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Preface

The importance of chirality is well recognized related to the fact that nearly all natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which will interact only with molecules of the proper absolute configuration. Indeed, the use of chiral drugs in enantiopure form is now a standard requirement for virtually every new chemical entity, and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies. Asymmetric synthesis constitutes one of the main strategies to gain access to enantioenriched compounds, involving the use of either chiral auxiliaries or catalysts.

Even 134 years after the synthesis of the first cyclopropane derivative, the synthesis of chiral three-membered (hetero)cycles remains a considerable challenge. Their strained structures, interesting bonding characteristics, and value as an internal mechanistic probe have attracted the attention of the physical organic chemistry community. Moreover, organic chemists have always been fascinated by these subunits, which have been playing a prominent role in organic chemistry. In fact, while three-membered rings are highly strained entities, they are nonetheless found in a wide variety of naturally occurring compounds including terpenes, pheromones, fatty acid metabolites, and unusual amino acids, among others. Indeed, the prevalence of three-membered-containing (hetero)compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis. The main strategy to gain access to these enantioenriched compounds involve the use of either chiral auxiliaries or catalysts that can in turn be metal-centered, small organic asymmetric molecules or enzymes.

This book collects all the developments achieved in the last 12 years in the fields of asymmetric cyclopropanation, aziridination, epoxidation, oxaziridination, azirination, and thiirination reactions. In addition to describing the large number of highly efficient processes based on the use of various chiral auxiliaries or substrates, this book demonstrates that the most important achievements in asymmetric synthesis of three-membered rings are the spectacular expansion of novel chiral catalysts, including the especially attractive chiral organocatalysts, which have been recently applied to these reactions. Indeed, a collection of new chiral Lewis-acid catalysts and organocatalysts have provided new opportunities for these enantioselective reactions and widely expanded their scope.

Each chapter of the book covers issues related to the title reactions and includes selected applications of the multiple synthetic methodologies discussed to prepare pharmaceuticals, natural or biologically active compounds. All the chapters include synthetic procedures based on the use of chiral pools and auxiliaries, which were employed in the earlier times, but also more convenient catalytic approaches based on the use of chiral metal catalysts and more recently organocatalysts.

Chapter 1, by R. Dalpozzo, deals with the synthesis of chiral cyclopropanes through asymmetric cyclopropanation. The more efficient methodologies employed are the well-known Simmons–Smith reaction, the transition-metal-catalyzed decomposition of diazo compounds, and the irreversible Michael-initiated ring closure (MIRC), among others. For all these procedures, the use of chiral substrates or auxiliaries as well as that of chiral metal- and organocatalysts is covered.

Chapter 2, by H. Pellissier, collects the recent developments in asymmetric aziridination. The use of chiral substrates in addition reactions to alkenes, imines, and azirines as well as in intramolecular substitutions among other reactions is developed in a first section. The second section deals with enantioselective metal- and organocatalyzed carbene transfers to imines and nitrene transfers to alkenes along with catalytic kinetic resolutions of racemic aziridines among other reactions promoted by chiral catalysts of all types.

Chapter 3, by A. Lattanzi, demonstrates the important progress achieved in the past decade in the vast area of asymmetric synthesis of epoxides. Important enantioselective metal- and organocatalyzed epoxidations of alkenes are firstly covered, while other sections deal with kinetic resolution of racemic epoxides, asymmetric sulfur-ylide-mediated epoxidations of carbonyl compounds, asymmetric Darzens reactions, and biocatalyzed synthesis of epoxides, among other methodologies.

Chapter 4, by H. Pellissier, deals with asymmetric oxaziridination, which can be achieved by using chiral substrates or chiral catalysts and kinetic resolutions. It is the smallest chapter of the book, demonstrating that this field is still in its infancy because it has been overshadowed for a long time by the fact that electron-deficient oxaziridines can be employed as convenient and stable sources of electrophilic oxygen.

Chapter 5, by H. Pellissier, collects the advances in asymmetric azirination and thiirination using chiral reagents as well as chiral catalysts, focusing on those published in the last 12 years.

The authors hope that this book will provide an insight into the present stage of asymmetric synthesis of three-membered rings and stimulate chemists to future discoveries to fulfill the enormous potential in this area, opening the way to the synthesis of a number of important products.

List of Abbreviations

2,6-DCPNO	2,6-dichloropyridine *N*-oxide
acac	acetylacetonate
ACDC	asymmetric counteranion-directed catalysis
Ad	1-adamantyl
AKR	aminolytic kinetic resolution
Anth	anthryl
Ar	aryl
BARF	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BHT	2,6-di-*t*-butyl-4-methylphenyl
BINAM	1,1′-binaphthyl-2,2′-diamine
BINAP	2,2′-bis(diphenylphosphino)-1,1′- binaphthyl
BINOL	1,1′-bi-2-naphthol
BMEH	Bacillus megaterium epoxide hydrolase
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Box	bis(oxazoline)
Bs	benzenesulfonyl
Bt	benzotriazole
BUDAM	tetra-*tert*-butyldianisylmethyl
Bz	benzoyl (PhCO)
CAN	ceric ammonium nitrate
CBS	oxazaborolidine Corey–Bakshi–Shibata catalyst
Cbz	benzyloxycarbonyl
CHP	cumyl hydroperoxide
Cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
CPO	chloroperoxidase
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DAM	dianisylmethyl
DAP	diaminopimelic acid
DBN	3,5-dinitrobenzoyl
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide

DCE	1,2-dichloroethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
Dec	decyl
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIC	diisopropylcarbodiimide
DIPEA	diisopropyl ethyl amine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMD	dimethyl dioxirane
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMM	dimethoxymethane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
E	electrophile
EDA	ethyl diazoacetate
ee	enantiomeric excess
EH	epoxide hydrolase
EPR	electron paramagnetic resonance
ESI-MS	electrospray ionization–mass spectrometry
Esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionate
EWG	electron-withdrawing group
FAD	flavin adenine dinucleotide
FG	functional group
Fu	furyl
GDH	glucose dehydrogenase
HDHH	halohydrin dehalogenase
Hept	heptyl
Hex	hexyl
HKR	hydrolytic kinetic resolution
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramine
JHC	Jørgensen–Hayashi catalyst
KSAE	Katsuki–Sharpless asymmetric epoxidation
L	ligand
LA	Lewis acid
LDA	lithium diisopropylamide
LDHs	layered double hydroxides
L-DET	L-diethyl tartrate
L-DIPT	L-diisopropyl tartrate
LEH	limonene 1,2-epoxide hydrolase
LG	leaving group
LIDAKOR	lithium diisopropylamide-potassium *t*-butoxide

LTMP	lithium 2,2,6,6-tetramethylpiperidine
M	metal
MCPBA	3-chloroperoxybenzoic acid
MEDAM	tetramethyldianisylmethyl
MEDPM	tetramethyldiphenylmethyl
MEM	methoxyethoxymethyl
MEOX	methyl 1-oxo-(2-oxazolidine)-4-carboxylate
MEPY	methyl 2-oxopyrrolidine-5-carboxylate
Mes	mesyl
MIB	morpholino isoborneol
MIRC	Michael-initiated ring-closure
MOM	methoxymethyl
Ms	mesyl ($MeSO_2$)
MS	molecular sieves
MSH	*O*-mesitylenesulfonylhydroxylamine
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
Mts	2,4,6-trimethylphenylsulfonyl
NADH	dihydronicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
Naph	naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMP	*N*-methyl pyrrolidinone
NOBIN	1-amino-1′-hydroxylbinaphthyl
Non	nonyl
Npt	naphthyl
Ns	nosyl
NsNIPh	[(nosylimino)iodo]benzene
Nttl	1,8-naphthanoyl-*tert*-leucine
Nu	nucleophile
Oct	octyl
PEG	polyethylene glycol
Pf	phenylfluorenyl
Pfm	perfluorobutyramide
PG	protecting group
Phen	phenanthryl
Phth	phthaloyl
Piv	pivaloyl (*t*-BuCO)
PLA	poly-L-alanine
PLL	poly-L-leucine
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
PNB	*para*-nitrobenzyl
PNNP	*N,N′*-bis[*o*-(diphenylphosphino)-benzylidene]cyclohexane-1,2-diamine
PPTS	pyridinium *p*-toluenesulfonate
PTAB	phenyltrimethylammonium tribromide

PTC	phase-transfer catalyst
PTFE	polytetrafluoroethylene
Py	pyridyl
Pybox	pyridylbis(oxazoline)
r.t.	room temperature
Salen	salicylidenethanediamine
Segphos	5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SEM	2-(trimethylsilyl)ethoxymethyl
Ses	trimethylsilylethanesulfonyl
SIPr	*N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene
SMO	styrene monooxygenase
SPC	sodium percarbonate
Su	succinimidyl
TADDOL	α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutyl ammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
TCPTTL	*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate
TEA	triethylamine
TEBAC	benzyl triethyl ammonium chloride
TEEDA	tetraethylethylene diamine
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thio	thiophene
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMOF	trimethylorthoformate
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	4-methylphenyl
TON	turnover number
TPPP	tetraphenylphosphonium monoperoxybisulfate
TPS	triphenylsilyl
Tr	trityl (Ph_3C)
TRIP	3,3′-bis-(2,4,6-triisopropyl-phenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate
Tris	2,4,6-triisopropylbenzenesulfonyl

Troc	2,2,2-trichloroethoxycarbonyl
Ts	tosyl (4-$MePhSO_2$)
UHP	urea hydrogen peroxide complex
XMO	xylene monooxygenase
Xyl	dimethylphenyl

1

Asymmetric Cyclopropanation

1.1 Introduction

Organic chemists have always been fascinated by the cyclopropane subunit [1]. Its strained structure[1] and interesting bonding characteristics have attracted the attention of the physical organic community [2]. Due to the limited degrees of freedom, these conformationally constrained molecules have very pronounced steric, stereoelectronic, and directing effects, which make them versatile probes for the study of regio-, diastereo-, and enantioselectivity [3].

On the other hand, the cyclopropane subunit is present in many biologically important compounds including terpenes, pheromones, fatty acid metabolites, and unusual amino acids [1j, 4], and it shows a large spectrum of biological properties, including enzyme inhibition and insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor, and antiviral activities [5]. This fact has inspired chemists to find novel and diverse approaches to their synthesis, and thousands of cyclopropane compounds have been prepared [6]. In particular, naturally occurring cyclopropanes bearing simple or complex functionalities are chiral compounds; thus, the cyclopropane motif has long been established as a valuable platform for the development of new asymmetric technologies [7]. The enantioselective synthesis of cyclopropanes has remained a challenge, since it was demonstrated that members of the pyrethroid class of compounds were effective insecticides [8]. Asymmetric synthesis constitutes the main strategy to gain access to enantioenriched compounds, involving the use of either chiral auxiliaries or catalysts that in turn can be metal-centered, small organic asymmetric molecules or enzymes. New and more efficient methods employing all these methodologies to gain enantiomerically enriched cyclopropanes are still evolving, covering all the main cyclopropanation reactions: those are the well-known Simmons–Smith reaction [9], the transition-metal-catalyzed

[1] The strain energy is the difference between the observed heat of formation of a strained molecule and that expected for a strain-free molecule with the same number of atoms.

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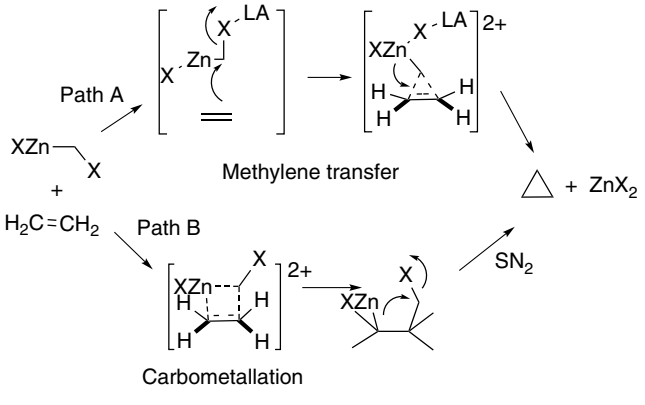
decomposition of diazo compounds [10],[2] and the irreversible Michael-initiated ring-closure (MIRC) [11].

1.2 Simmons–Smith Cyclopropanation

In the late 1950s, Simmons and Smith discovered that the reaction of alkenes with diiodomethane in the presence of activated zinc afforded cyclopropanes in high yields [12]. 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 [13]. The popularity of the Simmons–Smith reaction arose from the broad substrate generality, the tolerance of a variety of functional groups, the stereospecificity with respect to the alkene geometry, and the *syn*-directing and rate-enhancing effect observed with proximal oxygen atoms [14].

In spite of the practical importance of the asymmetric Simmons–Smith cyclopropanation, the reaction pathway is not completely clear yet [15]. Theoretically, the Simmons–Smith cyclopropanation can proceed via a concerted [2+1] methylene transfer (Scheme 1.1, path A), in which the pseudo-trigonal methylene group of a halomethylzinc halide adds to an alkene π-bond and forms two new carbon—carbon bonds simultaneously, accompanying a 1,2-migration of the halide anion from the carbon to the zinc atom. Alternatively, a [2+2] carbometallation mechanism, in which the halomethyl group and the zinc halide add to both termini of the alkene π-bond followed by intramolecular nucleophilic substitution of the pseudo-carbanion, can be supposed (Scheme 1.1, path B). Experimental studies show that, using a zinc carbenoid, the cyclopropanation very likely proceeds by the [2+1] pathway, primarily because the carbon—zinc bond is covalent and unpolarized. In 2003, Nakamura *et al.* studied the reaction pathways of cyclopropanation using the Simmons–Smith reagent by means of the B3LYP



Scheme 1.1 Possible mechanisms for the Simmons–Smith reaction.

[2] The high reactivity of diazo compounds counterbalances the ring strain generated in the newly formed cyclopropane unit.

hybrid density functional method, confirming that the methylene-transfer pathway was the favored reaction course [15]. It took place through two stages, an S_N2-like displacement of the leaving group by the olefin, followed by a cleavage of the C—Zn bond to give the cyclopropane ring. However, the alternative carbometallation and cyclization pathway was found to be preferred when the carbon—metal bond is more polarized, such as in lithium carbenoids, and this hypothesis has received experimental support [16].

Kinetic studies on the cyclopropanation of dihydropyrroles show an induction period that is consistent with a change in the structure of the carbenoid reagent during the course of the reaction. This mechanistic transition is associated with an underlying Schlenk equilibrium that favors the formation of monoalkylzinc carbenoid $IZnCH_2I$ relative to dialkylzinc carbenoid $Zn(CH_2I)_2$, which is responsible for the initiation of the cyclopropanation. Density functional theory (DFT) computational studies were also conducted to study the factors influencing reaction rates and diastereoselectivities [17].

1.2.1 Chiral Substrates

The simplest method to obtain chiral compounds is to start from enantiopure substrates, and the built-in chirality is then preserved in the remainder of the reaction sequence. However, this requires the availability of enantiopure substances with the right configuration, and the cheapest ones are amino acids and sugars, which are available in nature as single enantiomers. In the present case, only the cyclopropanation of various asymmetric acyclic allylic alcohols has been widely developed instead, using the heteroatom as the directing group, by chelation with the zinc reagent. Most of them are prepared by enantioenriched reduction of unsaturated carbonyl compounds or by cleavage of chiral epoxides. This Simmons–Smith reaction has distinct advantages over the reaction with a simple olefin in relation to the reaction rate and stereocontrol [18]. Moreover, these reactions have been shown to be much faster than those with simple olefins, and the reaction with a cyclic allylic alcohol took place, forming the cyclopropane ring on the same side as the hydroxyl group [13, 19].

1.2.1.1 Chiral Allylic Alcohols

The cyclopropanations of 1-cycloalken-3-ols with five-, six-, and seven-membered rings generally produced very good *syn*:*anti* ratios, while a reversal of selectivity was observed with larger eight- or nine-membered ring [7a]. This can be explained on the basis of simple conformational analysis of the ground state [20]. For instance, in their approach to enantiomerically pure cyclopropyl ketones, Johnson and Barbachyn showed that β-hydroxysulfoximines derived from cyclic enones could produce the cyclopropane *syn* to the hydroxy group [21]. In addition, the synthesis of cyclopropanated sugars is diastereoselective. In particular, the *syn*-isomer was obtained as the major product with halomethylzinc reagents, whereas the *anti*-isomer could be prepared by a multistep sequence [22].

The stereoselective cyclopropanation of a chiral, acyclic allylic alcohol using the Simmons–Smith reagent (Zn–Cu, CH_2I_2) was first reported by Pereyre and

coworkers in 1978 [23]. They observed that very high *syn*-selectivity (>200:1) was achieved with (*Z*)-disubstituted olefins, but much lower with (*E*)-disubstituted olefins (<2:1). Charette showed that the nature of the Zn carbenoid used in these reactions is very important for achieving high diastereoselectivities, especially with (*E*)-disubstituted olefins [24]. The stereochemical outcome of these reactions can be qualitatively predicted by assuming an oxygen-group-assisted delivery of the reagent from a conformation in which the minimization of the $A^{1,3}$-strain is the predominant controlling element, but other elements have to be taken into account.

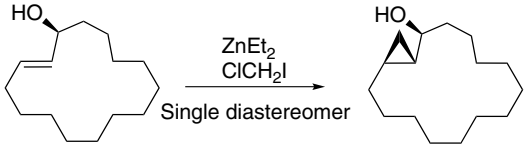
Most of asymmetric cyclopropanations are key steps in the synthesis of natural products of biological interest. For instance, the elegant synthesis of (*R*)-muscone reported by Oppolzer features a diastereoselective cyclopropanation of a chiral macrocyclic (*S*,*E*)-allylic alcohol (Scheme 1.2) [25].

Takemoto and coworkers afforded an asymmetric total synthesis of halicholactone, in which the regio- and stereoselective cyclopropanation is the key step (Scheme 1.3) [26]. It should be noted that the right choice of protecting groups was crucial for the regioselectivity and the occurrence of the reaction.

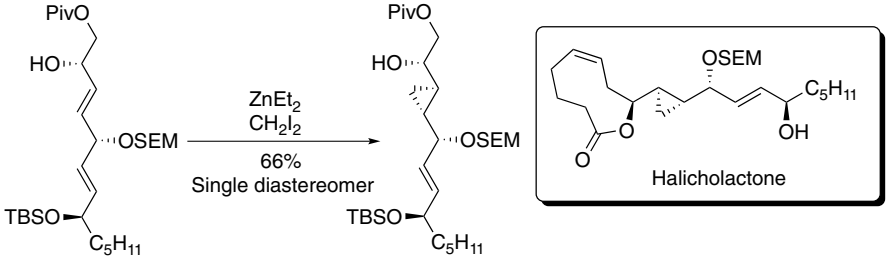
Smith and coworkers afforded the total synthesis of the marine diolide (–)-clavosolide A by direct Simmons–Smith cyclopropanation of an *N*-methoxyamide (Scheme 1.4) [27].

White *et al.* developed a total synthesis of solandelactones E and F (two biologically active oxylipins), having another similar directed Simmons–Smith cyclopropanation as the key step, leading to a single diastereomer, as shown in Scheme 1.5. From this synthesis, authors confirmed that the structures of the two solandelactones were epimeric at C11 [28].

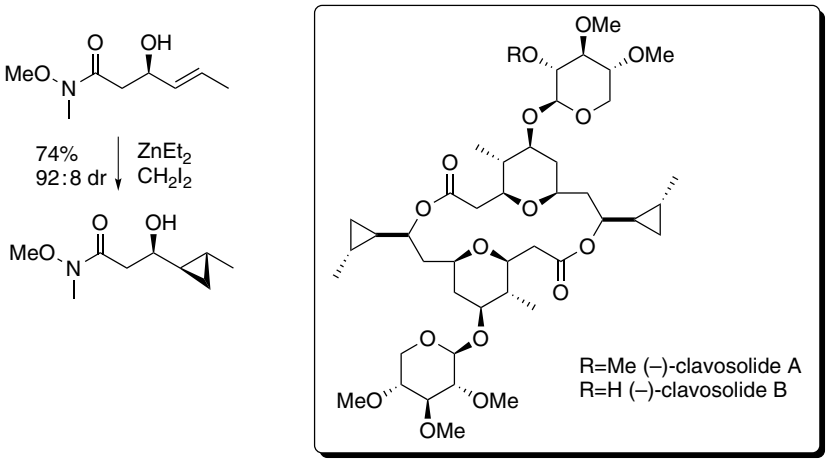
Brevipolides are extracted from the invasive tropical plant of *Hyptis brevipes* and showed interesting drug properties. A diastereoselective synthesis of C1–C12



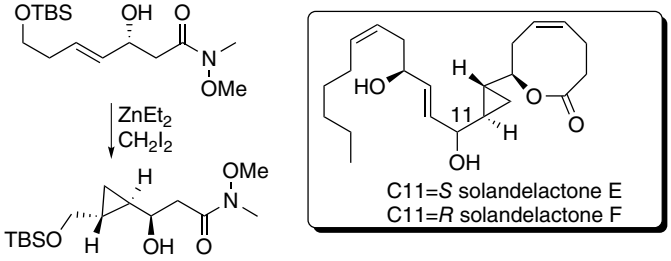
Scheme 1.2 Synthesis of (*R*)-muscone.



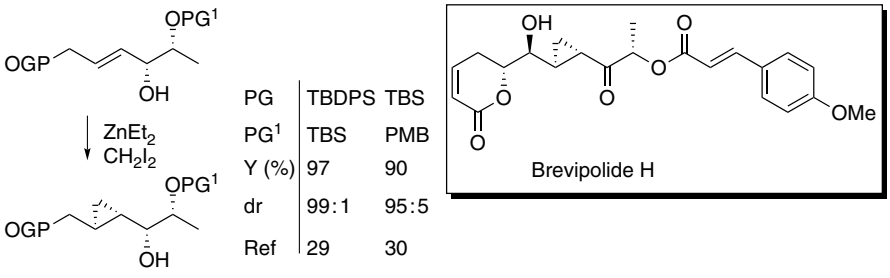
Scheme 1.3 Key step in the asymmetric total synthesis of halicholactone.



Scheme 1.4 Key step in the total synthesis of (–)-clavosolide A.



Scheme 1.5 Key step in the total synthesis of solandelactones E and F.



PG	TBDPS	TBS
PG[1]	TBS	PMB
Y (%)	97	90
dr	99:1	95:5
Ref	29	30

Scheme 1.6 Diastereoselective synthesis of C1–C12 fragment of brevipolide H.

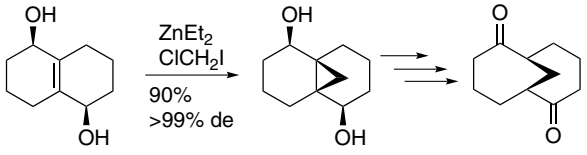
fragment of brevipolide H was synthesized by Mohapatra's group (Scheme 1.6) [29]. More recently, a similar reaction was proposed by Kumaraswamy and coworkers, but with inferior results for the synthesis of 11′-*epi*-brevipolide H [30].

Schmalz's group developed a fully enantioselective synthesis of a C_2-symmetric bicyclo[4.4.1]undecanedione based on a diastereoselective cyclopropanation [31]. It should be noted that the usual Simmons–Smith conditions failed, due to complete decomposition; thus, the desired cyclopropanation was successfully

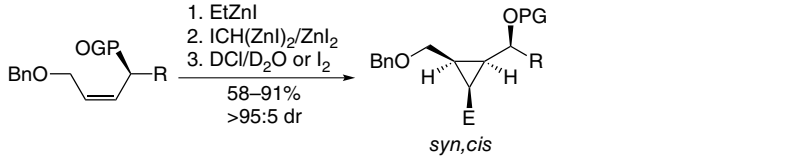
achieved using a $ZnEt_2/ClCH_2I$ reagent, providing the corresponding tricyclic diol as a single diastereomer (Scheme 1.7).

Charette *et al.* reported that the directed cyclopropanation of chiral acyclic allylic alcohols using *gem*-dizinc carbenoids was highly stereoselective, yielding either the *syn* or the *anti*-cyclopropane, depending upon the substitution pattern of the alkenes [32]. Thus, the zinc cyclopropanation of several *cis*-disubstituted allylic alcohols occurred with excellent facial selectivity for the attack of the *gem*-zinc carbenoid, leading to the corresponding *syn*, *cis*-cyclopropyl derivatives in high diastereomeric ratios for a wide range of sterically demanding substituents at the allylic position, even with protected allylic alcohol. The zinc cyclopropanation of the corresponding *trans*-isomer was less stereoselective. However, the introduction of a TMS substituent at either the R^1 or the R^2 position led to the exclusive formation of the *anti*, *cis* or of the *syn*, *trans*-isomer, as shown in Scheme 1.8.

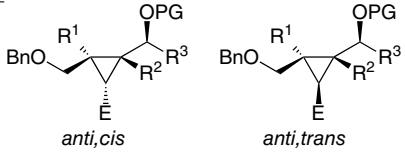
Occhiato's group prepared substituted cyclopropane pipecolic acids as conformationally restricted templates for linear and cyclic peptidomimetics [33]. The synthesis started from commercially available enantiopure γ-hydroxymethyl-γ-butyrolactones, leading to product with complete stereoselectivity even with remote directing group (Scheme 1.9). It should be noted that, sometimes, the reaction conditions deprotected the nitrogen atom, thus avoiding cyclopropanation.



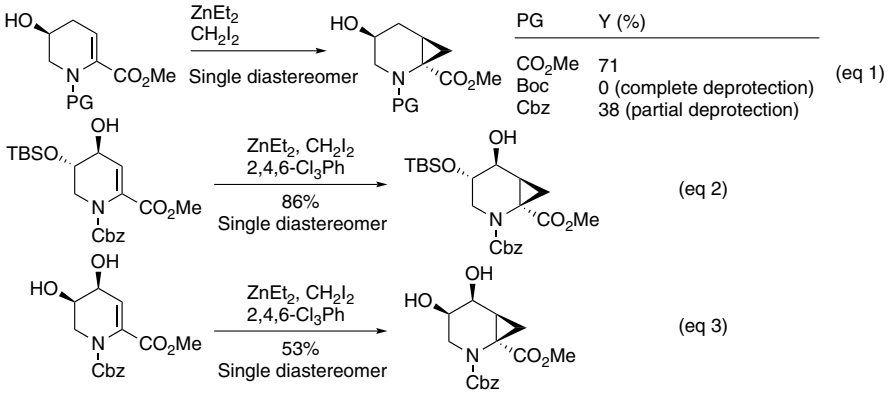
Scheme 1.7 Enantioselective synthesis of a C_2-symmetric bicyclo[4.4.1]undecanedione.



PG	R^1	R^2	R^3	E	Y (%)	*syn:anti*	*cis:trans*
H	H	H	Me	I	85	60:40	28:72
H	H	H	*t*-Bu	D	73	94:6	28:72
TIPS	H	H	*t*-Bu	D	64	>95:5	75:25
H	H	TMS	Me	D	68	<5:95	>95:5
H	H	TMS	*t*-Bu	D	77	<5:95	>95:5
H	TMS	H	*t*-Bu	D	84	>95:5	<5:95
H	TMS	H	*t*-Bu	I	81	>95:5	<5:95



Scheme 1.8 Cyclopropanation of chiral allylic alcohols using *gem*-dizinc carbenoids.



Scheme 1.9 Synthesis of substituted cyclopropane pipecolic acids.

1.2.1.2 Chiral Allylic Amines

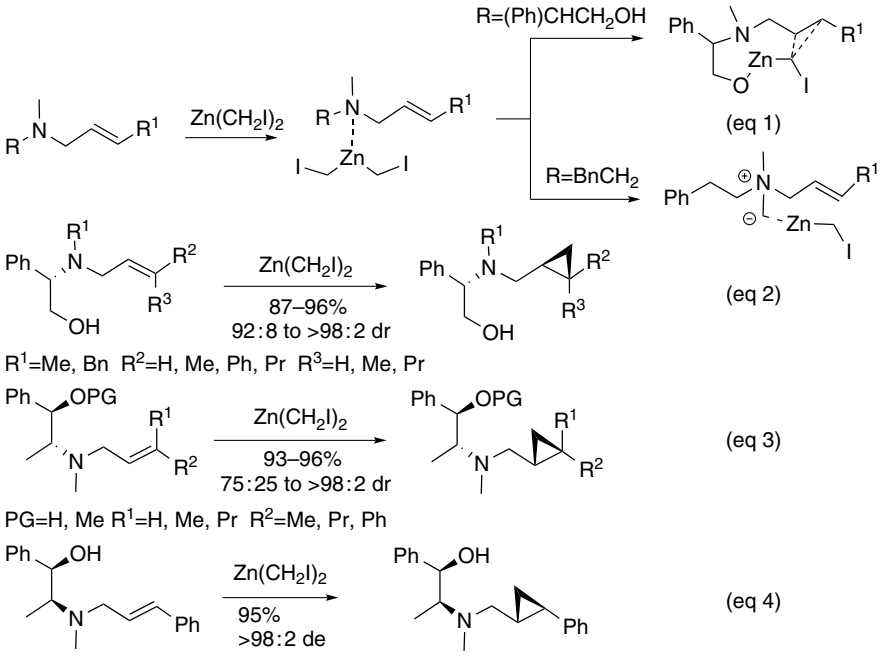
Even though amines have the same potential for binding with the zinc reagent as oxygen functional groups, allylic amines have been much less explored compared to their corresponding alcohols.

Aggarwal and coworkers reported the first highly diastereoselective cyclopropanation of allylic tertiary amines using the Simmons–Smith reagent [34]. They found a divergent behavior of simple allylic amines and those bearing additional chelating groups. In both cases, the reaction was initiated by complexation of the amine with the zinc reagent. However, in the case of a simple allyl-substituted amine (R = $BnCH_2$, Scheme 1.10, eq 1), this species underwent a 1,2-shift to furnish a zinc-complexed ammonium ylide. In the case of an amino alcohol (R = (Ph) $CHCH_2OH$, Scheme 1.10, eq 1), a more stable chelate zinc complex was considered to be formed that did not readily undergo the 1,2-shift. Because of the proximity of the olefin to the tightly held zinc carbenoid, however, cyclopropanation occurred instead. On these bases, they used a range of chiral amino alcohols such as phenylglycinol (Scheme 1.10, eq 2), pseudoephedrine (Scheme 1.10, eq 3), and ephedrine (Scheme 1.10, eq 4), to achieve cyclopropanation with very high diastereoselectivity.

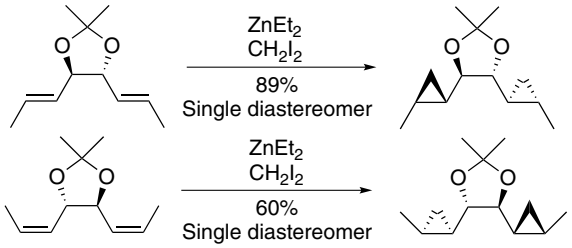
1.2.1.3 Chiral Acetal-Directed Cyclopropanations

Diastereoselective acetal-directed cyclopropanations constitute the key step of some important natural products or drugs containing cyclopropane moieties. The double asymmetric Simmons–Smith cyclopropanation of the (*E*)- and (*Z*)-bis(olefins) could be successfully used to prepare enantioenriched 1,2-bis(2-methylcyclopropyl) ethenes with excellent stereocontrol (Scheme 1.11) [35].

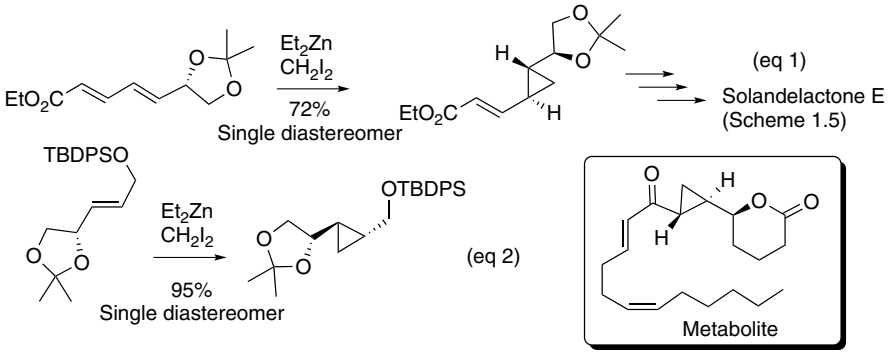
Diastereoselective acetal-directed cyclopropanations also constituted the key step of a total synthesis of solandelactone E (Scheme 1.12, eq 1) [36] and of a total synthesis of a marine fatty acid metabolite having lipoxygenase-inhibiting activity (Scheme 1.12, eq 2) [37], both providing the corresponding cyclopropyl derivative in excellent yield and with high stereoselectivity.



Scheme 1.10 Cyclopropanation of allylic tertiary amines.



Scheme 1.11 Double asymmetric Simmons–Smith cyclopropanation of bis(olefins).



Scheme 1.12 Diastereoselective acetal-directed cyclopropanations.

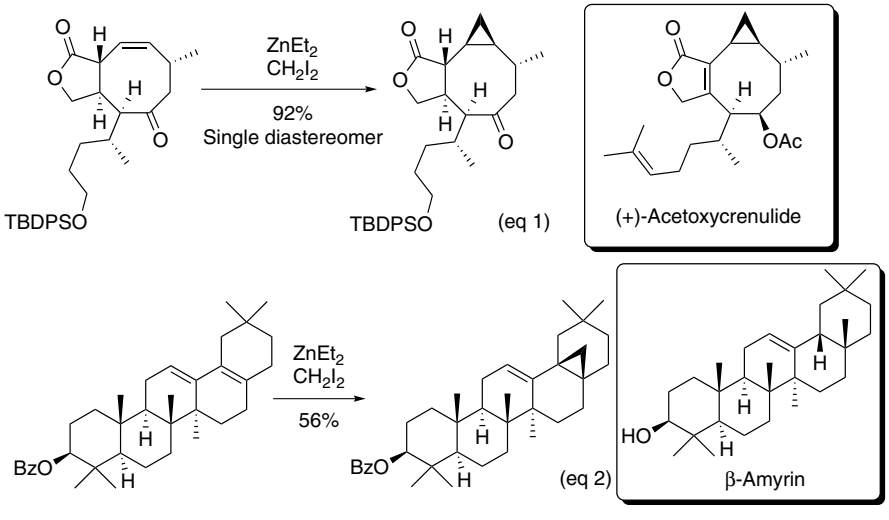
Finally, fluorocyclopropanation of *trans*-styryldioxolane derived from D-glyceraldehyde acetonide afforded the desired cyclopropane in 73% yield, in 94 : 6 dr, and with 99% ee, with the fluorine substituent being oriented *trans* to the dioxolane. The *cis*-isomer led to a 75 : 25 dr, and the major isomer, isolated in 62% yield and with 99% ee, was found to be the all-*cis*-fluorocyclopropane [38].

1.2.1.4 Simple Chiral Alkenes

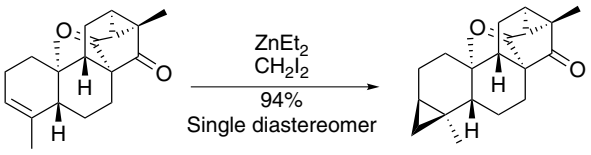
In the absence of a directing group, the cyclopropanation of cyclic olefins is generally subjected to steric effects. The level of stereochemical induction is usually very high, and the sense can be predicted on the basis of the prevailing ground-state conformation of the starting olefin. For instance, a stereoselective cyclopropanation from the more accessible β-face produced a key intermediate in the synthesis of (+)-acetoxycrenulide, as a single isomer (Scheme 1.13, eq 1) [39]. Another stereoselective cyclopropanation was used by Corey and Lee in their β-amyrin total synthesis (Scheme 1.13, eq 2) [40]. The regioselective methylenation of the 17–18 double bond should be also outlined, since the analogous reaction using dibromocarbene added exclusively to the 12–13 double bond.

The stereocontrol in the cyclopropanation of acyclic alkenes, in which the basic group that directed the reagent is not on a stereogenic center, usually was not very high, except when the allylic position bore a bulky dimethylphenylsilyl group. In fact, the cyclopropanation of functionalized (*E*)-crotylsilanes bearing a bis-homoallylic hydroxyl group gave reasonably good diastereoselectivities depending on the nature of the groups on the homoallylic position (the best results are 81% yield and 95 : 5 *anti:syn* ratio). It is worth noting that $AlMe_3$ was the organometallic species generating the carbenoid, because both the zinc- and samarium-derived reagents failed to produce the desired product [41].

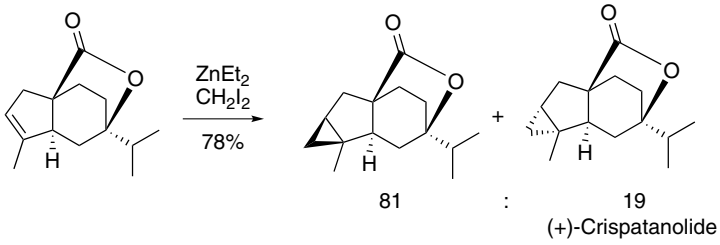
Standard Simmons–Smith conditions were applied by Abad *et al.* to the cyclopropanation of a tetracyclic diterpene [42]. The cyclopropanation took place



Scheme 1.13 Cyclopropanation of simple chiral cyclic olefins.



Scheme 1.14 Cyclopropanation of a tetracyclic diterpene.

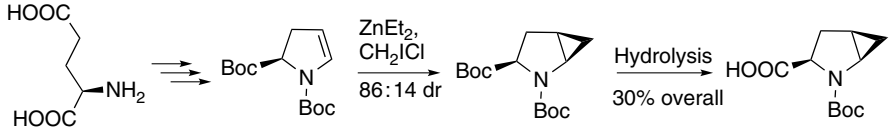


Scheme 1.15 Last step of a total synthesis of (+)-crispatanolide.

stereoselectively from the less hindered β-side of the double bond, affording the expected cyclopropane in excellent yield and diastereoselectivity (Scheme 1.14). This tricyclo[3.2.1.0]octane moiety was a key intermediate in the synthesis of trachylobane-, beyerane-, atisane-, and kaurane-type diterpenes.

Based on the same considerations on the steric effects of bulky polycyclic systems, Tori and coworkers applied standard Simmons–Smith conditions in the last step of a total synthesis of (+)-crispatanolide (Scheme 1.15) [43]. Surprisingly, the major product was not the expected (+)-crispatanolide, but a diastereomer, very likely because of the directing effect of the lactone carbonyl group. However, this synthesis allowed similarly assignment of the absolute configuration to the natural (+)-crispatanolide.

Moreover, 2-azabicyclo[3.1.0]hexane-3-carboxylic acids were obtained from chiral 2,3-dihydropyrroles derived from (*R*)-glutamic acid. The asymmetric Simmons–Smith reaction and hydrolysis reaction mainly led to the all-(*R*)-product. In this Simmons-Smith reaction the reaction time was found to influence the *E/Z* ratio and the best ratio was reached after 19.5 h (Scheme 1.16) [44].[3]



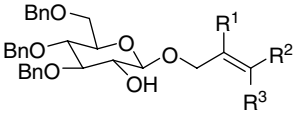
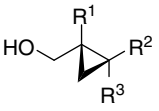
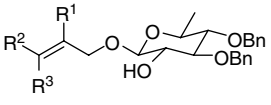
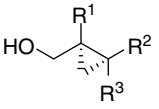
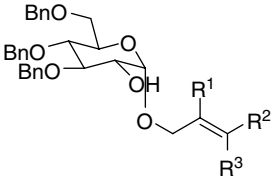
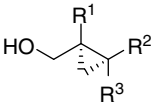
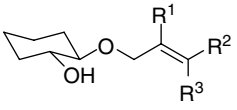
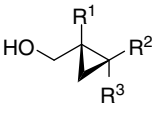
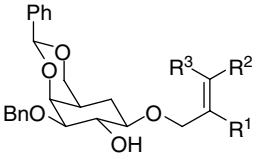
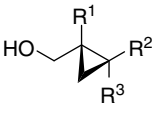
Scheme 1.16 Synthesis of 2-azabicyclo[3.1.0]hexane-3-carboxylic acid.

[3] The paper has only the abstract in English. There the formation of all-(*S*)-product is reported, but schemes report unnatural glutamic acid and it is always numbered R#. Sometimes among Chinese characters some products named S# are reported. Perhaps the reaction was performed from both enantiomers of glutamic acid.

1.2.2 Chiral Auxiliaries

The strategy that uses chiral auxiliaries is based on the transformation into "chiral product equivalents" by binding an enantiomerically pure derivative to the starting material. These compounds are then stereoselectively transformed into new chiral intermediates that contain new stereogenic centers in high diastereomeric excess, with diastereoselectivity being controlled by the presence of the chiral auxiliary fragment. Subsequent cleavage of the chiral auxiliary moiety affords a chiral compound containing a stereogenic center in high enantiomeric excess.[4] Thus, a number of auxiliary-based approaches, which can be encompassed in four general classes, have been reported for the Simmons–Smith cyclopropanation (Table 1.1). Most of these reactions led to cyclopropylmethanols (Scheme 1.17).

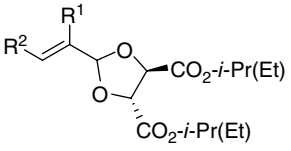
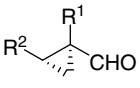
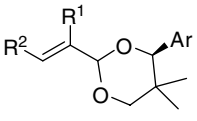
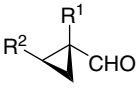
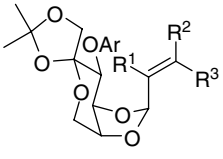
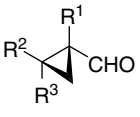
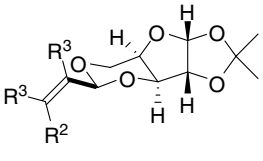
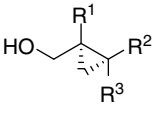
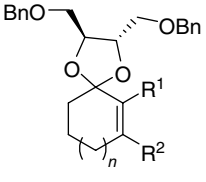
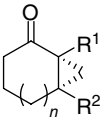
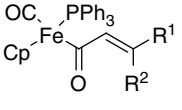
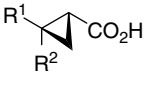
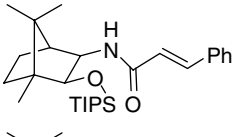
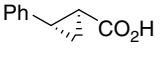
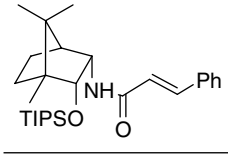
Table 1.1 Chiral auxiliaries for Simmons–Smith reaction using $ZnEt_2$, CH_2I_2.

Starting material	Yield (%)	de (%)	Product	References
Allylic ethers				
	≥95	≥98		[45]
	≥95	≥98		[45]
	83–93	92–94		[46]
	90–98[a]	≥93		[47]
	67–95[b]	Up to 100		[48]

(Continued)

[4] The need for additional steps to add and remove the chiral auxiliary reduces the overall yields and leads to wastage of material. However, this strategy was the first used by chemists to obtain enantioenriched products, and only later, the chiral catalysis emerged.

Table 1.1 (Continued)

Starting material	Yield (%)	de (%)	Product	References
Acetals				
	50–95	93–97		[49]
	34–67	66–92		[50]
	45–90	21–81		[51]
	69–87[b]	50–100		[52]
	54–99[c]	88–95		[53]
α,β-Unsaturated carbonyl derivatives				
	49–86[d]	94–97		[54]
	62[e]	99		[55]
	56[e]	99		[55]