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Applications of Chiral Three-Membered Rings for Total Synthesis: A Review

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Abstract: This review updates recent applications of asymmetric aziridination, azirination, thiirination, epoxidation, and cyclopropanation in the total synthesis of biologically active compounds, including natural products, using chiral substrates or chiral catalysts, covering the literature since 2000. The interest towards these synthetic methodologies of chiral three-membered rings has increased in the last decade, dictated either by the biological activities that display many naturally occurring products bearing a three-membered unit or by the ring strain of three-membered rings making them useful precursors of many more complex interesting molecules. Classic as well as modern protocols in asymmetric aziridinations, azirinations, epoxidations, thiirinations, and cyclopropanations have been widely applied as key steps of a number of syntheses of important products. Although the use of chiral substrates and auxiliaries is still highly employed particularly in asymmetric aziridination and cyclopropanation, the development of enantioselective catalytic methodologies has witnessed exponential growth during the last decade. The present review is subdivided into three parts, dealing successively with the use of chiral nitrogen-containing three-membered rings, chiral epoxides and thiiranes, and chiral cyclopropanes in total synthesis.

1. INTRODUCTION

Chiral three-membered rings are useful building blocks in synthesis, as well as important synthetic targets. The interest towards synthetic methodologies for their preparation has increased in the last decade, dictated either by the biological activities displayed by many naturally occurring products bearing a three-membered unit or by being useful precursors for accessing more complex interesting molecules [1]. The goal of the present review is to highlight the major developments and applications in the use of asymmetric three-membered ring formations in total synthesis reported in the last fifteen years. It must be noted that a range of reviews, which will be cited in the respective sections of the present review, have been separately devoted to asymmetric aziridinations, epoxidations, or cyclopropanations [2]. On the other hand, to the best of our knowledge, no previous review compiling all types of chiral three-membered rings and their synthetic applications exists. In 2000, a book dedicated to cyclopropanes in synthesis was published by de Meijere [3], while a special issue published in Chemical Reviews in 2014 was consecrated to small heterocycles in synthesis but did not especially focus on the asymmetric total synthesis of bioactive and natural products [4]. The present review is subdivided into three parts, dealing successively with the use of chiral nitrogen-containing three-membered rings, chiral epoxides and thiiranes, and chiral cyclopropanes in total synthesis. The first part is subdivided into two sections successively devoted to chiral aziridines and

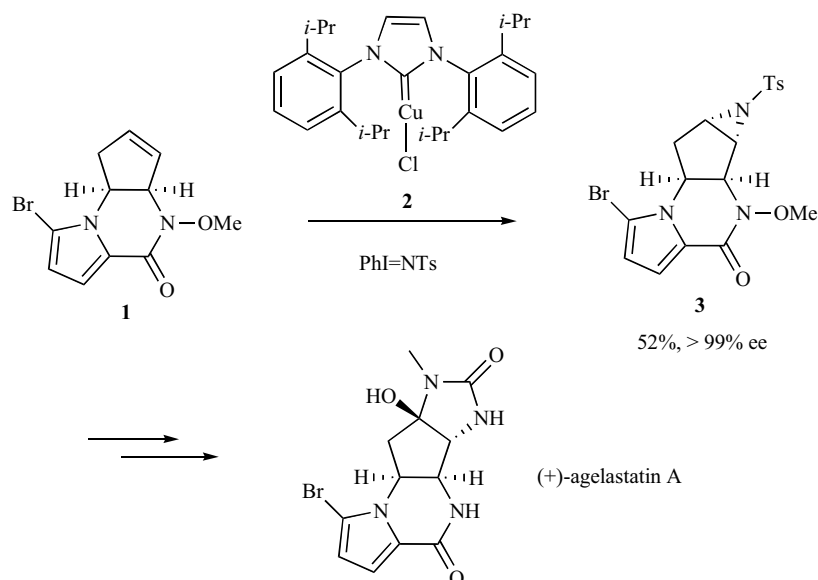
chiral azirines. The second part of the review is also subdivided into two sections, dealing successively with chiral epoxides and thiiranes. The third part of the review is subdivided into four sections, treating successively asymmetric Simmons–Smith cyclopropanations as key steps, asymmetric transition-metal decomposition of diazoalkanes as key steps, asymmetric Michael-initiated ring closures as key steps, and miscellaneous asymmetric cyclopropanations as key steps.

2. CHIRAL NITROGEN-CONTAINING THREE-MEMBERED RINGS IN TOTAL SYNTHESIS

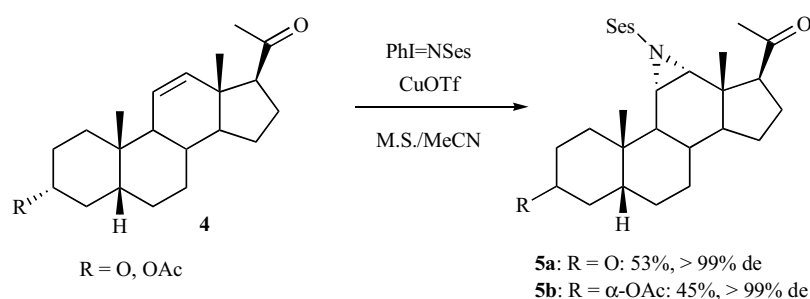
2.1. Chiral Aziridines

Aziridines are among the most fascinating heterocyclic intermediates in organic synthesis [5], acting as precursors of many complex molecules including natural and biologically active products due to the high strain incorporated in their skeletons [6]. The last decade has witnessed tremendous activity in the area of discovering new methodologies for their synthesis and transformations [7]. This growing interest is related to their striking chemical properties. The high strain energy associated with the aziridine ring enables easy cleavage of the C–N bond, leading to a series of important nitrogen-containing products [8]. Obtaining aziridines, especially optically active aziridines, has become of great importance in organic chemistry for many reasons. These reasons may include the antitumor, antibacterial and other biological properties associated with a great number of aziridine-containing compounds, such as mitomycins, azinomycins, and epothilones [9]. Indeed, as powerful alkylating agents, aziridines have an inherent *in vivo* potency through their ability to act as DNA cross-linking agents *via* nucleo-

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Scheme 1. Synthesis of (+)-agelastatin A.



Scheme 2. Synthesis of a pregnanolone and minaxolone analogue.

philic ring opening of the aziridine moiety. Structure–activity relationships have identified the aziridine ring is very essential for the antitumor activity, and a vast amount of work has concentrated on synthesizing derivatives of these natural products with increased potency. Various antitumor agents related to mitosanes and mitomycins, for example, have been synthesized and demonstrated to possess activity against a variety of cancers. A number of other synthetic chiral aziridines have also been shown to exhibit other useful biological properties such as enzyme-inhibitory activities. In addition to these important biological activities related to the aziridine unit, these molecules constitute key chiral building blocks for the easy construction of other types of biologically relevant as well as naturally occurring chiral nitrogen-containing compounds. Chiral aziridines can be prepared by either asymmetric catalytic methods or from chiral substrates. The main approaches to the synthesis of chiral aziridines can be classified as asymmetric nitrene transfer to alkenes, asymmetric carbene transfer to imines such as ylide-mediated aziridinations, asymmetric cyclization reactions through addition/elimination processes such as Gabriel–Cromwell reactions, and miscellaneous asymmetric reactions such as intramolecular substitutions [7].

2.1.1. Asymmetric Aziridinations of Chiral Substrates as Key Steps

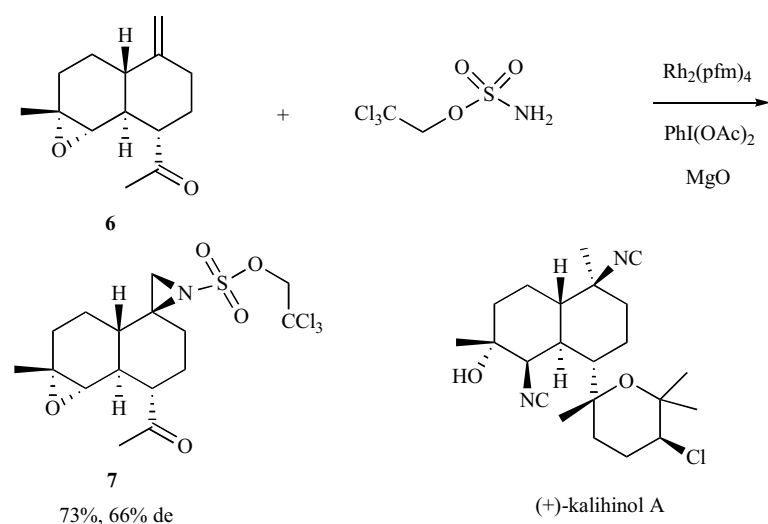
Nitrene Transfer to Alkenes

Nitrogen-atom transfer to alkenes is a particularly appealing strategy for the generation of aziridines because of the ready avail-

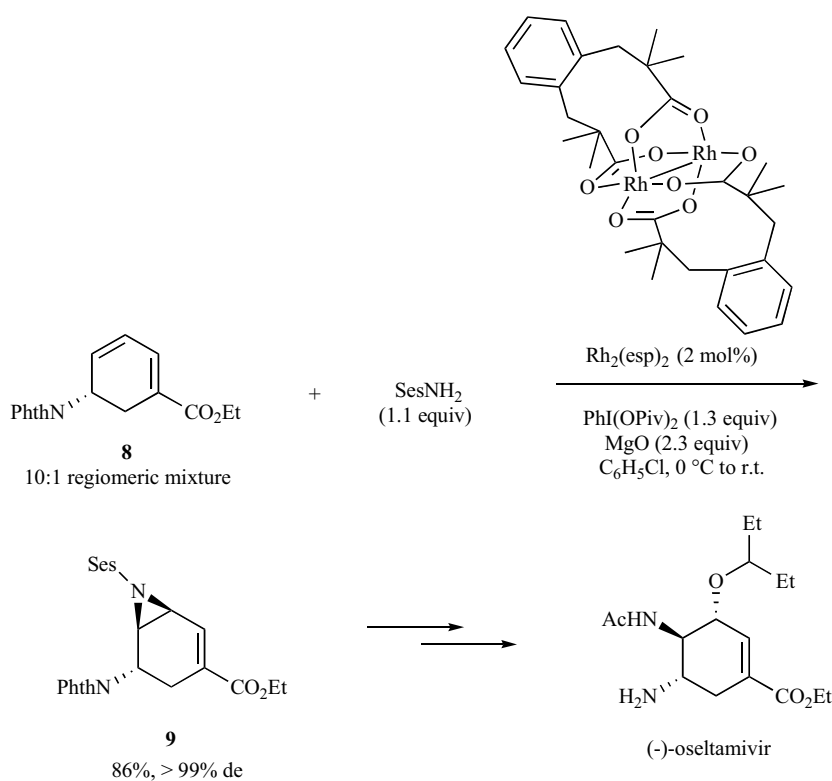
ability of olefinic starting materials and the direct nature of such a process.

The nitrene (or nitrenoid) source for this reaction can be generated from various methodologies, such as the metal-catalyzed reaction of [*N*-(*p*-toluenesulfonyl)imino]aryliodanes [10]. In 2006, Trost and Dong reported a total synthesis of (+)-agelastatin A, possessing nanomolar activity against several cancer cell lines, which was based on the aziridination of chiral piperazinone **1** (Scheme 1) [11]. This process was performed in the presence of PhI=NTs as the nitrene source and a catalytic amount of copper *N*-heterocyclic carbene complex **2**, providing the corresponding aziridine **3** as the only detected stereoisomer in 52% yield. This chiral aziridine was further converted into the expected (+)-agelastatin A in four supplementary steps. This natural product is also known to inhibit glycogen synthase kinase-3 β , a behaviour that might provide an approach for the treatment of Alzheimer's disease.

In 2003, Dauban and Dodd applied the Ses iminoiodane (PhI=NSes) to the copper-catalyzed aziridination of 11-pregnane derivatives to prepare chiral 11,12-aziridino analogues of neuroactive steroids [12]. As shown in Scheme 2, the reaction of chiral 11-pregnone-3,20-dione **4a** or 3- α -acetoxy-11-pregnen-20-one **4b** with PhI=NSes in the presence of CuOTf led to the corresponding α,α -11,12-aziridino steroids **5a-b** in moderate yields (45–53%). The 3 α -acetoxy-11-pregnen-20-one derivative **5b** was further converted *via* TASF-mediated removal of the *N*-Ses blocking group into *N*-methyl-11,12-aziridino-3 α -hydroxy-5 β -pregnan-20-one, which is a conformationally constrained analogue of the endogenous neuros-



Scheme 3. Formal synthesis of (+)-kalinol A.



Scheme 4. Synthesis of (-)-oseltamivir.

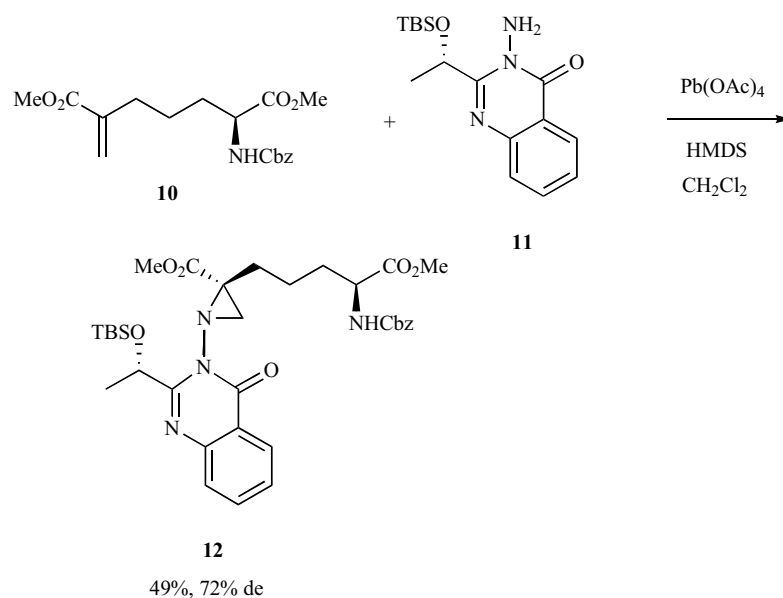
teroid, pregnanolone, and a structural analogue of the synthetic general anesthetic, minaxolone.

In 2005, Wood and Keaney explored the use of rhodium perfluorobutyramide ($\text{Rh}_2(\text{pfm})_4$) for the aziridination of olefins [13]. The authors found that the treatment of chiral olefin **6** by trichloroethylsulfamate ester in the presence of a combination of $\text{Rh}_2(\text{pfm})_4$ with $\text{PhI}(\text{OAc})_2$ provided the expected trichloroethoxy-sulfonylaziridine **7** in good yield and moderate diastereoselectivity (66% de), as shown in Scheme 3. Notably, this product constituted a potent intermediate for the formal synthesis of (+)-kalinol A.

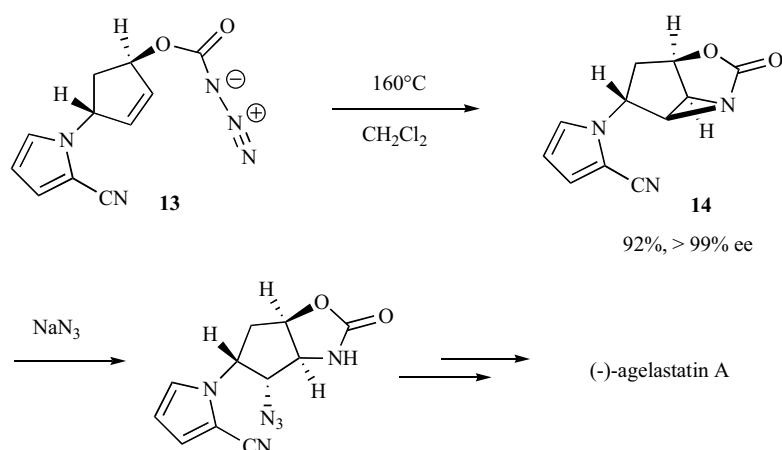
With the aim of developing a synthesis for the orally active neuraminidase inhibitor, (-)-oseltamivir, Trost and Zhang investigated the asymmetric aziridination of chiral diene **8** (Scheme 4)

[14]. In this case, the best result for the aziridination was obtained when the reaction was performed in the presence of SesNH_2 as the nitrene source, $\text{PhI}(\text{OPiv})_2$ as the oxidant, bis-[rhodium($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionate)] [$\text{Rh}_2(\text{esp})_2$] as the catalyst, and chlorobenzene as the solvent, as shown in Scheme 4. Under these reaction conditions, the corresponding γ,δ -aziridine **9** was obtained as the only detected stereoisomer in 86% yield. This chiral product was further converted into required (-)-oseltamivir through four supplementary steps with an overall yield of 30%.

Another methodology to generate nitrenes consists of the *in situ* oxidation of hydrazine derivatives in the presence of $\text{Pb}(\text{OAc})_4$. In 2005, Vederas *et al.* applied this methodology to the asymmetric aziridination of a camphor derivative in the presence of 3-amino-2-



Scheme 5. Synthesis of an analogue of diaminopimelic acid.



Scheme 6. Synthesis of (-)-agelastatin A.

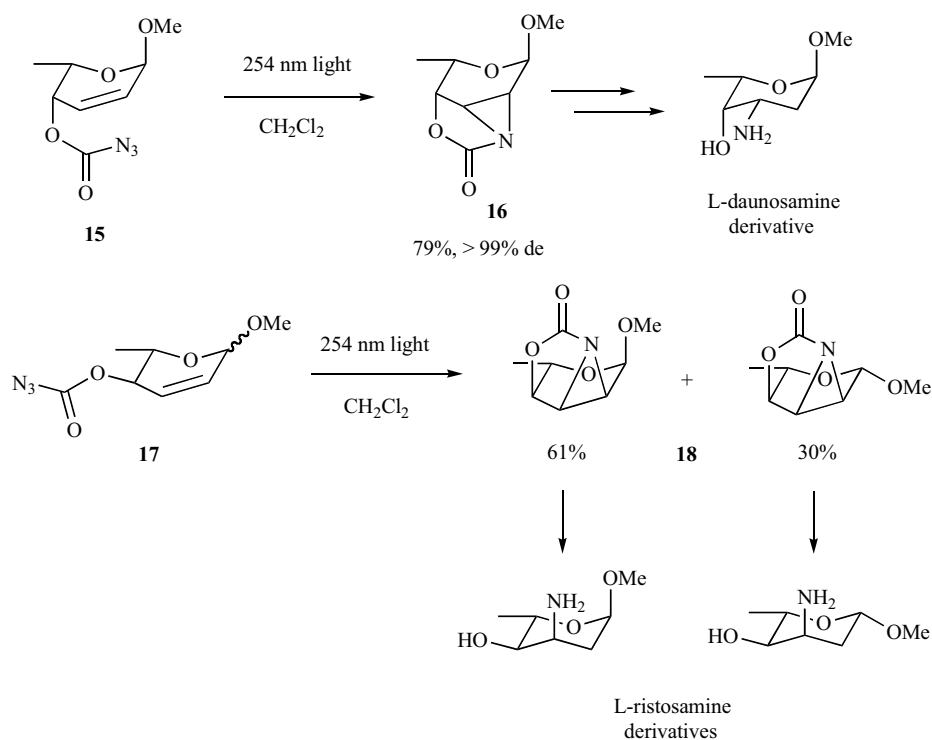
ethyl-3,4-dihydroquinazolin-4-one combined with Pb(OAc)_4 and hexamethyldisilazide (HMDS) [15]. An asymmetric version of this method was developed by these authors by using chiral 3-acetoxyaminoquinazolinones for the aziridination of unsaturated α -aminopimelic ester in order to prepare aziridine analogues of diaminopimelic acid which is an inhibitor of diaminopimelic acid epimerase [15]. As shown in Scheme 5, the reaction of chiral alkene **10**, performed in the presence of chiral aminoquinazolinone **11** and Pb(OAc)_4 , led to the expected corresponding aziridine **12** in 49% yield along with moderate diastereoselectivity of 72% de.

Another methodology to prepare aziridines is based on the thermolytic or photolytic decomposition of organic azides [16]. In 2008, Tanaka *et al.* employed this methodology as key step of a total synthesis of (-)-agelastatin A, a potent antineoplastic agent [17]. Indeed, the nitrogen functionality of the agelastatin core was installed through thermolytic intramolecular aziridination of chiral azidoformate **13**. The formed tricyclic aziridine **14** obtained as the only detected stereoisomer was further submitted to a regioselective azidation, leading to *trans*-diamination of the double bond. The obtained chiral azide was subsequently converted into the expected (-)-agelastatin A (structure in Scheme 1), as shown in Scheme 6.

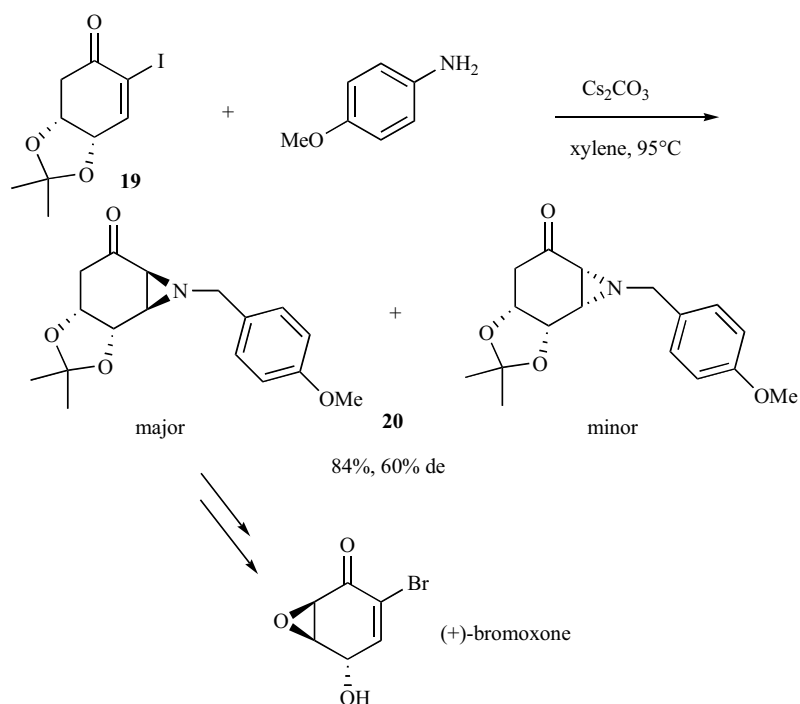
Earlier in 2006, Lowary *et al.* reported the synthesis of L-daunosamine and L-ristosamine glycosides based on photoinduced intramolecular aziridinations of acylnitrenes derived from L-rhamnose [18]. As shown in Scheme 7, upon exposure to UV light (254 nm), chiral acyl azide **15** was converted to the corresponding aziridine **16** in 79% yield and as the only detected stereoisomer through the generation of a presumed acylnitrene intermediate. This aziridine was further converted into expected glycoside L-daunosamine derivative. Similarly, the irradiation of a 2:1 α : β anomeric mixture of acyl azide **17** of an L-*erythro*-hex-2-enopyranoside derivative led to a mixture of the corresponding aziridines **18** in 91% yield (Scheme 7). These products were further separated by chromatography and then converted into important glycoside L-ristosamine derivatives.

Gabriel–Cromwell Reactions

The Gabriel–Cromwell aziridine synthesis involves a nucleophilic addition of a formal nitrene equivalent to a 2-haloacrylate or similar reagent. It involves an initial Michael addition, followed by protonation and 3-*exo-tet* ring closure. In 2003, Maycock *et al.* reported the Gabriel–Cromwell reaction of chiral α -iodocyclohex-



Scheme 7. Syntheses of L-daunosamine and L-ristosamine derivatives.



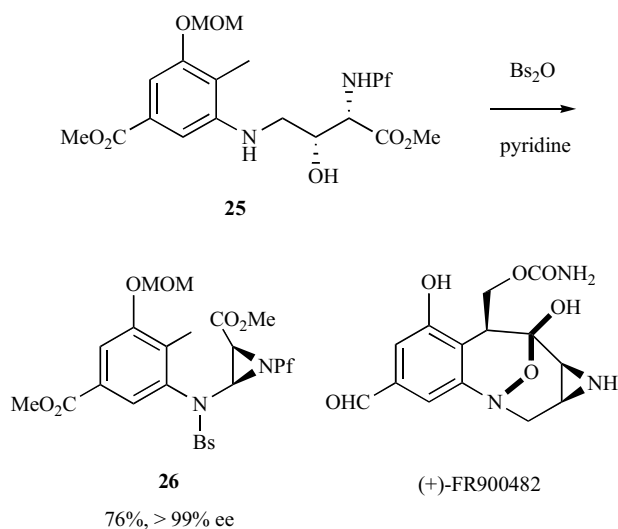
Scheme 8. Synthesis of (+)-bromoxone.

none **19** derived from (–)-quinic acid [19]. The aziridination, performed in the presence of 4-methoxybenzylamine and Cs_2CO_3 as a base, afforded the corresponding aziridine **20** in good yield (84%) as an 80:20 mixture of diastereomers, as shown in Scheme 8. This reaction constituted the key step of a short synthesis of (+)-bromoxone, the acetate of which showed potent antitumor activity.

In the same context, Dodd *et al.* have developed a total synthesis of the non-natural enantiomer of polyoxamic acid on the basis of the domino aza-Michael-type addition/elimination reaction of chiral

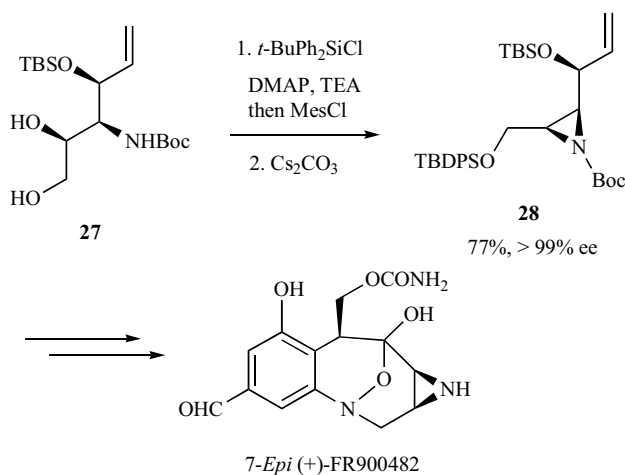
triflate **21** derived from D-ribonolactone [20]. This triflate reacted with 3,4-dimethoxybenzylamine to provide the corresponding aziridine **22** as the only detected stereoisomer in good yield (Scheme 9). The complete diastereoselectivity of the reaction was explained as a result of a aza-Michael-type addition of 3,4-dimethoxybenzylamine to the face opposite to that of the bulky silyl group at C-5. This aziridine was further converted through six supplementary steps into the expected (–)-polyoxamic acid with an overall yield of 10%.

key step of a formal synthesis of the antitumor antibiotic, (+)-FR900482, developed by Paleo *et al.*, was based on the aziridination of chiral 1,2-amino alcohol **25** derived from L-vinylglycine mediated by benzenesulfonic anhydride in pyridine (Scheme 11) [22]. The formed aziridine **26** was obtained as the only detected stereoisomer and further converted into a protected precursor of (+)-FR900482.



Scheme 11. Formal synthesis of (+)-FR900482.

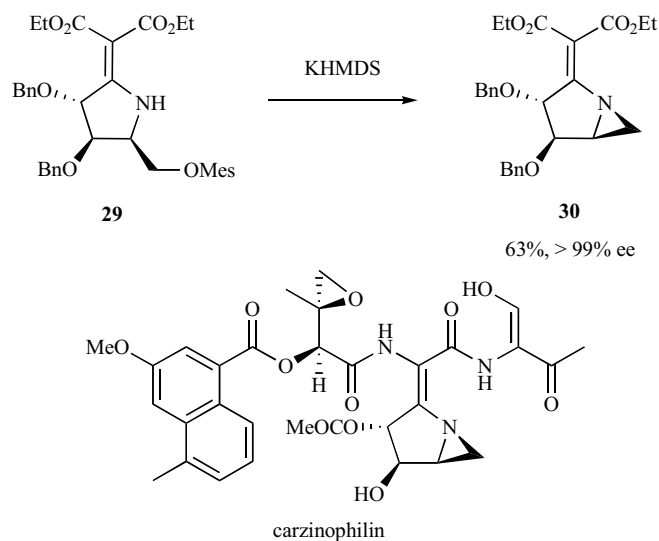
A total synthesis of 7-*Epi* (+)-FR900482, exhibiting equal potency as antitumor agent than natural product (+)-FR900482, was later reported by Trost and O'Boyle, involving the asymmetric aziridination of chiral amino diol **27** (Scheme 12), which was selectively silylated and mesylated [23]. The mesylate was then exposed to cesium carbonate, affording the expected aziridine **28** as the only detected stereoisomer in 77% yield, which was further transformed into expected 7-*Epi* (+)-FR900482.



Scheme 12. Synthesis of 7-*Epi* (+)-FR900482.

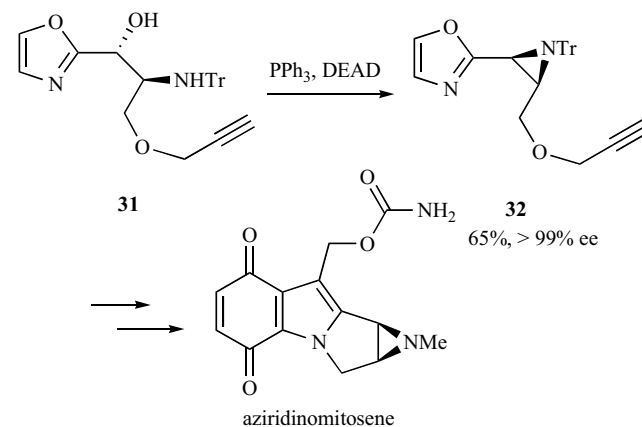
In 2003, Terashima *et al.* developed the synthesis of the C1-C17 fragment of the antitumor antibiotic, carzinophilin, that involved as a key step the asymmetric aziridination of chiral pyrrolidin-2-ylidenemalonate **29** derived from β -D-arabinofuranose [24]. As shown in Scheme 13, the treatment of this pyrrolidin-2-ylidenemalonate with KHMDS as base provided the corresponding aziridine **30** as the only detected stereoisomer in 63% yield. The

latter was further converted into the expected C1-C17 fragment of carzinophilin.



Scheme 13. Synthesis of the C1-C17 fragment of carzinophilin.

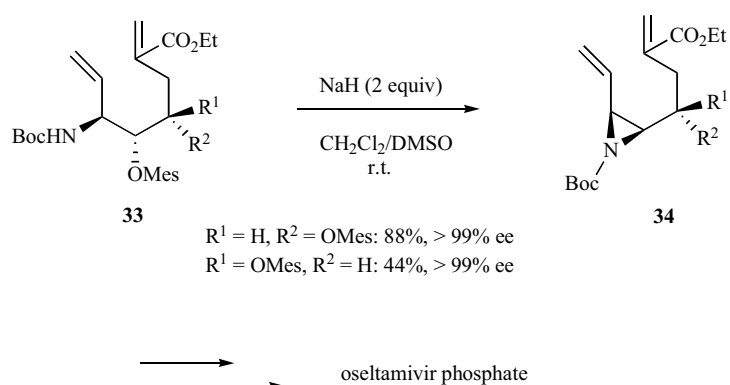
Later, Vedejs *et al.* reported the synthesis of enantiopure aziridinomitosenes, the key step of which was the asymmetric aziridination of chiral oxazole 1,2-amino alcohol **31** derived from L-serine (Scheme 14) [25]. The reaction yielded the corresponding aziridine **32** as the only detected stereoisomer in 65% yield which was further converted into aziridinomitosenes among which the first C6,C7-unsubstituted one, a DNA alkylating agent depicted in Scheme 14.



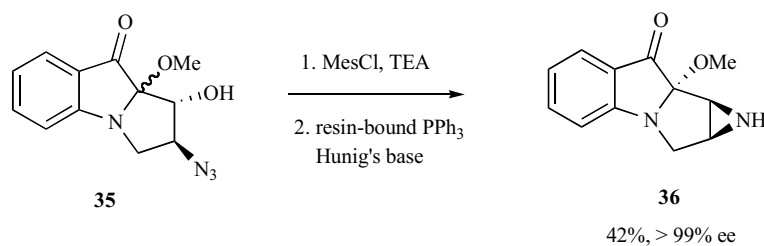
Scheme 14. Synthesis of an aziridinomitosenes.

In 2015, Kongkathip *et al.* reported a novel total synthesis of oseltamivir phosphate (structure of oseltamivir in Scheme 4) which was based on the asymmetric aziridination of chiral 1,2-amino mesylate **33** derived from D-glucose into aziridine **34** as the only detected stereoisomer, as shown in Scheme 15 [26]. The complete strategy gave rise to oseltamivir phosphate in 7.2% overall yield.

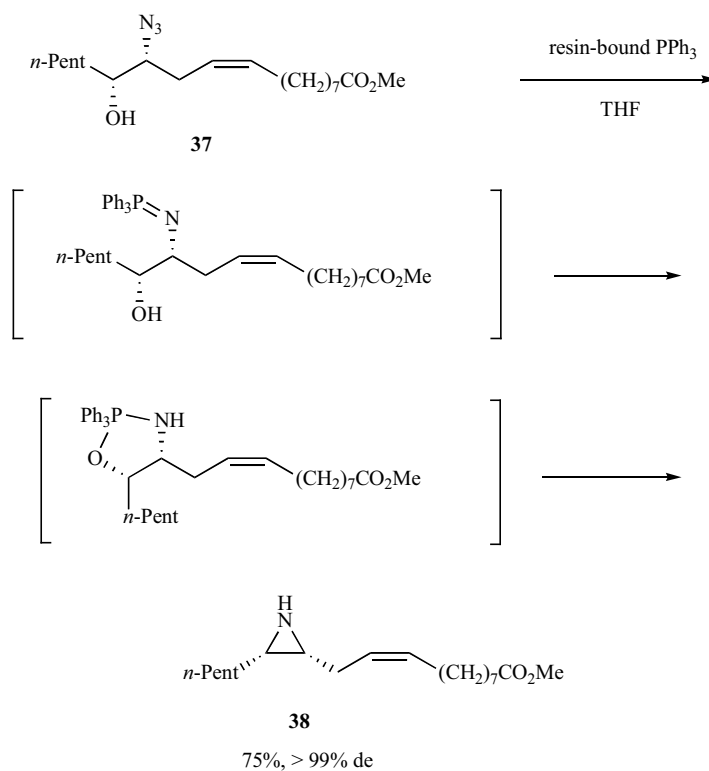
The last step of an enantioselective synthesis of an aziridinomitosenes, reported by Miller *et al.*, was based on the cyclization of chiral tricyclic 1,2-azido alcohol **35** into aziridine **36** as the only detected stereoisomer (Scheme 16) [27]. This process was achieved in two steps with resin-bound PPh₃, affording the expected enantiopure aziridinomitosenes with the *trans* configuration in moderate yield (Scheme 16).



Scheme 15. Synthesis of oseltamivir phosphate.



Scheme 16. Synthesis of an aziridinomitosane.

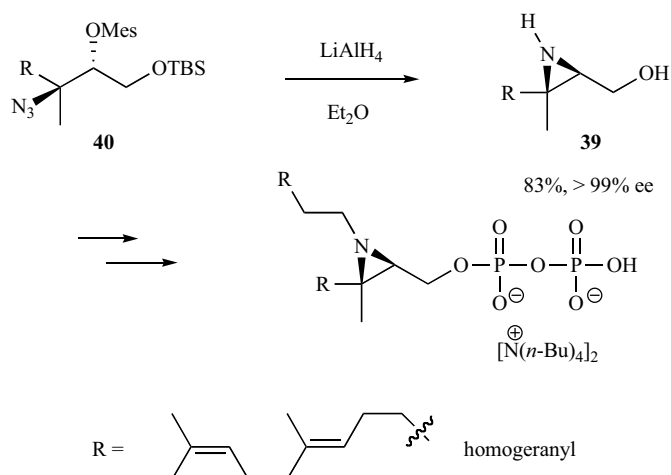


Scheme 17. Synthesis of a fat-derived chiral aziridine.

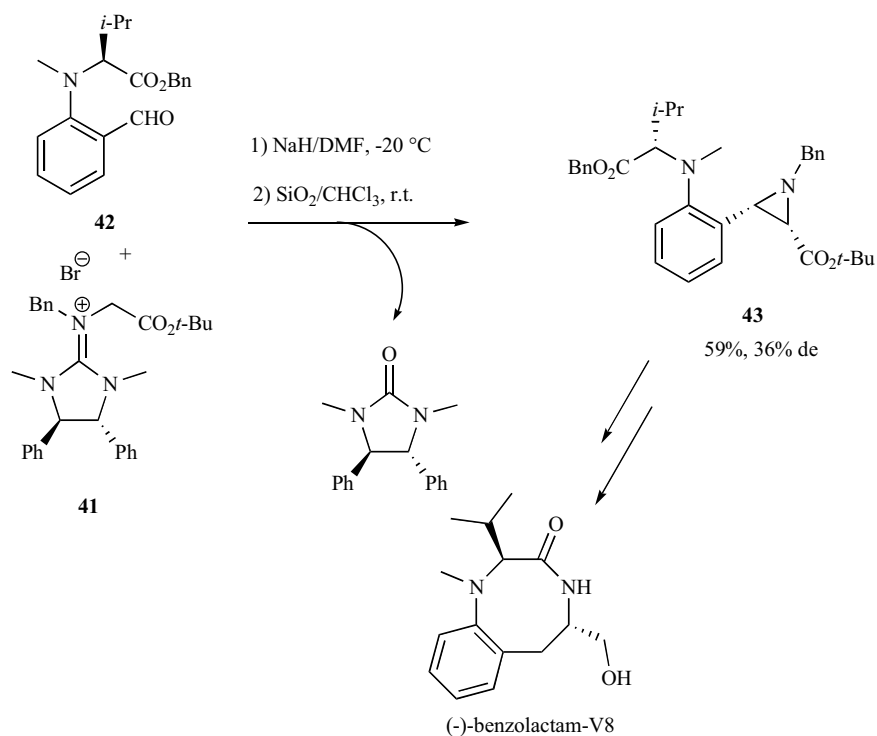
In the same area, Metzger and Fürmeier reported the first preparation of chiral fat-derived aziridines, with the aim of gaining insight into their biological properties [28]. The same methodology as described in Scheme 16, based on the use of resin-bound PPh₃, was applied to the enantiopure azido alcohol **37** derived from chiral methyl vernolate (Scheme 17). Under these reaction conditions, the corresponding unsaturated *cis*-aziridine **38** was isolated in 75% yield as the only detected stereoisomer, according to the mechanism

summarized in Scheme 17. This represented the first enantiomerically pure aziridine based on fats and oils.

In 2010, the cyclization of other chiral 2-azido alcohols was investigated by Coates *et al.* in the course of synthesizing aziridine analogues of presqualene diphosphates as inhibitors of squalene synthase [29]. As shown in Scheme 18, 2,3-aziridinofarnesol **39** was prepared as the only detected stereoisomer in 83% yield from the corresponding azido mesylate **40** by treatment with LiAlH₄. The



Scheme 18. Synthesis of a squalene synthase inhibitor.



Scheme 19. Synthesis of (-)-benzolactam-V8.

latter was subsequently converted into a diphosphate exhibiting squalene synthase inhibitory activity.

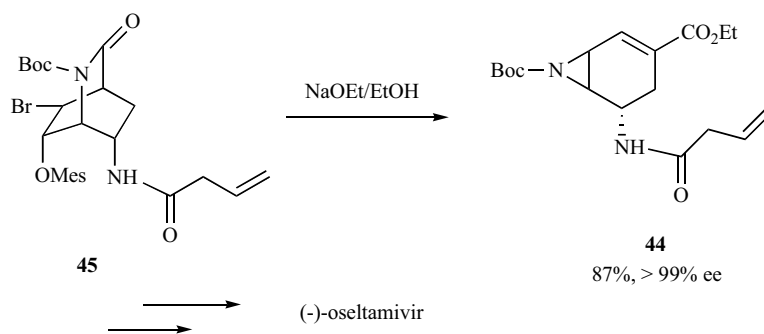
Miscellaneous Aziridinations

In 2012, Ishikawa *et al.* reported the synthesis of (-)-benzolactam-V8, an artificially-designed cyclic dipeptide exhibiting strong tumor-promoter activity [30]. The key step of the synthesis consisted in the reaction of chiral guanidinium bromide **41** with benzyl (*S*)-*N*-(2-formylphenyl)-*N*-methylvalinate **42** to give the corresponding *syn*-aziridine **43** in 59% yield and a moderate diastereoselectivity of 36% de (Scheme 19). The latter was further converted into the expected (-)-benzolactam-V8 in five supplementary steps.

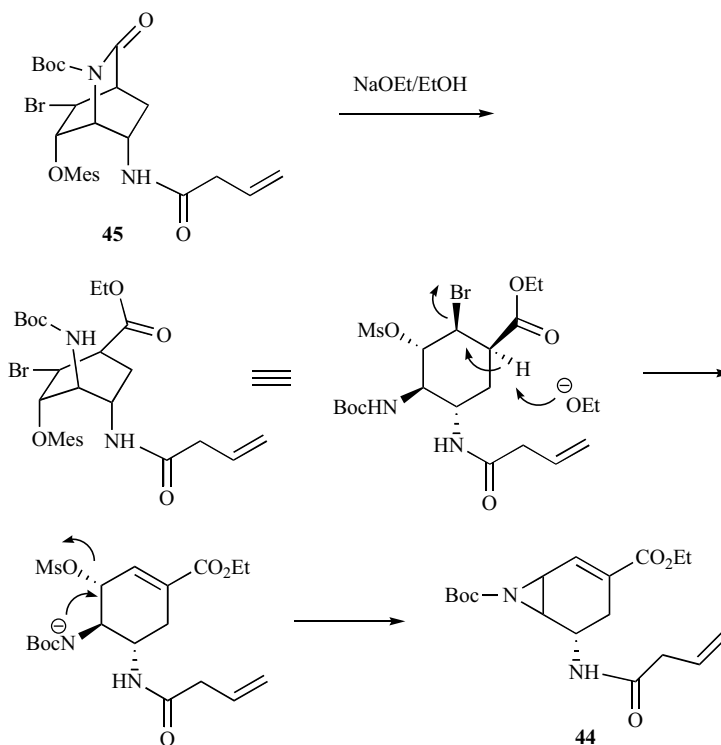
The total synthesis of (-)-oseltamivir, elaborated by Fukuyama *et al.* in 2007, included the formation of a bicyclic aziridine **44** by rearrangement of chiral allyl carbamate **45** [31]. Therefore, treat-

ment of this carbamate with NaOEt resulted in ethanolysis of *N*-Boc lactam, dehydrobromination, and aziridine formation, which provided the desired aziridine **44** as the only detected stereoisomer in high yield (87%), as shown in Scheme 20. This aziridine was further converted into the final (-)-oseltamivir (structure in Scheme 4) in four steps.

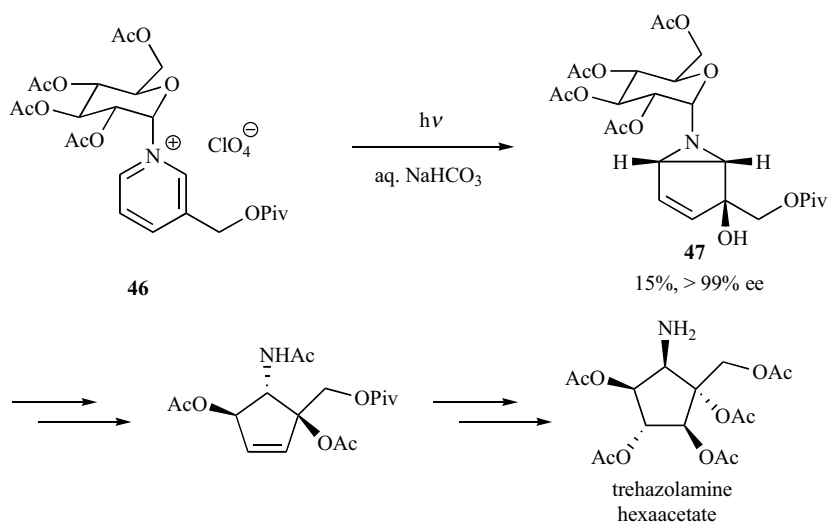
In 2005, a photocyclization reaction providing chiral aziridines was developed by Mariano *et al.*, starting from chiral pyridinium perchlorate **46** derived from D-glucose [32]. Irradiation of this substrate in aqueous NaHCO₃ produced a mixture of isomeric *N*-glycosyl-bicyclic-aziridines, which could be partially separated by chromatography to yield the major aziridine **47** (Scheme 21) as the only detected stereoisomer in 15% yield. This aziridine was subsequently converted into trehalosamine which is the aminocyclitol core of the potent trehalase inhibitor, trehalosin.



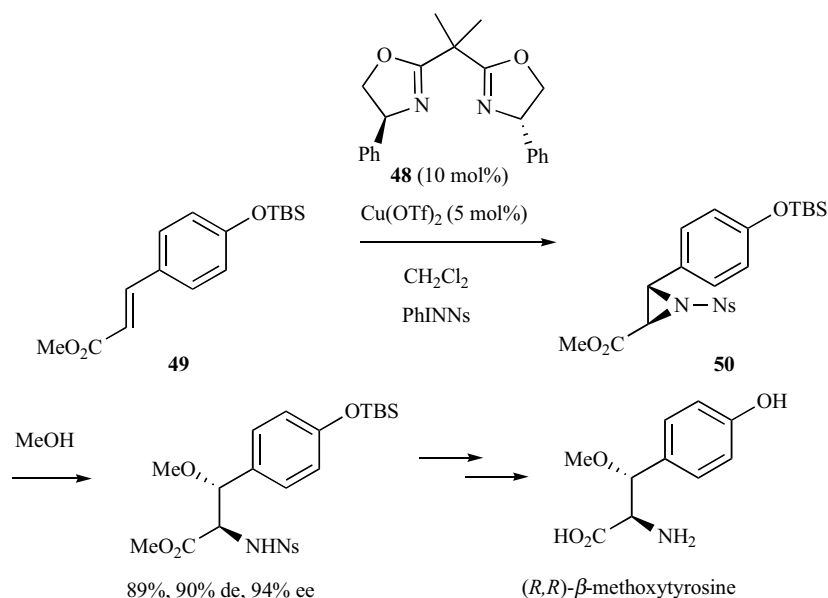
proposed mechanism for the formation of the aziridine intermediate:



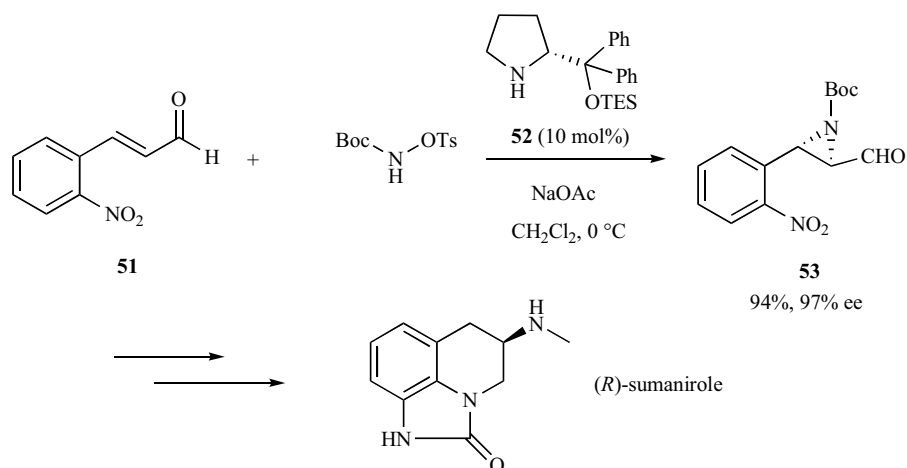
Scheme 20. Synthesis of (-)-oseltamivir.



Scheme 21. Synthesis of hexaacetylated trehalamine.



Scheme 22. Synthesis of (*R,R*)- β -methoxytyrosine.



Scheme 23. Synthesis of (*R*)-sumanirole.

2.1.2. Enantioselective Aziridinations as Key Steps

Copper-Catalyzed Nitrene Transfer to Alkenes

In addition to chiral dirhodium catalysts [33], the most commonly employed chiral catalyst systems in enantioselective aziridination *via* nitrene transfer to alkenes are based on copper complexes of chiral bisoxazolines early reported by Evans *et al.*, in 1991 [34]. In 2007, Cranfill and Lipton reported the use of Evans' bisoxazoline ligand **48** for the asymmetric aziridination of α,β -unsaturated ester **49** in the presence of $\text{Cu}(\text{OTf})_2$ and PhINNs (*N*-(*p*-nitrophenylsulfonyl)iminophenylidodane) as the nitrene source [35]. This process allowed the corresponding chiral *trans*-aziridine **50** to be obtained in 89% yield, and with 90% de and 94% ee, (Scheme 22). This nice reaction constituted the key step of a total synthesis of (*R,R*)- β -methoxytyrosine, which is a constituent of several cyclic depsipeptide natural products.

Organocatalyzed Nitrene Transfer to Alkenes

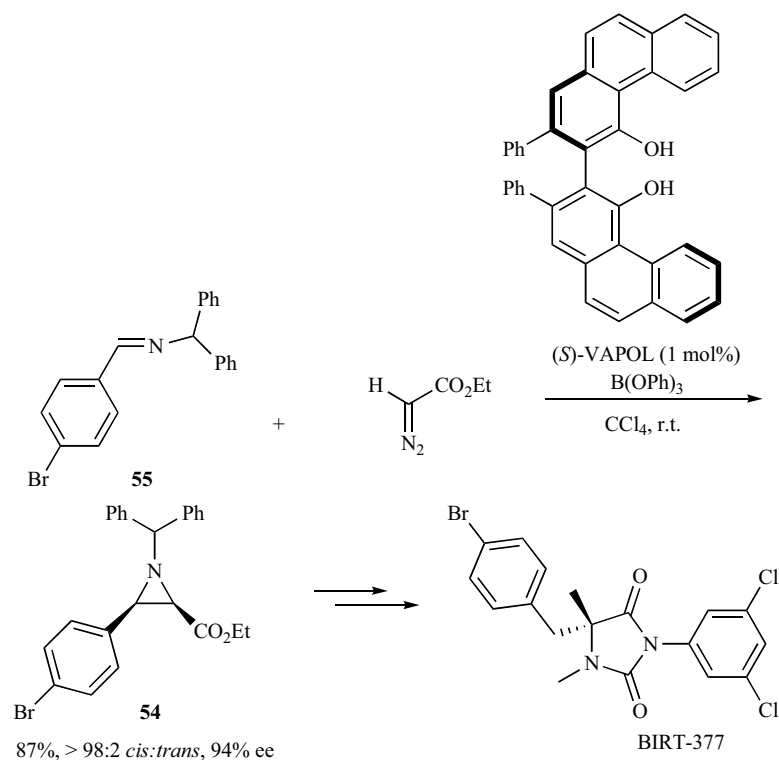
In 2014, Hamada *et al.* developed a total synthesis of (*R*)-sumanirole that exhibits selective dopamine D2 receptor agonist activity [36]. The key step of the synthesis was the aziridination of α,β -unsaturated aldehyde **51** organocatalyzed by chiral diphenyl-

prolinol triethylsilyl ether **52** in the presence of three equivalents of a base, such as NaOAc, allowing the key intermediate aziridine **53** to be obtained in 94% yield and 97% ee (Scheme 23) [37]. The latter was subsequently converted into the desired (*R*)-sumanirole.

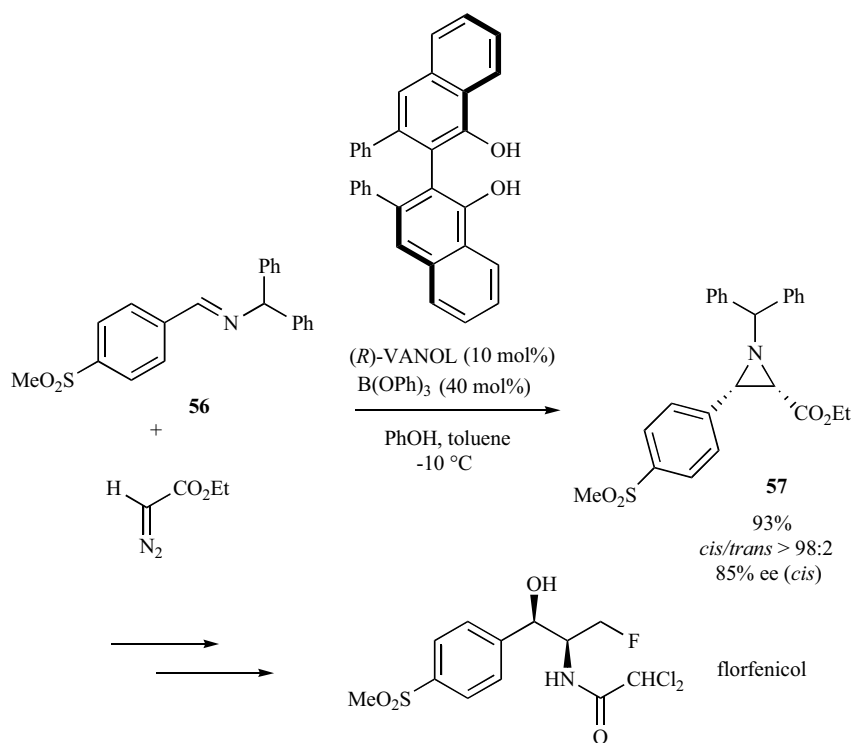
Carbene Transfer to Imines Through Carbene Methodology

Although most of the catalytic methods for synthesizing chiral aziridines proceeded through the transfer of a nitrogen group to an alkene, methods based on the less-studied enantioselective transfer of a carbenoid to an imine have been successfully developed in recent years [38]. For example, the formation of aziridines based on transition metal- or Lewis acid-catalyzed decomposition of diazo compounds in the presence of imines is well established. The synthetic utility of this approach was illustrated by Wulff *et al.* in the total synthesis of a leukointegrin LFA-1 antagonist, BIRT-377, an agent for the treatment of inflammatory and immune disorders [39]. As shown in Scheme 24, the key step of this synthesis provided chiral *cis*-aziridine **54**, arisen from the reaction of ethyl diazoacetate with *N*-benzhydryl imine **55** in the presence of a combination of $\text{B}(\text{OPh})_3$ as Lewis acid and (*S*)-VAPOL as chiral ligand.

In 2011, the highly efficient asymmetric Wulff's aziridination methodology was applied by Chen *et al.* to develop a total synthesis



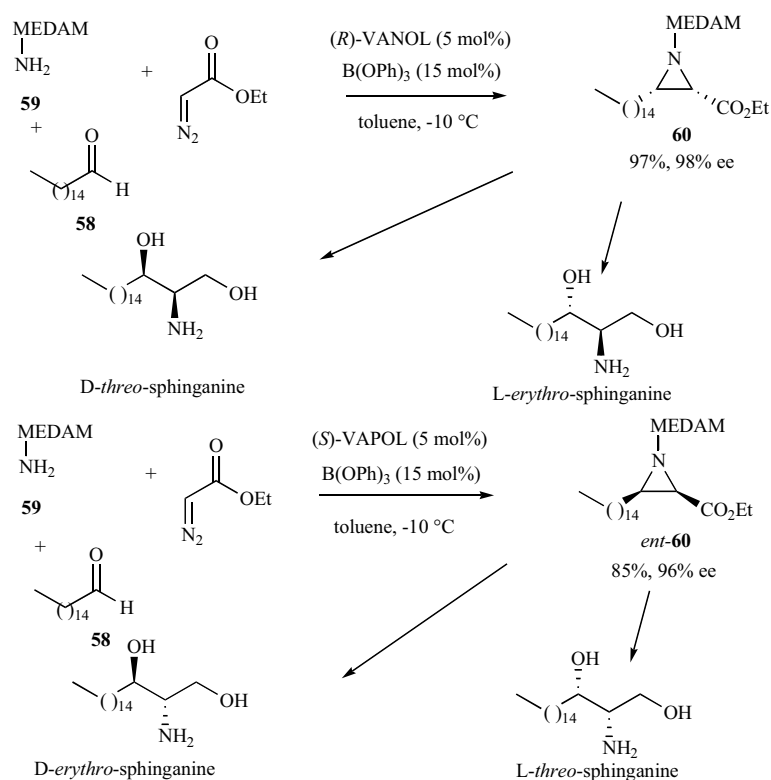
Scheme 24. Synthesis of BIRT-377.



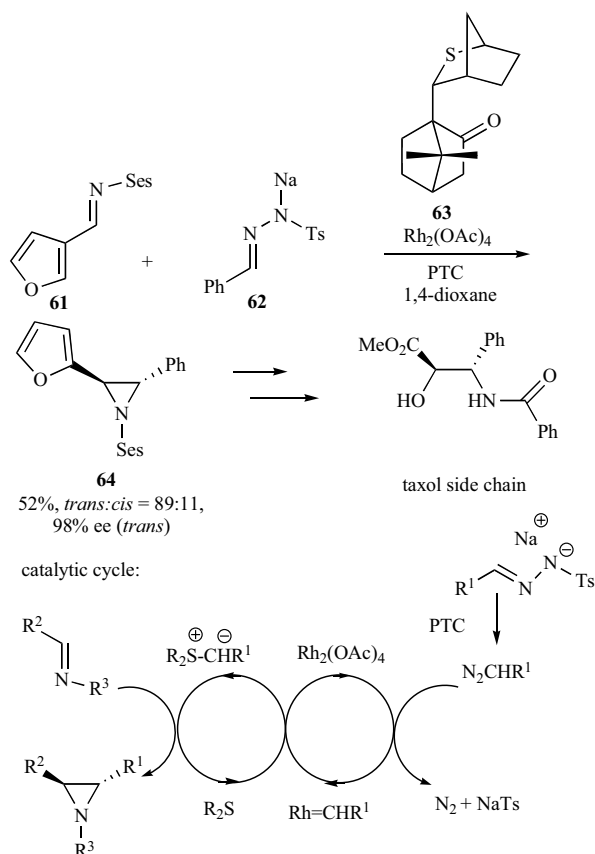
Scheme 25. Synthesis of florfenicol.

of antibacterial florfenicol shown in Scheme 25 [40]. In this case, the authors employed (*R*)-VANOL-boroxinate to aziridinate benzhydryl aldimine **56** with ethyl diazoacetate, providing the key chiral aziridine intermediate **57** in 93% yield as a single *cis*-diastereomer in 85% ee. The latter was further converted into expected florfenicol in 45% overall yield from commercially available *p*-(methylsulfonyl)benzaldehyde.

In 2014, Wulff *et al.* reported a three-component version of their methodology to the synthesis of all four stereoisomers of sphinganine, an important biologically active sphingolipid involved in cell structure and regulation [41]. As shown in Scheme 26, the syntheses all started from hexadecanal **58**, MEDAM amine **59**, and ethyl diazoacetate as starting materials. Using either (*R*)-VANOL- or (*S*)-VAPOL-boroxinate catalysts, the multicomponent reaction of



Scheme 26. Synthesis of four stereoisomers of sphinganine.



Scheme 27. Synthesis of taxol side chain.

hexadecanal with MEDAM amine and ethyl diazoacetate led to almost enantiopure aziridine-2-carboxylates **60** or *ent*-**60**, respecti-

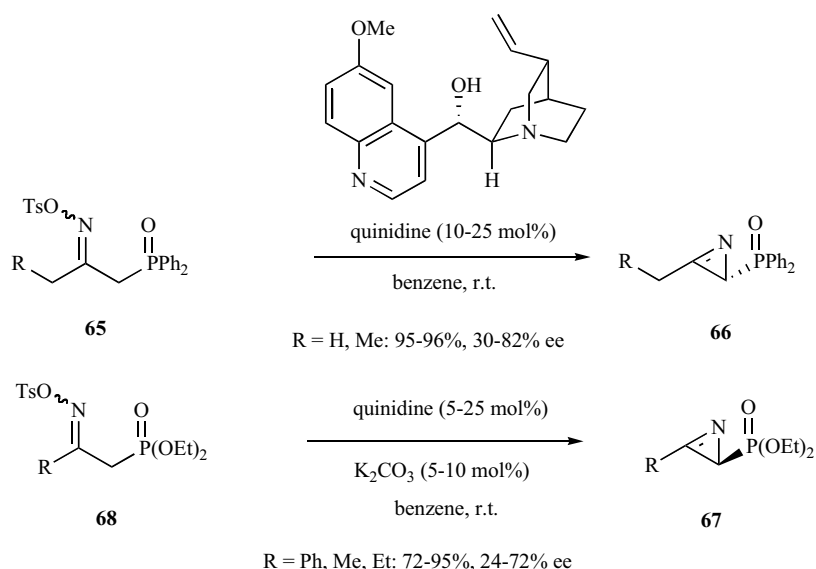
vely. Access to all four stereoisomers of sphinganine was achieved upon ring-opening of the enantiopure aziridine-2-carboxylate at the C-3 position through a direct S_N2 attack of an oxygen nucleophile, which occurred with inversion of configuration and by ring expansion of an *N*-acyl aziridine to an oxazolidinone followed by hydrolysis.

Carbene Transfer to Imines Through Sulfur Ylide-Mediated Aziridinations

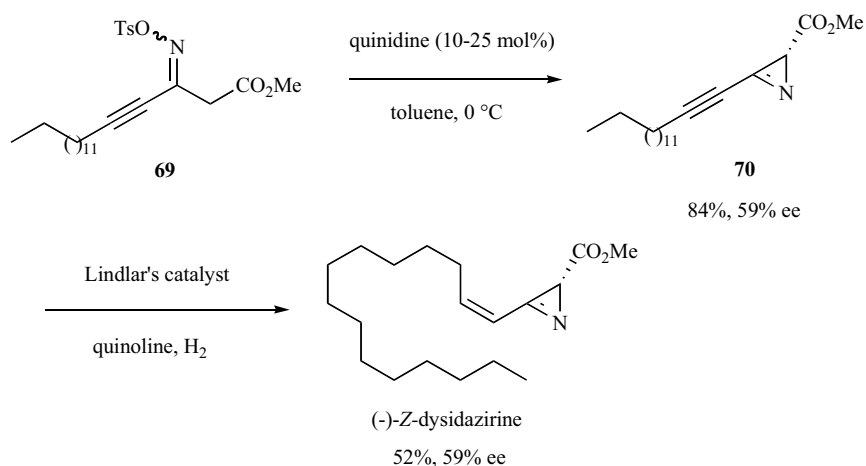
Aggarwal has developed an asymmetric aziridination methodology based on the generation of a carbene from diazo decomposition with $[Rh_2(OAc)_4]$, its association to a chiral sulfide, and subsequent transfer to an imine [42]. This approach was applied in 2003 to build the taxol side chain with a high degree of enantioselectivity via a *trans*-aziridine [43]. As shown in Scheme 27, the reaction of *N*-Ses imine **61** with tosylhydrazone salt **62** derived from benzaldehyde in the presence of a phase-transfer catalyst (PTC), $Rh_2(OAc)_4$, and 20 mol% of chiral sulfide **63** provided the corresponding aziridine **64** in 52% yield as a 89:11 *trans/cis* diastereoisomeric ratio. The expected *trans*-aziridine was obtained with an enantiomeric excess of 98% ee and was further converted into the desired final taxol side chain. A catalytic cycle was proposed, involving the decomposition of the diazo compound in the presence of the rhodium complex, to yield the metalcarbene. The latter was then transferred to the chiral sulfide, forming a sulfur ylide, which underwent a reaction with the imine to give the expected aziridine, returning the sulfide to the cycle to make it available for further catalysis (Scheme 27).

2.2. Chiral Azirines

2*H*-Azirines constitute the smallest nitrogen unsaturated heterocyclic system, bearing two carbon atoms and one double bond in a three-membered ring. Their stability can be attributed not only to



Scheme 28. Synthesis of constituents of naturally occurring antibiotics.



Scheme 29. Synthesis of (-)-Z-dysidazirine.

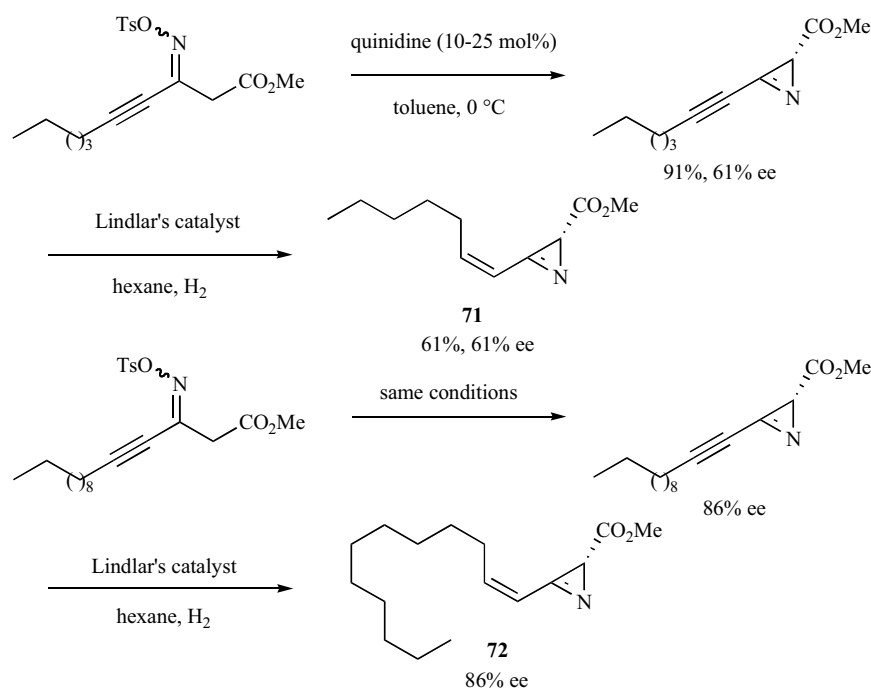
the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom [44]. The biological applications and the chemistry of these molecules have been widely investigated [8h, 45]. The chemistry of 2H-azirines is related to their ring strain, reactive π -bond, and ability to undergo regioselective ring cleavage. For example, they can act as nucleophiles as well as electrophiles in organic reactions, but they can also interact as dienophiles and dipolarophiles in cycloaddition reactions. Therefore, they constitute useful precursors for the synthesis of a variety of nitrogen-containing heterocyclic systems. In particular, 2H-azirines containing a carboxylic ester group are constituents of naturally occurring antibiotics. Several synthetic approaches are available to reach 2H-azirines, such as Neber rearrangement of oxime sulfonates, and elimination reaction of *N*-substituted aziridines, such as *N*-sulfinylaziridines or *N*-chloroaziridines. Several asymmetric versions of these methodologies have been recently applied in total synthesis.

2.2.1. Asymmetric Azirination Through Neber Approaches

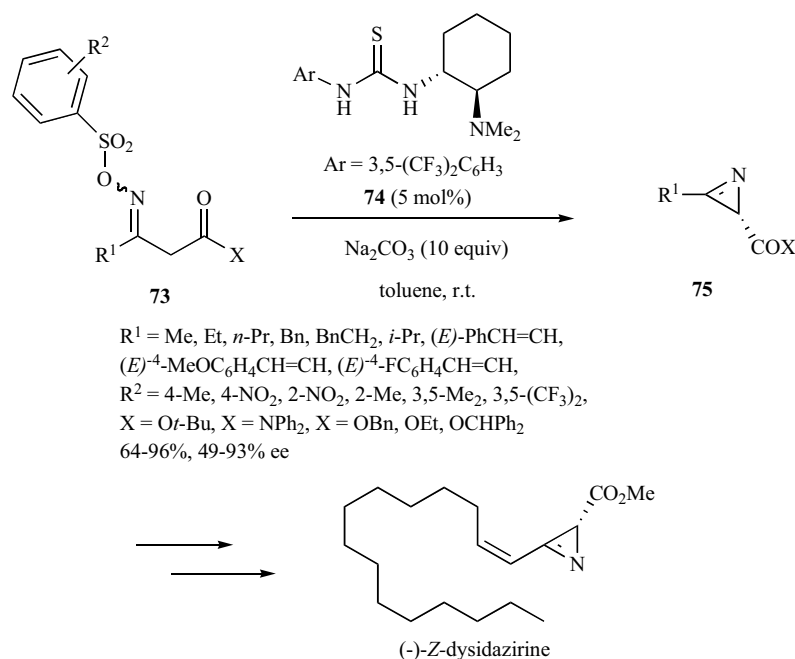
In 2000, an asymmetric Neber reaction was developed by Palacios *et al.* for the preparation of constituents of naturally occurring antibiotics, such as alkyl- and aryl-substituted 2H-azirines bearing a phosphonate group in the 2-position of the ring [46]. As shown in

Scheme 28, the Neber reaction of β -phosphorylated tosyloximes **65** provided the corresponding 2H-azirines **66** in excellent yields along with low to good enantioselectivities of up to 82% ee when employing quinidine as organocatalyst. The scope of this methodology was extended to the synthesis of enantioenriched 2H-azirines derived from phosphonates albeit with lower enantioselectivities ranging from 20 to 52% ee along with high yields (85-95%) [47]. Later, better enantioselectivities of up to 72% ee were reported by the same authors in the synthesis of chiral 2H-azirine phosphonates **67** performed with the same catalyst in the presence of K_2CO_3 (Scheme 28) [48]. These three-membered heterocycles constitute important building blocks in the preparation of biologically active compounds of interest in medicinal chemistry including naturally occurring antibiotics.

Later, Molinski *et al.* reported a total synthesis of marine natural and antifungal product (-)-Z-dysidazirine the key step of which was an enantioselective Neber reaction catalyzed by the same organocatalyst quinidine (Scheme 29) [49]. The Neber reaction of tosyloxime **69** derived from pentadecyne led to the corresponding key chiral azirine **70** in good yield and moderate enantioselectivity (59% ee). This product was further converted into expected (-)-Z-dysidazirine through partial hydrogenation using Lindlar's catalyst.



Scheme 30. Synthesis of shorter chain analogues of (-)-Z-dysidazirine.



Scheme 31. Synthesis of (-)-Z-dysidazirine.

In 2010, the same conditions were applied by these authors to the synthesis of shorter chain analogues **71** and **72** of (-)-Z-dysidazirine to be evaluated as antifungal agents [50]. As depicted in Scheme 30, these products were obtained in 61 and 86% ee, respectively. Their antifungal activity was found comparable to that of (-)-Z-dysidazirine.

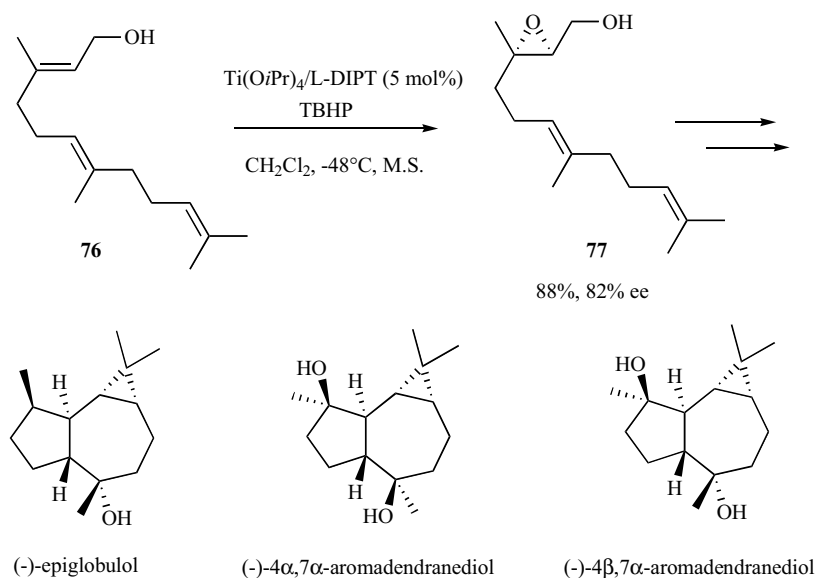
The first enantioselective Neber reaction of β -ketoxime sulfonates **73** catalyzed by bifunctional thiourea **74** was reported by Takemoto *et al.*, in 2011 [51]. The reaction was performed in the presence of only 5 mol% of catalyst loading and 10 equivalents of Na_2CO_3 to provide the corresponding 2*H*-azirine carboxylic esters **75** in good yields and moderate to high enantioselectivities of up to

93% ee (Scheme 31). The utility of this novel methodology was demonstrated by an asymmetric synthesis of (-)-Z-dysidazirine.

3. CHIRAL EPOXIDES AND THIIRANES IN TOTAL SYNTHESIS

3.1. Chiral Epoxides

Epoxides are strained three-membered rings of wide importance as versatile synthetic intermediates in total synthesis of a number of important products. Their strain energy allows an easy ring-opening by reacting with nucleophiles to provide a range of 1,2-functionalized products, such as amino alcohols, diols, hydroxy



Scheme 32. Synthesis of natural aromadendrane sesquiterpenes based on Katsuki-Sharpless asymmetric epoxidation.

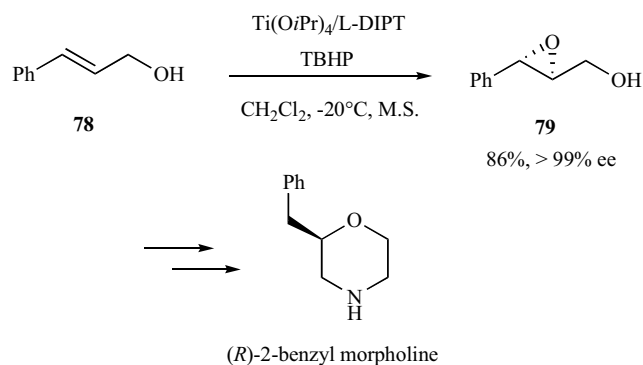
sulfides, hydrazino alcohols, 1,2-halohydrins, 1,2-cyanohydrins, alcohols and pharmaceuticals [81, 52]. Given the considerable number of asymmetric methodologies accessible to synthesize chiral epoxides, chemists have judiciously applied the combination of asymmetric epoxidation/ring-opening reactions to achieve various total syntheses of natural and biologically active compounds [53]. For example, β -adrenergic blocking agents used for the treatment of hypertension and angina pectoris, can be easily obtained from ring-opening of chiral terminal epoxides including (*S*)-propranolol [54], and (*R*)-dichloroisoproterenol [55]. Carboxypeptidase A, a zinc-containing proteolytic enzyme of physiological importance, has been found to be irreversibly inactivated, with the highest activity among all the possible stereoisomers, by terminal epoxide (2*R*,3*S*)-2-benzyl-3,4-epoxybutanoic acid via S_N2 type ring-cleavage [56]. Moreover, [3+2] asymmetric cycloaddition reactions of epoxides have also recently emerged as valuable tools to obtain chiral dihydro- or tetrahydrofuran derivatives, important core structures present in natural products [57]. Besides the relevance of chiral epoxides in synthesis, a great number of natural products and bioactive compounds exhibit the epoxide subunit in their structure as exemplified by sex pheromone for gypsy moth (+)-disparlure [58], antibiotic agent monocillin I [59], potent oral hypoglycemic and antiketogenic agent in mammals (*R*)-methyl palmoxirate [60], and anticancer agents ovalicin, fumagillin and ephothilones A and B [61]. The epoxidation of alkenes is undoubtedly the most investigated and convenient approach to obtain epoxides [62]. In the last decade, total syntheses of many important natural and biologically relevant products have been based on asymmetric metal- or organo-catalyzed epoxidations of alkenes, kinetic resolution of racemic epoxides, asymmetric sulfur ylide-mediated epoxidations of carbonyl compounds, and asymmetric Darzens reactions as key steps.

3.1.1. Asymmetric Metal-Catalyzed Epoxidations as Key Steps

In the last decade, many studies have focused on the development of asymmetric metal-catalyzed procedures for the epoxidation of alkenes [63]. As a recent example, Echavarren *et al.* have developed a short total synthesis of three natural aromadendrane sesquiterpenes, such as (-)-epiglobulol, (-)-4 α ,7 α -aromadendranediol, and (-)-4 β ,7 α -aromadendranediol, the first step of which was the Katsuki-Sharpless asymmetric epoxidation of (*E,E*)-farnesol **76**

(Scheme 32) [64]. These products, widespread in plant species, are endowed with a variety of antiviral, antibacterial, antifungal activities [65]. The epoxidation of **76** was performed in the presence of 5 mol% of $Ti(OiPr)_4/L-DIPT$ as catalyst system, leading to the corresponding chiral epoxy alcohol **77** in 88% yield and 82% ee. The latter was further converted into expected (-)-epiglobulol, (-)-4 α ,7 α -aromadendranediol, and (-)-4 β ,7 α -aromadendranediol.

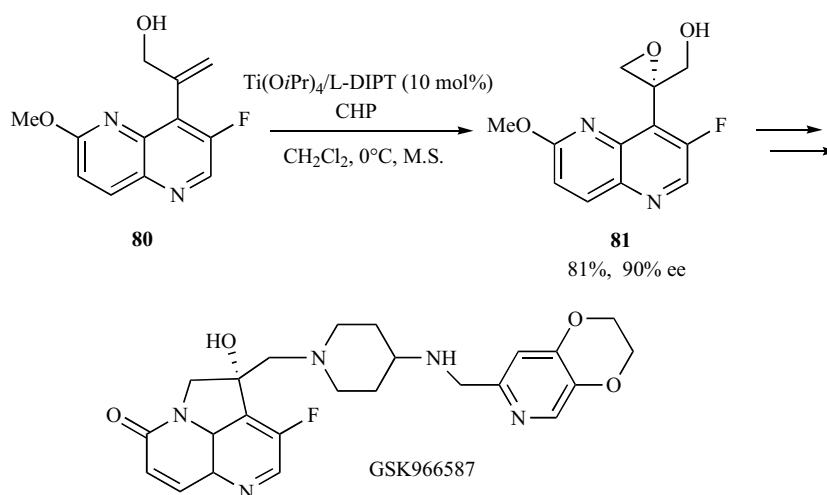
Very recently, this methodology was also employed by Muthukrishnan *et al.* as key step in a simple synthesis of (*R*)-2-benzylmorpholine, an appetite suppressant agent [66]. As shown in Scheme 33, the Katsuki-Sharpless asymmetric epoxidation of (*E*)-cinnamyl alcohol **78** led to the corresponding chiral epoxy alcohol **79** in high yield (86%) and excellent enantioselectivity under standard conditions. The latter was further converted into expected (*R*)-2-benzylmorpholine in 24% overall yield (Scheme 33).



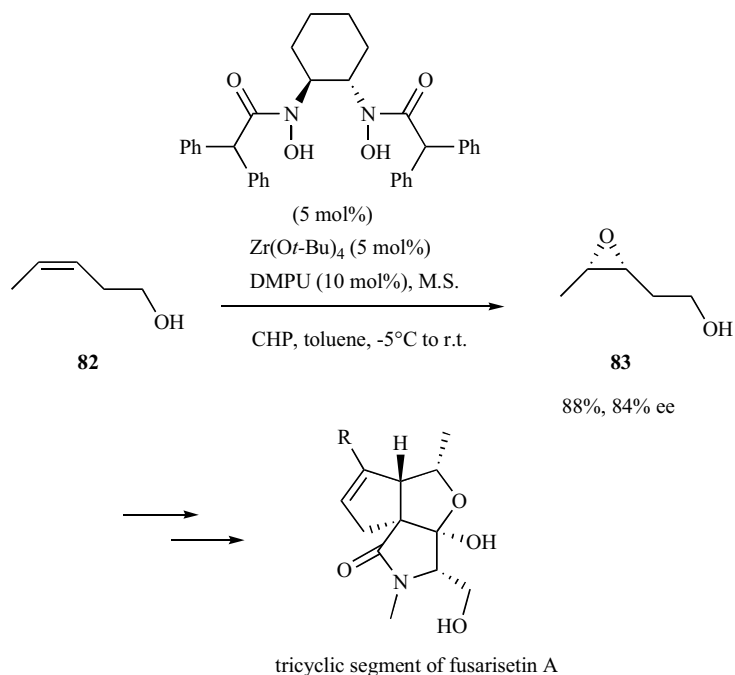
Scheme 33. Synthesis of (*R*)-2-benzylmorpholine based on Katsuki-Sharpless asymmetric epoxidation.

The Katsuki-Sharpless asymmetric epoxidation was also applied by Voight *et al.* to the total synthesis of potent antibiotic GSK966587 (Scheme 34) [67]. The epoxidation of allylic alcohol **80** smoothly proceeded with 10 mol% of the same metal complex, in the presence of cumyl hydroperoxide (CHP) to give the key chiral epoxy alcohol **81** in 81% yield and 90% ee. The synthesis afforded the target compound in eight steps and 25% overall yield.

Zirconium catalysts have been of limited use in the area of asymmetric epoxidation, with a particular focus on homoallylic



Scheme 34. Synthesis of GSK966587 based on Katsuki-Sharpless asymmetric epoxidation.



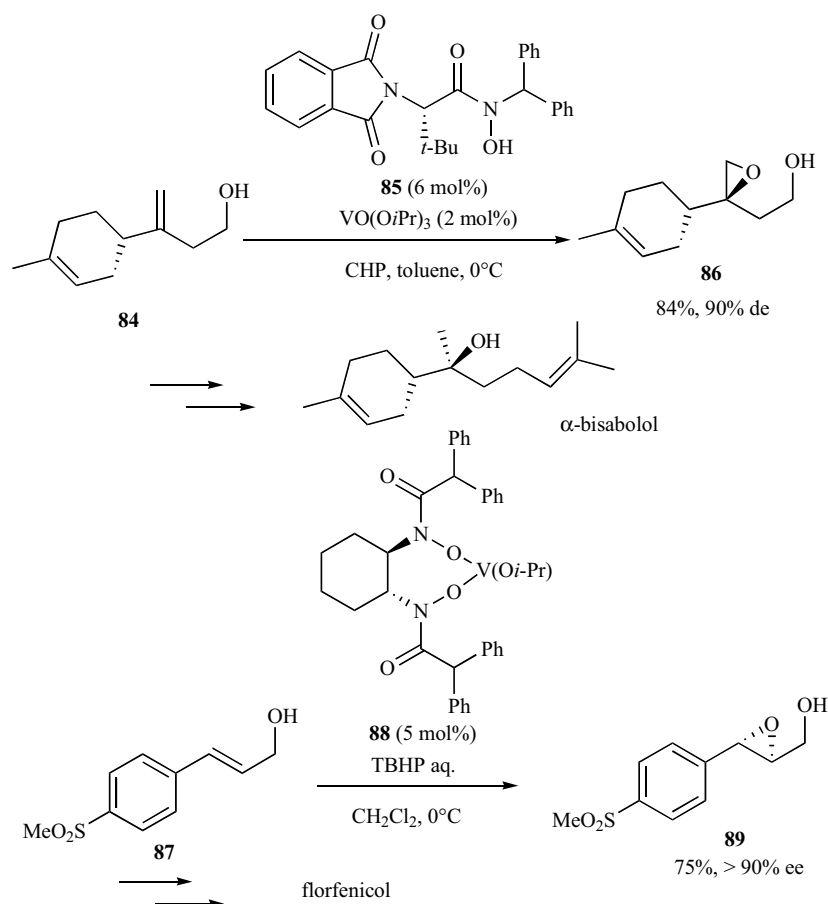
Scheme 35. Synthesis of the tricyclic polar segment of fusarisetin A through Zr-catalyzed epoxidation of an homoallylic alcohol.

alcohols. As a rare example, an asymmetric Zr(*Ot*-Bu)₄/bishydroxamic acid-catalyzed asymmetric epoxidation of an homoallylic alcohol was very recently applied as key step in the synthesis of the tricyclic polar segment of fusarisetin A [68], which is a fungal metabolite with anticancer activity, due to potent inhibition against acinar morphogenesis, cell migration, and cell invasion in MDAMB-231 cells [69]. The synthesis began with the epoxidation of (*Z*)-pent-3-en-1-ol **82**, which yielded the corresponding key chiral epoxyalcohol **83** in 88% yield with 84% ee (Scheme 35).

Chiral vanadium complexes have also been applied to catalyze asymmetric epoxidation. An example of the synthetic utility of this methodology was demonstrated in the synthesis of the fragrance abisabolol reported by Yamamoto *et al.*, in 2003 [70]. The key step to install the second stereocenter of the molecule was based on asymmetric epoxidation of the (*S*)-limonene-derived homoallylic alcohol **84** using the vanadium/ligand **85**/CHP catalytic system. The required epoxide intermediate **86** was isolated in good yield and

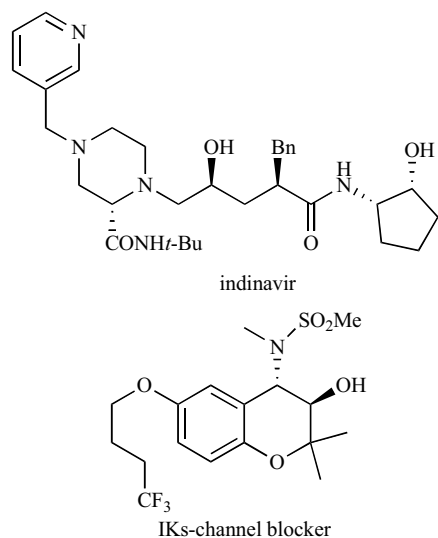
90% de (Scheme 36). More recently, an enantioselective synthesis of florfenicol, a fluorinated derivative of thiamphenicol albeit exhibiting superior antibacterial spectrum, was developed by Chen *et al.* [71]. The product was obtained in 37% overall yield from commercially available 4-methylthiobenzaldehyde. The key epoxidation step was performed on the *trans*-cinnamyl alcohol derivative **87** in the presence of 5 mol% of the Yamamoto vanadium complex **88** and TBHP to give the key epoxide **89** in 75% yield and > 90% ee (Scheme 36). This chiral epoxide was further converted into the antibacterial agent florfenicol (structure in Scheme 25).

In 1990, a pivotal discovery was illustrated by the groups of Jacobsen [72] and Katsuki [73], who independently reported the asymmetric epoxidation of a variety of unfunctionalized alkenes with optically pure Mn(III)/salen complexes using readily available PhIO, bleach, H₂O₂, oxone as the terminal oxidants, providing good levels of enantioselectivity [74]. Soon after their discovery, enantioselective epoxidations catalyzed by Jacobsen-Katsuki complexes



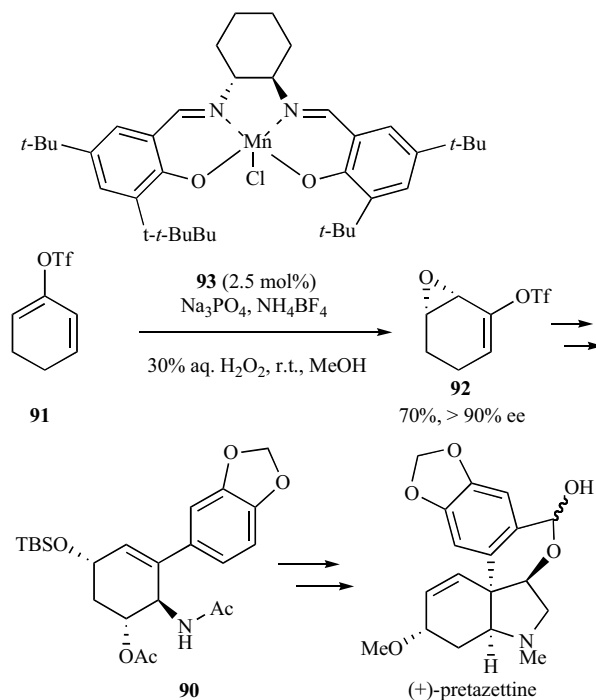
Scheme 36. Syntheses of α -bisabolol and florfenicol through V-catalyzed epoxidations.

were employed as key steps in the synthesis of biologically active products, such as anti-HIV compound indinavir (crivivan[®]) [75], and I_ks-channel blockers (Scheme 37) [76].



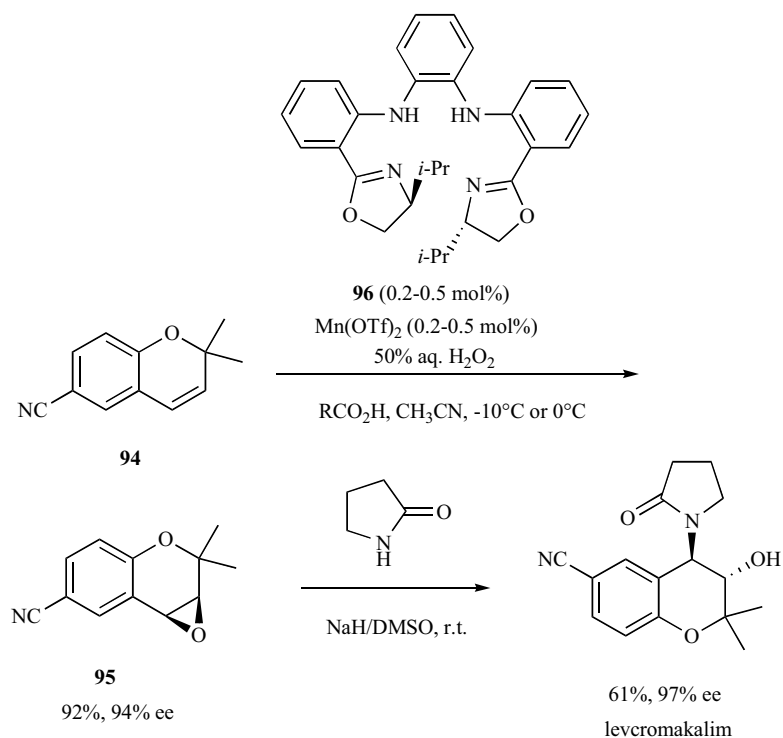
Scheme 37. Biologically active products synthesized through Jacobsen/Katsuki epoxidations.

In more than a decade, Fuchs *et al.* applied and optimized this methodology for the asymmetric epoxidation of cyclic dienyl sulfones and triflates to the corresponding chiral monoepoxides [77]. These compounds proved to be very useful intermediates to access

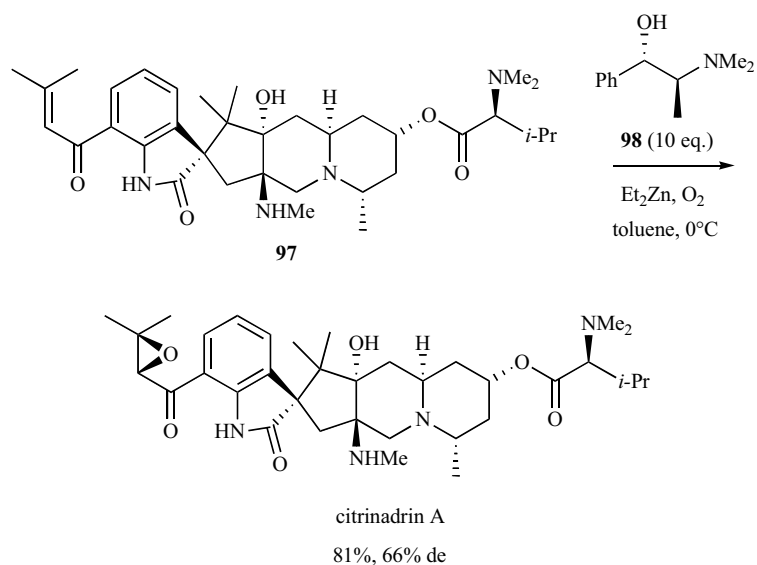


Scheme 38. Synthesis of (+)-pretazettine through Jacobsen/Katsuki epoxidation.

a variety of natural products such as (+)-pretazettine alkaloid core **90**. As shown in Scheme 38, the epoxidation of dienyl triflate **91**



Scheme 39. Synthesis of levcromakalim.



Scheme 40. Synthesis of citrinadrin A.

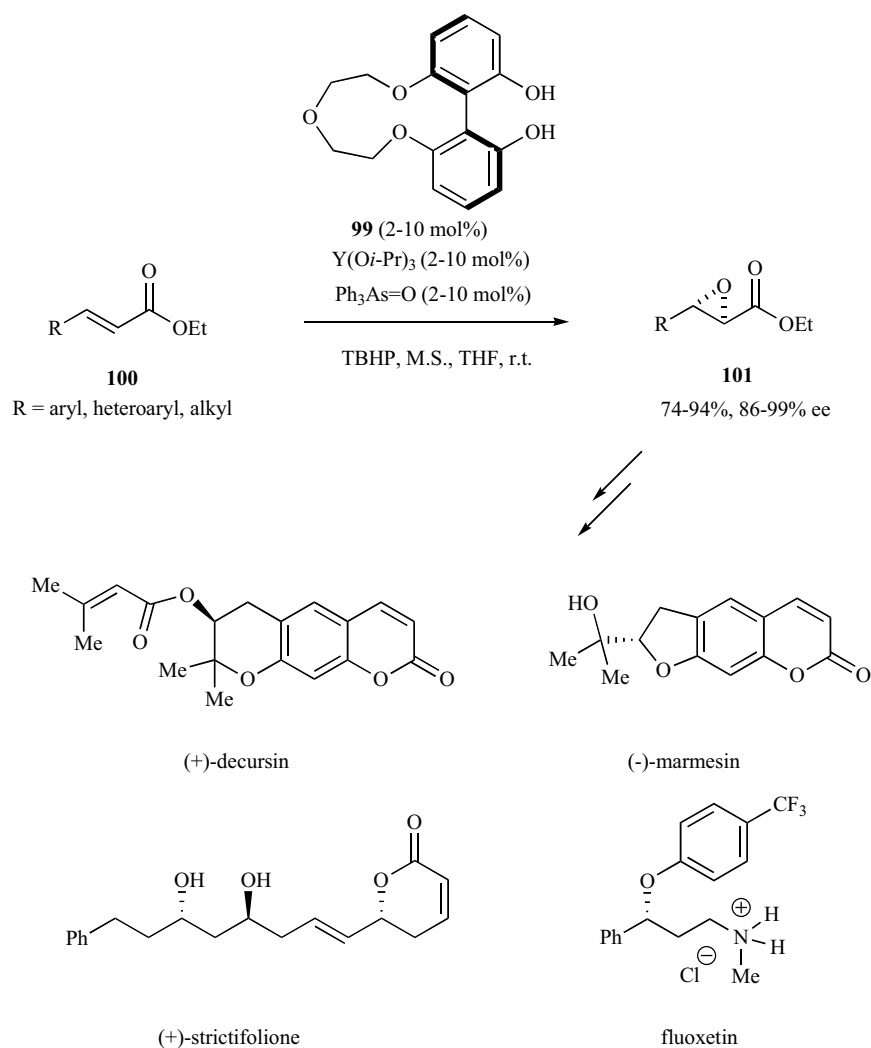
led to the key intermediate epoxide **92** in 70% yield and high enantioselectivity of > 90% ee by using catalyst **93** and H₂O₂ as oxidant. Epoxide **92** was further converted into (+)-pretazettine.

In 2013, Gao *et al.* reported the total synthesis of potassium channel activator levcromakalim the key step of which was the enantioselective Mn-catalyzed epoxidation of alkene **94** into functionalized epoxide **95** performed in the presence of porphyrin-inspired ligand **96** bearing chiral oxazoline groups as ligand with 92% yield and 94% ee (Scheme 39) [78].

Up to date, a few examples have been reported on stereoselective epoxidations mediated by chiral zinc complexes. In 2014, Martin *et al.* reported the epoxidation of *trans*- α,β -unsaturated ketone **97** mediated by overstoichiometric amounts of a complex generated

from Et₂Zn and (1*R*,2*R*)-*N*-methylpseudoephedrine **98** in the presence of molecular oxygen as a benign oxidant. This reaction constituted the final step in the total synthesis of citrinadrin A, an alkaloid isolated from marine-derived fungus *Penicillium citrinum* (Scheme 40) [79]. Indeed, the asymmetric epoxidation of enone **97** under these conditions led to citrinadrin A in 81% yield and moderate diastereoselectivity (66% de).

In 2005, Shibasaki *et al.* developed a catalytic system generated in the presence of molecular sieves from Y(O*i*-Pr)₃, (Ph)₃As=O as additive, and ligand **99** in 1:1:1 ratio, suitable for the asymmetric epoxidation of β -aromatic and aliphatic α,β -unsaturated esters **100** into epoxides **101** with up to 99% ee (Scheme 41) [80] Shibasaki's systems based on similar chiral-lanthanide catalysts and applied to



Scheme 41. Syntheses of biologically active products through Shibasaki's epoxidation.

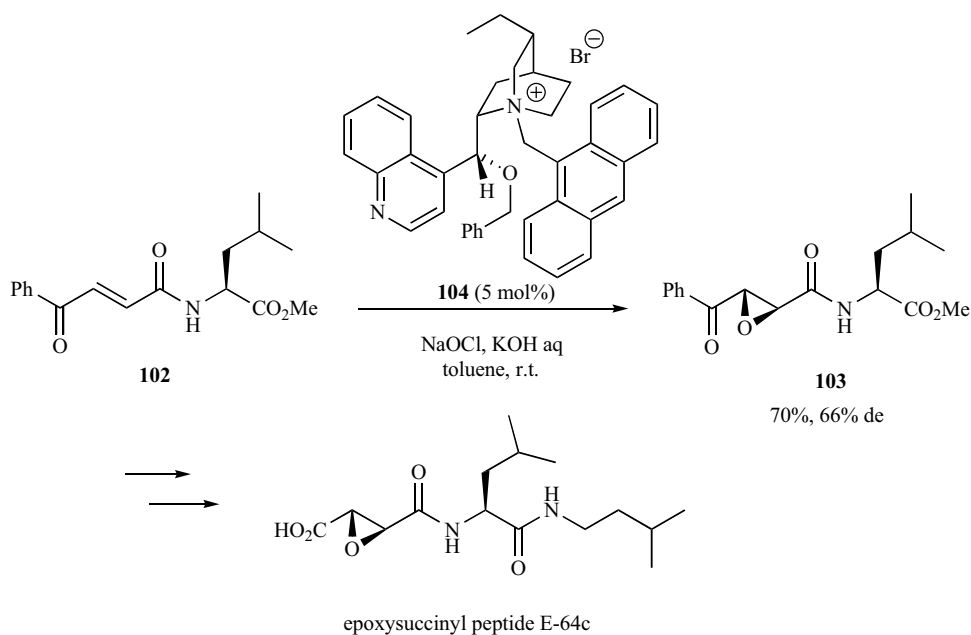
α,β -unsaturated amines [81] and imidazolides [82] have been successfully employed in key epoxidation steps of total syntheses of various biologically active products, such as anticancer agent (+)-decursin [83], antifeedant (-)-marmesin [84], antifungal agent (+)-strictifolione [85], and antidepressant drug fluoxetine [86] (Scheme 41).

3.1.2. Asymmetric Organocatalyzed Epoxidations as Key Steps

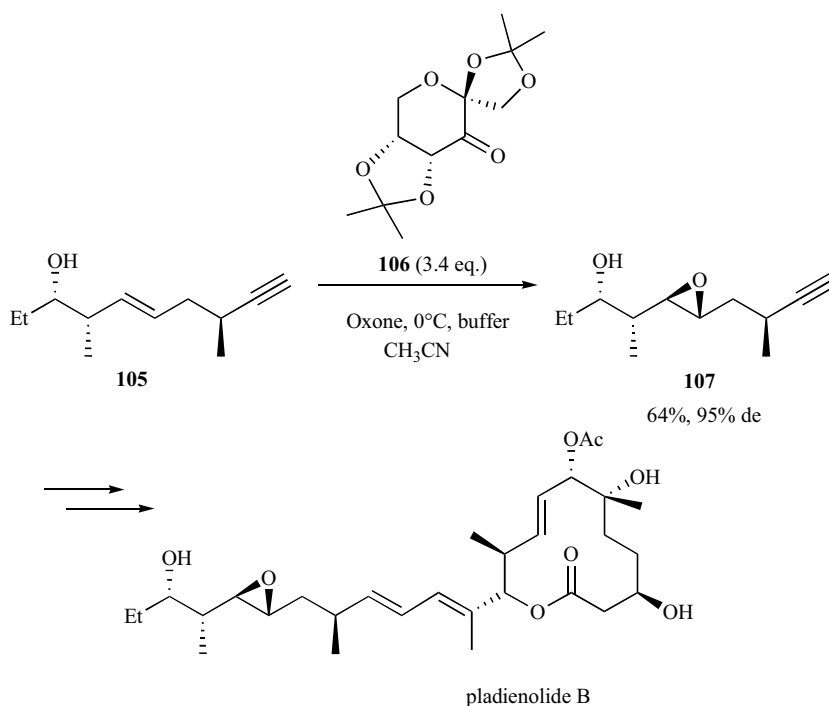
Asymmetric organocatalysis has increasingly become one of the most useful and practical tools to perform a synthetic transformation [87]. In particular, the organocatalyzed asymmetric epoxidation of olefins is an important part of this field, and a number of these processes have been successfully applied to the total synthesis of various important molecules in the last 15 years. Actually, this topic was reviewed in 2014 by Shi *et al.* [88], consequently only some representative examples will be detailed in this Section. The readers are invited to consult this comprehensive coverage for a complete coverage of the field. Asymmetric phase transfer catalysis (PTC) includes valuable methodologies for building carbon-carbon and carbon-heteroatom bonds [89]. The mildness and often environmentally friendly reaction conditions of asymmetric PTC reactions cope well for large-scale and industrial applications [90]. In 2006, an interesting application of the cinchona alkaloid-derived PTC-catalyzed diastereo- and enantioselective epoxidation to access

potent naturally-occurring cysteine protease inhibitor, the epoxy-succinyl peptide E-64c, was reported by Lygo *et al.* [91]. The key epoxidation of α,β -unsaturated amide **102** into the corresponding functionalized epoxide **103** occurred with 70% yield and moderate diastereoselectivity of 66% de when catalyzed with cinchona alkaloid salt **104**, as shown in Scheme 42.

The most efficient class of oxidants to perform the epoxidation of alkenes are dioxiranes [92]. In contrast to similar oxidizing agents, such as percarboxylic acids, the development of chiral dioxiranes for asymmetric epoxidations has met great success over the last decades [8, 93]. In late 1990s, Shi and co-workers introduced a variety of pseudo C_2 -symmetric six-membered carbocyclic ketones derived from quinic acid as stoichiometric precursors of *in situ* generated chiral dioxiranes to be used in asymmetric epoxidation of *trans*-disubstituted, trisubstituted, terminal alkenes, and electron-poor alkenes. Oxone was used in DME under basic buffered conditions at 0 °C in the presence of only 5-10 mol% of the chiral ketone [94]. More recently, a comparable methodology was applied by Chandrasekhar and Kumar to the total synthesis of pladienolide B, a natural anticancer macrolide [95]. The key step of the synthesis was the epoxidation of homoallylic alcohol **105** performed in the presence of superstoichiometric amounts of ketone **106** and oxone to give epoxide **107** in 64% yield and 95% de (Scheme 43).



Scheme 42. Synthesis of cysteine protease inhibitor peptide E-64c through PTC-catalyzed epoxidation.



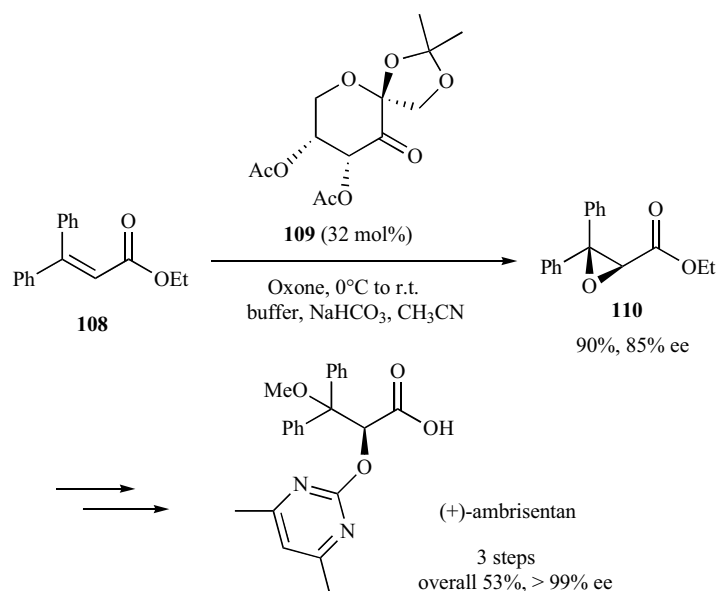
Scheme 43. Synthesis of pladienolide B through Shi's epoxidation.

In 2012, a simple total synthesis of (+)-ambrisentan, a drug clinically used for the treatment of pulmonary arterial hypertension, was reported by Shi *et al.* [96]. It began with the asymmetric epoxidation of ethyl 3,3-diphenylacrylate **108** (Scheme 44). This electron-poor alkene was epoxidized with the most effective ketone **109** to provide the corresponding chiral epoxide **110** in 90% yield and 85% ee. The reaction crude was then directly subjected to other steps to finally afford (+)-ambrisentan in 53% overall yield and >99% ee.

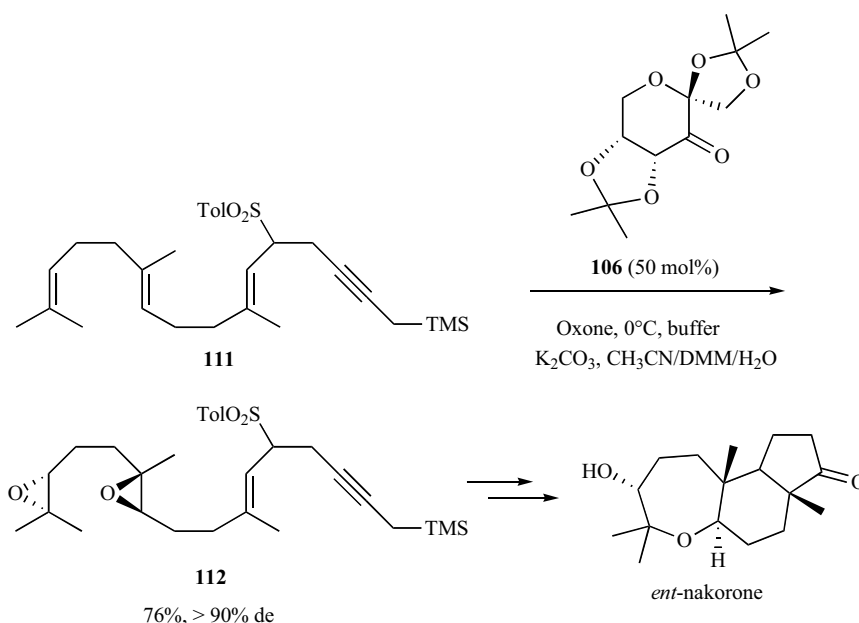
Biomimetic synthesis based on intramolecular cascade ring-opening reaction of chiral epoxides has been also reported by McDonald *et al.* (Scheme 45) [97]. With the aim of developing a

synthetic route to abudinolins A and B, oxygenated triterpenoid marine natural products, triene **111** was selectively epoxidized at two of its three carbon-carbon double bonds to give diepoxide **112** in good yield (76%) and high diastereoselectivity of > 90% de when using ketone **106** as the organocatalyst. The allylic electron-withdrawing group proximal to the other carbon-carbon double bond prevented its epoxidation. *ent*-Nakorone, an oxidative degradation product of abudinolins, was then obtained *via* TMSOTf-promoted cyclization with the propargylsilane nucleophile, followed by ozonolysis.

Conceptually similar chiral iminium salts/oxaziridinium salts systems have been introduced as epoxidizing systems since the late



Scheme 44. Synthesis of (+)-ambrisentan through Shi's epoxidation.



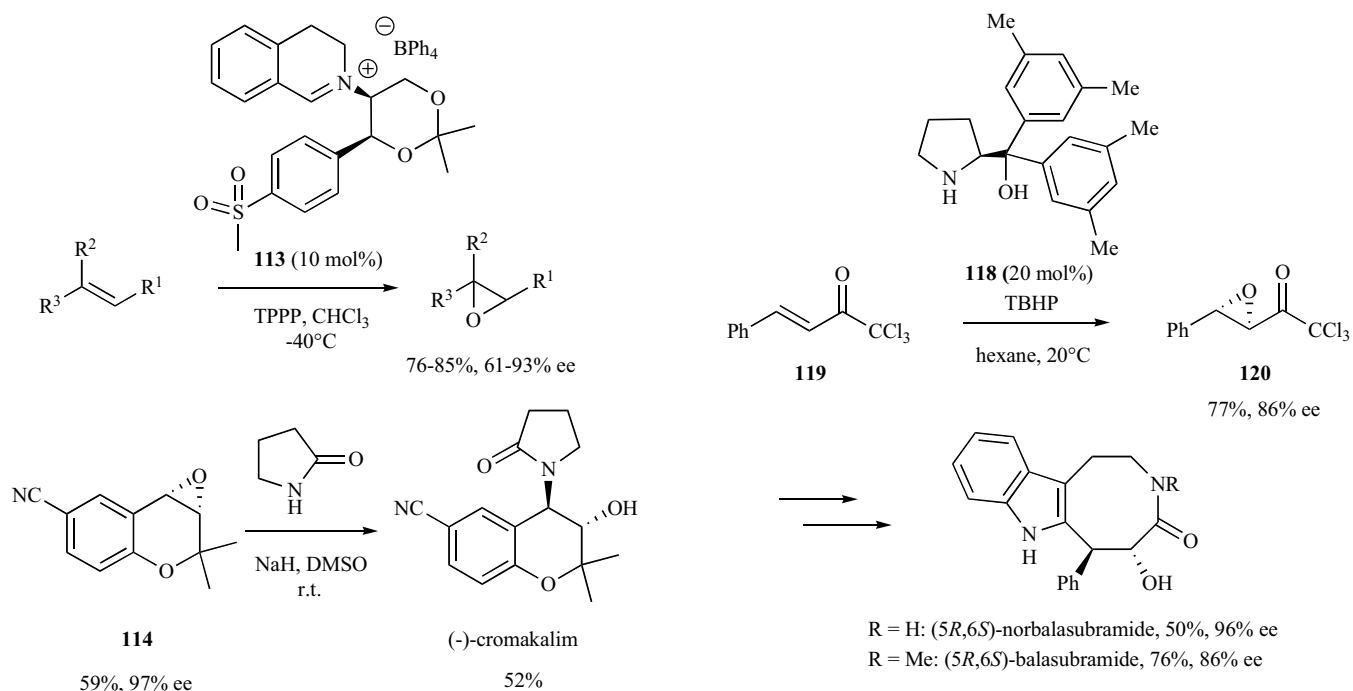
Scheme 45. Synthesis of *ent*-nakorone through Shi's epoxidation.

1980s [98]. A tetraphenylphosphonium monoperoxybisulfate (TPPP) [99] was employed as oxidant in combination with organocatalyst **113** in the asymmetric epoxidation of some *Z*-alkenes to the corresponding epoxides, which were isolated in good yields and good to high enantioselectivities of up to 97% ee (Scheme 46) [100]. In particular, the epoxidation of a benzopyran substrate into tricyclic epoxide **114** occurred with the highest efficiency, and was applied to synthesize the antihypertensive agent (-)-cromakalim with high stereoselectivity *via* ring-opening of the epoxide unit with pyrrolidone, as shown in Scheme 46. In addition, organocatalyst **113** was used in the key epoxidation step for a concise asymmetric synthesis of natural coumarin derivatives (-)-lomatin, and (+)-*trans*-khellactone [101].

Page and co-authors reported the application of another chiral iminium salt-catalyzed epoxidation as key step in the first highly enantioselective synthesis of (+)-scutellorin A, one of the numerous

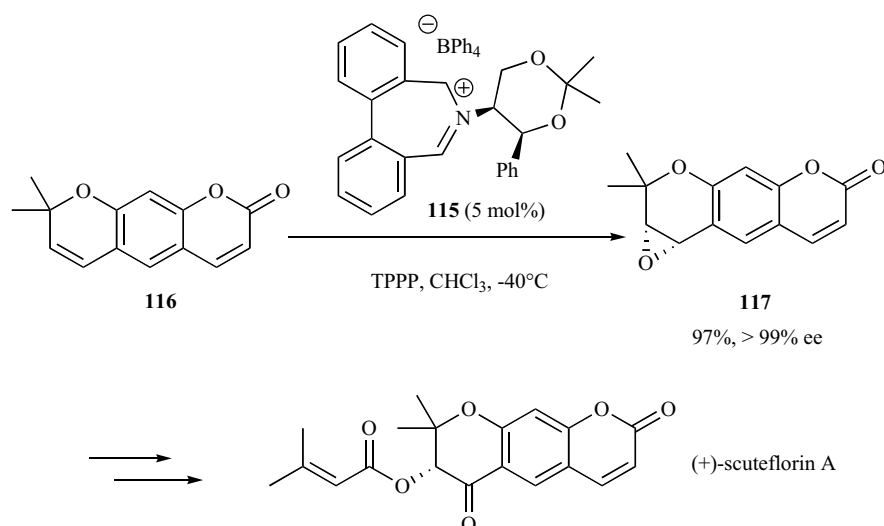
and pharmacological active compounds recently isolated from *Scutellaria* species (Scheme 47) [102]. A previously reported chiral iminium salt **115** [103] served as organocatalyst under non aqueous conditions, to epoxidize the starting *Z*-alkene **116** into the corresponding key enantiopure epoxide **117** in 97% yield. Epoxide hydrolysis/oxidation and esterification completed the synthesis.

The combination of diaryl prolinol **118** as organocatalyst with an alkyl hydroperoxide, such as TBHP, as oxidant in asymmetric epoxidation system was investigated by Zhao *et al.*, developing the first asymmetric epoxidation reactions of a variety of *trans*-disubstituted electron-poor alkenes, such as **119**, into the corresponding chiral epoxides, such as **120**, in good yields, complete diastereocontrol, and good enantioselectivities [104]. As an application, the authors developed a short synthesis of natural products (-)-(5*R*,6*S*)-norbalasubramide and (-)-(5*R*,6*S*)-balasubramide which is depicted in Scheme 48.



Scheme 46. Synthesis of (-)-cromakalim through chiral iminium salt-catalyzed epoxidation.

Scheme 48. Synthesis of (5*R*,6*S*)-norbalasubramide and (5*R*,6*S*)-balasubramide through epoxidation with L-prolinol/TBHP system.



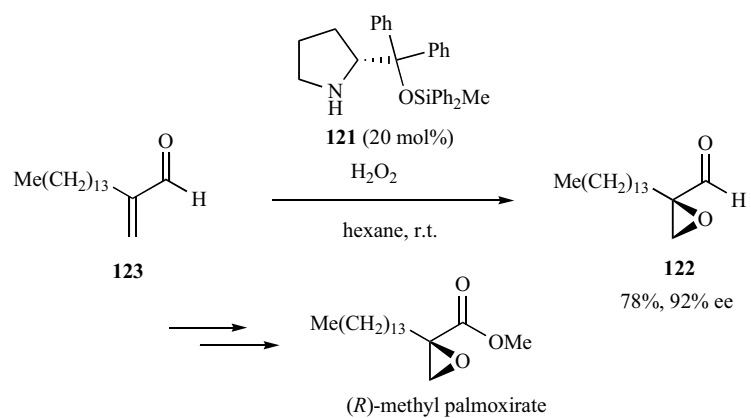
Scheme 47. Synthesis of (+)-scuteflorin A through chiral iminium salt-catalyzed epoxidation.

In 2010, Hayashi *et al.* reported a short synthesis of (*R*)-methyl palmoxirate, a potent oral hypoglycemic agent, based on the first successful asymmetric epoxidation of aliphatic α -substituted acroleins, that was catalyzed by diphenylprolinol silyl ether **121** and H_2O_2 as oxidant [105]. Terminal epoxide **122**, bearing a quaternary stereocenter, was obtained as key intermediate in good yield (78%) and high enantioselectivity (up to 92% ee) starting from alkene **123**, as shown in Scheme 49.

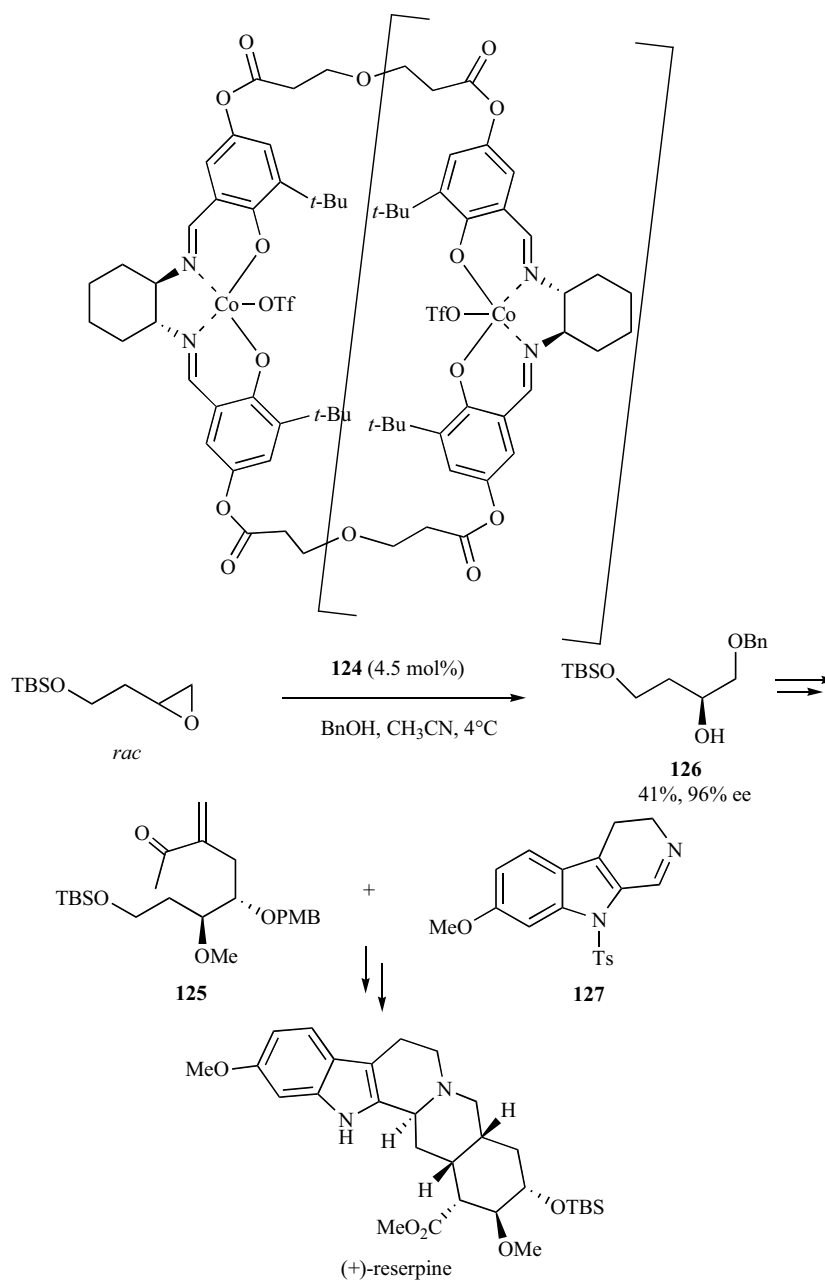
3.1.3. Kinetic Resolutions of Racemic Epoxides as Key Steps

Besides reactions mediated by metal complexes or organocatalysts, another important tool in asymmetric synthesis to obtain optically active products is the kinetic resolution of racemic molecules [106]. In 1990s, Jacobsen *et al.* demonstrated the exceptional catalytic performance of Cr(III)-salen complexes in the kinetic resolu-

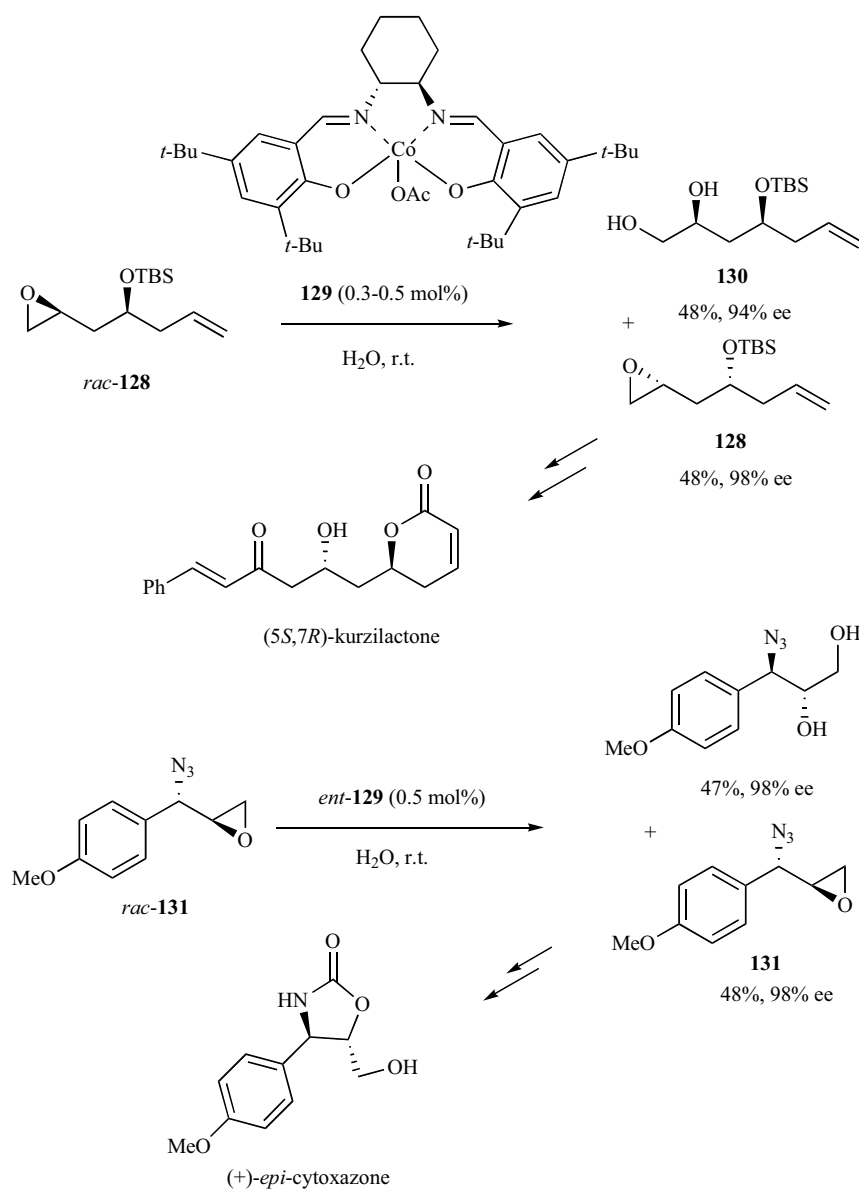
tion of racemic terminal monosubstituted and 2,2-disubstituted epoxides by TMSN_3 , which occurred with complete regioselectivity for the terminal position and very high stereoselectivity factors of up to 280 [107]. Later, these authors reported enhanced reactivity by using dimeric catalyst **124** in hydrolytic kinetic resolution of terminal epoxides (Scheme 50) [108]. A recent synthetic application of kinetic resolution using primary alcohols was illustrated by the same authors in the total synthesis of (+)-reserpine *via* intermediate enone **125** [109]. The kinetic resolution of a racemic epoxide performed in acetonitrile with 4.5 mol% of catalyst **128** and benzyl alcohol as the nucleophile, afforded the secondary alcohol **126** in 41% yield and 96% ee, which was further converted into enone **125**. Then, this product was coupled with dihydro- β -carboline **127** to access antipsychotic and antihypertensive drug (+)-reserpine.



Scheme 49. Synthesis of (*R*)-methyl palmoxirate.



Scheme 50. Synthesis of (+)-reserpine.



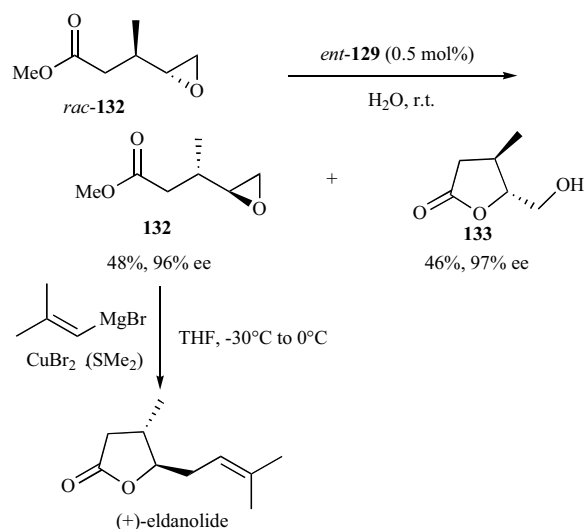
Scheme 51. Syntheses of (5*S*,7*R*)-kurzilactone and (+)-epi-cytosaxzone.

Rare examples of hydrolytic kinetic resolution of functionalized racemic epoxides bearing two stereocenters have been reported. The groups of Tae and Sudalai independently investigated the hydrolytic kinetic resolution of racemic *syn*- and *anti*-2-hydroxy-1-oxiranes in order to obtain both enantiomers of *syn*- and *anti*-epoxides (Scheme 51) [110]. Racemic *syn*-*O*-protected terminal epoxide **128** underwent hydrolytic kinetic resolution with chiral cobalt catalyst **129** to give enantioenriched *syn*-epoxide **128** along with 1,2-diol **130** in excellent conversions and enantioselectivities of up to 98% ee. Epoxide **128** was employed as the starting reagent for the total synthesis of the opposite enantiomer of natural product (5*S*,7*R*)-kurzilactone. Optically active *trans*-epoxide **131** was produced under comparable reaction conditions albeit using catalyst *ent*-**129** and further employed in a concise total synthesis of the cytokine modulator (+)-epi-cytosaxzone (Scheme 51).

The hydrolytic kinetic resolution methodology performed in the presence of cobalt catalyst *ent*-**129** also constituted the key step of a total synthesis of natural product (+)-eldanolide, a long range sex attractant, which was reported by Sudalai *et al.*, in 2013 [111]. As

shown in Scheme 52, racemic *anti*-3-methyl epoxy ester **132** led to the corresponding *trans*-3,4-disubstituted- γ -butyrolactone **133** along with unreacted chiral epoxide **132** both isolated in excellent enantioselectivities of 96-97% ee. Epoxide **132** was subsequently converted into expected natural product (+)-eldanolide. Another advantage of this methodology was the production of chiral 3,4-disubstituted γ -butyrolactones, which constitute important scaffolds endowed with several biological activities.

The hydrolytic kinetic resolution of terminal epoxides was recently applied in the total synthesis of the anti-Parkinson agent safinamide, starting from commercially available benzyl glycidyl ether (Scheme 53) [112]. Enantiopure epoxide **134** was obtained in good conversion (46%) *via* hydrolytic kinetic resolution of the corresponding racemic epoxide in the presence of *ent*-**129** as catalyst, which secured a highly enantioselective approach to safinamide *via* simple elaboration steps. In addition, the hydrolytic kinetic resolution of racemic epoxides has also been used in the synthesis of other natural and bioactive compounds, such as (*S*)-timolol [113], decarestrictine D [114], (+)-isolaurepan [115], (*R*)-tuberculostearic



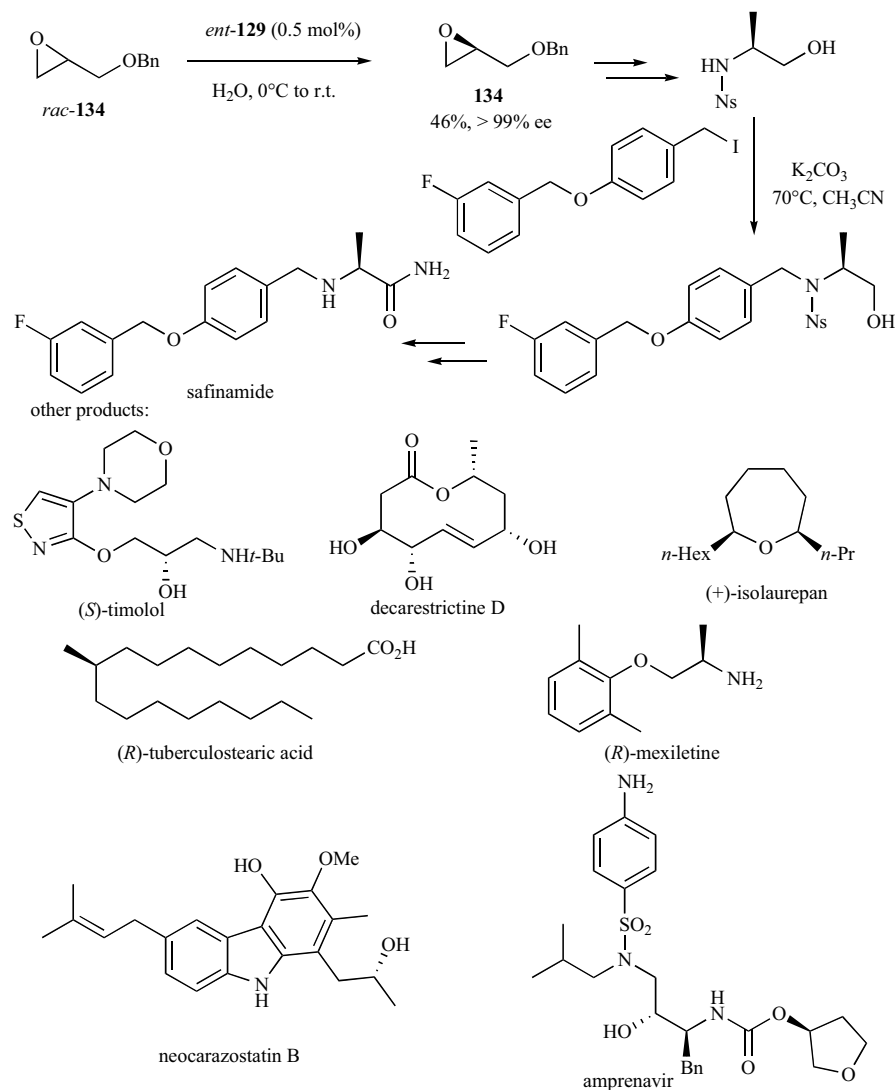
Scheme 52. Synthesis of (+)-eldanolide.

acid [116], (*R*)-mexiletine [117], neocarazostatin B [118], and amprenavir [119].

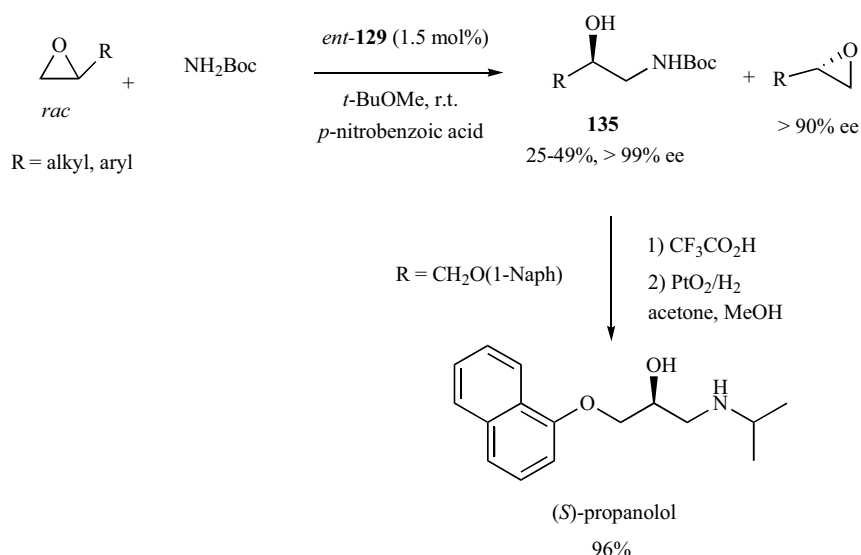
In 2004, Bartoli, Melchiorre *et al.* showed that the same cobalt catalyst *ent*-129 could also catalyze the highly regioselective kinetic resolution of epoxides with carbamates as nucleophiles in the presence of *p*-nitrobenzoic acid as an additive to provide the corresponding enantiopure chiral β -amino alcohols **135** (Scheme 54) [120]. The utility of this novel methodology was demonstrated in a total synthesis of the anti-hypertensive drug (β -blocker) (*S*)-propranolol.

3.1.4. Asymmetric Sulfur Ylide-Mediated Epoxidations as Key Steps

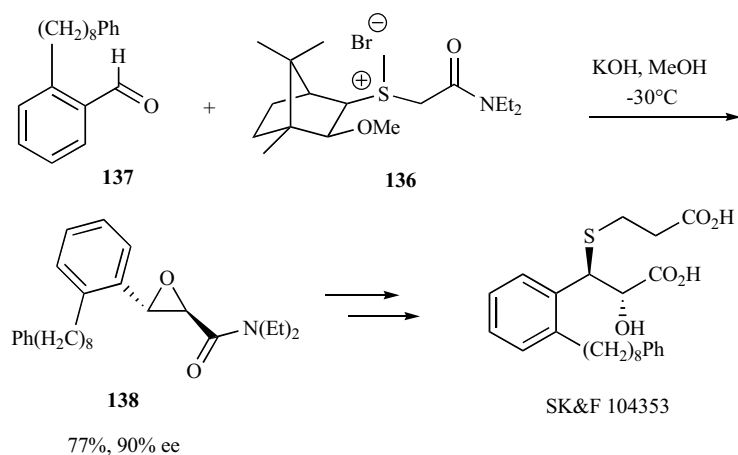
An alternative non-oxidative preparation of chiral epoxides relies on the use of chiral sulfur ylides and aldehydes as reactive partners [121]. This methodology has been the focus of significant interest to efficiently produce chiral epoxides in the last decade [87a, 122]. For example, Aggarwal *et al.* developed a total synthesis of SK&F 104353, a leukotriene D₄ inhibitor, that was based on the reaction of diastereoisomerically pure *O*-protected sulfonium salt **136** with aromatic hindered aldehyde **137**, performed in the presence of KOH at low temperature, to afford the corresponding chiral key *trans*-epoxide **138** in 77% yield and high enantioselectivity (90% ee) [123]. The latter was subsequently converted into expected SK&F 104353 (Scheme 55).



Scheme 53. Synthesis of safinamide and structures of other products.



Scheme 54. Synthesis of (*S*)-propranolol.



Scheme 55. Synthesis of SK&F 104353.

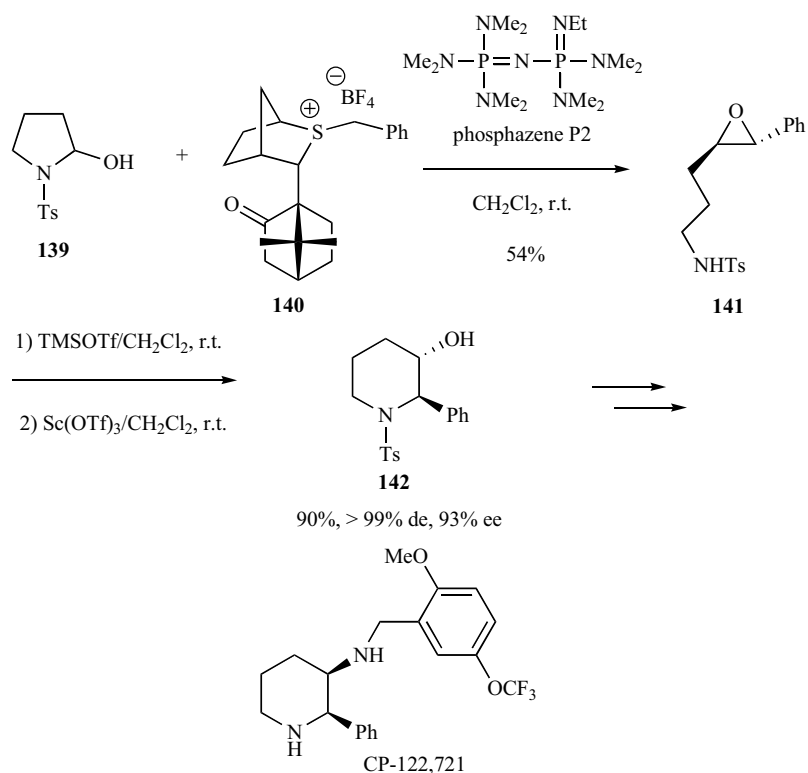
The same group also developed asymmetric sulfur ylide epoxidations of readily available hemiaminals [124]. As shown in Scheme 56, the reaction of cyclic hemiaminal **139** with chiral sulfonium salt **140** at room temperature in dichloromethane in the presence of a base, such as phosphazene P2 (*N,N,N',N'*-tetramethyl-*N'*-(tris(dimethylamino)phosphoranylidene) phosphoric triamide ethylimine), led to the corresponding chiral epoxide **141** in 54% yield. The latter was further successively submitted to TMSOTf and Sc(OTf)₃ to afford the corresponding chiral piperidine **142** as the only detected diastereomer in 93% ee and with 90% yield. The synthetic utility of this novel methodology was demonstrated by its application in the synthesis of the potent neurokinin-1 (NK-1) receptor antagonist CP-122,721, as depicted in Scheme 56.

Most of the recent efforts in the asymmetric ylide-mediated epoxidation were focused on the synthesis of readily accessible optically pure sulfides able to improve and extend the scope of epoxidation in order to apply this methodology in total synthesis [42, 125]. An innovative scaffold for the starting sulfide has been reported by Sarabia *et al.*, based on the use of easily available amino acids L- and D-methionines (Scheme 57) [126]. For example, sulfonium salt **143** was readily prepared in four steps and 70% overall yield from L-methionine. The reactions of **143** with various aldehydes were

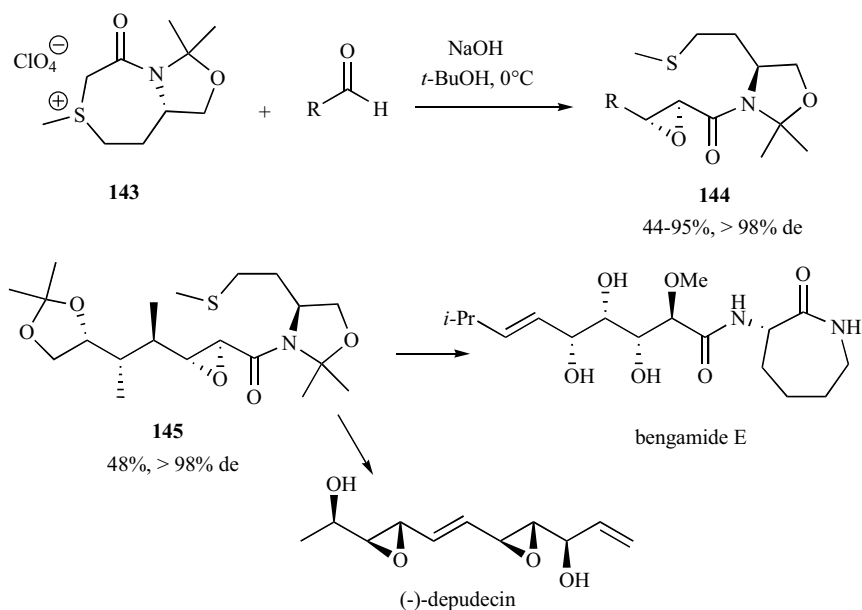
performed under basic conditions to give exclusively the corresponding chiral *trans*-epoxides **144** in almost diastereoisomerically pure form. Employment of enantiopure aldehydes as reagents enabled the preparation of complex epoxy amides, such as **145**, with an excellent control of the diastereoselectivity. This compound constituted a useful intermediate for the synthesis of macrolide-type natural products. The same group recently reported an in-depth study on the bicyclic core ring-size of sulfonium salts of type **143**, demonstrating that it was possible to increase the scope of simple and chiral aldehydes employable in the epoxidation, for instance heteroaromatic, vinyl, and hemiacetal [127]. The versatility of this methodology was demonstrated in the total syntheses of ben-gamides analogues [128], a family of marine natural products isolated from sponges, exhibiting prominent antitumor, antihelmintic, and antibiotic activities as well as natural product (-)-depudecin [129], an antiangiogenic microbial polyketide (Scheme 57). Further applications include the synthesis of cyclodepsipeptides globomycin and SF-1902 A5 [130], and sphingoid-type bases [131].

3.1.5. Catalytic Asymmetric Darzens Reactions as Key Steps

An important transformation to obtain epoxides bearing an electron-withdrawing groups is the Darzens reaction [132]. Since the first asymmetric metal-catalyzed Darzens reaction reported by



Scheme 56. Synthesis of CP-122,721.



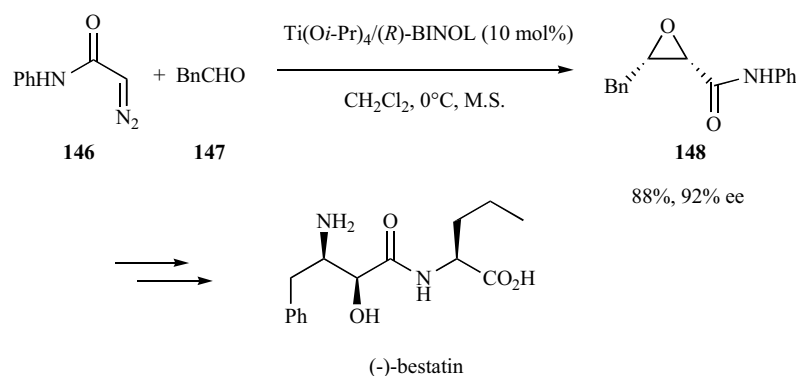
Scheme 57. Syntheses of bengamide E and (-)-depudecin.

North *et al.* in 2007 [133], successful examples of this type of methodology have been developed and applied in total synthesis. Therefore, Gong *et al.* have described an enantioselective titanium-catalyzed Darzens reaction as key step in the total synthesis of protease inhibitor (-)-bestatin [134]. The reaction was catalyzed by an *in situ* generated complex from $\text{Ti}(\text{O}i\text{Pr})_4$ and (*R*)-BINOL. It occurred between diazoacetamide **146** and aldehyde **147** in the presence of molecular sieves (Scheme **58**). A complete control of the diastereoselectivity was observed, providing the corresponding *cis*-glycidic amide **148** in good yield (88%) and high enantioselectivity

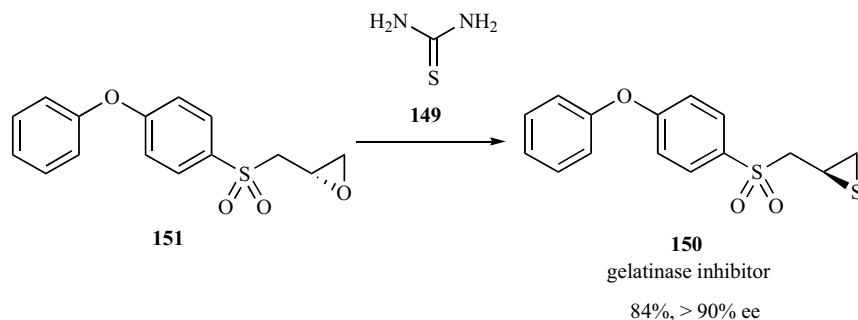
of 92% ee. This epoxide constituted a useful intermediate in the synthesis of (-)-bestatin.

3.2. Chiral Thiiranes

Sulfur-containing compounds are widespread among natural products and biologically active substances [135]. Consequently, great efforts have been devoted to develop stereocontrolled C–S bond-forming procedures [136]. In particular, thiiranes are suitable precursors of numerous products, including biologically active compounds. Several methods for thiirane preparation [137] have



Scheme 58. Synthesis of (-)-bestatin.



Scheme 59. Synthesis of a gelatinase inhibitor.

been reported, among which the most convenient one consists in the conversion of oxiranes into the corresponding thiiranes by an oxygen–sulfur exchange reaction. With this aim, various sulfur reagents have been investigated such as thiourea **149** [138]. In 2005, an asymmetric version of this methodology was applied by Mobashery *et al.* to the synthesis of chiral 1,2-(4-phenoxyphenyl-sulfonylmethyl)thiirane **150**, which is a selective gelatinase inhibitor active for cancer metastasis [139]. The key step of the synthesis consisted in the reaction of the corresponding (*S*)-epoxide **151** with thiourea **149** to give the expected (*R*)-thiirane **151** in good yield (84%) and high enantioselectivity (> 90% ee), as shown in Scheme 59.

4. CHIRAL CYCLOPROPANES IN TOTAL SYNTHESIS

The strained cyclopropane subunit [2a, 140] is present in a range of biologically relevant products, such as terpenes, pheromones, fatty acid metabolites, and unusual amino acids [141], among others. These compounds exhibit a large spectrum of biological properties, including enzyme inhibition and insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor, and antiviral activities [3, 142]. This fact has inspired chemists to find novel approaches for their synthesis [143], and thousands of cyclopropane compounds have already been prepared [144]. In particular, the asymmetric synthesis of cyclopropanes has remained a challenge [2f, 145], since it was demonstrated that members of the pyrethroid class of compounds to be effective insecticides [146]. In the last decade, many important chiral cyclopropane derivatives have been synthesized according to three principal methodologies, including the Simmons–Smith reaction [147], the transition-metal-catalyzed decomposition of diazo compounds [2f, 148], and the Michael-initiated ring-closure (MIRC) [149]. In each case, the reactions can start from chiral substrates (or auxiliaries) or can be promoted by chiral catalysts.

4.1. Asymmetric Simmons–Smith Cyclopropanations as Key Steps

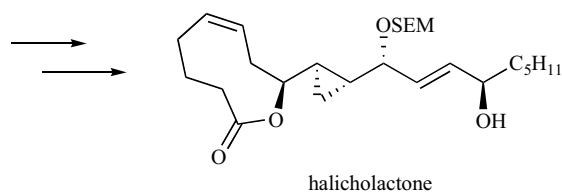
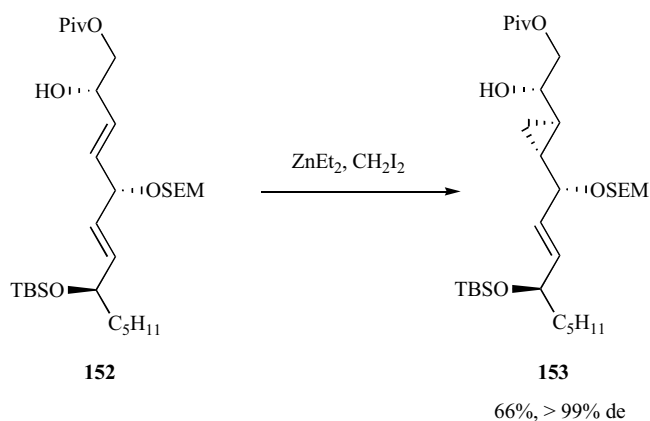
In 1950s, Simmons and Smith reported the reaction of alkenes with diiodomethane performed in the presence of activated zinc which afforded cyclopropanes in high yields [150]. The reactive intermediate is an organozinc species and the preparation of such species, including $RZnCH_2I$ or $IZnCH_2I$ compounds and samarium derivatives, was developed in the following years [151]. Ever since, asymmetric versions of the Simmons–Smith reaction [152] have been developed and applied to the synthesis of various biologically active products using either chiral substrates or chiral catalysts.

4.1.1. Using Chiral Substrates

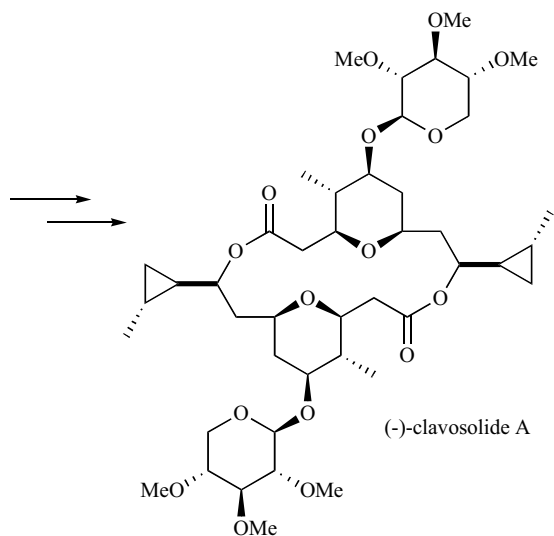
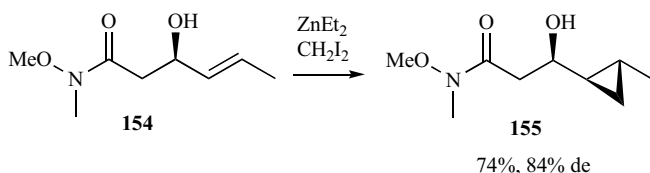
Various asymmetric cyclopropanations of acyclic allylic alcohols have been reported, using the heteroatom as the directing group, through chelation with the zinc reagent. This Simmons–Smith reaction has distinct advantages over the reaction with a simple olefin in relation to the reaction rate and stereocontrol [153]. Many asymmetric cyclopropanations of chiral allylic alcohols have been used as key steps in total synthesis of natural products of biological interest. For instance, Takemoto *et al.* reported in 2000s an asymmetric total synthesis of natural product halicholactone, in which a regio- and stereoselective cyclopropanation of chiral diene **152** into epoxide **153** obtained as the only detected stereoisomer constituted the key step (Scheme 60) [154].

In 2006, Smith and Simov developed the total synthesis of the marine diolide (-)-clavosolide A on the basis of the direct Simmons–Smith cyclopropanation of chiral *N*-methoxyamide **154**, providing the corresponding key cyclopropane intermediate **155** in 74% yield and diastereoselectivity of 84% de, as shown in Scheme 61 [155].

In 2007, a total synthesis of the two biologically active oxylipins solandelactones E and F was described by White *et al.* [156].



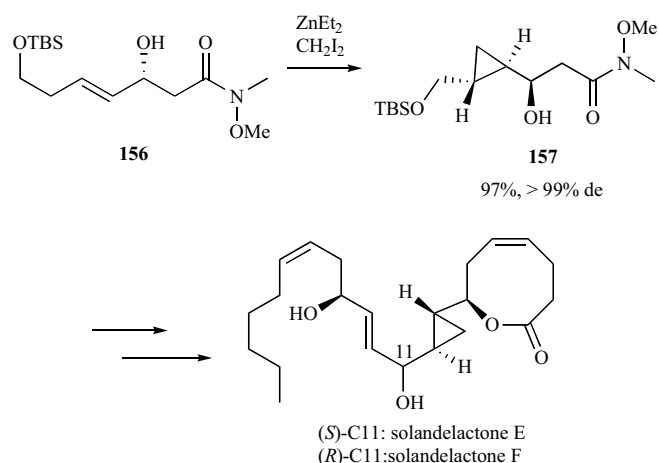
Scheme 60. Synthesis of halicholactone.



Scheme 61. Synthesis of (-)-clavosolide A.

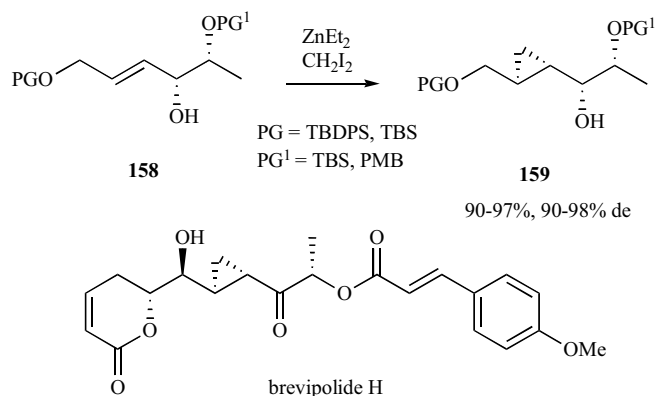
The key step was a comparable Simmons-Smith cyclopropanation of chiral *N*-methoxyamide **156** which provided the corresponding functionalized cyclopropane **157** as the only detected stereoisomer in almost quantitative yield, as shown in Scheme **62**. The authors confirmed that the structures of the two solandelactones were epimeric at C11.

Brevipolides are extracted from the invasive tropical plant of *Hyptis brevipes*, and exhibit interesting drug properties. Recently, Mohapatra *et al.* developed a highly diastereoselective synthesis of the C1–C12 fragment of brevipolide H (Scheme **63**) [157]. The key



Scheme 62. Synthesis of solandelactones E and F.

step was the cyclopropanation of chiral alkene **158** into **159** in excellent yield (up to 97%) and diastereoselectivity (up to 98% de). A similar reaction was previously reported by Kumaraswamy *et al.*, but with inferior results in the synthesis of another representative member of the brevipolide family [158].

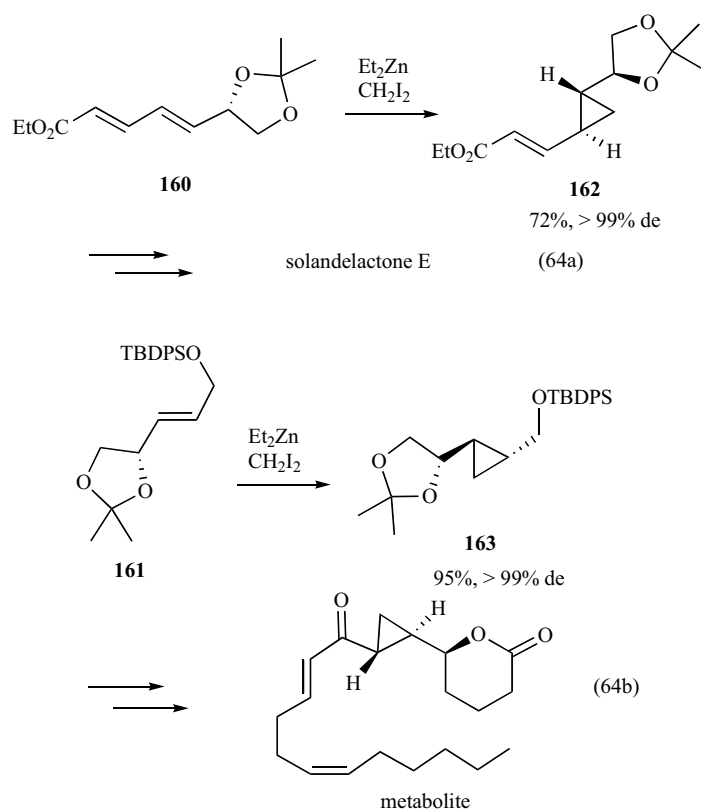


Scheme 63. Synthesis of the C1–C12 fragment of brevipolide H.

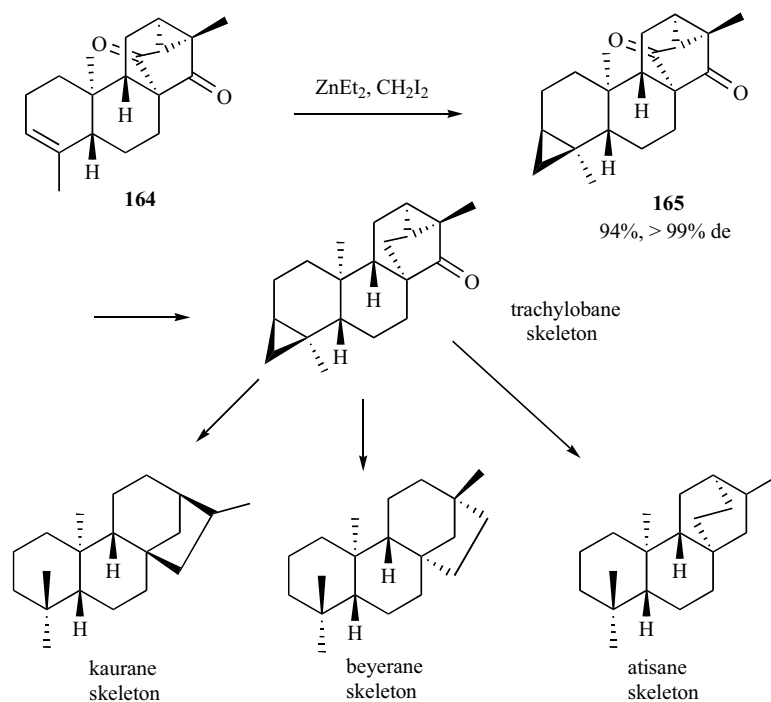
In addition to chiral allylic alcohols, chiral acetals bearing an alkene function, such as **160** and **161**, have been used in diastereoselective acetal-directed cyclopropanations as key steps of total syntheses of solandelactone E (Scheme **64a**, structure in Scheme **62**) [159], and a marine fatty acid metabolite exhibiting lipoxygenase-inhibiting activity (Scheme **64b**) [160], both providing the corresponding cyclopropane derivatives **162** and **163**, respectively, in good to excellent yields (72-95%) and as the only detected stereoisomers.

In 2006, standard Simmons-Smith conditions were also applied by Abad *et al.* to the cyclopropanation of diterpene **164** [161]. The reaction occurred stereoselectively from the less hindered b-side of the double bond, affording the expected cyclopropane **165** in 94% yield and as the only detected stereoisomer (Scheme **65**). This tricyclo[3.2.1.0]octane moiety constituted the key intermediate in the synthesis of biologically interesting trachylobane-, beyerane-, atisane-, and kaurane-type diterpenes.

In 2015, Tori *et al.* applied similar Simmons-Smith conditions to the last step of a total synthesis of natural product (+)-crispatanolide starting from chiral alkene **166**, as shown in Scheme **66** [162]. Surprisingly, the major product was not the expected (+)-



Scheme 64. Syntheses of solandelactone E and a marine fatty acid metabolite.

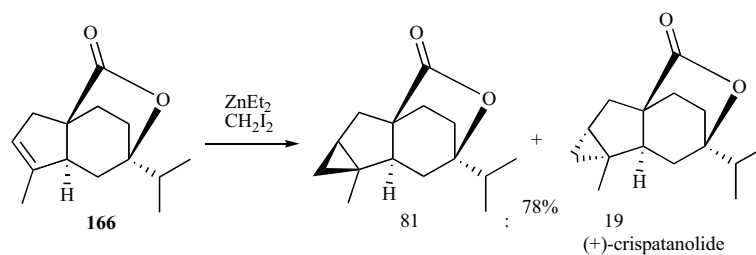


Scheme 65. Syntheses of trachylobane-, kaurane-, beyerane- and atisane-type diterpenes.

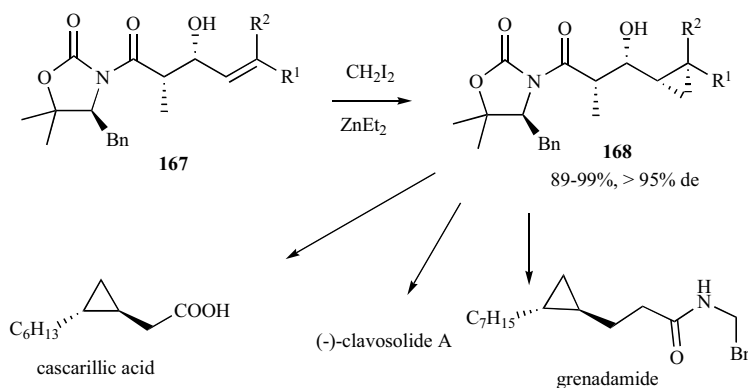
crispatanolide, but a diastereomer, very likely because of the directing effect of the lactone carbonyl group. However, this synthesis allowed likewise assigning the absolute configuration of the natural (+)-crispatanolide.

In addition, various types of recoverable chiral auxiliaries have been successfully employed in asymmetric Simmons-Smith cyclo-

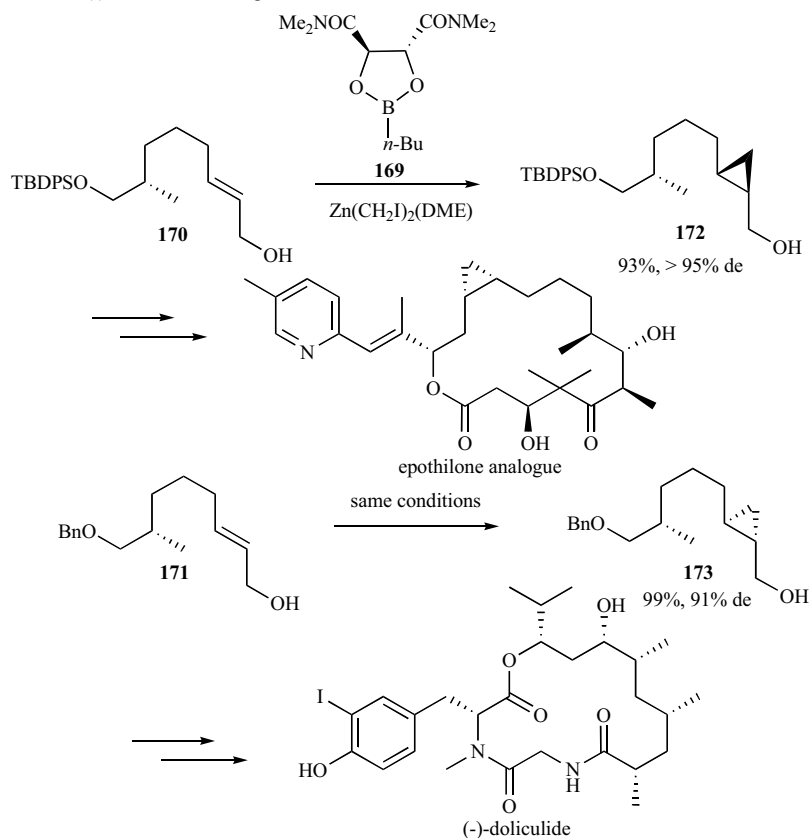
propanations as key steps of total syntheses of various natural products. For example, the asymmetric Simmons-Smith cyclopropanation of chiral allylic alcohol **167** led to the corresponding cyclopropanes **168** in high to quantitative yields and as almost single diastereomers (> 95% de) [163] to be used as key intermediates in several natural products, such as cascarillic acid [164],



Scheme 66. Synthesis of (+)-crispatanolide and its diastereomer.



Scheme 67. Syntheses of cascarillic acid, (-)-clavosolide and grenadamide.



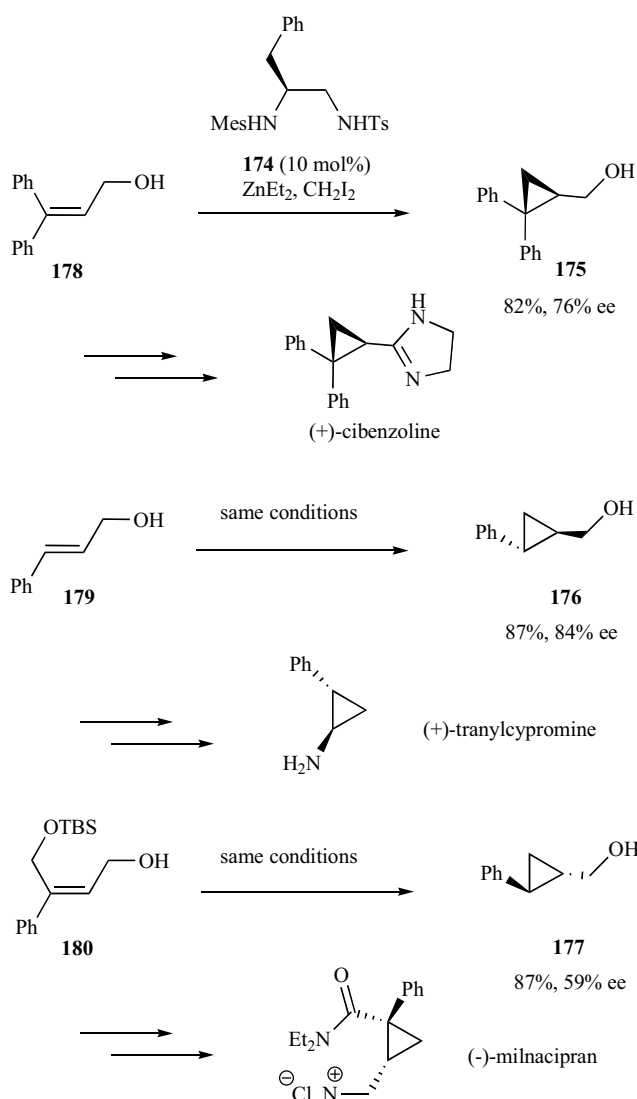
Scheme 68. Syntheses of an epothilone analogue and (-)-doliculide through Charette's cyclopropanations.

(-)-clavosolide A (structure in Scheme 61) [165], and grenadamide [166] (Scheme 67).

4.1.2. Using Chiral Catalysts

In 2001, Liu and Ghosh reported the cyclopropanation of *cis*- and *trans*-disubstituted allylic alcohols, such as **170** and **171**, per-

formed in the presence of chiral dioxaborolane ligand **169**, which led to the corresponding chiral cyclopropylmethanols **172** and **173**, respectively, in diastereoselectivities of up to > 95% de. These reactions constituted the key steps for biologically active product synthesis, such as an epothilone analogue [167], and (-)-doliculide [168], as shown in Scheme 68. It must be noted that in fact these



Scheme 69. Syntheses of (+)-cibenzoline, (+)-tranilcypromine and (-)-milnacipran.

results arose from a double induction since the starting materials were also chiral.

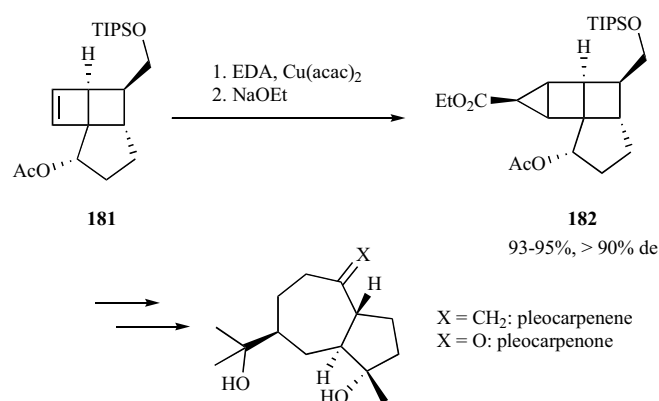
In 2006, (*S*)-phenylalanine-derived disulfonamide **174** was applied as chiral ligand to promote the cyclopropanation of a range of 3,3-diaryl-2-propen-1-ols in the presence of Et_2Zn and CH_2I_2 , providing the corresponding cyclopropylmethanols with moderate to good enantioselectivities (59–84% ee), as shown in Scheme 69 [169]. Chiral cyclopropanes **175**, **176** and **177**, derived from the corresponding allylic alcohols **178**, **179**, and **180**, were further converted into (+)-cibenzoline, an antiarrhythmic agent [170], (+)-tranilcypromine, a strong monoamine oxidase inhibitor, and (-)-milnacipran, a serotonin-noradrenaline reuptake inhibitor, respectively [171].

4.2. Asymmetric Transition-Metal Decomposition of Diazoalkanes as Key Steps

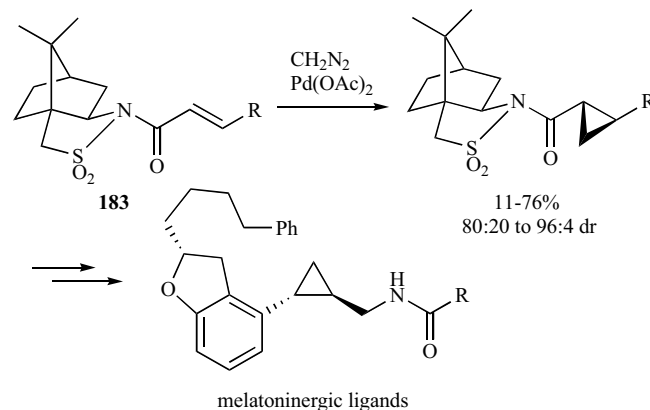
4.2.1. Intermolecular Cyclopropanations

Chiral Substrates

Since the pioneering work of Nozaki and Noyori reported in 1966 [172], the transition-metal-catalyzed cyclopropanation of



Scheme 70. Synthesis of pleocarpenene and pleocarpenone.



Scheme 71. Synthesis of melatonergic ligands.

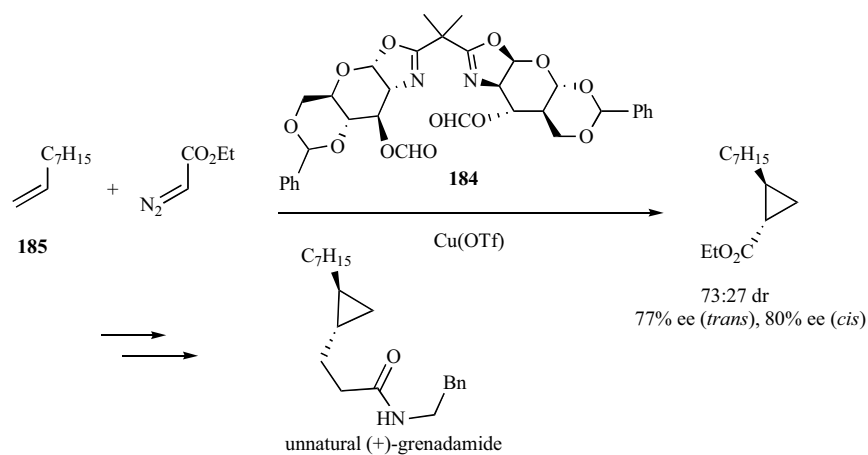
alkenes with diazo compounds has emerged as one of the most highly efficient routes to functionalized cyclopropanes. These reactions have been applied in total synthesis, starting from chiral substrates, but also in the presence of chiral catalysts. As a rare example of reaction involving a chiral substrate, Snapper *et al.* developed the asymmetric cyclopropanation of chiral tricyclic alkene **181** as key step in total syntheses of natural products pleocarpenene and pleocarpenone [173]. The authors observed a high stereochemical control (> 90% de) in the cyclopropanation with ethyl diazoacetate (EDA) into compound **182** followed by deacetylation reaction using $\text{Cu}(\text{acac})_2$ as the catalyst (Scheme 70).

Moreover, Oppolzer's chiral sultam **183** was applied for the synthesis of novel melatonergic agents, as shown in Scheme 71 [174].

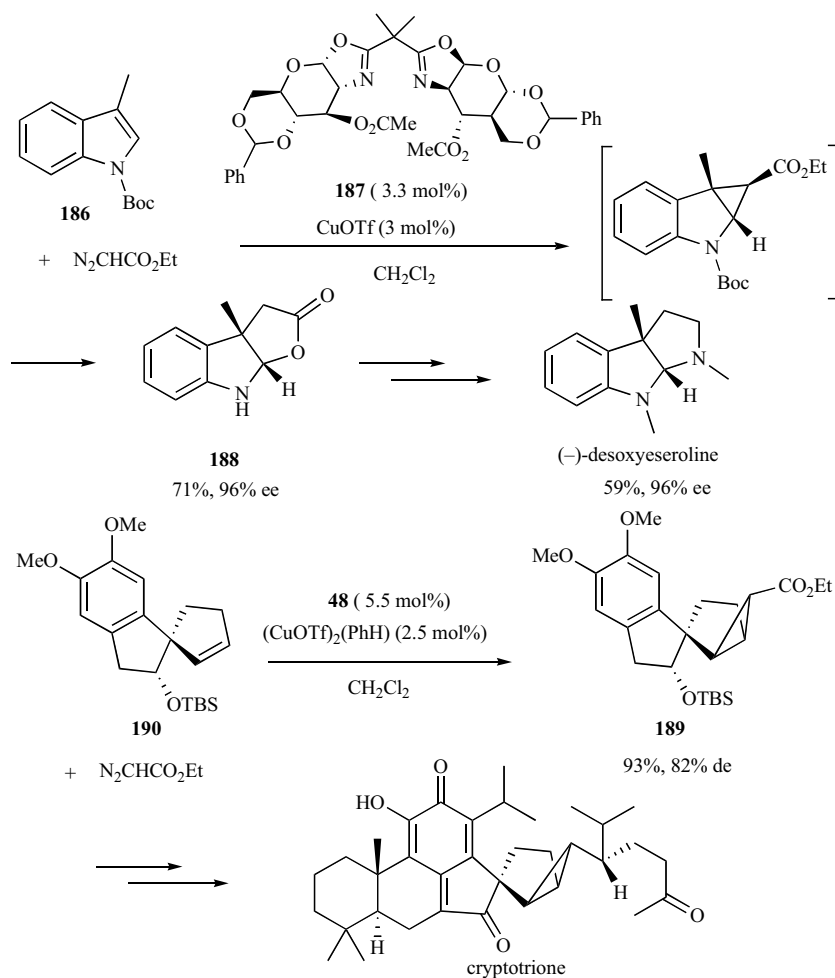
Chiral Catalysts

Chiral copper catalysts are among the most effective catalysts for the preparation of the *trans*-isomer of cyclopropanes with the widest reaction scope. Among them, non-racemic C_2 -symmetric bidentate bisoxazoline ligands [34] have been used in cyclopropanation reactions with copper for more than thirty years (see also subsection entitled "Copper-catalyzed nitrene transfer to alkenes") [175]. Some of these copper-catalyzed reactions have been included into multistep syntheses of natural products [176]. For example, carbohydrate-based bis(oxazoline) ligand **184** and copper(I) triflate were used in the reaction of non-1-ene **185** and EDA for the total synthesis of unnatural (+)-grenadamide [177] (Scheme 72).

In 2012, the cyclopropanation of *N*-Boc-3-methylindole **186**, performed in the presence of bisoxazoline ligand **187** in combination with CuOTf , yielded a key building block **188** for the synthesis



Scheme 72. Synthesis of unnatural (+)-grenadamide.



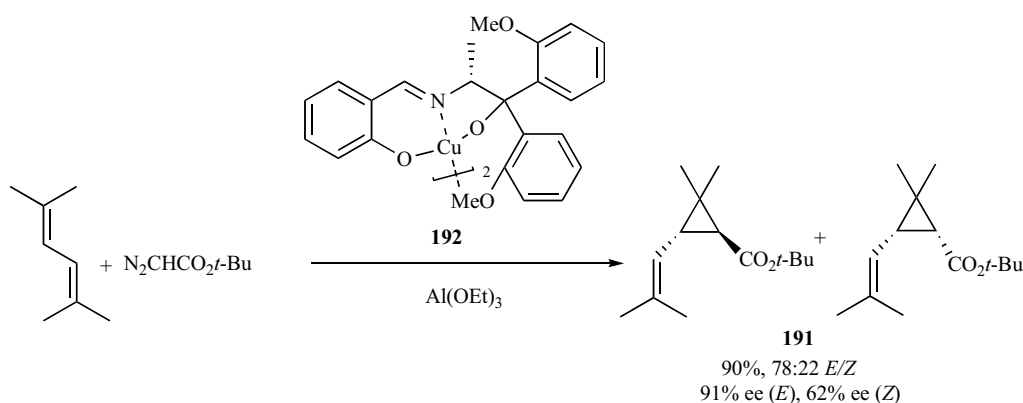
Scheme 73. Syntheses of (-)-desoxyeseroline and cryptotrine through copper-catalyzed cyclopropanations.

of the indole alkaloid (-)-desoxyeseroline that was isolated in 59% overall yield and 96% ee (Scheme 73) [178]. Moreover, the use of ligand **48** allowed the stereoselective preparation of the tetracyclic core and key intermediate **189** in a total synthesis of cryptotrine to be achieved (Scheme 73). The key cyclopropane intermediate **189** was obtained in 93% yield and 82% de starting from alkene **190** [179].

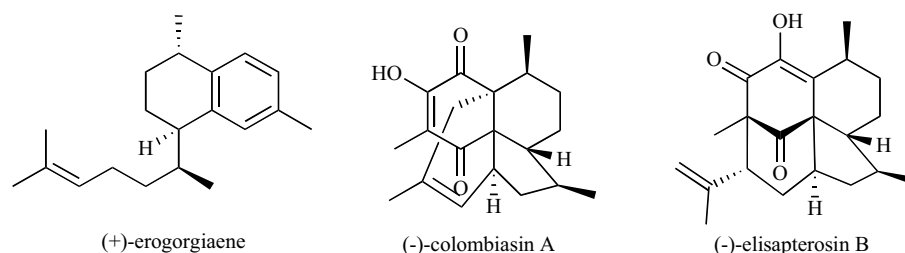
Copper-salen catalysts were found particularly efficient in the synthesis of chrysantemate esters, and (1*R*,3*R*)-chrysanthemic acid

ester **191** was prepared in the presence of Cu(I)-salen complex **192** in 90% yield with 78:22 dr and enantioselectivities of 91% and 62% ee for the *trans*- and *cis*-diastereomers, respectively [180] (Scheme 74).

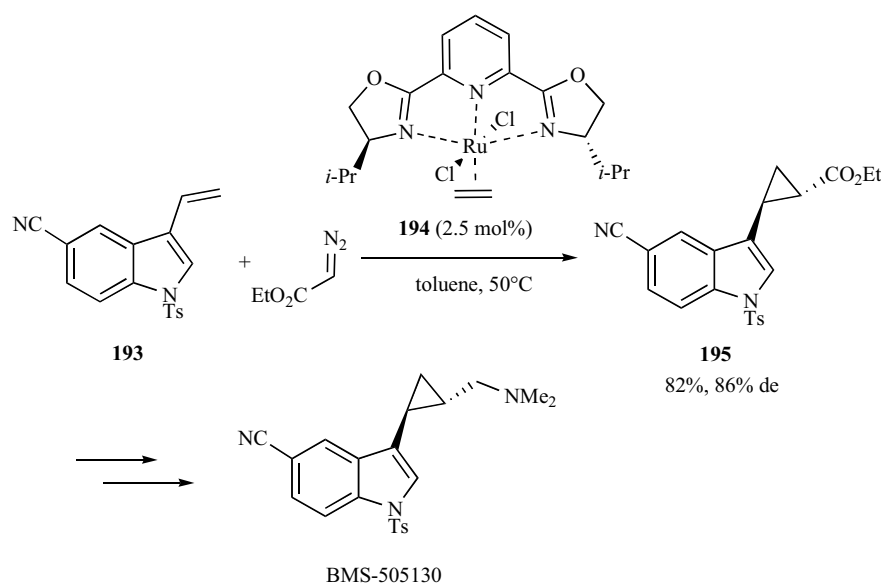
Chiral dirhodium carboxamide catalysts were originally developed by Doyle for enantioselective cyclopropanations [181]. In the presence of these catalysts, allylic substrates and in particular dihydronaphthalene have a potentially competing pathway to cyclopropanation, such as allylic C–H insertion. An example was developed



Scheme 74. Synthesis of chrysanthemic acid ester.



Scheme 75. Natural products synthesized through chiral dirhodium catalysis.



Scheme 76. Synthesis of BMS-505130 through ruthenium-catalyzed cyclopropanation.

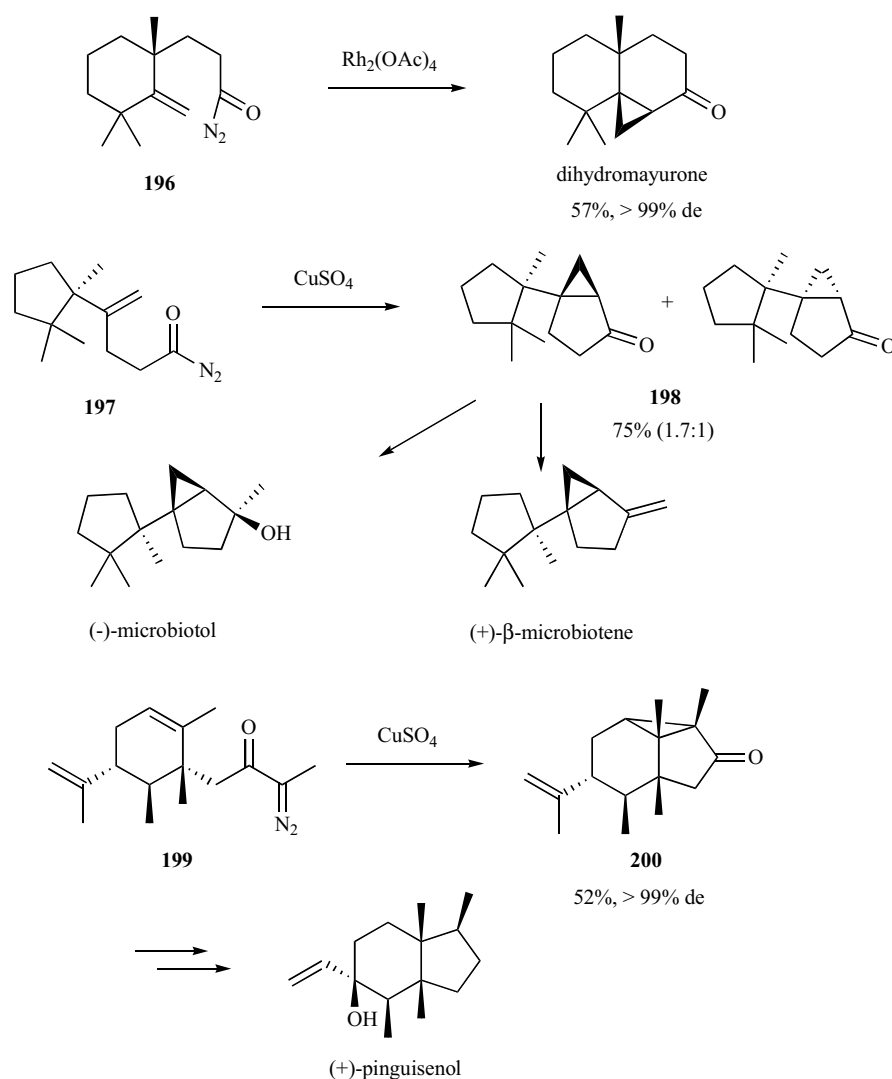
by Davies *et al.* with the total synthesis under $\text{Rh}_2(\text{R-DOSP})_4$ catalysis of the natural products (+)-erogorgiaene, and (-)-colombiasin A, (-)-elisapterosin B through cyclopropanation and C-H insertion, respectively, of the same dihydronaphthalene derivative [182] (Scheme 75).

Moreover, chiral ruthenium catalysts have also been applied to the field of catalytic enantioselective cyclopropanation. This approach was employed by Marcin *et al.* as key step in a total synthesis of BMS-505130, a selective serotonin reuptake inhibitor [183]. As shown in Scheme 76, 1-tosyl-3-vinylindole **193** was cyclopropanated by Nishiyama's catalyst **194** with ethyl diazoacetate to give the corresponding key cyclopropane **195** in 82% yield and 86% de. The latter was further converted into expected BMS-505130.

4.2.2. Intramolecular Cyclopropanations

Chiral Substrates

Initially, intramolecular cyclopropanation reactions were performed with appropriate chiral substrates, and generally occurred with complete stereocontrol, leading to the exclusive formation of one stereoisomeric product. Copper and rhodium complexes are the most popular catalysts for these reactions. For example, $\text{Rh}_2(\text{OAc})_4$ was shown to promote the last step in the synthesis of terpenes, such as dihydromayurone, as the only detected stereoisomer [184]. As shown in Scheme 77, this step evolved through the intramolecular cyclopropanation of chiral diazoketone **196** with complete diastereoselectivity and moderate yield (57%). On the other hand, a



Scheme 77. Syntheses of dihydromayurone, (-)-microbiotol, (+)- β -microbiotene and (+)-pinguisenol.

copper-catalyzed intramolecular cyclopropanation, occurring with low diastereoselectivity of 26% de, constituted the key step in the synthesis of sesquiterpenes (-)-microbiotol and (+)- β -microbiotene starting from chiral diazoketone **197** derived from cyclogeraniol (Scheme 77) [185]. The key cyclopropane intermediate **198** was obtained in good yield (75%). In addition, the key step to construct the bicyclic system of another sesquiterpene (+)-pinguisenol was based on the diastereoselective copper-catalyzed intramolecular cyclopropanation of chiral diazoketone **199** into cyclopropane **200** obtained as the only detected stereoisomer with moderate yield (52%), followed by regioselective cyclopropane cleavage (Scheme 77) [186].

Chiral Catalysts

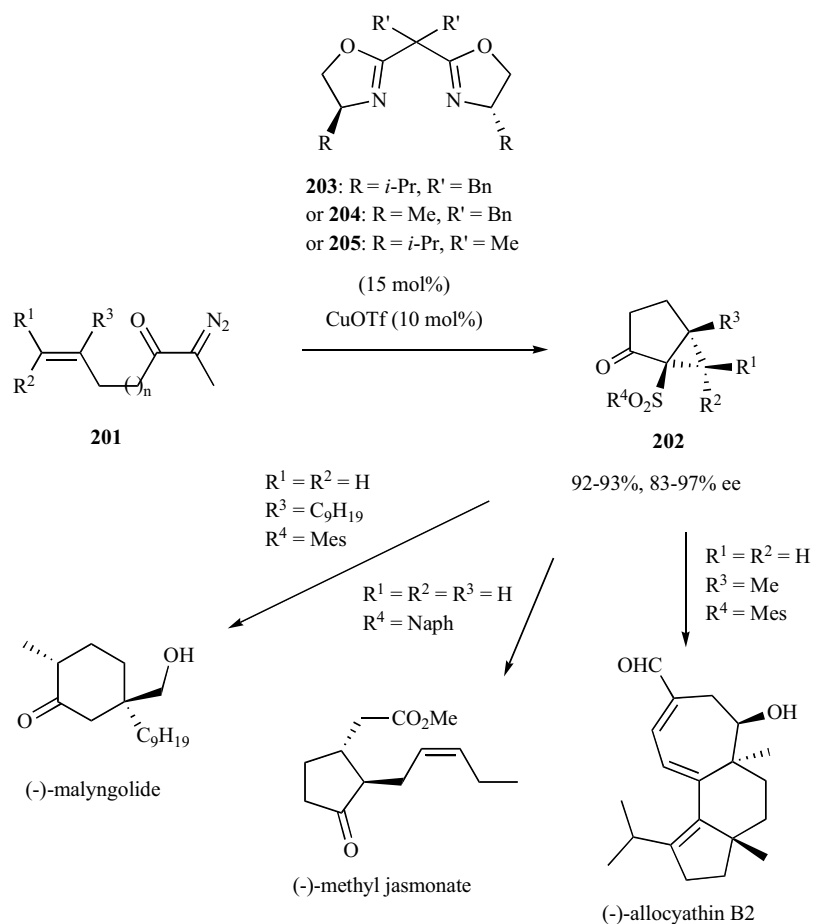
A number of chiral catalysts have been successfully applied to the enantioselective intramolecular cyclopropanation of unsaturated diazoketones as key steps in total synthesis. For example, Nakada *et al.* investigated the enantioselective copper-catalyzed intramolecular cyclopropanation of α -diazo- β -keto sulfones (Scheme 78) [187]. The success of this methodology was illustrated by its application to the total syntheses of several biologically active products, such as (-)-alocycathin B₂ [188], (-)-malyngolide [189], and, (-)-methyl jasmonate, as illustrated in Scheme 78 [190]. Key intermediates

202a-c of these syntheses were produced with up to 97% ee and 93% yield through intramolecular cyclopropanation of the corresponding unsaturated diazoketones **201a-c** catalyzed with a combination of CuOTf with a chiral bisoxazoline ligand among **203-205**.

The same group also developed the enantioselective preparation of tricyclo[4.4.0.0]dec-2-ene derivatives [191] and tricyclo[4.3.0.0]nonenones **206** by using CuOTf combined with chiral ligand **205** [192]. The resulting chiral cyclopropanes **207** were employed as key intermediates in the (formal) total syntheses of natural and biologically active products, such as (+)-busidarasin C and acetoxytubipofuran [191], (+)-digitoxigenin [193], (-)-platensimycin and (-)-platencin [192], as well as nemorosone, garsubellin A, clusianone, and hyperforin [194] (Scheme 79).

A related methodology was also applied to the intramolecular cyclopropanation of various α -diazo- β -oxo-5-hexenyl phosphonates **208** [195]. In the presence of a combination of CuBF₄ and bisoxazoline ligand **203** (structure in Scheme 78), (1*R*,5*S*)-bicyclo[3.1.0]hexane **209** was obtained in good yield (79%) and high enantioselectivity of 91% ee and was further converted into natural and bioactive product (+)-colletoic acid (Scheme 80).

Moreover, asymmetric Rh₂(*S*-MEPY)₄-catalyzed cyclization of allylic diazoacetates led to chiral 1,2,3-trisubstituted cyclopropanes,



Scheme 78. Syntheses of (-)-malyngolide, (-)-methyl jasmonate and (-)-alloyathin B₂ through copper-catalyzed cyclopropanations.

as rigid replacements of dipeptide arrays in several biological systems, with excellent enantioselectivities [196]. For example, Martin *et al.* reported that allylic diazoacetate **210** underwent rhodium-catalyzed cyclopropanation with high diastereo- and enantiocontrol (100% de, 92% ee) since the corresponding cyclopropane **211** was obtained in 80% yield as almost single stereoisomer (Scheme **81**). The latter constituted a key intermediate in a total synthesis of natural biologically active product ambruticin S [197]. Furthermore, the reaction of secondary divinyl diazoacetate **212** led to the corresponding cyclopropane derivative **213** as a 50:50 mixture of two diastereomers each obtained in 94% ee and quantitative yield (Scheme **81**) [198]. This mixture was further employed as key intermediate in the total synthesis of natural products, tremulenediol A and tremulenolide A [199], and to that of various cyclopropane-derived peptidomimetics [200].

In 2015, Chanthamath and Iwasa reported the enantioselective intramolecular cyclopropanation of electron-deficient allylic diazoacetate **214**, performed in the presence of ruthenium catalyst **215** that provided the corresponding diastereo- and enantiopure cyclopropane-fused γ -lactone **216** in high yield (90%) [201]. The latter was employed as building block in the total syntheses of drug DCG-IV and natural product dysibetaine CPa (Scheme **82**).

4.3. Asymmetric Michael-Initiated Ring Closures as Key Steps

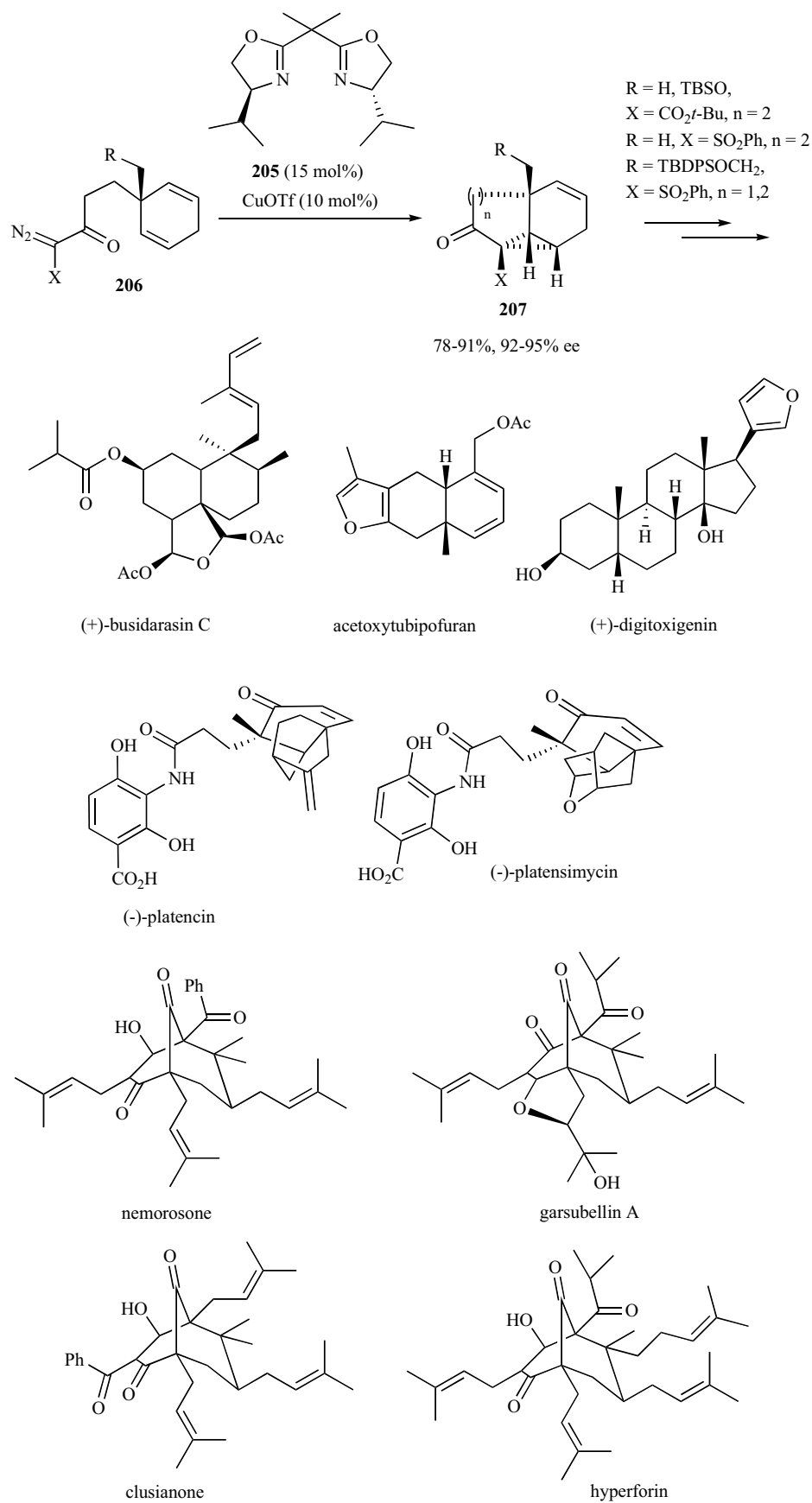
Michael-initiated ring-closing (MIRC) reactions also constitute highly efficient routes to cyclopropanes. These reactions involve a conjugate addition to an electrophilic alkene generally to produce an enolate, which then undergoes an intramolecular ring closure. A

range of asymmetric Michael-initiated ring-closing reactions based on the use of chiral substrates have been applied to the synthesis of important products. As a recent example, Marek *et al.* have developed the MIRC reaction of chiral alkylidene bis(*p*-tolylsulfoxides) **217** with trimethylsulfoxonium ylide **218**, leading to the corresponding chiral bis(*p*-tolylsulfinyl) cyclopropane **219** with a moderate diastereoselectivity of 72% de, which was further used to prepare enantiomerically enriched polyalkylated cyclopropane derivatives [202]. As illustrated in Scheme **83**, this methodology was applied to the synthesis of (9*R*,10*S*)-dihydrosterculic acid, a natural fatty acid [203].

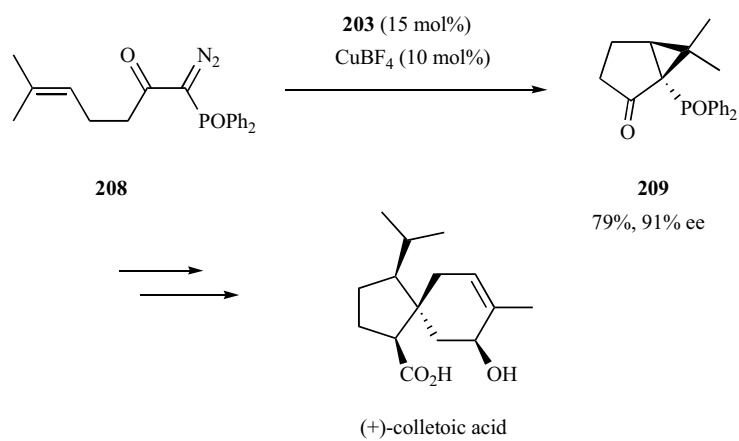
4.4. Miscellaneous Asymmetric Cyclopropanations as Key Steps

Enantioenriched cyclopropane derivatives, such as **220**, can also be efficiently prepared from the addition of the dianion of (-)-dimenthylsuccinate **221** to bromochloromethane **222** (Scheme **84**) [204]. This method, providing up to 98% de and 87% yield, was used in the total synthesis of natural bioactive callipeltoside [205], and to that of the first peptide nucleic acid (PNA) bearing a cyclopropane, (*S,S*)-*tcpr*PNA [206].

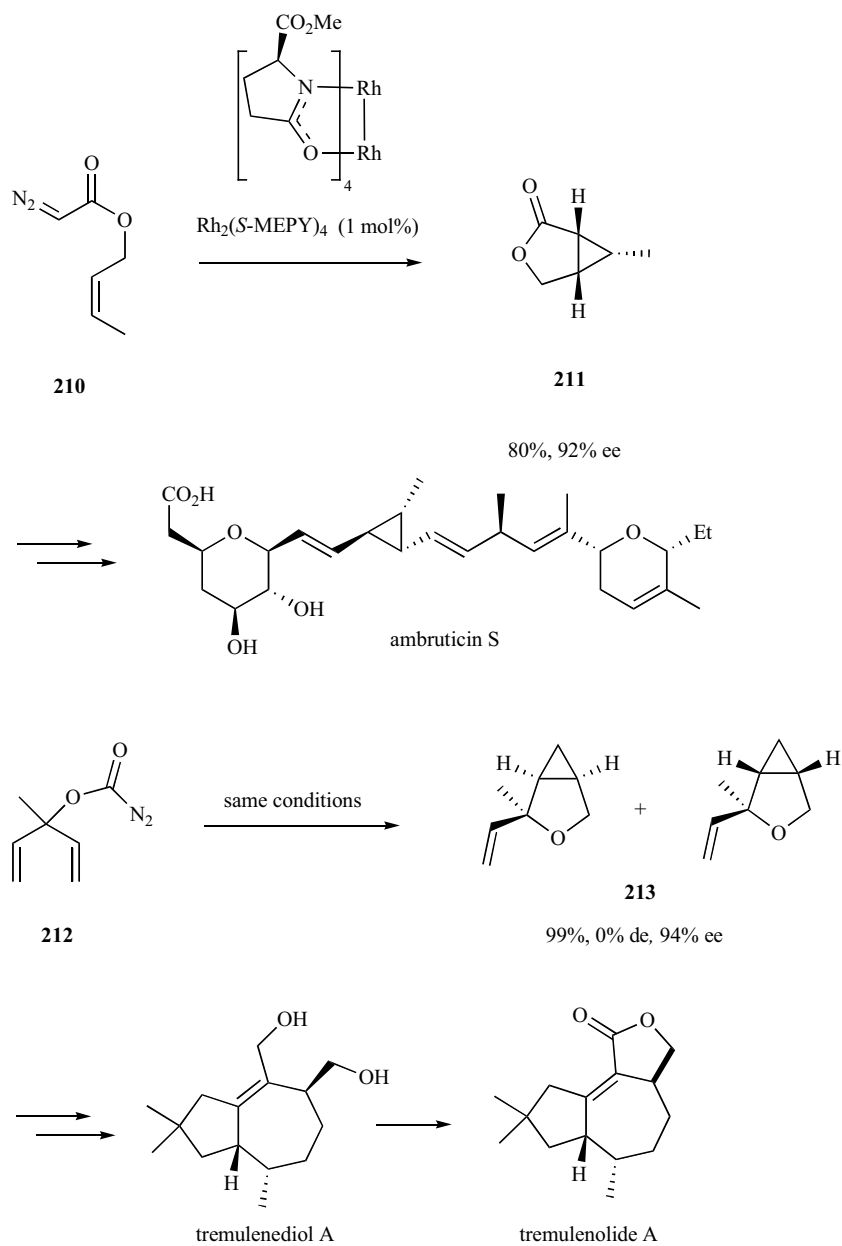
LTMP-induced intramolecular cyclopropanation of unsaturated terminal epoxides provided an efficient and completely stereoselective entry to bicyclo[3.1.0]hexan-2-ols and bicyclo[4.1.0]heptan-2-ols. This methodology was applied to a total synthesis of natural product (+)-cuparenone, starting from chiral chlorohydrin **223** that was converted into the corresponding bicyclohexanol **224** as almost single stereoisomer (> 99% de, 97% ee) in 59% yield (Scheme **85**) [207].



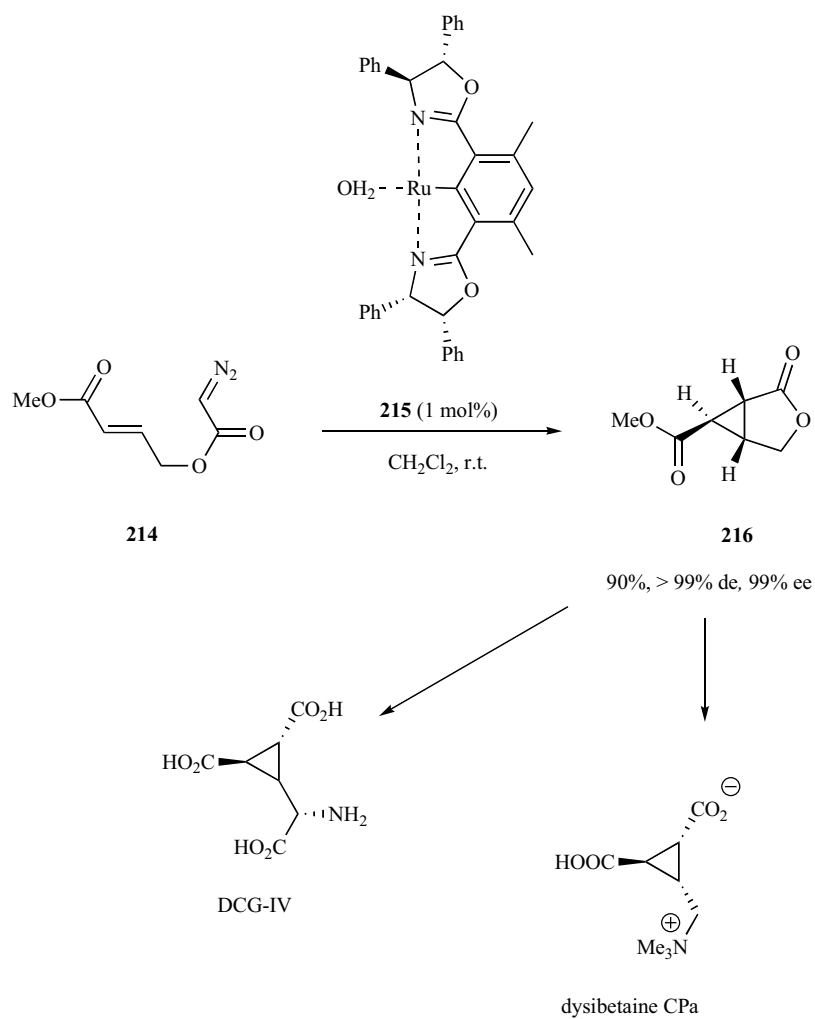
Scheme 79. (Formal) syntheses of (+)-busidasarin C, acetoxytubipofuran, (+)-digitoxigenin, (-)-platencin, (-)-platensimycin, nemorosone, garsubellin A, clusianone, and hyperforin through copper-catalyzed cyclopropanations.



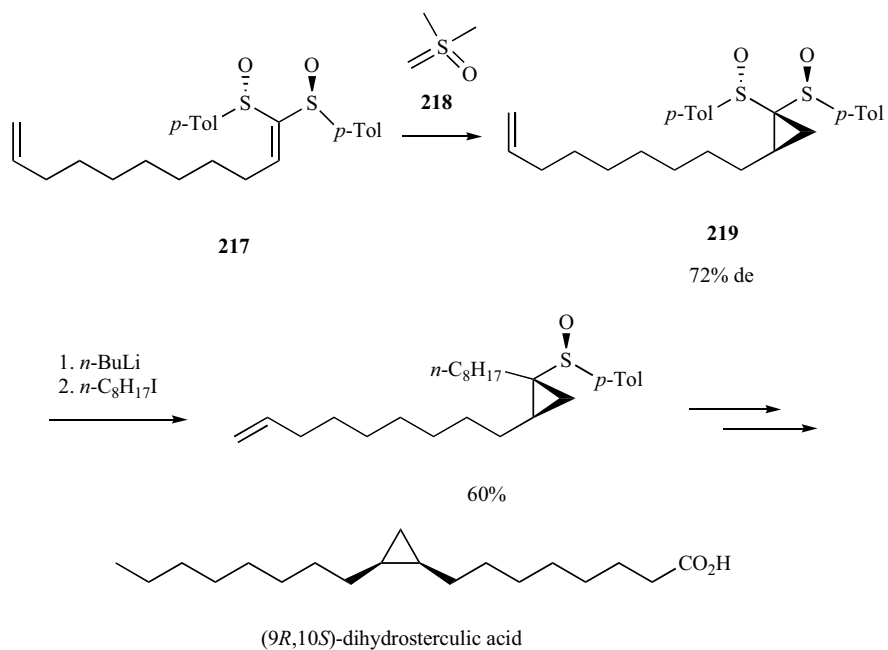
Scheme 80. Synthesis of (+)-colletoic acid through copper-catalyzed cyclopropanation.



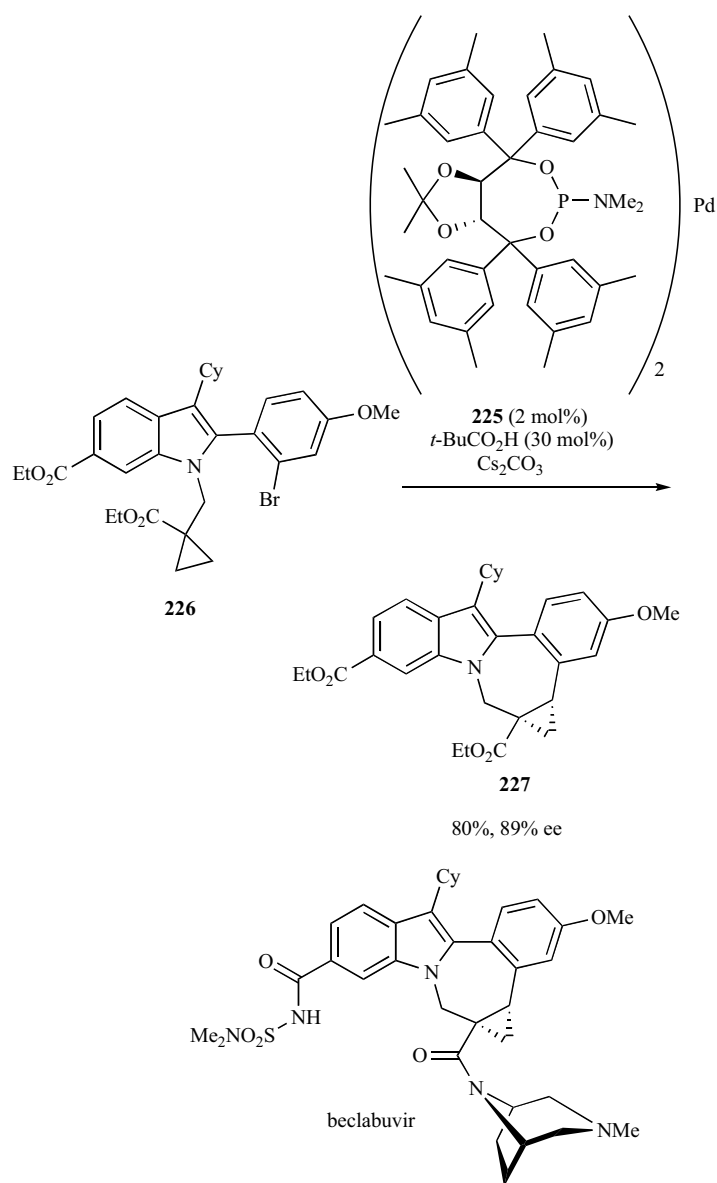
Scheme 81. Syntheses of ambruticin S, tremulenediol A and tremulenolide A through rhodium-catalyzed cyclopropanations.



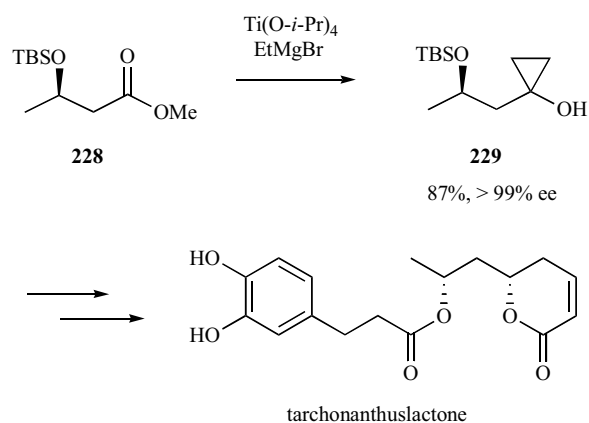
Scheme 82. Syntheses of DCG-IV and dysibetaine CPa through ruthenium-catalyzed cyclopropanation.



Scheme 83. Synthesis of (9*R*,10*S*)-dihydrosterculic acid.



Scheme 86. Synthesis of the cyclopropylindolobenzazepine core of beclabuvir.

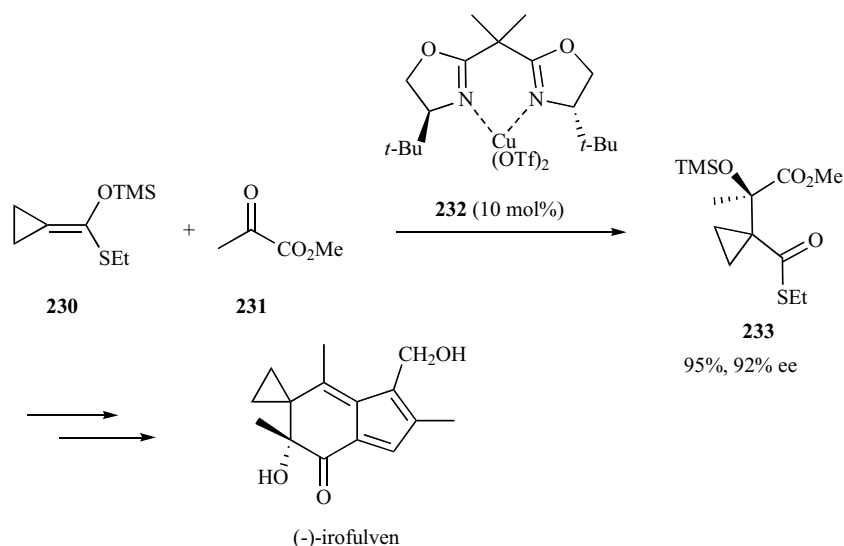


Scheme 87. Synthesis of tarchonanthuslactone.

further converted into expected (–)-irofulven, as shown in Scheme 88.

5. CONCLUSION

This review highlighted major total syntheses of biologically active compounds, including natural products, using chiral three-membered rings as key intermediates. The interest towards synthetic methodologies for their preparation has increased in the last decades, dictated either by the biological activities that display many naturally occurring products bearing a three-membered unit or by their ring strain making them useful precursors of more complex interesting molecules. Classic as well as modern protocols, such as organocatalyzed reactions, have been applied to make asymmetric aziridination, azirination, epoxidation, thiirination, and cyclopropanation key steps of a wide number of syntheses of important products. The use of classical methods which employ chiral substrates and auxiliaries is still highly frequent particularly for asymmetric aziridination and cyclopropanation. On the other hand, the development of enantioselective catalytic methodologies has witnessed exponential growth during the last decade, in particular, in the area of asymmetric organocatalytic epoxidations. The development of new catalytic systems including organocatalysts or chiral



Scheme 88. Synthesis of (-)-irofulven.

ligands for metal catalysts for the synthesis of the other three-membered rings is still in its infancy. However, their expansion is awaited in the coming few years, opening the way to the synthesis of other biologically important products. Undoubtedly, the chemistry of three-membered rings will continue to play a dominant role in the history of total synthesis for many years.

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