocyclic system **62** leading to the oxazolinylaryl alkanone **65** through first the oxiranyllithium **63** and then the enolate **64**.

It has been successively found that the fate of the *ortho*-lithiated aryloxiranes of the type of **61** depends on the way it has been generated. Indeed, *ortho*-lithiated oxazolinyl aryloxiranes, generated by lithium-bromine exchange performed on the corresponding *ortho*-bromo aryloxirane, in the presence of an excess of organolithium, give 2,3-dihydro-10b*H*-oxazolo-[2,3-a]isoquinolines (Scheme 26) going through the same type of spirocyclic lithiated intermediate **62**, which further reacts with excess RLi.[40]

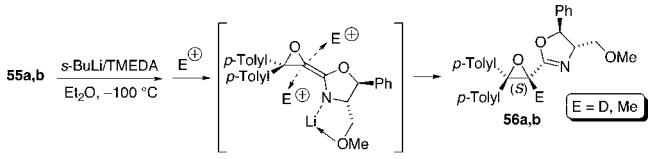
Scheme 21



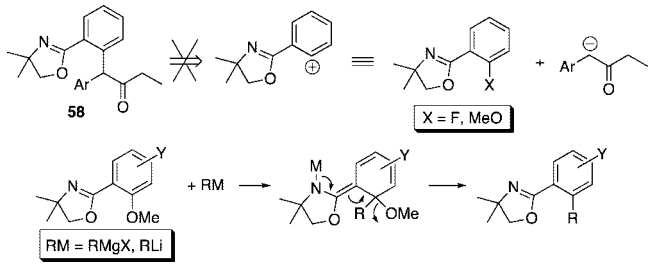
Scheme 22



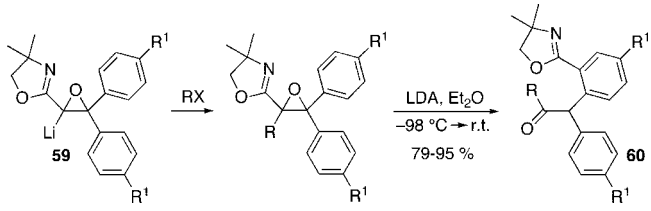
Scheme 23



Scheme 24



Scheme 25



4.1.2. Synthesis of α-Epoxy-β-amino Acids

In another synthetic application, it has been developed a method of synthesis of novel nonnatural α-epoxy-β-amino acids such as **68**, via the elaboration of dispirocyclic compounds **66** and epoxy-isoxazolidinones **67**, just combining the chemistry of oxiranyllithiums with that of nitrones, as envisaged in the following retrosynthetic approach (Scheme 27).[41]

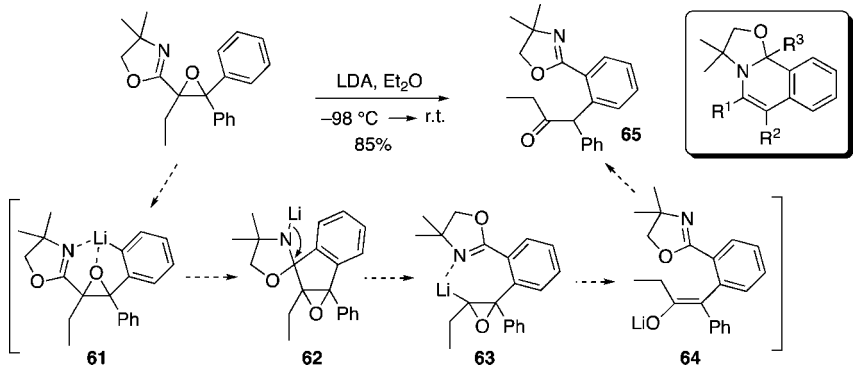
2-Lithiooxirane **69** was reacted with the *Z-N-t*-butyl-α-phenylnitrone **70a** affording a good yield of the 7,7-dimethyl-2,2,11-triphenyl-10-*tert*-butyl-1,5,9-trioxa-8,10-diazadispiro[2.0.4.3]undecane **71a** as a single diastereomer (Scheme 28). To explain the observed diastereoselectivity, a mechanism that involves a highly ordered transition state (TS-1), which originates from the addition of the oxiranyllithium to the nitrone (*re* face) ending up with the formation of **71a** after the acidic quenching, has been proposed (Scheme 28). Steric effects as well as lithium chelation may be playing a crucial role.

The reaction of **69**, leading to the dispirocyclic compound of the type of **71a**, was not restricted to the nitrone **70a**: it worked well also with other nitrones **70** affording dispirocyclic products **71** (Scheme 29). All the reactions occurred with the same excellent diastereoselectivity as with **70a**.

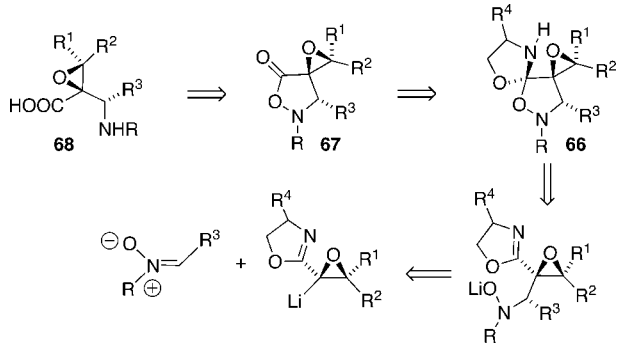
Aliphatic other than aromatic substituents are tolerated on the β-position of the starting epoxide.

Hydrolysis of the dispirocyclic compounds **71** with aq. oxalic acid furnished the 5-isoxazolidinones **72** in good yields. Interestingly, all the epoxy-5-isoxazolidinones **72** could be easily and quantitatively reduced (H_2, Pd/C, MeOH, rt, 3 h) to the α-epoxy-β-amino acids **73** (Scheme 30). It seems that the hydrolysis of compounds **71** to the 5-isoxazolidinones **72** depends upon the substituents on the β-position of the oxirane ring: the transformation occurs

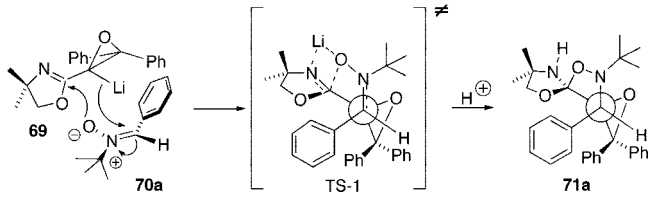
Scheme 26



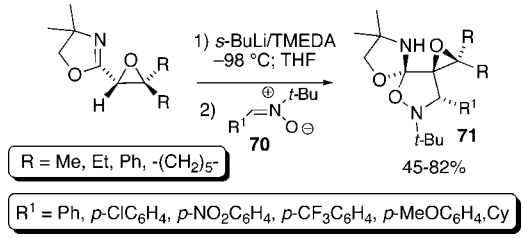
Scheme 27



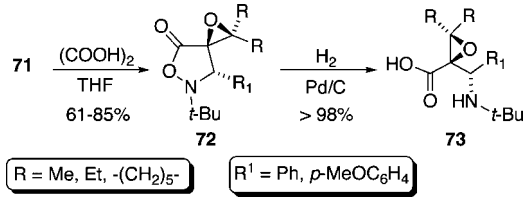
Scheme 28



Scheme 29



Scheme 30



when aliphatic substituents are present and it does not with aromatic groups.

Analogously, starting from an optically active oxazolinyloxirane such as (*S*,*S*)-**74** (Scheme 31), which could be obtained from the (4*S*)-4-isopropyl-2-chloromethyl-2-oxazoline via lithiation, lithium−titanium transmetalation and then coupling with acetone (Scheme 21), it was possible to prepare, after α-lithiation, coupling with the nitrone **70a**, the highly enantiomerically enriched dispirocyclic compound (3*R*,4*R*,7*S*,11*S*)-(+)-**75** as a single diastereoisomer in a very good yield (75%). The explanation for the observed diastereoselectivity resides in the way the lithiated oxazolinyloxirane and the nitrone interact each other. It is worth pointing out that the configuration at the C-3 of (+)-**75** was ascertained to be opposite (*R*) to that for the starting oxazolinyloxirane (*S*,*S*)-(−)-**74**, indicating that an inversion had occurred at this carbon. Configuration of the three newly created stereogenic centers is presumably established in the transition state **TS-1** (Scheme 31) which results from the nucleophilic addition of the lithiated oxirane **74-Li** on the *re* face of **70a**. Such a transition state may be justified assuming that the lithiated oxiranes (*S*,*S*)-(−)-**74-Li** and (*S*,*R*)-(−)-**74-Li** interconvert each other; then, the diastereomeric lithiated oxirane (*S*,*R*)-(−)-**74-Li** (having the isopropyl group on the C-4 of the oxazoline ring far away from the oxirane C−Li bond) preferentially reacts with the nitrone for experiencing a lower steric hindrance to produce (+)-**75**. Treatment of (+)-**75** with aq. oxalic acid afforded optically active 5-isoxazolidinone (+)-**76** highly enantioenriched (ee >99%) and in good yield (76%) (Scheme 31).[41]

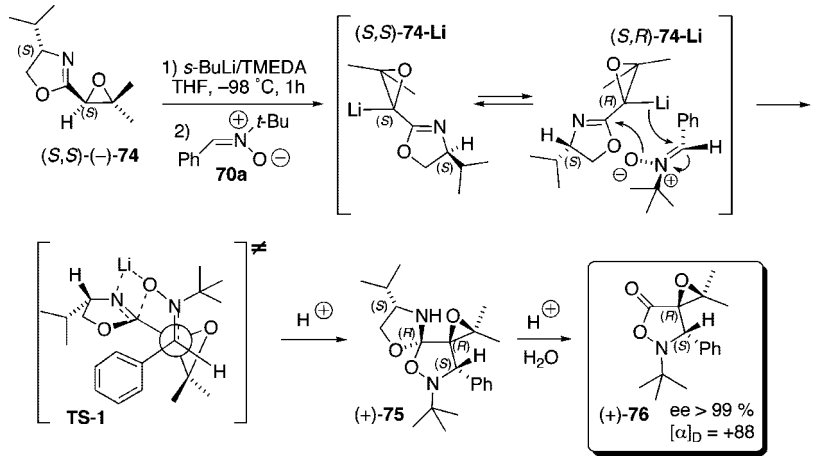
4.1.3. Synthesis of Cyclopropane-γ-butyrolactones

Cyclopropane-γ-butyrolactones such as **77** (Scheme 32) are useful synthetic intermediates[42] and key precursors of biologically important target molecules of pharmaceutical interest such as (+)-ambruticine S,[43] furofuran lignans,[44] NMDA receptor antagonist,[45] ligands of histamine H_3 receptors,[46] and Grb_2-SH2 domain.[47] A useful synthetic strategy has been developed for the preparation of this type of substances by combining the oxiranyllithium-based methodology with a Michael addition reaction to a masked and more reactive form of a carbonyl compound, as illustrated in the following retrosynthetic approach (Scheme 32).[48]

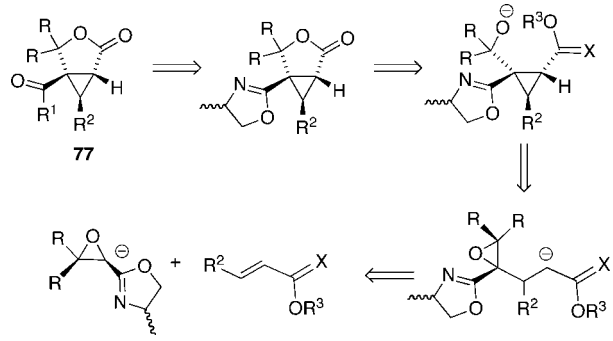
With a cascade reaction which initiated with the addition of lithiated oxazolinyloxirane **78** (Scheme 33) to the tungsten Fischer carbene complex **79**, followed by the oxirane ring-opening-promoted cyclopropanation, lactonization and then oxidation, it was possible to synthesize polysubstituted cyclopropane-γ-butyrolactones **80** as single diastereomers.

A reasonable rationale for the observed diastereoselectivity is illustrated in Scheme 34 which involves the addition of the lithiated oxirane on the *re* face of the carbene complex via a preliminary coordination on the oxygen of the methoxy group of the metal complex.

Scheme 31



Scheme 32



4.2. β-Lithiated Oxazolinyloxiranes

4.2.1. Synthesis of α,β-Epoxy-γ-butyrolactones

β-Lithiated aryl-substituted oxazolinyloxiranes **81** and **82** proved to be configurationally stable. Indeed, once generated, they could be trapped with a series of electrophiles with complete retention of configuration at the β-carbon (Scheme 35).[16,49]

In particular, the trapping reaction of **81** with carbonyl compounds has been exploited for the preparation of α,β-epoxy-γ-butyrolactones **83** (Scheme 35).[16]

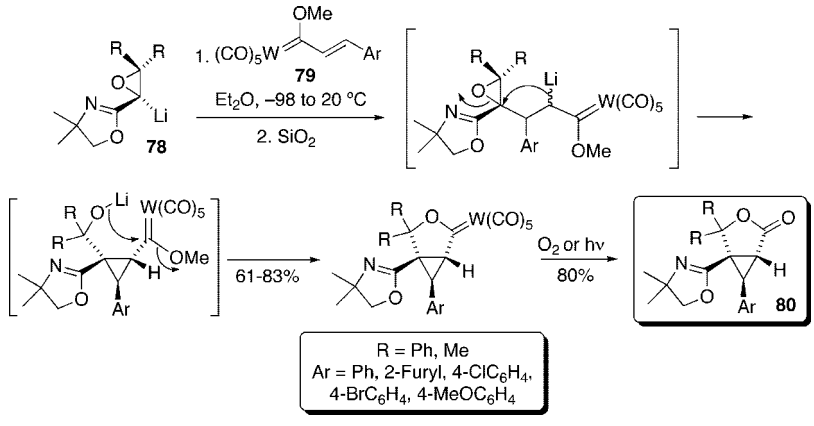
Almost optically pure α,β-epoxy-γ-butyrolactones, such as **86**−**88**, could be obtained starting from the chiral nonracemic oxazolinyloxirane **84** (dr *trans*/*cis* 90:10, er *trans* > 99:1)[16] (Scheme 36). The reaction of the intermediate lithiated oxirane **85** with aldehydes was poorly diastereoselective, but the diastereomers could be easily separated and transformed into the corresponding epoxylactones **87** and **88**, almost optically pure.

4.2.2. Synthesis of α,β-Epoxy-γ-amino acids and α,β-Epoxy-γ-butyrolactams

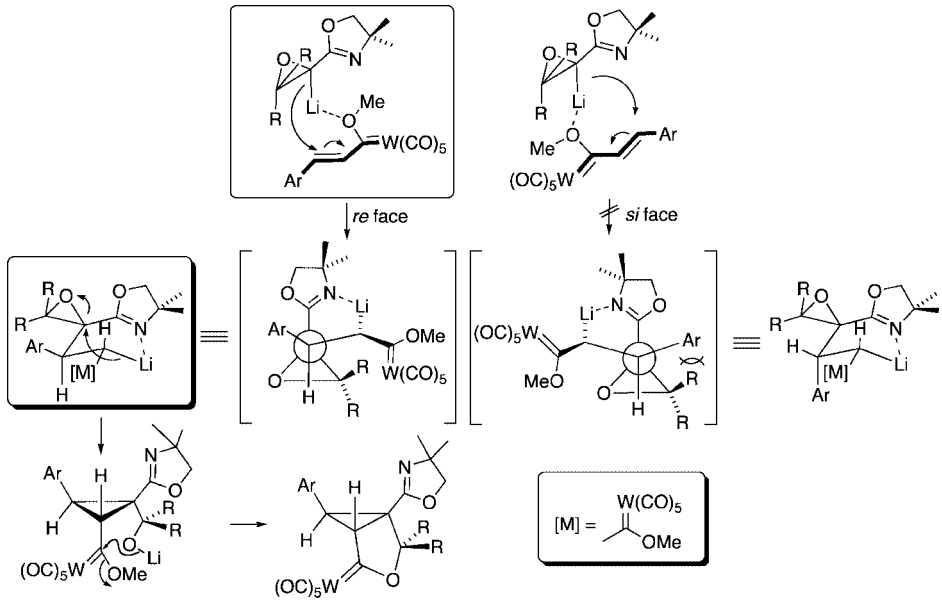
The synthesis of 4,5-epoxy-1,2-oxazin-6-ones and very rare α,β-epoxy-γ-amino acids, based on the reaction of β-lithiated oxazolinyloxiranes with nitrones, has been developed.[50] When β-lithiated (1*R**,2*S**)-1-methyl-1-oxazolinyloxirane **89** was reacted with (*Z*)-*N*-*t*-butylnitrones **91**, 9,10-epoxy-1,6-dioxa-4,7-diazaspiro[4.5]decanes **92** formed in good yields (42−71%) and diastereoselectively (dr > 98/2) (Scheme 37). In $CDCl_3$ solution, as well as in THF-d_8, spirocyclic compounds **92** equilibrate with the hydroxyl-amino forms **93** and *diast*-**92**. Trifluoroacetic acid (TFA)-catalyzed hydrolysis of compounds **92**, carried out in dioxane/H_2O, afforded in good yields (40−94%) and diastereoselectivity (dr > 98/2) 4,5-epoxy-1,2-oxazin-6-ones **95** (R^1 = *t*-Bu) (Scheme 37). The intermediacy of the epoxy-hydroxyamides **94** in the transformation of **92** to **95** was proved by quenching the reaction mixture at shorter reaction times (16 h).

The *N*-*t*-butyl substituent of **95** could not be removed. Therefore, attention was addressed to *N*-cumyl nitrones. 4,5-Epoxy-1,2-oxazinones **95** (R^1 = cumyl) could be prepared by hydrolysis of compounds **92** (R^1 = cumyl) (67−88%), which, in turn, had been obtained by the addition of **90** to *N*-cumylnitrones **91** (R = cumyl) (52−78%) (Scheme 37).

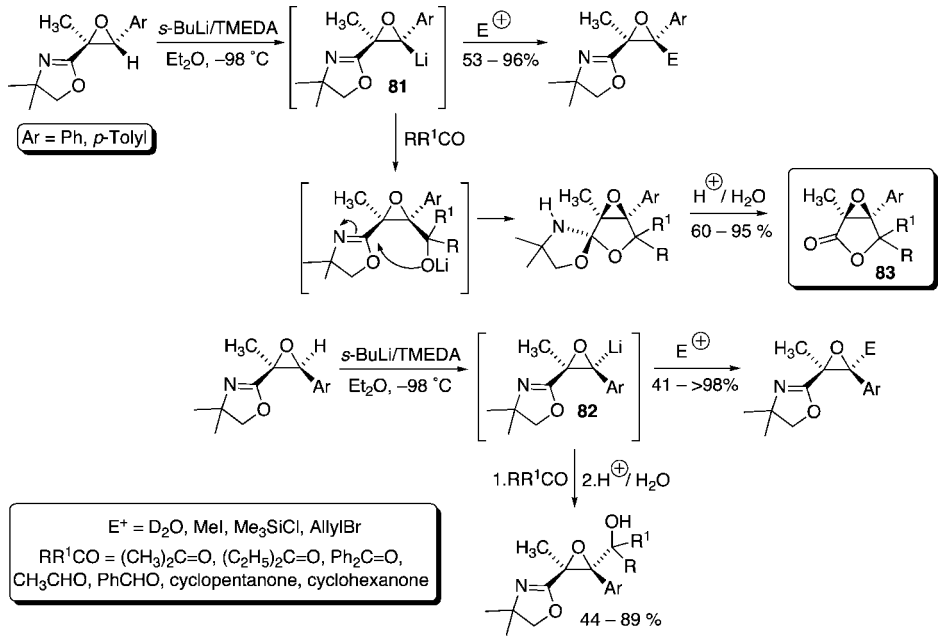
Scheme 33



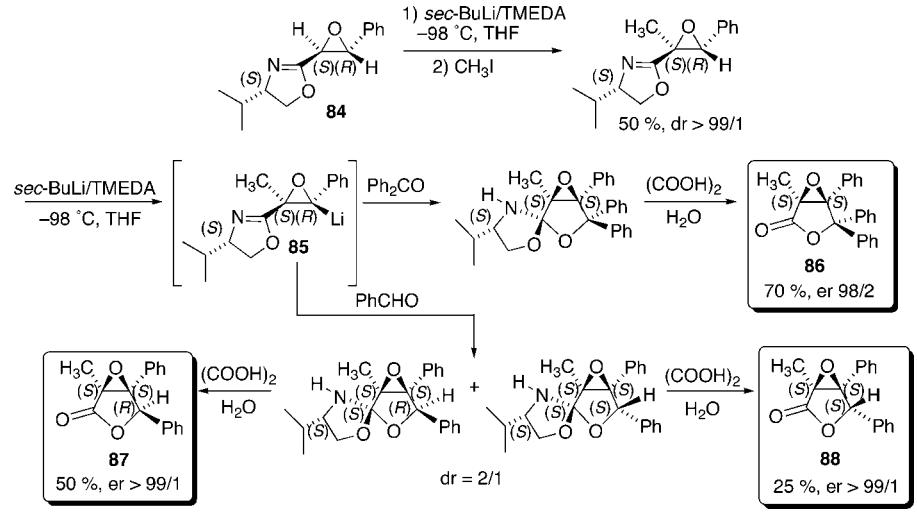
Scheme 34



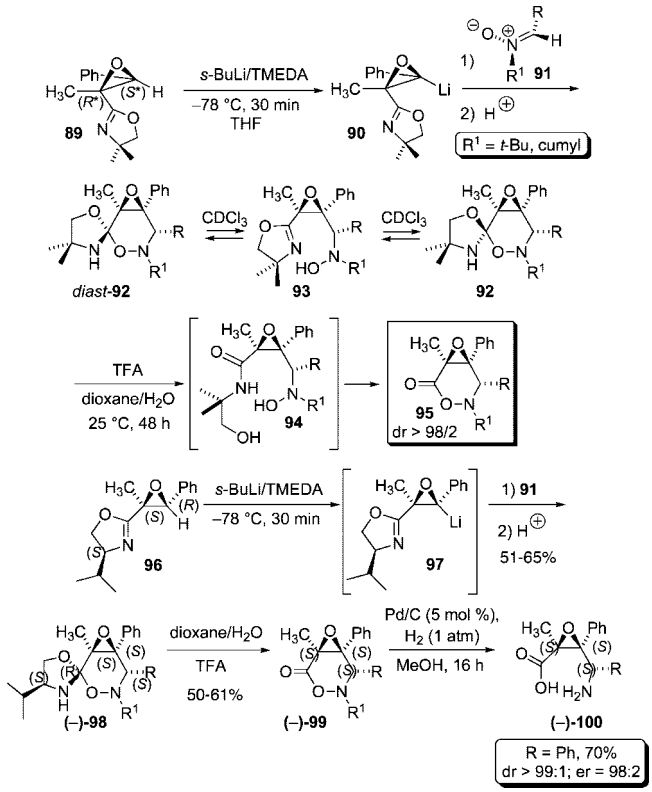
Scheme 35



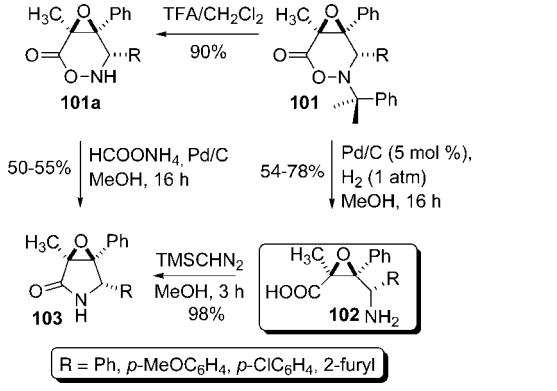
Scheme 36



Scheme 37



Scheme 38



Lithiation of the optically active oxazolinyloxirane **96** (er = 98/2),[16,45] followed by the coupling of the corresponding lithiated intermediate **97** with *N*-*tert*-butyl- and *N*-cumylnitrones **91**, gave spirocyclic compounds (−)-**98** with complete diastereoselectivity. Hydrolysis (TFA) of (−)-**98** furnished highly enantioenriched *N*-*t*-butyl- and *N*-cumylepoxy-1,2-oxazinones (−)-**99**, which are amenable to the corresponding α,β-epoxy-γ-amino acids, as in the case of (−)-**100** (Scheme 37).

Reduction [H_2, 1 atm, Pd/C (5% mol)] of *N*-cumylepoxy-1,2-oxazinones **101** provided the α,β-epoxy-γ-amino acid **102** in good yields (54−78%) with the free amino group (Scheme 38). Moreover, treatment of **102** with Me_3SiCHN_2 in dry MeOH gave α,β-epoxy-γ-butyrolactams **103** quantitatively. *N*-Cumylepoxy-1,2-oxazinones **101** could be also selectively *N*-deprotected under acidic conditions (TFA, CH_2Cl_2) to give epoxy-1,2-oxazinones **101a** with very good yields whose reduction led finally to α,β-epoxy-γ-butyrolactams **103** (Scheme 38).

4.2.3. Synthesis of Polysubstituted Cyclopropanes

The addition of β-lithiated aryl-substituted oxazolinyloxiranes **104** and **105** to tungsten Fischer carbene complexes **79** resulted in the formation of polysubstituted cyclopropanes **106** and **107**, respectively (Scheme 39).[43]

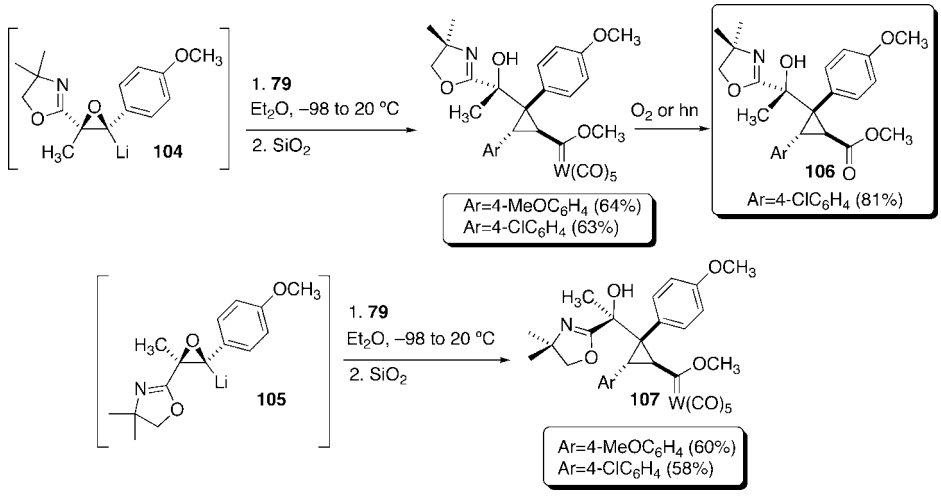
As illustrated in the following mechanistic model (Scheme 40), the reaction initiates with the coordination with the methoxy group followed by the attack on the *re* face of the α,β-unsaturated Fischer carbene complex.

From the above results it follows that lithiated oxazolinyloxiranes can be easily generated and that the α-lithiated derivatives are only thermally stable at low temperature but configurationally unstable, whereas the β-lithiated counterparts are kinetically configurationally stable. Moreover, some preliminary results of a multinuclear spectroscopic investigation, as well as ab initio calculations, suggest that α-lithiated derivatives do not tend to delocalize the negative charge onto the oxazoline moiety; that is, they are not azaenolates.[51]

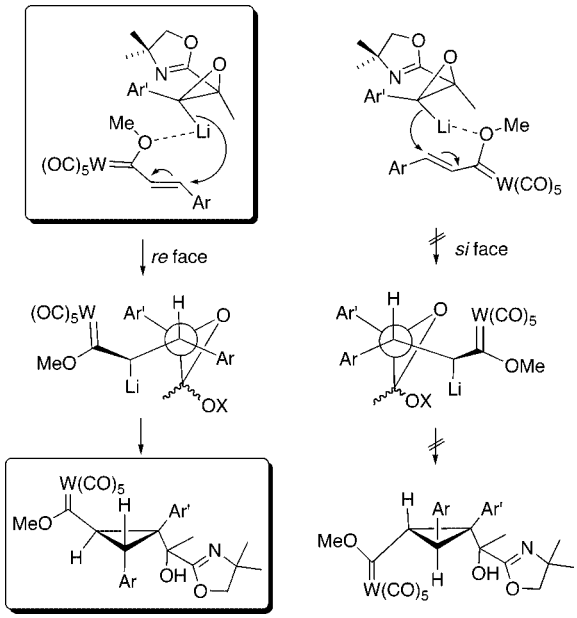
5. α-Lithiated Sulfonyloxiranes

Sulfonyloxiranes can be easily prepared. Because of its well-known strong electron-withdrawing effect, it is expected that the sulfonyl may act as a good stabilizing group for related oxiranyllithiums. What, moreover, adds value to its ability as a stabilizing group is the fact that the sulfonyl group can be easily removed from the epoxide or suitably elabo-

Scheme 39



Scheme 40



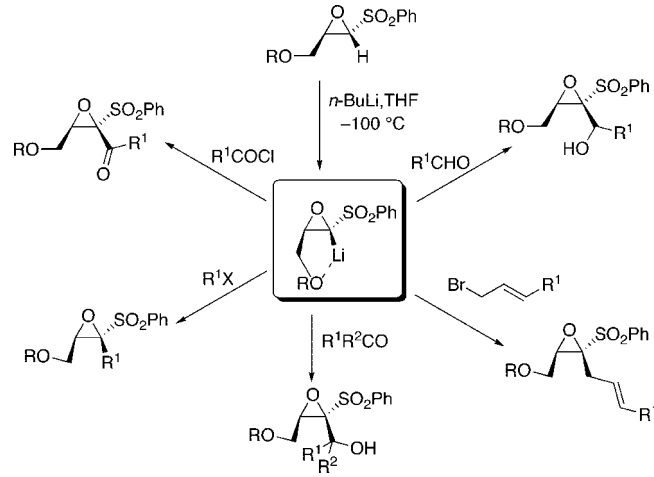
rated. It follows that sulfonyl-stabilized oxiranyl anions and their reactions with electrophiles have been extensively studied.

After the pioneering results by Tavares[52] on the reaction of *β*-*p*-tolylsulfonyl styrene oxide with $NaOCH_3$ in CD_3OD and by Eisch in the lithiation-deuteration sequence of 2-*p*-tolylsulfonyl-2,3-octene oxides,[5b,53] most of the work in this field has been reported by Jackson[54] who, toward the end of the 80s and the beginning of the 90s, extensively investigated the lithiation of sulfonyl-substituted oxiranes and reaction of the resulting α-lithiated oxiranes with a series of electrophiles under varied experimental conditions in terms of temperature, reaction time, Lewis acid, demonstrating that such sulfonyl-stabilized lithiated oxiranes are usually rather unstable at temperatures higher than −102 °C and that the configurational stability depends upon the geometry of the starting oxiranes. Lithiated oxiranes derived from *trans* epoxysulfones proved to be configurationally stable, whereas those generated from *cis* epoxysulfones were not due to their bias to isomerize to the more stable *trans*-isomers. However, the lithiation carried out at −100 °C, under Barbier conditions, circumvents this isomerization and degradation. It was also demonstrated that coordinating substituents on the oxirane ring, such as silyloxy and benzyloxy groups, capable of lithium chelation, increase the stability and control the reactivity. These lithiated oxiranes, indeed, can be generated from −95 to −90 °C and captured with a variety of electrophiles to give functionalized epoxides susceptible of synthetic elaboration to α-bromo-*β*-hydroxy ketones, acylepoxides, lactones, spiroacetals, α-halothioesters, *and* α-haloacylsilanes (Scheme 41). Lithiated *cis*-oxiranes proved to be more reactive than the *trans* counterparts for steric reasons.

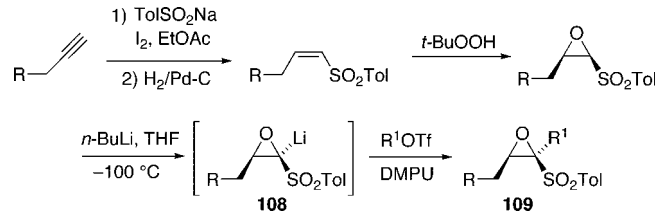
Many of these organometallic reagents have been found to couple with electrophiles in a stereospecific manner. Thus, as shown in Schemes 42 and 43, trapping of lithio sulfonyl-oxiranes of opposite configuration, such as **108** and **110**, afforded substituted epoxysulfones **109** and **111**, respectively.[55]

Following their work based on the generation and capture of some stabilized α-lithiated epoxides with triflates to give

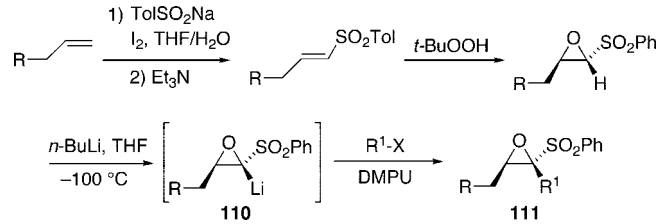
Scheme 41



Scheme 42



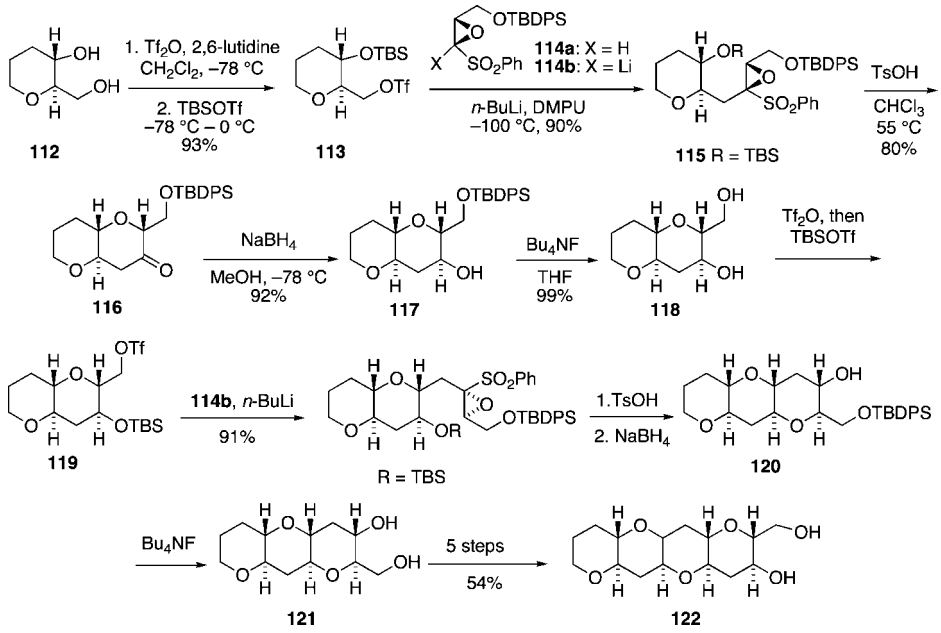
Scheme 43



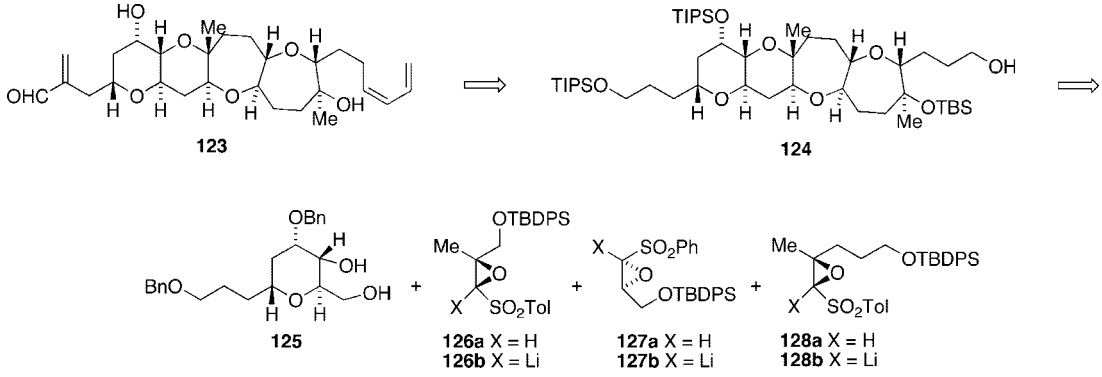
polysubstituted epoxides,[56] Mori developed a general and iterative procedure for the synthesis of polytetrahydropyrans based on the oxiranyl anion strategy in which alkylation of a sulfonyl-stabilized oxiranyl anion and the subsequent 6-*endo* cyclization were employed as key reactions, the 6-*endo* cyclization being complementary to that of the *π*-orbital-assisted cyclization developed by Nicolau. It was a new strategy for the synthesis of trans-fused tetrahydropyran systems using epoxysulfones as the source of the C_3 oxiranyl anion unit (Scheme 44).[57]

The synthesis started from diol **112** which was treated with triflic anhydride and 2,6-lutidine in CH_2Cl_2 followed by *t*-butyldimethylsilyl triflate (TBSOTf) to give triflate **113**. Then, in view of the well-known thermal instability of sulfonyl-substituted *cis*-oxiranyl anions, such as **114b**, a mixture of epoxy sulfone **114a** and triflate **113** was treated with *n*-BuLi at −100 °C to give compound **115** in high yield. The 6-*endo* cyclization of **115** was effected by heating with *p*-TsOH to afford bicyclic ketone **116** in 80% yield with complete regio- and stereoselectivity. Reduction with $NaBH_4$ generated the alcohol **117**. Successive desilylation provided bicyclic diol **118** ready for a further cyclization. Indeed, the second cycle of the five-step operation afforded tricyclic diol **121** in 52% overall yield from **118**. The second key coupling reaction of **119** with the oxiranyl anion **114b** and subsequent endo mode of cyclization proceeded uneventfully. The diastereomeric excess of the hydride reduction was 96%.

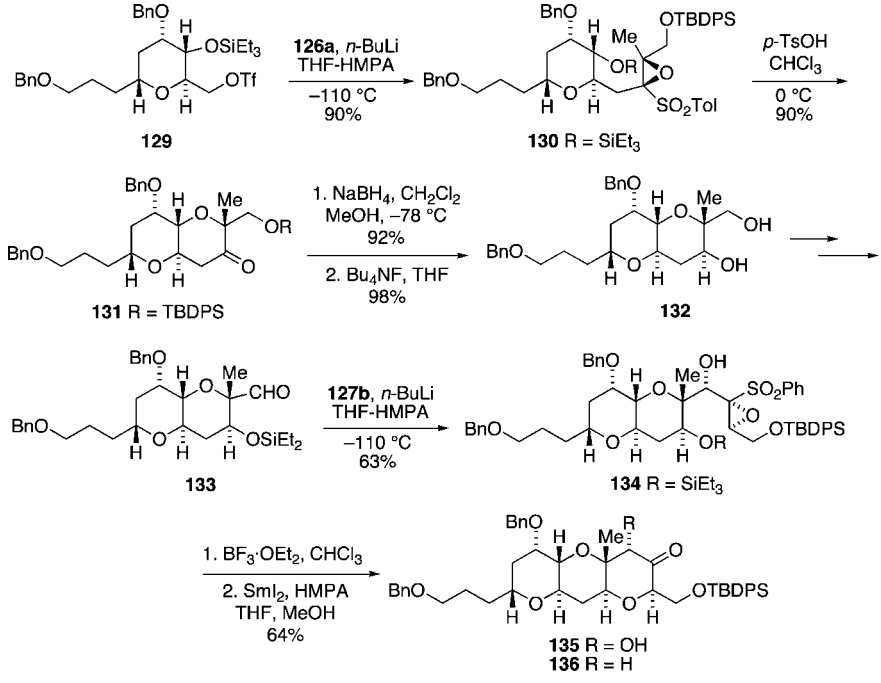
Scheme 44



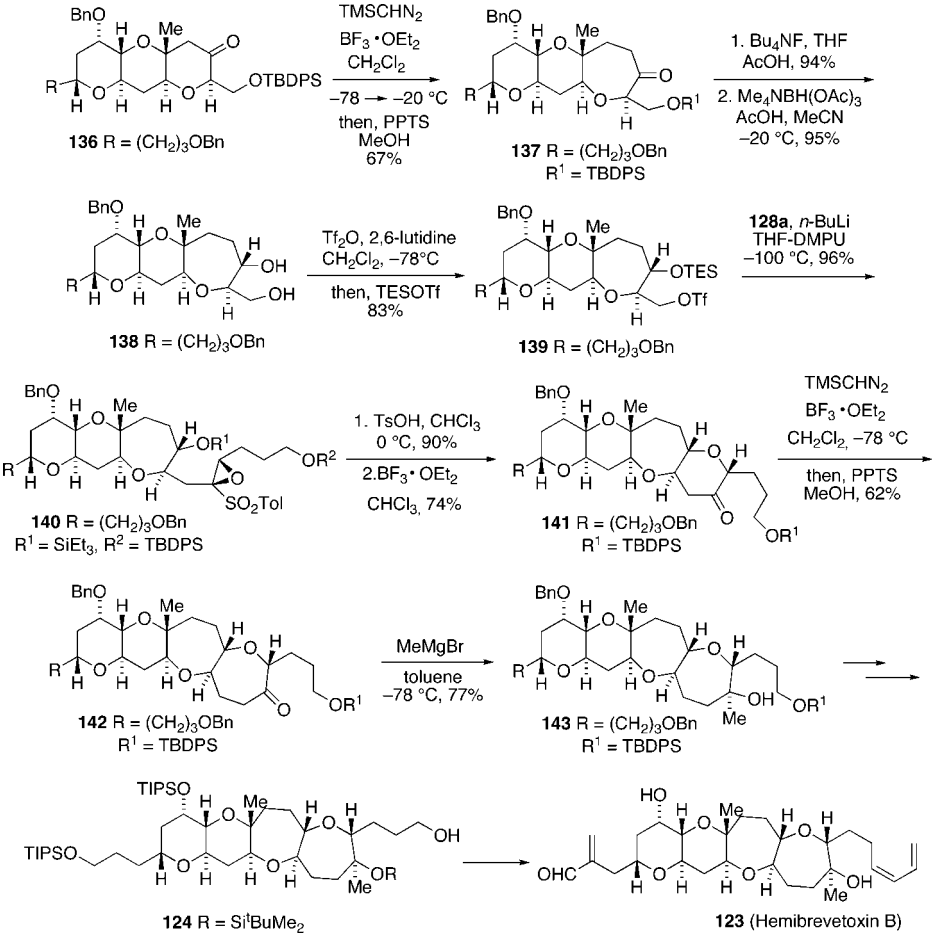
Scheme 45



Scheme 46



Scheme 47



Since **121** contains two hydroxyl groups, the sequence reported here was reiterated to construct the 6,6,6,6-tetracyclic all-trans-fused framework **122** in 54% overall yield (dr 97:3). Therefore, a highly effective method for the construction of *trans*-fused tetrahydropyran ring systems has been developed.

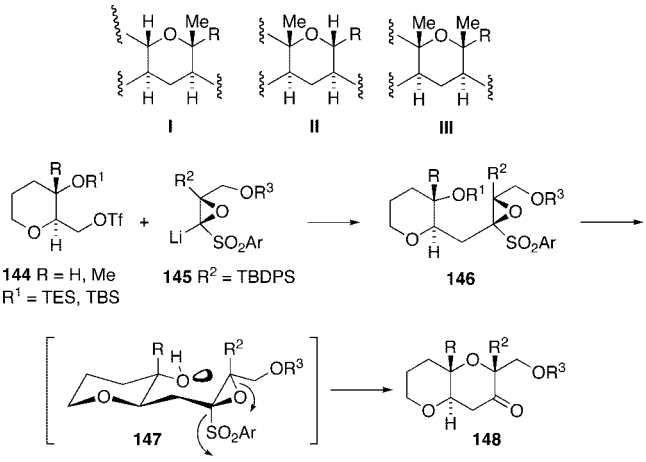
A new approach to the synthesis of Hemibrevetoxin B **123** (Scheme 45) based on the oxiranyl anion methodology has been successively developed by Mori.[58] The strategy is illustrated by the stereocontrolled synthesis of **124**, which is elaborated by sequential coupling of three sulfonyl-stabilized oxiranyl anions **126b**, **127b**, and **128b** to the monocyclic diol **125**.

Since oxiranyl anions-substituted by a sulfonyl group are unstable even at low temperatures, the reaction of a triflate and oxiranyl anions such as **126b**−**128b** has to be carried out by an *in situ* trapping method in order to minimize decomposition of the transient lithiated epoxides prior to electrophile trapping. Thus, a mixture of a triflate and an epoxy sulfone, in THF at −100 °C and in the presence of DMPU or HMPA, has been treated with *n*-BuLi to afford a cyclization precursor in high yield. Treatment of a mixture of **126a** and **129** (Scheme 46) with *n*-BuLi in THF/HMPA at −110 °C provided the coupled product **130** in 90% yield. Stereospecific 6-*endo*-cyclization of **130** using *p*-TsOH led to the bicyclic ketone **131**, whose reduction with $NaBH_4$, followed by desilylation, gave bicyclic diol **132** as the sole product. Installation of the third ring involved the challenging preparation of the oxepane ring. Compound **132** was converted into the aldehyde **133** by bis(silylation) followed by regioselective mono(desilylation) and SO_3•pyr oxidation. The addition of the oxiranyl anion **127b** to **133** was carried out with the *in situ* trapping method, as described for the transformation **129** to **131**, furnishing a 3:1 mixture of products from which **134** was isolated in 63% yield.

Exposure of **134** to BF_3•Et_2O caused its clean cyclization to the tricyclic hydroxy ketone **135**. Removal of the hydroxy group by treatment with SmI_2 led to the ketone **136** in 64% yield. The crucial oxepane formation was accomplished by one carbon homologation of a 3-oxotetrahydropyran ring (Scheme 47).

The reaction of **136** with (trimethysilyl)diazomethane ($TMSCHN_2$), in the presence of BF_3•Et_2O, gave the seven-membered ring ketone **137** in 67% yield after acid hydrolysis of the intermediary α-trimethylsilyl ketone. Compound **137** was then desilylated and subjected to hydroxy-directed reduction with $Me_4NBH(OAc)_3$ providing the *trans*-alcohol **138** as a single diastereomer. The third coupling of triflate **139** with the oxiranyl anion **128b** (generated from epoxy sulfone **128a**), having a C_3 side chain, proceeded uneventfully to give **140** (98% yield) which, upon treatment with *p*-TsOH followed by BF_3•Et_2O, gave the tetracyclic ketone **141**. Repetition of the ring expansion with $TMSCHN_2$ provided ketone **142** in 62% yield. The addition of MeMgBr in toluene led to a 4:1 epimeric mixture of products from which **143** was isolated in 77% yield. Finally, desilylation of **143** followed by bis(silylation) with *t*-butyldimethylsilyl trifluoromethanesulfonate, debenzylation, bis(silylation) with triisopropyl-

Scheme 48



silyl trifluoromethanesulfonate and regioselective removal of the primary TBS group provided the alcohol **124**, the precursor of Hemibrevetoxin B **123**, in 48% overall yield. This synthesis of Hemibrevetoxin B, using oxiranyl anions, represents a conceptually new approach to marine polycyclic ethers containing six- and seven-membered rings.

Taking advantage of this methodology, it was discovered a way for making the 6-membered ether ring systems of the kind **I**−**III** (Scheme 48), containing angular methyl groups adjacent to the ring oxygen.[59] Such ring systems are frequently encountered as structural units of polycyclic ether marine toxins and several synthetic efforts have been reported. A particularly attractive feature of this approach is that the methyl-substituted keto tetrahydropyran **148** could be easily accessed by assembling triflate **144** and lithiated epoxy sulfone **145** (see above) followed by 6-*endo* cyclization of **146** via hydroxy epoxy sulfone **147** (Scheme 48). With reference to the stereochemistry, the cyclization proceeded stereoselectively with inversion of the stereogenic center of the epoxide likely through the chair-like transition state **147** as shown in Scheme 48.

In an effort to extend the 6-*endo* cyclization reaction to a seven-membered ring alcohol,[59] the bicyclic ketone **149** was prepared from the keto tetrahydropyran **148a** by a ring expansion reaction with trimethylsilyldiazomethane (Scheme 49). Then, the required α-methyl isomer **150** was prepared by a four-step manipulation in 69% overall yield: methylenation with Tebbe reagent, epoxidation with *m*-CPBA (α/*β* = 3:1), reduction with $LiEt_3BH$, and desilylation with TBAF. Subsequent *O*-triflation and *O*-triethylsilylation in one pot gave triflate **151** in 88% yield. Reaction of **151** with the oxiranyllithium generated from **126a** gave the cyclization precursor **152** in 91% yield. Exposure of **152** to $BF_3 \cdot OEt_2$ in the presence of $Tl(TFA)_3$ at 0 °C and at room temperature gave **153** in 74% yield.

Finally, the BF_3-promoted cyclization conditions were applied to epoxy sulfone **156**, which has a silylene protective group and was prepared by the reaction of triflate **154** and the oxiranyl anion generated from epoxy sulfone **155** (Scheme 50). Treatment of **156** with $BF_3 \cdot OEt_2$ in the presence of 4 Å MS led to the formation of the 6,6,7,6-tetracyclic ketone **158** in 58% yield and the partially deprotected tricyclic ketone **157** in 36% yields, respectively. Although the silylene protective group was not compatible under these reaction conditions, the total yield of the cyclization was very high. Fortunately, the byproduct **157** could be transformed into the desired ketone **158**, in 79% yield, by heating with $TsOH \cdot H_2O$ in benzene.

Therefore, a powerful method to construct *trans*-fused 6,6- and 6,7,6-cyclic systems having angular methyl groups adjacent to the ring oxygen from precursors, which were synthesized by the coupling reaction of a suitable triflate and an oxiranyl anion stabilized with a sulfonyl group followed by cyclization, has been also developed.[60]

6. α-Lithiated-α-Silyl-, Aryl-, Cyano- and Sulfonyl-Substituted Oxiranes: Lithium−Aluminum and Lithium−Zirconium Transmetalation

Reactions of silyl-, phenyl-, cyano-, and sulfonyl-substituted α-lithiated oxiranes with organoaluminum, organozinc and zirconacycles (as electrophiles) have been reported as a route of making functionalized alkenes. Oshima and Utimoto[61] developed an efficient synthesis of triphenylsilyl-substituted alkenes **163** based on the reaction of α-lithiated triphenylsilyl-substituted oxirane **160** (generated by deprotonation of the corresponding epoxide **159** with *s*-BuLi) with alkyl-, alkenyl- and alkynyl-organoaluminum (Scheme 51). Equally efficient was the reaction with diethylzinc.

A mechanism involving attack of the oxiranyllithium on the alluminium atom of the organoalluminium to produce alluminium ate complex **161**, followed by a 1,2-migration of an R group, cleavage of the oxirane ring and *syn*-elimination of R_2Al and OLi from **162** to generate the olefinic bond of **163**, was proposed.

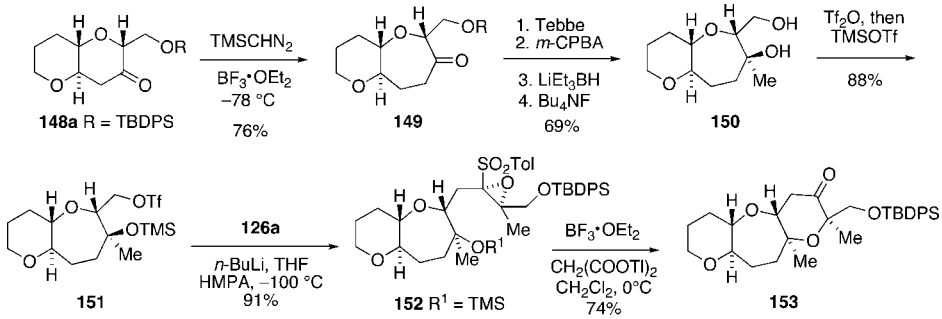
Whitby and Kasatkin have shown that silyl-stabilized α-lithiated oxiranes such as **165** (Scheme 52) react with zirconacycles, via lithium−zirconium transmetalation and formal insertion into a C−Zr bond, giving vinylsilanes.[62] Deprotonation of *cis*-1-trimethylsilyl-1,2-epoxyoctane **164** with *s*-BuLi/TMEDA, followed by addition of zirconacycle **166** in Et_2O afforded, after quenching with 2 M HCl, (*Z*)-alkenylsilane **167**. A reasonable mechanism for this transformation is described in Scheme 52.

Similarly, α-lithiated styrene oxide **13** reacts with zirconacycle **168** to give α-substituted styrene **169**, whereas reaction of lithiated epoxynitrile **170** with zirconacycle **171** gives cyanoalkene **172** (Scheme 53).[62]

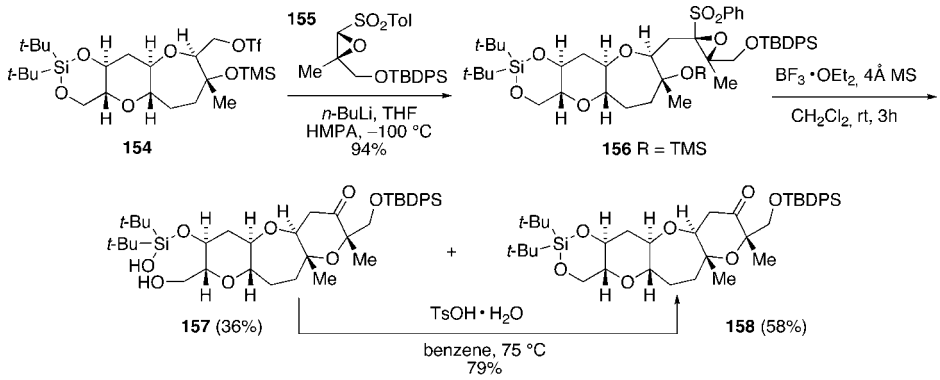
α,*β*-Epoxynitriles are readily deprotonated with LDA but, in the absence of an electrophile, they undergo extremely rapid self-condensation even at −90 °C. However, slow addition of LDA to a mixture of (*E*)-1-octenylzirconocene chloride **173** (readily available by hydrozirconation of 1-octyne with the Schwartz reagent) and epoxynitrile **174** in THF at −90 °C, followed by warming to −60 °C and acidic hydrolysis, ends up with the formation of (*E*)-2-cyano-1,3-diene **177** (Scheme 54). A reasonable mechanism for the above transformation includes, after a preliminary lithium−zirconium transmetalation between lithiated epoxynitrile **175** and alkenylzirconocene chloride **176**, epoxide ring-opening by 1,2-migration of the alkenyl fragment in the 'ate'-complex **176** followed by *syn*-*β*-elimination of the zirconium alkoxide.[63]

The lack of stereoselectivity ascertained in the reaction of **173** with *β*-monosubstituted epoxynitriles has been explained in terms of a configurational instability ascribed to α-lithiated oxiranes **178** and **179** which are believed to

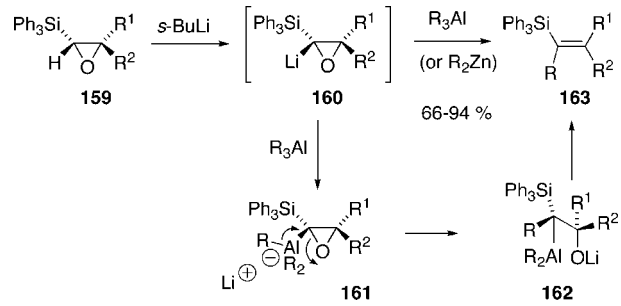
Scheme 49



Scheme 50



Scheme 51



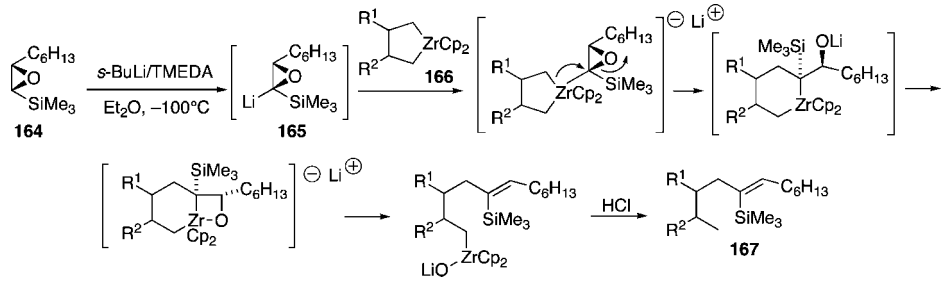
interconvert rapidly under the reaction conditions (Scheme 55). Moreover, the reaction of **173** with (*R**,*S**)-isomer **178**, to afford (*Z*,*E*)-cyanodienes, was found to be faster than with (*R**,*R**)-isomer **179**, probably due to the steric repulsion between a *trans*-*β*-substituent in **179** and the Cp-ligands.

Whitby and Kasatkin have recently reported the addition of *β*,*β*-disubstituted-α-lithiated phenylsulfonyloxiranes to alkenylzirconocene chlorides, derived by hydrozirconation of alkynes, to give zirconyloxiranes which smoothly rearrange by either α- or *β*-C−O bond cleavage to afford regiodefined zirconium enolates which may be further synthetically elaborated.[64] A reasonable mechanism is the attack of the *β*,*β*-disubstituted-α-lithiated phenylsulfonyloxirane **180** on the alkenylzirconocene chloride **181** to form an "ate" complex **182** which undergoes a 1,2-metalate rearrangement with loss of phenylsulfinate to afford the zirconyloxirane **183**, in the first example of reaction of a metallated oxirane with a nucleophile which does not directly cleave the oxirane ring (Scheme 56). Presumably, the difference in behavior compared with cyanooxiranes (see above) is due to the much greater stability of the phenylsulphinate anion compared with that of cyanide (pK_a values of phenylsulphinic acid and hydrogen cyanide in water are 2.1 and 9.2, respectively).

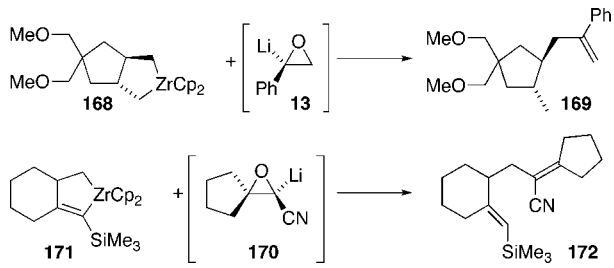
Rearrangement of the zirconyloxirane **183**, likely involving an unusual cleavage of the *β*-C−O bond which can be viewed either as an electrocyclic ring opening or as a 1,2-elimination, then affords the zirconium enolate **184** which may be protonated to give ketone **185** or oxidized on aqueous quenching in air to give the alcohol **186** or, finally, reacted with aldehydes to provide aldol-type products **187** (Scheme 56). Rearrangement of zirconyloxiranes to ketones following a *β*-C−O bond breaking is rather surprising as usually this occurs by cleavage of the α-C−O bond, except few cases regarding lithiated oxazolinyloxiranes (see ahead) and terminally lithiated monosubstituted oxiranes.[65,33] A very similar mechanism has been also suggested for Lewis acid catalyzed rearrangements of *β*,*β*-disubstituted silyloxiranes.[66]

The reaction of α-lithiated *β*-monosubstituted-(*E*)-phenylsulphonyloxiranes **188** with (*E*)-1-octenylzirconocene chloride **173**, followed by aqueous quenching, gave *β*,*γ*-unsaturated ketones **192** implying enolates **191** as intermediates (Scheme 57). The reaction thus follows a similar course to that shown in Scheme 57 as far as zirconyloxirane **189** is concerned, but now opening of the oxirane occurs with cleavage of the bond between oxygen and the metallated carbon (α-cleavage). As a possible mechanism, an initial α-elimination of zirconium alkoxide to afford the carbene **190** which inserts into the *β*-C−H bond to afford the enolate **191** (*path a*, Scheme 57) may be favored by the strong affinity of zirconium for oxygen. Alternatively, cleavage of the α-C−O bond accompanied by 1,2-H migration to give the α-zirconylketone **193** (*path b*, Scheme 57), which may rearrange to the enolate **191**, has precedent in the Lewis acid-catalyzed rearrangement of silyloxiranes to *β*-silyl ketones. The above are two extreme forms of a mechanism in which α-elimination of zirconium alkoxide is concerted with migration of the *β*-hydride to afford **191** directly. The transition state **194** for this process resembles that of the

Scheme 52



Scheme 53



Simmons Smith cyclopropanation; however, initial orbital alignment is very poor implying a late transition state with very much of the character of **190**.

The remarkably facile rearrangement of α-zirconyloxiranes to zirconium enolates, and the difference in behavior of *β*-monosubstituted and *β*,*β*-disubstituted phenylsulfonyloxiranes in giving regioisomeric dienolates **184** and **191**, respectively, have been addressed an explanation. The action of the zirconium as a Lewis acid toward the oxirane oxygen during these rearrangements is important. The structure of $Cp_2Zr(Cl)(CH_2OMe)$ shows strong bonding between the oxygen and zirconium, and its reactivity is consistent with an "oxonium ion" depiction. The rearrangements of zirconyloxiranes to enolates could thus be considered to be both "pushed" by the anionic character of the carbon to which zirconium is attached, and "pulled" by the Lewis acid interaction of the zirconium with the oxirane oxygen. The transition state for rearrangement of the zirconyloxiranes **183** to enolates **184** (*β*-C−O cleavage) must involve substantial positive charge build-up on the carbon *β* to the zirconium since the zirconium−carbon bond is initially close to orthogonal to the breaking C−O bond's *σ** orbital. The *β*-C−O bond cleavage will thus be strongly favored when the *β*-position is tertiary, as in **184** (cf. secondary as in **189**). In **189** breaking of the *β*-C−O bond is disfavored as positive charge build-up would be on a secondary center, and the observed 1,2-shift favored by the good migrating group ability of hydride.

7. α-Lithiated Benzothiazolyloxiranes

The first heteroaryl-substituted lithiated epoxides to be reported were the α-lithiated benzothiazolyloxiranes **196** that could be generated by deprotonation of the corresponding 2-benzothiazolyl epoxides **195**.[67] Upon treatment with *n*-BuLi (or LDA) in THF at −90 °C, the oxiranes **195** underwent rapid lithiation which was complete in less than 10 min to generate **196**, as proved by its quick trapping with Me_3SiCl and MeI to give **197** (90%) and **198** (50%), respectively (Scheme 58). It was demonstrated that **196** tends to isomerize to the benzothiazolyl isopropyl ketone **199** upon warming to room temperature, likely through an electrocyclic process or an E_1cb-like mechanism. Trapping of **196** with cyclopentanone resulted in the formation of the corresponding hydroxyalkylepoxide **200** (63%), whereas the reaction with aldehydes gave mixtures of diastereomeric *syn*- and *anti*-hydroxyalkyl epoxides **201** (61−83%) and reaction with 2-cyclopent-1-one furnished a mixture of 1,2- and 1,4-addition products **202** (37%) and **203** (16%), respectively (Scheme 58).

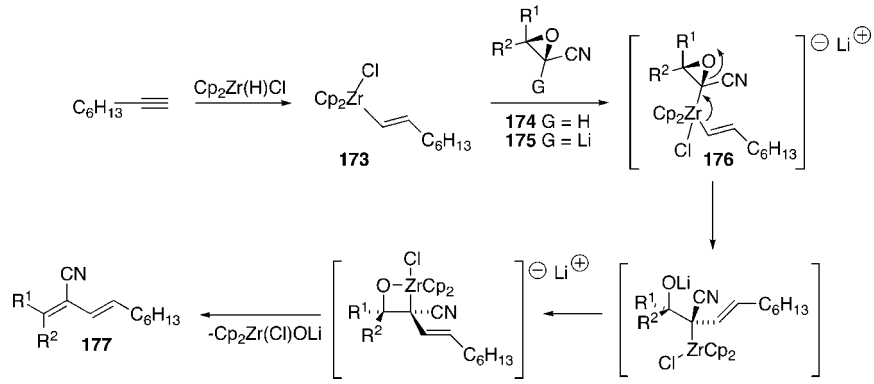
It is worth noting that the deprotonation reactions of *cis*- and *trans*-benzothiazolyl epoxides, such as **204** and **205** with *n*-BuLi (in contrast with Molander's statement that cis epoxides are more prone to lithiation than the trans isomers) took place with comparable rates, and subsequent reaction of the resulting oxiranyllithiums **206** and **207** with PhCHO led to the same epoxy alcohol **208** (Scheme 59).[66] Such a stereoconvergency was explained with the assumption that oxiranyllithiums **206** and **207** equilibrate each other and the attack of PhCHO on these lithiated oxiranes would take place from the less sterically hindered site of the equilibrating oxiranyllithiums to give **208**. It might be asserted that conjugation with the aza group of the benzothiazolyl moiety might facilitate the interconversion process in contrast with the reported configurational stability of many lithiated oxiranes.

8. α-Lithiated Benzotriazolyloxiranes

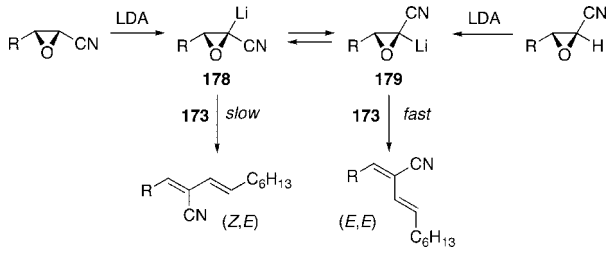
In contrast to other oxiranyl anions, usually generated from −90 to −110 °C, lithiation of 3,3-disubstituted benzotriazolyloxiranes **209**, at −78 °C in THF with *n*-BuLi, furnished lithiated oxiranes **210**, which proved to be stable at the above temperature and could be successfully trapped with a variety of electrophiles to give the corresponding α-substituted products **211** in very good yields (Scheme 60).[68] In the case of aldehydes, such as PhCHO, the desired epoxy alcohols were obtained as a mixture of syn and anti isomers in a 1:1 ratio, while the trapping reaction of **210** with ethyl benzoate provided the corresponding α-acylated products **212** in good yield. The procedure worked well also with Schiff's bases: reaction of **210** with *N*-(phenylmethylidene)aniline furnished the addition product **213** as a mixture of three isomers in a 2:1:1 ratio.

Attempts to generate acylbenzotriazoles via base-promoted rearrangement of α-lithiated benzotriazolyloxirane **214** failed leading instead to the formation of the acyl epoxide **217** which likely is the result of an addition of the benzotriazolyloxiranyllithium **214** to the intermediate ketene **216**, generated by the loss of the benzothiazolyl group from the enolate **215** (Scheme 61).

Scheme 54



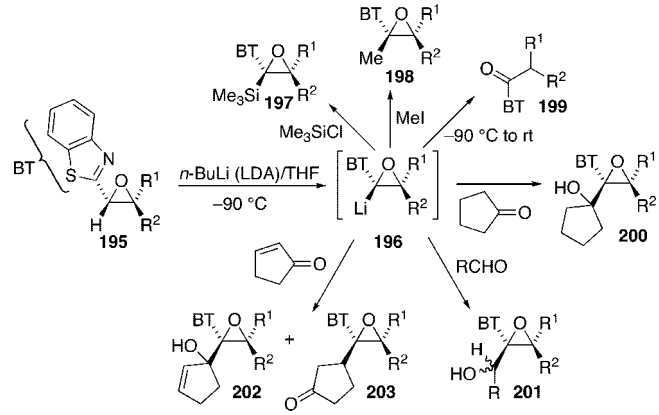
Scheme 55



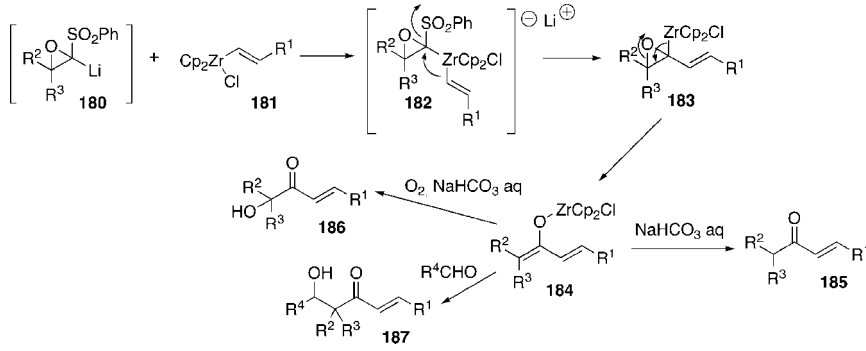
9. α-Lithiated Alkenyl- and Alkynyloxiranes

Compared to other stabilized lithiooxiranes, organyl-stabilized α-lithiated oxiranes, such as alkenyl and alkynyl lithioxiranes, have been studied much less. Most of the work in this field has been reviewed[1,9] showing that some of this type of lithiated oxiranes, once generated, are thermally and configurationally stable and can be trapped with electrophiles, whereas some vinyl-stabilized lithiooxiranes reveal a strong electrophilic character and undergo rearrangement reactions. It has also been reported[69] that while *cis*-(α,*β*-epoxy-*γ*,*δ*-alkenyl)-*t*-butyldimethylsilane **218** is cleanly deprotonated by *s*-BuLi at −116 °C at the silylated oxiranyl carbon atom sterospecifically and successfully

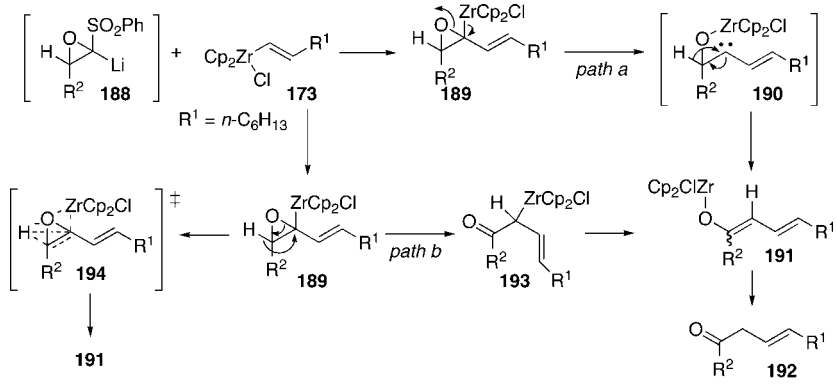
Scheme 58



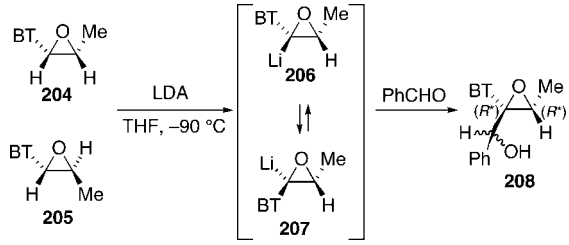
Scheme 56



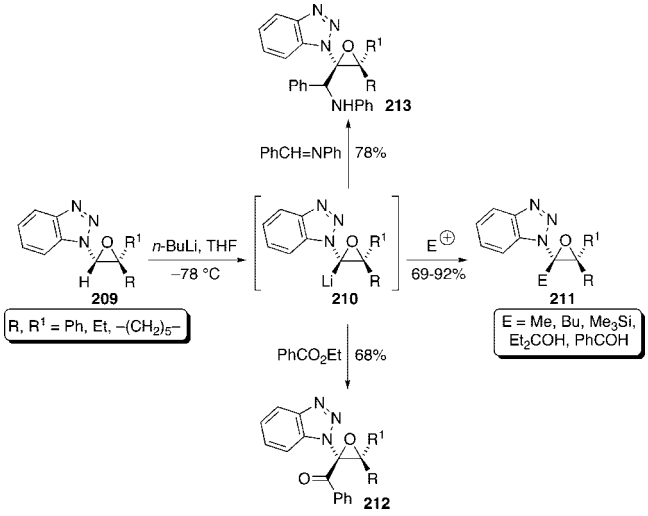
Scheme 57



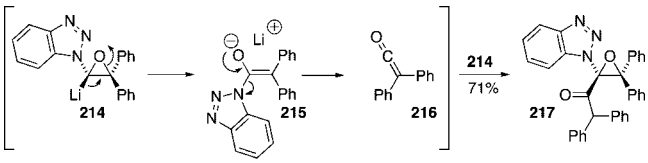
Scheme 59



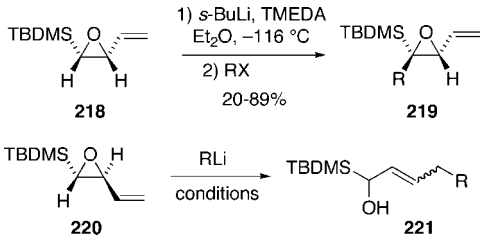
Scheme 60



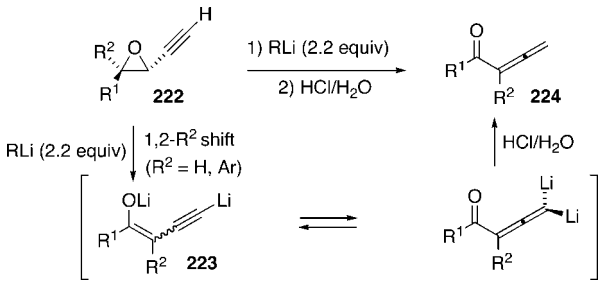
Scheme 61



Scheme 62

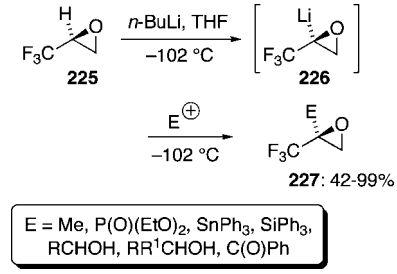


Scheme 63

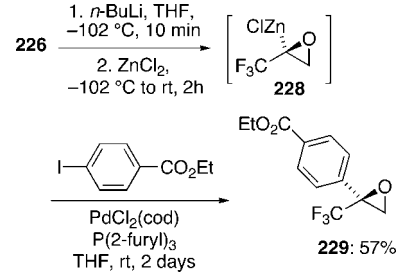


trapped with electrophiles to give silylated vinyloxiranes **219** with a quaternary carbon in the α-position to the silicon, the corresponding *trans* isomer **220**, when treated with powerful bases such as *s*-BuLi, *t*-BuLi, and *t*-BuOK/*n*-BuLi, undergoes 1,4-nucleophilic addition on the vinyloxirane moiety resulting in the formation of S_N2' adducts **221**. For the latter, the selectivity sometimes observed in the formation of the new C=C double bond resulted to be highly dependent on the nature of the nucleophile and on the experimental conditions (Scheme 62).

Scheme 64



Scheme 65



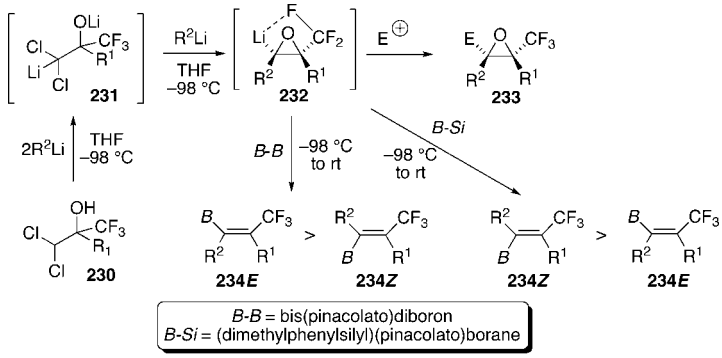
It has been recently reported[70] that *cis*- and *trans*-propargylic oxiranes **222** isomerized to allenic ketones **224** when treated with 2.2 equiv of organolithium (Scheme 63). It has been proposed, on the basis of experimental evidence, that the above isomerization occurs through the formation of a new dilithium ynenolate species **223**. The mechanism of such ynenolate formation has been shown to follow an unprecedented double deprotonation reaction taking place at the acetylenic and propargylic positions of the acetylenic oxiranes, followed by a 1,2-H or 1,2-Ar shift (Scheme 63). The interesting result of this work is the development of a new method of preparation of allenic ketones, useful Michael acceptors and Diels−Alder dienophiles, which compares quite well with other previously reported synthetic procedures.

10. α-Lithiated Trifluoromethyloxiranes

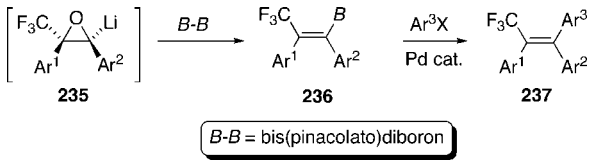
The trifluoromethyl group proved to be a very good stabilizing group for lithiated oxiranes. Indeed, optically active 2,3-epoxy-1,1,1-trifluoropropane **225** can be lithiated at very low temperature (−102 °C) and the resulting lithiated oxirane **226** reacts with electrophiles, such as aldehydes, ketones, Weinreb amide and halides, to give the corresponding α-adducts **227** in moderate to good yields (42−99%). The whole reaction occurs with retention of configuration at the stereogenic carbon center (Scheme 64).[71]

The oxiranyllithium **226** is very sensitive to temperature; thus, the reaction should be performed under low temperature conditions. Indeed, **226** was found to be stable at −78 °C even for 1 h but to decompose at around −70 °C. At a reaction temperature above −40 °C, **226** was completely decomposed, as proved by an ^{19}F NMR analysis. A metal exchange by $ZnCl_2$ gave the thermally stable species **228**, of which the detailed structure is still unknown. The zinc species **228** underwent a coupling reaction with aryl halide with the aid of a Pd complex at rt to give the arylated compound **229** (Scheme 65).

Scheme 66



Scheme 67



The products of these reactions are versatile synthetic intermediates as a wide variety of highly functionalized α-trifluoromethylated alcohols with quaternary chiral carbon centers may be synthesized.

The trifluoromethyl group, which provides stabilization to α-lithiated trifluoromethyl oxirane, proved to be a good stabilizing group for β-lithiated trifluoromethyl oxiranes other than for β-oxido carbenoids.[72] Indeed, CF_3-substituted oxiranyllithiums **232** can be generated by reacting, at −98 °C in THF, readily available acyclic CF_3-containing dichlorohydrins **230** with organolithium reagents R^2Li via novel reaction involving β-oxido carbenoids **231** (Scheme 66). Noteworthy is that the generation of **232** proceeds with high stereoselectivity that involves CF_3 and Li being cis thus favoring a stabilizing intramolecular coordination between the above groups. The oxiranyllithiums **232** react stereospecifically not only with various kinds of electrophiles to give tri- and tetrasubstitued oxiranes **233** but also with either organoborane or silyl borane reagents to afford, stereoselectively, tetrasubstituted alkenes **234E** and **234Z**, respectively (Scheme 66). This type of compounds serve as highly versatile intermediates for stereocontrolled synthesis of CF_3-containing complex organic molecules of potential interest in pharmaceutical and material sciences fields.

On this basis, a convenient and versatile synthetic strategy for CF_3-substituted triaryl ethenes **237**, through stereoselective preparation of **236** and its Pd-catalyzed cross-coupling, and that has in oxiranylithium **235** the key intermediate, has been recently set up (Scheme 67).[73] This method has been applied to diverse CF_3-substituted triaryl ethenes, including panomifene, a potent nonsteroidal antiestrogen.

11. Final Conclusions

The understanding of the chemistry of α-lithiated-α-substituted oxiranes over the last fifty or so years has advanced to such a level that their use in organic synthesis has become almost routine. After the pioneering work by Cope and Crandall toward the end of the fifties and the achievements by Eisch and Galle in the middle of the 70s, several research groups have addressed their attention to the chemistry of lithiated oxiranes over the last fifteen to twenty years and still their work continues to unveil new aspects of their reaction pathways and to develop these into synthetically useful processes. The synthetic utility of α-lithiated-α-substituted epoxides based on peculiar reactions such as stereoselective rearrangements, asymmetry induction and reductive alkylation, allowing access to polyfuctionalized alkenes, has been amply demonstrated. As described in the present review, the last ten years have witnessed very significant achievements in the use of stabilized α-lithiated epoxides as nucleophiles so that the reactions with a variety of electrophiles have given access to polyfunctionalised epoxides and products that can be derived from. What adds value to the stabilized α-lithiated epoxides is the fact that the stabilizing group is often amenable to synthetic elaborations as in the case of lithiated oxazolinyloxiranes that have become very useful building blocks for the synthesis of a variety of substances. In order to explain the reactivity as well as to strengthen the synthetic utility of α-lithiated-α-substituted epoxides, spectroscopic investigations have to be undertaken in view of the fact that almost nothing has been done sofar in this context.

12. Acknowledgments

Our own work described in this review was financially supported by many National PRIN Projects received throughout the years, by a FIRB project, by the University of Bari, and by the Italian Interuniversities Consortium CINMPIS. Particular thanks are also due to the enthusiastic young students and co-workers who have contributed to the success of all the work described here; without them, the insights revealed here could not have been gained.

13. References

(1) (a) For reviews and book on the synthesis and reactivity of oxiranes, see Crandall, J. K.; Apparu, M. *Org. React. (N. Y.)* **1983**, *29*, 345. (b) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337. (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625. (d) Hodgson, D. M.; Gras, E. In *Topics in Organometallic Chemistry*; Hodgson, D. M., Ed.; Springer: Berlin, 2003, p 217. (e) Hodgson, D. M.; Bray, C. D. In *Aziridine and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, 2006; Chapter 5, p 145. (f) Padwa, A.; Murphree, S. *ARKIVOC* **2006**, 6.

(2) (a) Cope, A. C.; Tiffany, B. D. *J. Am. Chem. Soc.* **1951**, *73*, 4158. (b) Cope, A. C.; Martin, M. M.; Mckervey, M. A. *Q. Rev. (London)* **1966**, *20*, 119.

(3) Cope, A. C.; Lee, H.-H.; Petree, H. E. *J. Am. Chem. Soc.* **1958**, *80*, 2849.

(4) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428.

(5) (a) Eisch, J. J.; Galle, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4646. (b) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1976**, *121*, C10. (c) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835.

(6) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303.

(7) Mori, Y. *Rev. Heteroat. Chem.* **1997**, *17*, 183.

(8) (a) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, *1*, 1. (b) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625. (c) Hodgson, D. M.; Humphreys, P. G.; Hughes, S. P. *Pure Appl. Chem.* **2007**, *79*, 269.
(9) Chemla, F.; Vrancken, E. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley and Sons: New York, 2004; p 1165.
(10) (a) For a special issue on oxiranyl and aziridinyl anions, see *Oxiranyl and Aziridinyl Anions as Reactive Intermediates in Synthetic Organic Chemistry*, Tetrahedron Symposia-in-Print; Florio, S., Ed. *Tetrahedron* **2003**, *59*, 9693. (b) Capriati, V.; Florio, S.; Luisi, R. *Synlett* **2005**, *9*, 1359.
(11) Closs, G. L.; Moss, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4062.
(12) Hodgson, D. M.; Norsikian, S. L. M. *Org. Lett.* **2001**, *3*, 461.
(13) (a) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697. (b) A recent computational investigation on the "unstabilized" lithiated ethylene oxide revealed that its properties appear to be really intermediate between a chelated alkyllithium and a lithium carbenoid, with the monomeric structure being more carbenoid-like, and the dimer and the tetramer more alkyllithium-like; see Pratt, L. M.; Ramachandran, B. *J. Org. Chem.* **2005**, *70*, 7238.
(14) Chaiyanurakkul, A.; Jitchati, R.; Kaewpet, M.; Rajviroongit, S.; Thebtaranonth, Y.; Thongyoo, P.; Watcharin, W. *Tetrahedron Lett.* **2003**, *59*, 9825.
(15) (a) Hattori, K.; Nagano, M.; Kato, T.; Nakanishi, I.; Imai, K.; Kinoshita, T.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2821. (b) Di Fabio, R.; Pietra, C.; Thomas, R. J.; Ziviani, L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 551. (c) Sher, P. M.; Mathur, A.; Fisher, L. G.; Wu, G.; Skwish, S.; Michel, I. M.; Seiler, S. M.; Dickinson, K. E. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1583.
(16) Capriati, V.; Degennaro, L.; Favia, R.; Florio, S.; Luisi, R. *Org. Lett.* **2002**, *4*, 1551.
(17) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445.
(18) (a) Takahashi, K.; Ogata, M. *J. Org. Chem.* **1987**, *52*, 1877. (b) Ogata, M.; Matsumoto, H.; Tawara, K.; Ishiguro, T.; Hatta, T. (Shionogi and Co., Ltd., Japan) *Eur. Patent Appl.* EP 117578 A2 19840905, 1984.
(19) Capriati, V.; Florio, S.; Luisi, R.; Nuzzo, I. *J. Org. Chem.* **2004**, *69*, 3330.
(20) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615.
(21) (a) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4527. (b) Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943.
(22) Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049.
(23) (a) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042. (b) Molander, G. A.; Mautner, K. *Pure Appl. Chem.* **1990**, *62*, 707.
(24) Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2359.
(25) (a) Cope, A. C.; Trumbull, P. A.; Trumbull, E. R. *J. Am. Chem. Soc.* **1958**, *80*, 2844. (b) Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* **2004**, *6*, 4191.
(26) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.
(27) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone, A. *J. Org. Chem.* **2006**, *71*, 3984.
(28) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone, A.; Gasparrini, F. *Org. Lett.* **2005**, *7*, 4895.
(29) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Barluenga, J. *J. Org. Chem.* **2005**, *70*, 5852.
(30) (a) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A.; Cuocci, C. *Org. Lett.* **2006**, *8*, 3923. (b) For a recent review on the chemistry of oxazetidines, see: Florio, S.; Capriati, V.; Luisi, R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ed.; Pergamon: Oxford, 2008; Chapter 2.14: Four-Membered Rings with One Oxygen and One Nitrogen Atom, p 689.
(31) The two competitive mechanistic pathways depicted in Scheme 18 refer, in particular, to the addition of **13,18a,28** to the *re* or *si* face of the *N*-*t*-butylphenyl nitrone.
(32) (a) Florio, S.; Capriati, V.; Di Martino, S. *Tetrahedron Lett.* **1998**, *39*, 5639. (b) Florio, S.; Capriati, V.; Di Martino, S.; Abbotto, A. *Eur. J. Org. Chem.* **1999**, 409.
(33) Capriati, V.; Florio, S.; Luisi, R.; Russo, V.; Salomone, A. *Tetrahedron Lett.* **2000**, *41*, 8835.
(34) Dunn, D.; Chatterjee, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1273.
(35) Shafer, C. M.; Molinsky, T. F. *J. Org. Chem.* **1996**, *61*, 2044.
(36) Luisi, R.; Capriati, V.; Carlucci, C.; Degennaro, L.; Florio, S. *Tetrahedron* **2003**, *59*, 9707.
(37) Florio, S.; Capriati, V.; Luisi, R.; Abbotto, A. *Tetrahedron Lett.* **1999**, *40*, 7421.
(38) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.
(39) Perna, F. M.; Capriati, V.; Florio, S.; Luisi, R. *Tetrahedron Lett.* **2002**, *43*, 7739.
(40) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M. *J. Org. Chem.* **2007**, *72*, 6316.
(41) Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Org. Lett.* **2003**, *5*, 2723.
(42) (a) von Angerer, S. In *Carbocyclic Three-and Four-Membered Ring Compounds. Methods of Organic Chemistry*; de Meijere, A., Ed.; Houben-Weyl: New York, 1997; Vol. E17, p 2121. (b) Wong, H. N.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
(43) Berberich, S. M.; Cherney, R. J.; Colucci, J.; Courillon, C.; Geraci, L. S.; Kirkland, T. A.; Marx, M. A.; Schneider, M. F.; Martin, S. F. *Tetrahedron* **2003**, *59*, 6819.
(44) Swain, N. A.; Brown, R. C. D.; Bruton, G. *J. Org. Chem.* **2004**, *69*, 122.
(45) Kazuta, Y.; Tsujita, R.; Yamashita, K.; Uchino, S.; Kohsaka, S.; Matsuda, A.; Shuto, S. *Bioorg. Med. Chem.* **2002**, *10*, 3829.
(46) Braña, M. F.; Guisado, C.; Alguacil, L. F.; Garrido, E.; Pérez-García, C.; Ruiz-Gayo, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3561.
(47) Plake, H. R.; Sundberg, T. B.; Woodward, A. R.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1571.
(48) Florio, S.; Perna, F. M.; Luisi, R.; Barluenga, J.; Fananas, F. J.; Rodriguez, F. *J. Org. Chem.* **2004**, *69*, 9204.
(49) Capriati, V.; Favia, R.; Florio, S.; Luisi, R. *ARKIVOC* **2003**, *xiv*, 77.
(50) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Punzi, P. *Org. Lett.* **2006**, *8*, 4803.
(51) Capriati, V.; Florio, S.; Luisi, R. Unpublished results.
(52) Vogt, P. F.; Tavares, D. F. *Can. J. Chem.* **1969**, *47*, 2875.
(53) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1988**, *341*, 293.
(54) (a) Ashwell, M.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1988**, 645. (b) Ashwell, M.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. I* **1989**, 835. (c) Hewkin, C. T.; Jackson, R. F. W.; Clegg, W. *J. Chem. Soc., Perkin Trans. I* **1991**, 3091. (d) Hewkin, C. T.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. I* **1991**, 3103. (e) Jackson, R. F. W.; Standen, S. P.; Clegg, W. *Tetrahedron Lett.* **1991**, *32*, 5393. (f) Ashwell, M.; Clegg, W.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. I* **1991**, 897. (g) Dunn, S. F. C.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. I* **1992**, 2863.
(55) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731.
(56) Mori, Y.; Yaegashi, K.; Iwase, K.; Yamamori, Y.; Furukawa, H. *Tetrahedron Lett.* **1996**, *37*, 2605.
(57) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158.
(58) (a) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917.
(59) Furuta, H.; Takase, T.; Hayashi, H.; Noyori, R.; Mori, Y. *Tetrahedron* **2003**, *59*, 9767.
(60) (a) Other synthetic applications to polyciclic ethers are the following: Mori, Y.; Takase, T.; Noyori, R. *Tetrahedron Lett.* **2003**, *44*, 2319. (b) Mori, Y.; Nogami, K.; Hayashi, H.; Noyori, R. *J. Org. Chem.* **2003**, *68*, 9050. (c) Furuta, H.; Hase, M.; Noyori, R.; Mori, Y. *Org. Lett.* **2005**, *7*, 4061.
(61) Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, *32*, 2783.
(62) Kasatkin, A.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 5275.
(63) Kasatkin, A.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 6201.
(64) Kasatkin, A.; Whitby, R. J. *Tetrahedron* **2003**, *59*, 9857.
(65) Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2103.
(66) (a) Colvin, E. In *Silicon in Organic Synthesis*; Butterworths: London, 1981; p 83. (b) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. I* **1984**, 119.
(67) Florio, S.; Ingrosso, G.; Troisi, L.; Lucchini, V. *Tetrahedron Lett.* **1993**, *34*, 1363.
(68) Katritzky, A. R.; Manju, K.; Steel, J. *J. Org. Chem.* **2003**, *68*, 407.
(69) (a) Marié, J.-C.; Courillon, C.; Malacria, M. *Synlett* **2002**, *4*, 553. (b) Courillon, C.; Marié, J.-C.; Malacria, M. *Tetrahedron* **2003**, *59*, 9759.
(70) Denichoux, A.; Ferreira, F.; Chemla, F. *Org. Lett.* **2004**, *6*, 3509.
(71) Yamauchi, Y.; Kawate, T.; Katagiri, T.; Uneyama, K. *Tetrahedron* **2003**, *59*, 9839.
(72) (a) Shimizu, M.; Fujimoto, T.; Minezaki, H.; Hata, T.; Hiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 6947. (b) Shimizu, M.; Fujimoto, T.; Liu, X.; Minezaki, H.; Hata, T.; Hiyama, T. *Tetrahedron* **2003**, *59*, 9811.
(73) Liu, X.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 879.

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