Chapter 4

ASYMMETRIC CYCLOPROPANATION

4.1 INTRODUCTION

This chapter deals with asymmetric cyclopropanations of 2-alkenyl acetals **2.19.** Two methods were tried to achieve a diastereoselective carbene addition to the carbon-carbon double bond.

The Simmons-Smith reaction was used to add a methylene carbene to the double-bond. Moderate diastereoselectivities were achieved by this method. An oxidative deprotection method, using ozone, was performed to obtain trans cyclopropanecarboxylic acids **4.12.**

Another method, which uses transition metal catalyzed decomposition of α-diazoester, failed to give cyclopropanes.

4.2 CYCLOPROPANES: PROPERTIES AND SYNTHESIS

Cyclopropanes receive a continuous interest of both theoretical and synthetic chemists. Ring strain, the nature of the ring carbon-carbon bonds, and the unique chemical reactivity, as a consequence of the first two aspects, fascinate theoreticians. From the synthetic point of view it is a challenge to develop general synthetic methods for cyclopropanes, especially stereochemiscal syntheses is a developing field of interest. Numerous natural products and agrochemicals possess a cyclopropane unit. These and other aspects of cyclopropane chemistry have been repeatedly reviewed over the years.[1-5]

4.2.1 **Bonding modes and ring strain in cyclopropane**

Three major theories of cyclopropane bonding have been developed over the years.[5,6] The Coulson-Moffit model,[7] the Walsh model,[8] and the concept of σ-aromaticity,[9,10] are all used to explain the physical properties and the chemical reactivity of cyclopropanes.

In the Coulson-Moffit model the three carbon atoms are sp^3 hybridized. This approach results in an orbital overlap occurring outside the internuclear line,[7] i.e. so called bent bonds (or banana bonds) are formed. In this model the angle strain is a

consequence of the diminished orbital overlap. In the Walsh model the carbon atoms are sp^2 hybridized.[8] One sp^2 orbital on every carbon atom is directed to the center of the three membered ring, and form together the lowest bonding molecular orbital. The three p-orbitals form also two bonding molecular orbitals.

The strain in the Walsh model has the same origin as in the Coulson-Moffit model. The ring strain is the consequence of poor orbital overlap in the distorted carbon-carbon bonds.

A modern theory is the concept of σ-aromaticity.[9,10] Dewar views cyclopropane as a flat cyclic array of six electrons.[9] In this view cyclopropane is aromatic ($4n+2$ π electrons). In Cremer's version, the σ-aromaticity is the consequence of the three center two electron bond in the Walsh model. Both these theories hold that cyclopropane is more stable than one would expect from angle strain considerations,[11,12] and that the reason for this extra stability is to be found in σ-aromaticity. The experimental strain energy of 116 kJ/mole[11] is indeed substantially lower than the calculated value of 437 kJ/mole.[12]

With any of these three models certain unexpected properties of cyclopropane can be explained, examples being: angle strain, the NMR chemical shifts of cyclopropyl protons, and the reactivity towards electrophiles. The difference between experimental and calculated values for angle strain have been mentioned in the preceeding paragraph.[11,12] In ^{1}H-NMR spectra the cyclopropyl protons show an upfield shift as a result of ring current effects. Coupling constants ($J_{^1H-^{13}C}$; $J_{^{13}C-^{13}C}$) can be understood if the carbon atoms are sp^2 hybridized. The enhanced reactivity towards electrophiles is explained through the aromaticity that is maintained in the transition state.[9]

The Coulson-Moffit model is likely too primitive to describe cyclopropane satisfactorily. On the other hand σ-aromaticity looks somewhat artificial, but together with the Walsh model it can explain many of the properties of cyclopropane.

4.2.2 Cyclopropanes in natural products and in synthetic intermediates

One reason that cyclopropane chemistry is gaining considerable attention in the literature is the occurrence of this ring system in natural products. A few examples are given below (Fig. 4.1).

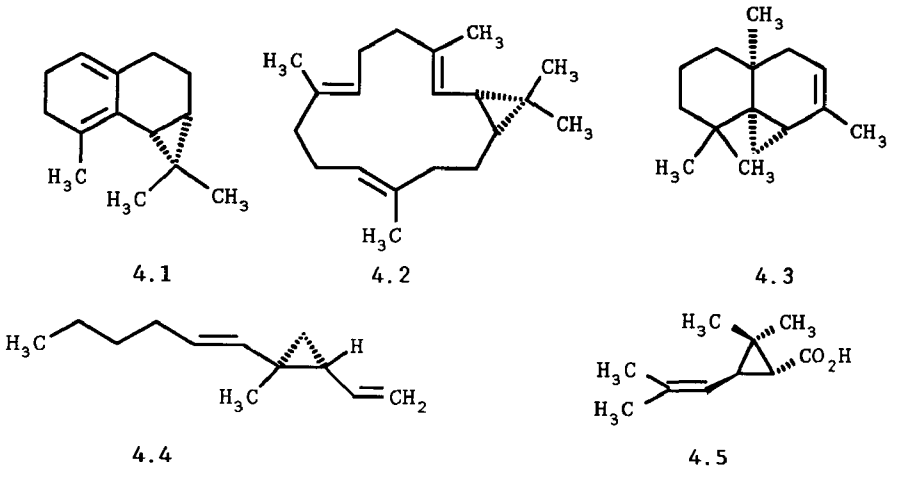
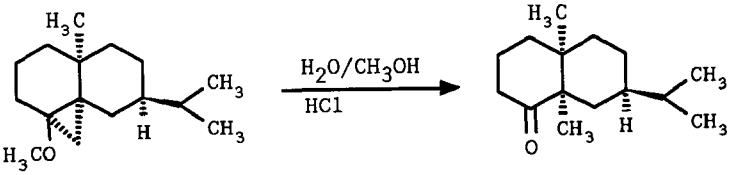


Fig. 4.1 Cyclopropanes in natural products

Bicyclogermacrene (**4.1**) was isolated from the shrub Citrus tunos by Nishimura[13] and casbene (**4.2**) was found in the castor bean Ricinus cummunis.[14] Both terpenes have been synthesized by McMurry.[15] One of the compounds found in the wood oil of the Japanese hiba tree is the tricyclic sesquiterpene (-)thujopsene (**4.3**).[16] Moore determined the structure of a few components of the oils of sea weed found on the shores of Hawaiian islands.[17] One of these components in this oil was dictyopterene A (**4.4**). Chrysanthemic acid (**4.5**), that is used as an insecticide, is probably the best known example of a class of compounds found in the Pyrenthrum flowers.



(-)-Valeranone (4.6)

Scheme 4.1 (-)-Valeranone synthesis

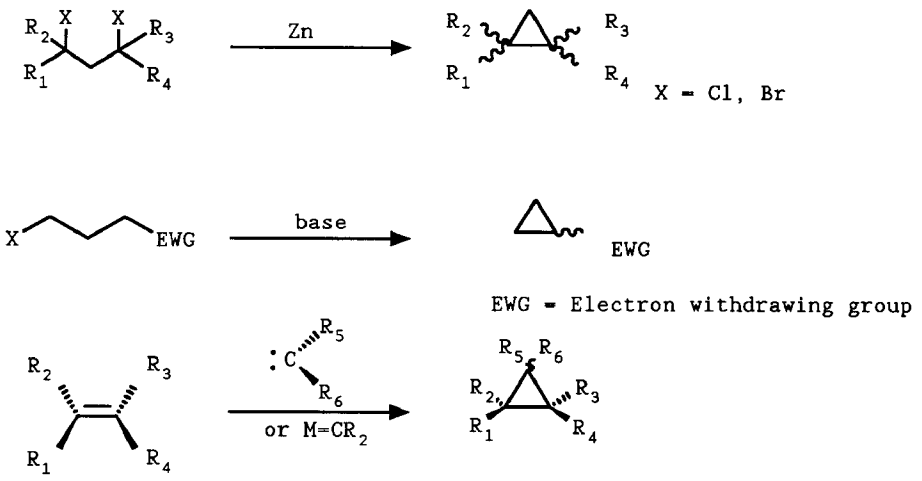
The use of cyclopropanes as intermediates in natural product syntheses is widespread.[3-5] Regioselective electrophilic and nucleophilic ring openings are often possible. One example is given. Enol ethers can be cyclopropanated and after that the cyclopropane ring can be regioselectively opened by acid. This procedure yields an α-methylated ketone. This strategy was used in the (-)-valeranone (**4.6**) synthesis shown in Scheme 4.1.[19]

4.2.3 Cyclopropane syntheses

The three most important routes to synthesize cyclopropanes are the following:[21] (a) dehalogenation of 1,3-dihalo compounds

(b) cyclization of ß-halo esters, nitriles, aldehydes or ketones

(c) carbene addition to alkenes or aromatic compounds



Scheme 4.2 Routes to cyclopropanes

Dehalogenation of 1,3-dihalo compounds suffers from serious limitations, because alkene formation is a common side reaction. Cyclization of ß-halo esters, nitriles,

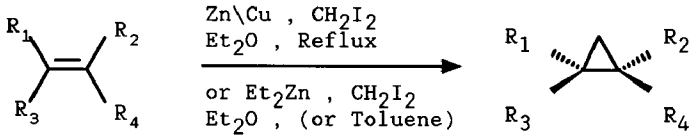
aldehydes or ketones is a good, generally applicable reaction. Instead of chlorine or bromine, a tosyl group can also undergo the reaction. The addition of carbenes to alkenes and aromatic compounds has gained in importance after the development of metal-carbenoid reactions. Nowadays relatively stable metal complexes are known that give cyclopropanes with alkenes. In contrast the high reactivity and relatively low selectivity of free carbenes limit applications severely. Metal carbenoid addition to alkenes will be discussed in a more extensive manner in the next Section.

4.3 METAL-CARBENOID ADDITION TO ALKENES

Metal carbenoid addition to alkenes can be performed either via the Simmons-Smith procedure or by means of a transition metal catalyzed decomposition of diazo compounds. Both strategies will be discussed in this paragraph.

4.3.1 The Simmons-Smith cyclopropanation

In the original Simmons-Smith procedure diiodomethane is used in combination with a zinc/copper couple to cyclopropanate alkenes.[21,22] Inherent to this method are the usually low yield and poor reproducibility. The cause of these complications is imputed to be in the synthesis of the zinc/copper couple.[23] A new procedure was therefore developed by Furukawa and coworkers which does not suffer from these difficulties.[24,25]



Scheme 4.3 The Simmons-Smith reaction of alkenes

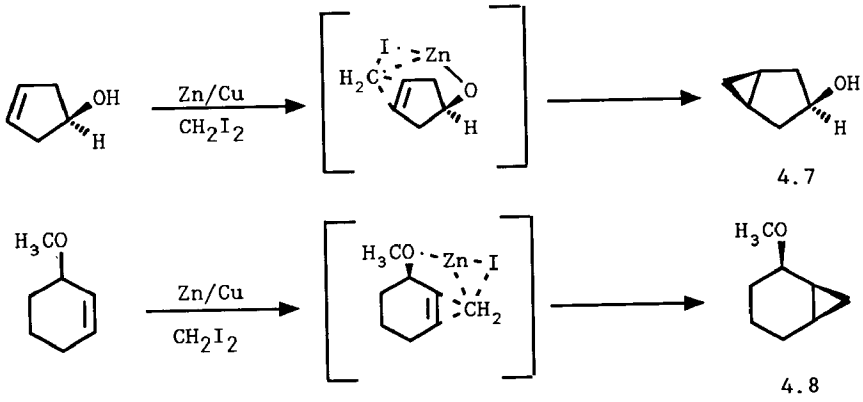
In this new procedure diethylzinc in ether, hexane or toluene, in combination with diiodomethane or another diiodoalkyl compound, is used (Scheme 4.3). With this modification the reaction can be carried out at a wide range of temperatures, depending on the substrate. Diethylzinc is now commercially available as a 1.1M solution in n-hexane or toluene. With this method cyclopropanation is easily carried out, and has

developed to a standard synthetic reaction. Recently, the original procedure was modified by Friedricht et al.,[26] who found that a catalytic amount of $TiCl_4$ facilitates the cyclopropanation reaction.

Numerous studies on the nature of the zinc reagent and on the mechanism of the Simmons-Smith reaction have been undertaken.[21,27] All parties involved seem to be more or less in agreement about the fundamental aspects. The following conclusions have been drawn from these studies concerning the nature of the active zinc reagent:

1. the only role of the copper is to activate the zinc surface;
2. all dihalo methylene compounds are capable of forming a methylene transfer reagent, but diiodomethane is the most reactive one;
3. in the case of the $Zn/Cu/CH_2I_2$ reagent the active species is probably ICH_2ZnI and when Et_2Zn/CH_2I_2 is used it is $ICH_2ZnC_2H_5$ that transfers the methylene group;[21,27]
4. solvation of the zinc reagent takes place in solvents like ether and THF;
5. higher order type zinc species are present at elavated temperatures.

The presence of a hydroxyl or an ether functionality in the substrate molecule can direct the stereochemistry of cyclopropanation of a carbon-carbon double bond (Scheme 4.4).[28-30] The use of this principle will be discussed in the next Section.



Scheme 4.4 Oxygen directed diastereoselective Simmons-Smith reaction

Although the transition state in the methylene transfer to carbon-carbon double bonds is not precisely defined, the following facts characterize it:[21]

1. addition preferably takes place to double bonds from the less hindered site of the

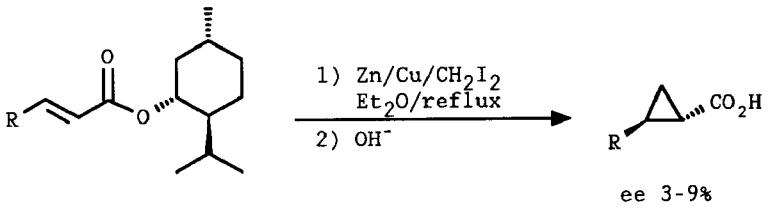
molecule;

2. the reaction is first order in both the alkene and the zinc reagent;
3. the addition is stereospecific with respect to the alkene;
4. the zinc reagent possesses weak electrophilic properties;
5. both new carbon-carbon bonds are formed simultaneously.

The above mentioned facts make the involvement of cations, carbanions or radicals in the reaction highly unlikely.

4.3.2 Asymmetric Simmons-Smith reactions

The first example of an asymmetric Simmons-Smith cyclopropanation was published in 1968 by Inouye and coworkers,[31] who cyclopropanated (-)-menthyl esters of α,β- and β,γ-unsaturated carboxylic acids in 3-9% optical yield (Scheme 4.5). To explain the stereochemistry of the acids formed, they postulated a [3.1.0]bicyclic transition state in which the zinc atom was coordinated to the ester carbonyl group.



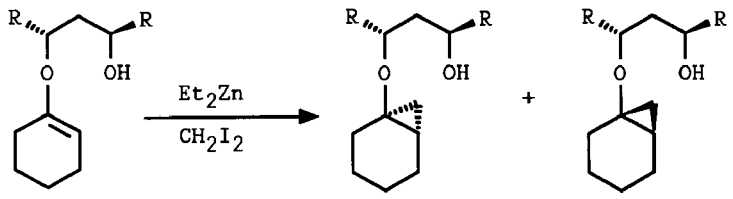
Scheme 4.5 First stereoselective Simmons-Smith reaction

To obtain this transition state a twisted cisoidal conformation of the α,β-unsaturated ester is necessary. Although the chemical and optical yields were not too high, the results showed that optical induction in the Simmons-Smith reaction is possible by using a chiral auxiliary that is capable of coordinating a zinc atom.

Johnson et al. used a chiral sulfoxime to protect α,β-unsaturated cyclic ketones.[32] The diastereoselectivity in this reaction was only moderate, but fortunately the diastereomers could be separated quite easily by column chromatography. The subsequent cyclopropanation (zinc-silver, diiodomethane) proceeded with high diastereoselectivity and cis to the hydroxyl group. After a thermolytic deprotection,

cyclopropane ketones were obtained. This strategy was used to synthesize the tricyclic sesquiterpene, (-)thujopsene.[32]

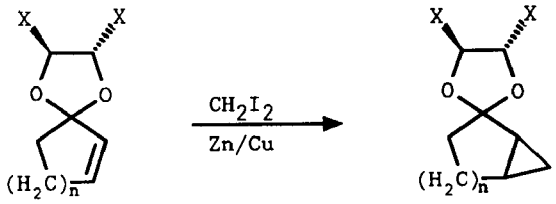
Enol ethers can also be cyclopropanated with an excess of diethylzinc and diiodomethane. Tai and coworkers used (2R,4R)-2,4-pentanediol and (3S,4S)-2,6-dimethyl-3,5-heptanediol as chiral auxiliary in the cyclopropanation of cyclohexanone enol ethers (Scheme 4.6).[33] With the more bulky isopropyl substituent, de's of more than 98% were obtained in hexane or ether as the solvent.



R = CH_3
$i\text{-}C_3H_5$

Scheme 4.6

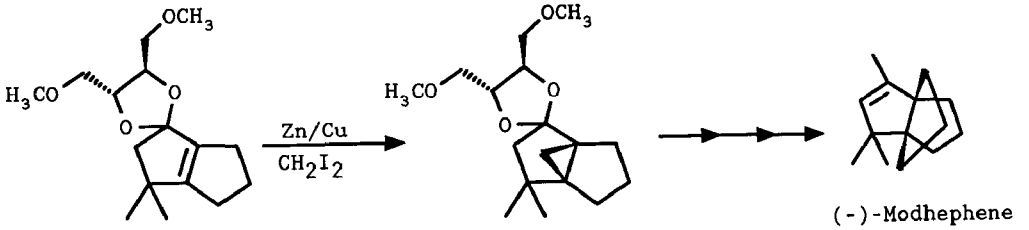
Tartaric acid derivatives have gained considerable interest as chiral auxiliaries, and they have also been tested in Simmons-Smith type reactions. The group of Mash made use of 1,4-di-o-benzyl-l-treitol to protect α,β-unsaturated aldehydes and ketones.[34] Cyclopropanation of these acetals and ketals proceeded in diastereomeric ratios varying from 20:1 to 2:1. Cyclic ketones gave the best results. Aldehydes and non-cyclic ketones gave moderate diastereomeric excesses (Scheme 4.7).



n = 1,2,3
X = $CH_2OCH_2C_6H_5$
CH_2OH
$CO_2C_2H_5$

Scheme 4.7

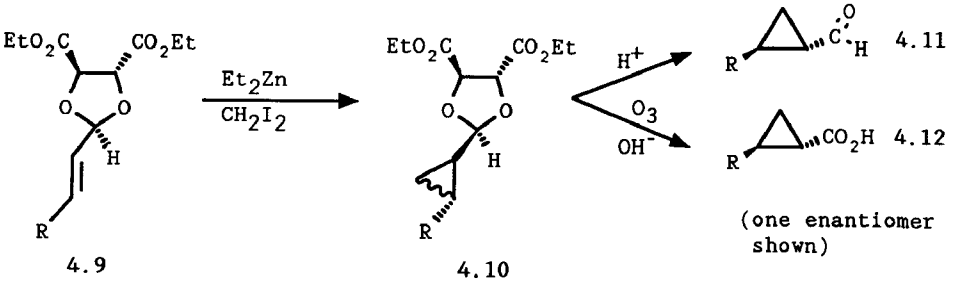
A comparative study of cyclohexenone ketals of other 1,2-diols led Mash to conclude that appendage oxygens, which might coordinate the zinc atom, were not necessary to obtain a high diastereoselectivity (Scheme 4.7).[34a] An asymmetric Simmons-Smith reaction was also employed by Mash in the total synthesis of the sesquiterpene (-)-modhephene[35] (Scheme 4.8).



(4.10)

Scheme 4.8 Synthesis of medhephene (**4.10**)

Acetals of chiral diethyl tartrate were subjected to asymmetric cyclopropanation by Yamamoto.[35] He achieved diastereoselectivities of 85% to 94% in the reaction with excess diethylzinc and diiodomethane (Scheme 4.9). These results were



4.9 4.10

Scheme 4.9 Diastereoselective Simmons-Smith reaction of acetal of diethyl tartrate

compared with the cyclopropanations of unsaturated acetals derived from (2R,4R)-2,4-pentantediol.[36] In that case diastereoselectivities of only 30% to 70% were achieved. In contrast to the diethyl tartrate ketals of cyclohexenone of Mash,[34a] a second complexation site for the zinc atom gave good results for acetals. After acid hydrolysis or ozonolysis and subsequent hydrolysis in base, cyclopropane aldehydes or cyclopropane carboxylic acids were obtained.

Cleavage reactions of C-2 symmetric cyclic acetals catalyzed by Lewis acids preferably take place at the oxygen adjacent to the axial substituent. These sites are denoted with an * in Fig. 4.2. To explain the stereochemistry of the products, given the prefered coordination site, it is necessary to assume conformations **b** and **c** to be the most reactive ones. This assumption seems reasonable because the carbon-carbon double bond is in a better position to be cyclopropanated by a coordinated zinc-carbene complex.

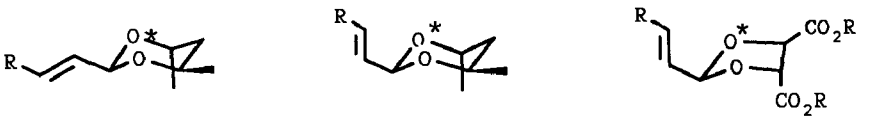


Fig. 4.2

Although the exact mechanism of the Simmons-Smith cyclopropanation is not known, a few conclusions from the above mentioned asymmetric modifications can be drawn:

1. coordination sites for zinc atoms facilitate the carbene transfer to the carbon-carbon double bond. Asymmetric induction is possible as a consequence of this coordination despite the fact that an excess of zinc and diiodomethane is used.
2. most results indicate that the use of an apolar solvent gives higher optical inductions. This observation can be understood by assuming the absence of a competitive coordination site when an apolar solvent is used.
3. the classical procedure (Zn/Cu-couple/CH_2I_2) gave good diastereomeric excesses despite the elevated reaction temperature (refluxing diethyl ether).

In view of the general applicability and the results of the asymmetric modifications of the Simmons-Smith procedure, we decided to perform this reaction on our diastereomerically pure unsaturated acetals **2.19**. We had three major goals in mind:

1. to achieve a high diastereomeric selectivity in the cyclopropanation step.
2. to develop a good deprotection strategy. Normal acid hydrolysis would provide cyclopropane aldehydes; ozonolysis would lead to cyclopropanecarboxylic acids.
3. to gain more insight in the stereochemical aspects of the reaction.

4.4 THE SIMMONS-SMITH REACTION OF OPTICALLY PURE 2-ALKENYL-4-ARYL-5,5-DIMETHYL-1,3-DIOXANES 2.19

4.4.1 Introduction

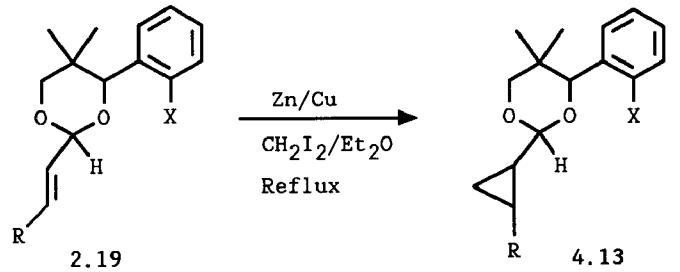
Because we observed a preferential complexation of Lewis acids to the benzylic oxygen of acetals **2.19** derived from 1-aryl-2,2-dimethyl-1,3-propanediols **2.18**, we speculated that it would be possible to obtain good diastereoselectivities in reactions in which metal complexes were involved with moderate Lewis acid properties. From ring acetal opening reactions we have learned that weak Lewis acids were not able to activate the acetal carbon to such an extent that displacement of one of the oxygens became possible (see Chapter 3).

In a Simmons-Smith reaction zinc-carbenoid species are involved. The Lewis acid properties of these species are probably only weak. The same holds true for diethylzinc, which is often used in the most modern recipes for cyclopropanations. No side reactions during Simmons-Smith reactions arise that from the Lewis acid properties of the zinc species have been reported to our knowledge.

4.4.2 Experimental approach of the cyclopropanation of acetals 2.19

The first exploratory reactions to cyclopropanate our acetals were performed according to the classical Simmons-Smith procedure, using a zinc-copper couple and an excess of diiodo methane.[21,22] The zinc-copper couple was freshly prepared for each reaction, as described in Vogel's "Textbook of Practical Organic Chemistry".[23]

Conversion of the alkene moiety to a cyclopropane was observed with acetals **2.19** (Scheme 4.10) in refluxing diethyl ether over a period of 15 h. However, chemical yields were only poor. Only starting material and cyclopropane acetal **4.13** were isolated. The progress of the reaction could easily be determined by integration of the decreased alkene absorptions compared to the growth of the alkane absorptions in the δ 0.5-1.5 region of ^{1}H-NMR spectra. The products and the starting material were normally not separated, although this could be done by careful column chromatography.



R = phenyl X = H
CH_3 Cl

c.y. 10-25%

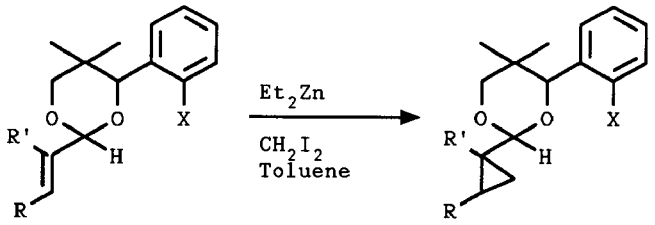
Scheme 4.10 Classical Simmons-Smith reaction of acetals **2.19**

The limiting factor is the preparation of the zinc-copper couple.[22,23] In our hands, a freshly prepared couple sometimes failed to give reaction; this behaviour was unpredictable. Good results, however, have been reported for this classical method, as was discussed in the previous section.[34,35] No further attempts to optimize the reaction were made.

Diethylzinc can be purchased as a 1.1 M solution in either toluene or n-hexane in 100 ml quantities. These apolar solvents are almost immediately assumed to be the solvents of choice, because competiting complexation of the zinc atom is minimized. The reaction is highly exothermic and may lead to explosions. Explosions have been reported due to too quick mixing of the reagents and insufficient cooling of the reaction mixture.[23,24] However, with small scale (1-10 mmol) experiments this was never encountered.

The unsaturated acetals **2.19** which were used in the cyclopropanation reactions, are given in Table 4.1. The reactions were run in freshly distilled toluene (from sodium/benzophenone, N_2-atm) under a dry nitrogen atmosphere. Diethylzinc in toluene was used and a ratio of 1:2 with diiodomethane was maintained in all reactions. An excess of these reagents, relative to the unsaturated acetal, was necessary to make sure that the cyclopropanation of the carbon-carbon double bond was complete. Progress of the reactions could be monitored by thin layer chromatography. In the crude product, the presence of starting material was easily detected by ^{1}H-NMR spectroscopy. It turned out that a three to five fold excess of diethylzinc/ diiodomethane was sufficient to

cyclopropanate the double bonds completely.



2.19 4.13

Entry	R	R'	X	$[\alpha]_{578}$[a] **2.19**	c.y.(%)	$[\alpha]_{578}$[a] **4.13**	d.e. (%)[b]
a	Ph	H	H	+38.9°	78	+3.57°	28
b	Ph	H	Cl	-2.60°	97	-7.27°	-
c	CH_3	H	H	+108°	96	+67.5°	75-78
d	CH_3	H	Cl	-67.9°	60	-39.9°	72-75
e	n-C_3H_7	H	H	+85.3°	97	+48.7°	56-60
f	n-C_3H_7	H	Cl	-61.7°	88	-33.3°	60
g	Ph	CH_3	H	+76.2°	66	+29.1°	-
h	Ph	CH_3	Cl	-19.2°	70	-6.30°	-

[a]: Measured in $CHCl_3$. For the concentrations see the experimental section **4.8**
[b]: Established via integration of the ^1H- or ^{13}C-nmr spectra. See section **4.33**

Table 4.1 Cyclopropanes **4.13** from 2-alkenylacetals **2.19**

The best way to perform these reactions is to add the diethylzinc in toluene to a solution of unsaturated acetal **2.19** in toluene at -30°C. At a low temperature there is no risk of acetal ring opening. Quenching such a solution with water or with trimethylsilyl cyanide gave, after extraction with ether, only unreacted acetal **2.19**. This holds for both saturated and unsaturated acetals **2.19**.

At -30°C, the pure diiodomethane was added carefully to let the temperature not rise above -20°C. At this temperature, after two to three hours of stirring, no starting spot could be seen on a thin layer plate. After standard work-up the products were purified by column chromatography or by bulb-to-bulb distillation. For exact details, the reader

is referred to the Experimental Section of this chapter.

The chemical yields of this modification of the Simmons-Smith reaction are good to excellent. No starting material could be detected in the crude product. The chemical yields in the table refer, however, to the yield of purified product. It was sometimes troublesome to get rid of the excess of diiodomethane. In a few cases this resulted in a somewhat lower yield (entries d, g). Conversions are, however, clean and so it is justified to conclude that this Simmons-Smith reaction is a good way to obtain cyclopropanes **4.13**.

It is striking that the specific rotations of the cyclopropanes tend to go to zero, compared to the specific rotations that were found for the unsaturated acetals. In other words, the cyclopropyl moiety has an opposite contribution in the optical rotation of **4.13** than the cyclic acetal moiety has. As was found later, deprotection of the acetals **4.13** to cyclopropane carboxylic acids gave the enantiomer in excess with a specific rotation with the opposite sign compared to that of the unsaturated acetal. Of course, from this observation no conclusions can be drawn about the diastereoselectivity of the process. However, the trend is general, for both phenyl and o-chlorophenyl derived acetals. This observation makes it likely that there exists a single mechanism in these reactions.

4.4.3 **Diastereoselectivity in the Simmons-Smith reaction of acetals 2.19**

Two diastereomeric compounds possess, in principle, different NMR spectra. These differences may be small; buth with the modern NMR spectrometers even small chemical shift differences can be made visible. Determination of diastereomeric excesses with NMR techniques (^{1}H-, ^{13}C-, ^{31}P- and ^{19}F-NMR) is nowadays common practice.[38] For determination of enantiomeric excess, chiral derivatising reagents are available.[39]

The diastereoselectivity in the cyclopropanation of 2-alkenyl acetals **2.19** can be established from their NMR spectra by virtue of the mentioned principle. Differences in the magnetic properties of various atoms in cyclopropane acetals **4.13**, however, are likely to be small, since the cyclopropyl substituent can freely rotate around the bond with the acetal carbon. This is illustrated in Fig. 4.3.

Both conformations, **2.19A** and **2.19B**, are present in solution. This was concluded from NOESY-NMR spectra of acetals **2.19** (see Chapter 2). Cyclopropanation of **2.19A** or **2.19B** from either side of the carbon-carbon double bond results in cyclopropane

conformations **4.13I** to **4.13IV**; of which **4.13I** and **4.13IV** are diastereomers of **4.13II** and **4.13III**. The parts of the NMR spectra, on which the de values in Table 4.1 are based, are shown in Fig. 4.4.

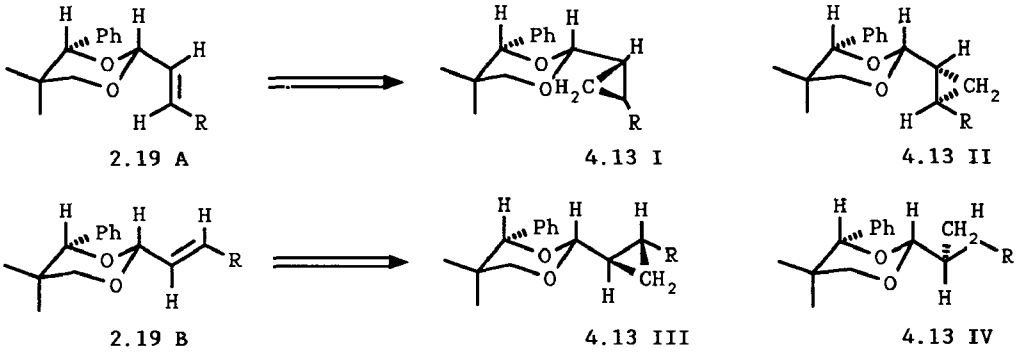
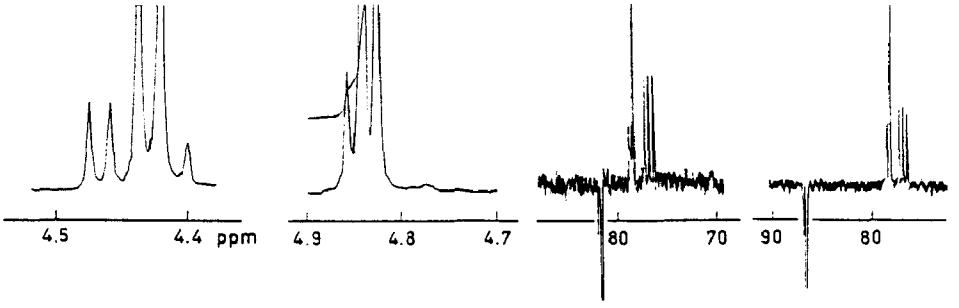


Fig. 4.3 Four possible conformations for cyclopropanes **4.13**



4.13f **4.13a** **4.13c** **4.13d**

Fig. 4.4

The signals for the acetal protons of cyclopropyl acetals **4.13a** and **4.13f** provided sufficiently separated doublets to make a reasonable integration possible. Acetal **4.13a** shows doublets that overlap partially, but integration of the outer lines indicate a de of about 28-30%. Integration of the well separated doublets for acetal **4.13f** gave a de value of 60%. Acetals **4.13c**, **4.13d** and **4.13e** showed double signals in the ^{13}C-NMR spectra for the benzylic carbon and for the -OCH_2-, in the same intensity ratio. Diastereomeric excesses, de-values, of 75-80%, 72-75%, 56-60% for **4.13c**, **4.13d** and **4.13e**, respectively, were estimated from these signals.

Enantiomeric excess values (ee.) for trans-2-phenylcyclo-propanecarboxylic acid and trans-2-methylcyclopropanecarboxylic acid (obtained after ozonolysis of the parent

acetal **4.13**), are in agreement with the estimated de-values (see Section 4.5.3 and 4.5.4).

4.5. DEPROTECTION OF ACETALS 4.13: OZONOLYSIS AND SUBSEQUENT HYDROLYSIS TO CYCLOPROPANE CARBOXYLIC ACIDS

4.5.1 General remarks on acetal hydrolysis

Acetal formation is catalyzed by acid. Hydrolysis entails shift of the equilibrium in the direction of the starting carbonyl compound and alcohol. Acid catalysis is also necessary to perform this operation.[45] Normal acidic reagents to accomplish acetal hydrolysis are: hydrochloric acid, hydrobromic acid, sulfuric acid and boron trichloride or boron tribromide.[45] Of course, the molarity of the acidic solution and the reaction temperature can be varied, depending on the resistence towards acid of the acetal under study.

It was quite clear to us, from the initial experiments to accomplish the hydrolysis of 2-phenyl-4-phenyl-5,5-dimethyl-1,3-dioxane, that it would be difficult to achieve this conversion.

Another problem could become the cyclopropane ring. It is known that cyclopropanes can be opened in the presence of strong Brönsted or Lewis acids.[1-4,46] Opening of the cyclopropane ring of course is only useful when it happens with high regioselectivity.

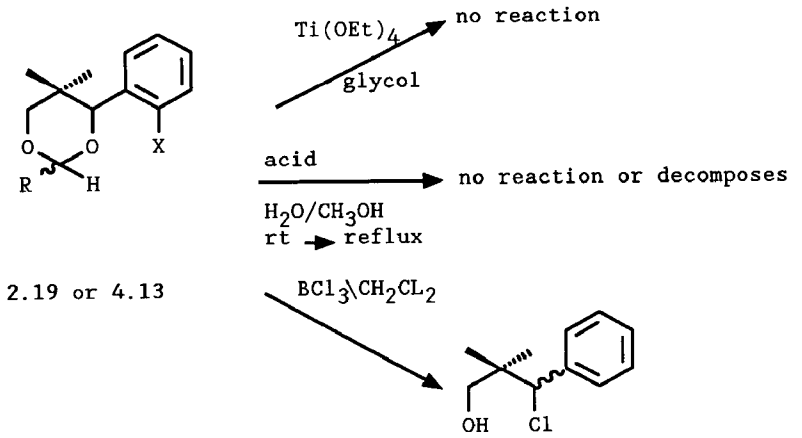
A variety of conditions were tried namely:

1. acidic hydrolysis in hydrochloric or hydrobromic acid
2. reaction with boron trichloride
3. transacetalization
4. ozonolysis and subsequent ester hydrolysis.

The first three methods will be discussed together (Section 4.5.2) and the fourth in Section 4.5.3, because ozonolysis of acetals is a completely different type of reaction compared to the other methods.

4.5.2 **Attempted hydrolysis of acetals 4.13**

A number of inorganic acids in a wide range of concentrations were used to effect hydrolysis of the acetal moiety in 1,3-dioxanes **2.19** and in cyclopropyl-1,3-dioxanes **4.13** (Scheme 4.11).



Scheme 4.11 Hydrolysis conditions for acetals **2.19** and **4.13**.

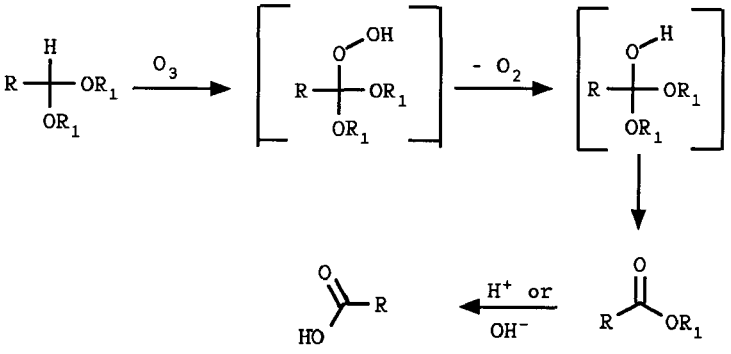
Hydrochloric acid, hydrobromic acid, and sulfuric acid were used to test the resistance of 2,4-diphenyl-5,5-dimethyl-1,3-dioxane towards acidic conditions. Methanol was added (10-20%) to enhance the solubility in water. Hydrolysis was not observed with acid concentrations of 1-5M after stirring at room temperature, nor after reflux for several hours. Decomposition was observed after reflux in concentrated acid solutions, although some benzaldehyde was liberated. Subjecting 2-cyclopropane acetals **4.13** to these acidic conditions gave a quantitative recovery of starting material (1M, room temperature), or led to cyclopropyl cleavage in an unselective manner (reflux). The mild trans-esterification catalyst $Ti(OEt)_4$ was used with ethylene glycol and did not result in any transacetalization of 2-cyclopropane acetals **4.13**, nor was cyclopropyl cleavage

observed. The formation of 1-chloro-1-phenyl-2,2-dimethylpropan-3-ol (**3.29**) in the reaction of acetals **2.19** with BCl_3 was described in Chapter 3. Reaction of cyclopropylacetals **4.13** with 1.0 equivalent of BCl_3 resulted in the formation of some ß-chloropropanols **3.29**, but extensive cyclopropane cleavage was also observed. Moreover, the reaction was incomplete and addition of more BCl_3 gave more unwarranted and unselective cyclopropane cleavage.

4.5.3 Ozonolysis and subsequent hydrolysis of cyclopropane acetals 4.13

Ozone is a highly reactive form of oxygen.[46] It was probably discovered by Schönbein[47] in 1840, who gave it its name. The name ozone is derived from the Greek word ozein, meaning "to smell". The smell of ozone in the air after a thunder and lightning storm has long been known and recognized. Homer refers to it in both the Odyssey and the Iliad,[48] and characterized it as "sulfurous".

Ozone can react as an 1,3-dipole, an electrophile or as a nucleophile. Probably the best known synthetic reactions are the ozonation of carbon-carbon double bonds and the ozone insertion in activated carbon-hydrogen bonds. The synthetic use of ozone is, however, limited because overoxidation takes easily place. A complete degradation of the compound is possible when the ozonation is performed for a long period.



Scheme 4.12 Mechanism of acetal oxidation by ozone

In reaction with compounds that contain an activated carbon-hydrogen bond, ozone can insert in this weakened bond. The reaction between an acetal and ozone is a good example of such a process.[50] In this reaction the acetal is oxidized to a carboxylic

ester (Scheme 4.12). The initial intermediate loses molecular oxygen, giving an instable compound in which the original acetal carbon is now attached to three oxygens. A hydrogen shift to one of the "acetal oxygens" will give the carboxylic ester and a molecule of alcohol. This mechanism was proposed by Deslongchamps.[51] Mechanistic investigations indicated that a "lone pair" of an acetal oxygen should be antiperiplanar to the acetal carbon-hydrogen bond. Attempted ozonolysis of rigid bi- or tricyclic acetals confirmed this precondition.

Because all other procedures to hydrolyze the acetals **4.13** had failed, we decided to attempt ozonolysis and to form the cyclopropanecarboxylic acids, by ester hydrolysis. In 1,3-dioxanes the axial acetal C-H bond possesses a trans diaxial relationship to one of the free electron pairs on both the oxygen atoms. This means that the precondition of antiperiplanarity between this acetal C-H bond and an oxygen "lone pair" is fulfilled.[51]

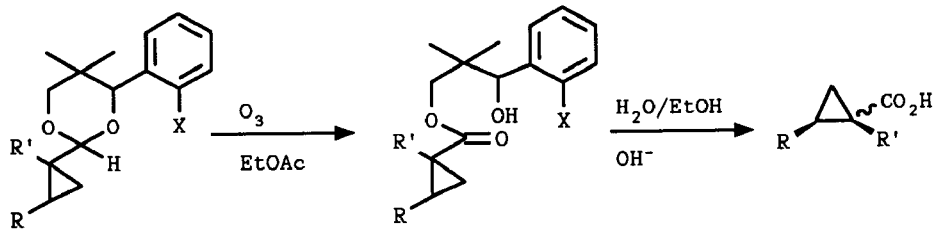
The ozonolysis of acetals **4.13** was performed in ethyl acetate by leading a stream of oxygen-ozone mixture through the solution. The results are summarized in Table 4.2. The ozone was generated by leading a stream of oxygen through an ozone generator. Details about the ozone content in this gas stream are given in the Experimental Section. An excess of ozone, however, was used in all reactions. Because ozone is a very strong oxidizing reagent, monitoring of the reaction was important. Azo dyes have been reported as ozone indicators in ozonation reactions of carbon-carbon double bonds.[52] Unfortunately consumption of ozone by the azo dye Sudan III was fast compared to the oxidation of acetals **4.13**. Ozonolysis of an acetal **4.13** in the presence of Sudan III showed that the use of azo dyes as ozone indicators is an inadequate method to monitor this reaction. After the colour of the Sudan III had disappeared, which happens within a few minutes, acetals **4.13** were recovered unchanged after evaporation of the solvent. Monitoring the reaction was possible with thin layer chromatography (SiO_2; hexane/ethyl acetate 2:1). The cyclopropyl acetals **4.13** have Rf values of approximately 0.8, whereas the ring-opened ester-alcohols **4.14** have typical Rf values of 0.25-0.40. By means of thin layer chromatography it was established that it took about 3,5-4 h until the spot of starting material was no longer detected by iodonation or ultraviolet light. When no more starting material was detected, the ethyl acetate was thoroughly evaporated, and an infrared spectrum was recorded. The ester carbonyl was detected at wave numbers of approximately 1730 cm^{-1}. Also a broad OH-absorption at 3000-3500 cm^{-1} was present in

the IR-spectra. NMR-spectroscopy confirmed the completion of the reaction, since no acetal C-H absorption was present in the crude reaction products **4.14a** or **4.14b**. Both regio isomers **4.14a** and **4.14b** are probably formed in the oxidation of acetals **4.13** with ozone. This is indicated in the NMR spectra of the crude reaction products, in which two benzylic hydrogens can be identified. No attempts were made to establish the ratio of **4.14a** and **4.14b**. The crude mixtures of carboxylic esters **4.14a** and **4.14b** were subjected to ester hydrolysis in a 1 M solution of KOH in water/ethanol 1:1 (v/v) at room temperature for 15-18 hours. A normal work-up procedure gave the carboxylic acids **4.12**. Further experimental details are given in the Experimental Section of this chapter.

The chemical yields in Table 4.2 refer to the isolated cyclopropanecarboxylic acids **4.12** and are the overall yields of this two step deprotection method of acetals **4.13**. The chemical yields are moderate, varying from 34% to 67%. Some over oxidation by ozone, leading to a diminished yield, is not completely avoidable. Probably an average yield of 60% can be reached after further optimalization of this reaction. The yields are reproducible when a stream of ozone/oxygen gas of the same ozone content is passed through the solution for corresponding periods.

Table 4.2 shows that the enantiomers of cyclopropane carboxylic acids **4.12** that are formed in excess have an optical rotation of opposite sign compared to the sign of the optical rotation of the parent unsaturated acetals **2.19** (see Chapter 2, Table 2.1). This is also opposite to the sign of the optical rotation of the parent 1-aryl-2,2-dimethyl-1,3-propanediol.

Trans-2-phenyl- and trans-2-methyl cyclopropanecarboxylic acid have been described previously in the literature.[53,54] Their absolute configurations were chemically correlated to each other and to the known (-)-(1R,2R)-trans-1,2-dimethylcyclopropane[55] by Inoue and coworkers.[53,54] Trans-2-phenyl-cyclopropanecarboxylic acid was obtained from 2-cyclopropane acetals (+)-**4.13a** and
(-)-**4.13b**, by the above described deprotection method, in 32% and 21% enantiomeric excess. As already mentioned, the opposite enantiomers were obtained from (+)-**4.13a** and (-)-**4.13b**. The same result gave deprotection of cyclopropane acetals (+)-**4.13c** and (-)-**4.13d**. Trans-2-methylcyclopropanecarboxylic acid was obtained in 73% and 78% enantiomeric excess from **4.13c** and **4.13d**, respectively.



4.13 4.14a 4.12

(+ regioisomer 4.14b)

entry	R	R'	X	$[\alpha]_{578}$[a] **4.13**	c.y (%)	$[\alpha]_{578}$[b] **4.12**	e.e(%)	config.
a	Ph	H	H	+38.9	67	-99.3[c]	32	R,R
b	Ph	H	Cl	-2.60	38	+64.1[c]	21	S,S
c	CH_3	H	H	+108	41	-57.4[d]	73	R,R
d	CH_3	H	Cl	-67.9	34	+60.9[d]	75	S,S
e	n-C_3H_7	H	H	+85.3	43	-48.1[e]	f	f
f	n-C_3H_7	H	Cl	-61.7	53	+58.0[e]	f	f
g	Ph	CH_3	H	+76.2	46	-63.0[e]	f	f
h	Ph	CH_3	Cl	-19.2	38	+103[e]	f	f

[a]: Rotation was measured in $CHCl_3$. For the concentration see the experimental section **4.8**

[b]: Rotion was measured in abs. EtOH. For the concentrations see the experimental section **4.8**

[c]: $[\alpha]_D$ (lit) 311 (abs. EtOH). see ref. 53

[d]: $[\alpha]_D$ (lit) 77.8 (abs. EtOH). see ref. 54

[e]: Rotation was measured in $CHCl_3$ at λ=578. No literature value is known.

[f]: Not Known.

Table 4.2: Cyclopropanecarboxylic acids **4.12** obtained from ozonolysis of cyclopropyl acetals **4.13**

Both trans-2-n-propylcyclopropane carboxylic acid (entries e and f in Table 4.2) and E-2-phenyl-1-methylcyclopropane carboxylic acid (entries g and h in Table 4.2) have not been described in the literature in optically pure or enriched form. For both acids in our cyclopropanation-deprotection sequence the (+)-acid is produced using a (-)-acetal

2.19 and the (-)-acid is obtained starting from a (+)-acetal **2.19**.

When we assume a mecanistic analogy in the formation of trans-2-n-propylcyclopropanecarboxylic acid (entries e and f in Table 4.2) with trans-2-phenyl- and trans-2-methylcyclopropanecarboxylic acid, then all three acids will have the absolute configuration (-)-(1R,2R), which is correlated with (-)-(1R,2R)-1,2-trans-dimethylcyclopropane.[55] This similarity seems reasonable, since no large difference in steric hindrance arising from the trans-2-n-propyl substituent with respect to the trans-2-phenyl- and trans-2-methyl-substituents is to be expected.

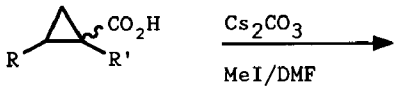
The absolute configuration of (E)-2-phenyl-1-methylcyclo-propanecarboxylic acid is less obvious because of the role which the 1-methyl substituent might play in the conformation of the carbon-carbon double bond in the transition state of the methylene transfer from the zinc carbenoid. The mechanistic and stereochemical analysis that we will present in the next section, however, led us predict an absolute configuration of (+)-(1S,2R) for (E)-2-phenyl-1-methylcyclopropanecarboxylic acid.

The ee.'s found for cyclopropanecarboxylic acids **4.12** that were obtained from cyclpropylacetals **4.13** are disappointingly low. These low ee.'s are, in our opinion, a result of the flexibility of the 2-alkenyl side chain in the parent acetals **2.19** (Table 4.1), that prevents a tight transition state. The use of a cyclic α,β-unsaturated ketone like 2-cyclohexenone would offer a possibility to create a transition state that possesses less rotational freedom. However, the use of ketones in the formation of acetals with diols **2.19** was not feasible (Chapter 2).

4.5.4 Attempts to establish the enantiomeric excess of cyclopropanecarboxylic acids 4.12 by NMR

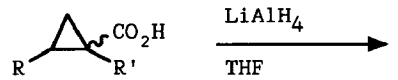
Since optical rotations of enantiomeric pure cyclopropane carboxylic acids **4.1** are only known for the trans-2-phenyl- (entries a and b, Table 4.2) and trans-2-methyl- (entries c and d, Table 4.2) substituted cyclopropanecarboxylic acid, additional experiments to establish the ee. of trans-2-n-propylcyclo-propanecarboxylic acid (entries e and f, Table 4.2) and (E)-2-phenyl-1-methylcyclopropanecarboxylic acid (entries g and h, Table 4.2) were necessary. NMR techniques with chiral shift reagents and with chiral derivatising agents provide good opportunities to do so. Cyclopropanecarboxylic acids

4.12 were transformed to suitable derivatives for NMR ee. determination with $Eu(hfc)_3$ (methyl ester)[39] and with Feringa's PCl_3 method[42] (alcohol). Methyl esters **4.14** were prepared by reaction of the acid cesium salt with methyl iodide in DMF, and alcohols **4.19** by reduction of the acid **4.12** with lithium aluminum hydride (Scheme 4.13). Yields of the reactions varied from moderate to good. Small sclae preparations probably prevent high chemical yields, due to isolation problems that are frequently encountered with LAH reductions.



4.12 → 4.14

	R	R'	cy(%)
a	C_6H_5	H	64
b	CH_3	H	57
c	n-C_3H_7	H	54



4.12 → 4.15

	R	R'	cy(%)
e	n-C_3H_7	H	52
h	C_6H_5	CH_3	69

Scheme 4.13

However, NMR experiments with $Eu(hfc)_3$ and PCl_3 to establish the enantiomeric excess of cyclopropane derivatives **4.14** and **4.15** were unavailing. Stepwise addition of $Eu(hfc)_3$ to a solution of methyl esters **4.14** in chloroform-d resulted in the expected downfield shift of the methyl signals in the ^{1}H-NMR spectra. Insufficient splitting of these signals was observed. The spectra became in fact vague because of peak broadening. Determination of the enantiomeric excess of cyclopropane alcohols **4.15** with the achiral derivatising reagent PCl_3 in the ^{31}P-NMR, according to a procedure of Feringa and Smaardijk,[41] was not feasible. The ^{31}P-NMR spectra of PCl_3 adducts with alcohols **4.15** showed several peaks of which none seemed to match with a reasonable enantiomeric excess. These unsuccessful experiments have led open the question about the enantiomeric purity of cyclopropanecarboxylic acids **4.12e** and **4.12g**.

4.6. DISCUSSION ON THE MECHANISM OF CYCLOPROPANATIONS OF 2-ALKENYL ACETALS 2.19: EXPLANATION OF THE OBSERVED STEREOCHEMISTRY IN CYCLOPROPANECARBOXYLIC ACIDS 4.12

In the preceeding section we provided arguments to illustrate that cyclopropanation of all 2-alkenyl acetals **2.19** by Et_2Zn/CH_2I_2 proceed via analogous transition states. The Zn-carbenoid is complexed to the benzylic ethereal oxygen in this transition state, and the 2-alkenyl side chain has assumed the same conformation in all cases. The general observations on which this idea is based are:

1. the specific rotation of all 2-alkenyl acetals **2.19** has the same sign as the specific rotation of the parent 1-aryl-2,2-dimethyl-1,3-propanediol **2.18** (see Chapter 2);
2. all cyclopropanated acetals **4.13** have a specific rotation that tends to go to zero. This means that the contribution of the new cyclopropane moiety to the total optical acitivity is opposite to the contribution of the chiral 1,3-dioxane ring;[58]
3. after ozonolysis of the acetals **4.13** and hydrolysis of the esters the cyclopropanecarboxylic acids **4.12** were obtained with the enantiomer in excess that showed an optical activity with opposite sign compared with the starting alkenyl acetal **2.19**;
4. the results in Chapter **3** on Lewis acid catalyzed cleavage of acetals **2.19** show that complexation of Lewis acids to the benzylic oxygen is favoured over complexation to the alkyl oxygen. We assume that the zinc carbenoid, being a weak Lewis acid is also complexed to the benzylic oxygen during the methylene transfer. This expectation is in agreement with the hard-soft acid and base principle.[56]

In Fig. 4.5 we propose a transition state in the cyclopropanation of 2-alkenyl acetals **2.19b,d** and **f**
(Table 4.1, entries b, d and f), derived from (-)-(1S)-1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol (**2.18b**). However, analogous structures can be drawn for acetals **2.19a**, **c** and **e** (Table 4.1, entries a, c and e). The conformation of the 2-alkenyl side chain determines to which side of the double bond the methylene is transfered.

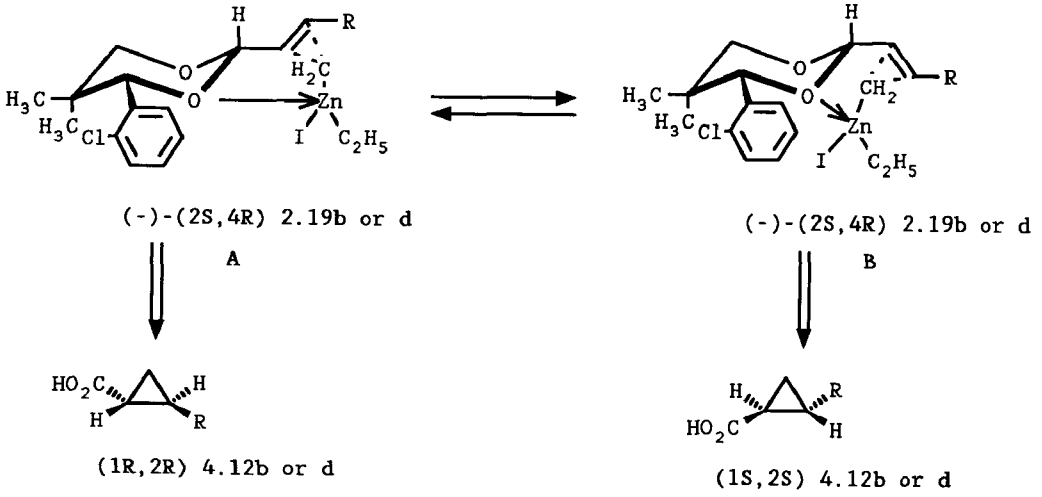


Fig. 4.5 Mechanism of cyclopropanation of acetals **2.19b** and **2.19d**

Kahn and Hehre have calculated minimum energy conformations of simple allyl ethers.[57] One important conformation is shown in Fig. 4.6 for 3-methoxy-1-butene. In this conformation the π-orbitals of the carbon-carbon double bond are oriented perpendicularly to the H-C(3) bond. We assume that in 2-alkenylacetals **2.19a** a similar minimum energy conformation exists. Two possible conformations are represented as **A** and **B** in Fig. 4.6. The π-orbitals of the double bond are perpendicular to the acetal carbon-hydrogen bond. Cyclopropanation of the double bond in **B** would result in the ultimate formation of the 2-substituted cyclopropanecarboxylic acid enantiomer, which is actually found in excess, whereas **A** would result in the opposite (wrong) enantiomer. The higher reaction rate of the cyclopropanation of **B** is a consequence of double bond being folded back towards the acetal ring, bringing it in a closer proximity to the zinc carbenoid compared to **A**.

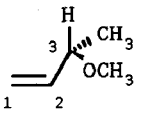


Fig. 4.6

The cyclopropanation of 2-alkenyl acetals **2.19g** and **2.19h** is more complicated by the presence of an additional methyl substituent (derived from α-methylcinnamic aldehyde). When we make the same assumptions as we did in Fig. 4.6; i.e. the zinc carbenoid is complexed to the benzylic oxygen and the alkene π-orbitals are oriented perpendicularly to the acetal carbon-hydrogen bond.[57] In addition, the presence of the α-methyl substituent will probably favour conformation B over A (Fig. 4.5). An analogous discussion leads us to predict an absolute configuration of (1S,2R) for the (+)-**4.12h**. Unfortunately, no references are available that permit us to verify this prediction. Work, however, by Brewster on the relation between optical rotation and the polarizability of substituents attached to the chiral center[58] indicates that the large positive optical rotation of (1S,2S)-2-transphenylcyclopropanecarboxylic acid (**4.12b**; Table 4.2) could not be altered into a negative rotation by substituting 1-H for a 1-CH_3 to form (1S,2R)-(E)-2-phenyl-1-methylcyclopropanecarboxylic acid **4.12h**. Thus the positive rotation found for the acid **4.12b** is a further indication that the enantiomer in excess has indeed the absolute configuration (1S,2R).

4.7 TRANSITION METAL CATALYZED DECOMPOSITION OF ETHYL DIAZOACETATE IN THE PRESENCE OF ACETALS 2.19

4.7.1 Introduction

Another general applicable method of cyclopropane formation in synthetic organic chemistry is the transition metal catalyzed decomposition of diazo compounds in the presence of alkenes.[59,60] Two distinct mechanisms can be given. The reaction pathway depends on the transition metal used. Electron rich and unactivated carbon-carbon double bonds can be cyclopropanated by a mechanism that involves a metal-carbene complex.[59,60] On the other hand, electron poor alkenes react through a dipolar addition mechanism.[59,60] Both mechanisms will be briefly discussed in the following Section.

4.7.2 Carbene addition to alkenes via use of diazo compounds

Electron rich and unactivated double bonds can be cyclopropanated by diazo

compounds in the presence of certain metal complexes. A transient metal-carbene complex is probably involved in the mechanism. The transition metal complex should possess at least one free coordination site. Examples of efficient cyclopropanation catalysts are: Rh^{II}-carboxylates, Cu^{II}-salts and Pd^{II}-complexes.[59,60] Some of these catalysts are commercially available. The mechanism is not completely understood. The crucial steps will be briefly mentioned.[59,61]

In the first step, coordination of the diazo compound to the metal complex takes place, forming a dipolar complex. Loss of nitrogen results in the formation of a metal stabilized carbene. The existence of this species was first proposed by Yates.[61] In the next step the carbene moiety is transferred to an electron rich alkene, at the same time releasing the metal catalyst.

All catalytically active complexes possess weak Lewis acid properties and are therefore subject to inhibition by electron donors. The most widely used catalyst in cyclopropanation reactions is $Rh_2(OAc)_4$, which is a dimer with a free coordination site on each rhodium atom. No association with alkenes, esters or ethers has been found.[58,62] However, adducts with strong electron donors (amines, nitriles) are easily formed.

In the brief discussion on the catalytic cycle, nothing was said about how the carbene transfer takes place. It is this step that determines the stereochemistry of the product. Any model about this carbene transfer should explain the observations of cis-trans isomers formed in the cyclopropanation. From published data, it was concluded that the nature of the diazo compound was the major factor that determines the stereochemistry of the cyclopropane. Alkyl and aryl diazo compounds gave predominantly (Z)-isomers, and α-carbonyl stabilized carbenes showed (E)-selectivity. The magnitude of the selectivity varies largely with the metal catalyst used. Copper^{II} gave in most cases the best results, followed by $Rh_2(OAc)_4$ and other Rh^{II}-carboxylates and Pd-complexes.

Casey et al. developed a model that explains the predominant formation of the Z-isomer in cyclopropanation with benzylidene carbene and alkenes.[63] The first step is the interaction of the carbene with one carbon atom of the alkene, at the same time developing an electrophilic center on the other (most substituted) carbon atom. Backside attack would then displace the metal and would lead to Z-cyclopropane. A metallocycle could also be a possible intermediate. Larger substituents on the carbon-carbon double bond would favour the formation of a (E)-cyclo-propane. The model of Casey offers no

explanation for the formation of the E-product with α-carbonyl stabilized carbenes.

Doyle described a model, that is largely an extension of the Casey model, in which he offers an explanation for the opposite stereochemistry found in reaction with α-diazocarbonyl compounds.[64] He suggests a stabilizing interaction between the developing electrophilic center on one terminus of the double bond with the carbonyl oxygen. A complicating factor in discussions about the mechanism of the carbene transfer to the carbon-carbon double bond is, however, the size of alkene substituents. Not all data can be completely understood, so that the exact nature of the carbene transfer remains rather vague and sometimes contradictory.

4.7.3 **Stereoselective metal-carbene addition to alkenes**

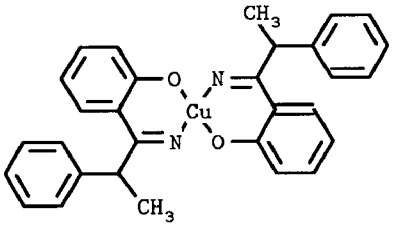
One can imagine three basic methods to achieve an asymmetric induction in a metal-carbene addition to alkenes:

1. the use of chiral ligands for the metal catalyst
2. the use of a chiral diazo compound
3. the use of a chiral alkene

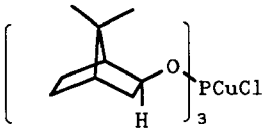
Most examples are known of procedures that make use of the first strategy.

The first report in this field was published by Nozaki et al.[65] Catalyzed decomposition of ethyl diazoacetate and diazomethane by copper(II) complex **4.16** (Fig. 4.7) resulted in an enantiomeric excess of only 6% for both cis and trans cyclopropanes. Mosher did not succeed in raising the optical induction by use of the copper(I) tribornyl phosphite **4.17.** Styrene was cyclopropanated by ethyl diazo acetate in only 3% ee.[66]

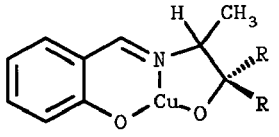
An important break-through was reported by Aratani et al.[67-69] The copper chelate **4.18** (Fig 4.12) produced optical yields of 68% in the cyclopropanation of 2,5-dimethyl-2,4-hexadiene to yield chrysanthemic acid ethyl ester. A cis/trans ratio of 9:1was achieved. Another important result was obtained by Nakamura in the cyclopropanation of styrene by α-diazoacetates,[70,71] who used the cobalt(II) complex **4.19** as a catalyst and achieved ee's of about 80% for both cis and trans cyclopropanes. More bulky alkyl groups gave better ee's and a better trans selectivity.



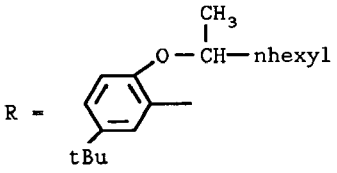
4.16 (Nozaki[62])

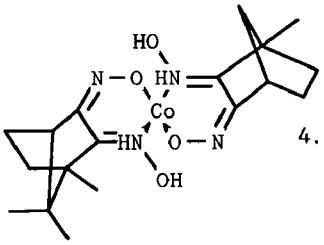


4.17 (Moser[63])



4.18 (Aratani[64-66])





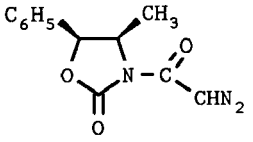
4.19 (Nakamura[67,68])

Fig. 4.7 Chiral cyclopropanation catalysts

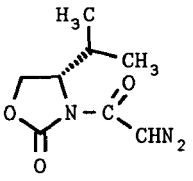
The use of chiral diazoacetates was less rewarding. The results were not very promising, probably due to the fact that the chiral center in chiral α-diazoacetates is at least four atoms away from the reaction center. Arantani et al. achieved only 0.7% ee in the cyclopropanation of styrene with l-menthyl diazo-acetate, catalyzed by copper powder.[69] Moderate results were obtained by Doyle and coworkers,[72] who used in a $Rh_2(OAc)_4$ catalyzed cyclopropanation of styrene the chiral diazo oxazolidones **4.20** and **4.21** (Fig. 4.8).

After transacetalization in ethanol cis- and trans-2-phenylcyclopropanecarboxylates were obtained with ee's of approximately 13-14%. The chemical yields, however, were low because of the intramolecular association of the oxazolidone carbonyl with the carbenoid center. Another explanation for the low yields could be the complexation of

the rhodium complex to the carbonyl oxygen.



4.20



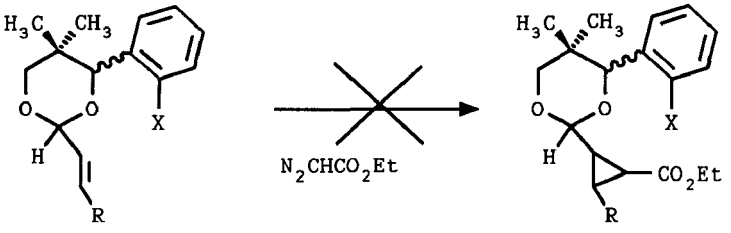
4.21

Fig. 4.8 Chiral diazoacetates

No additions of diazo compounds to chiral alkenes, catalyzed by transiton metal complexes, have been described to our knowledge. The reason that no chiral alkenes have been used in these type of reactions may be due to the experimental characteristics of these reactions. Normally the alkene is used in a large excess or simply as solvent. We tried our chiral 2-alkenylacetals **2.19** in these type of reactions, to test whether a large excess of alkene is indeed necessary, and, if not, whether chiral induction can be observed during the addition reaction (see Section 4.7.4).

4.7.4. Discussion on attempted addition of α-diazoethyl acetate to 2-alkenyl acetals 2.19

The most common way to perform a metal-catalyzed addition of a diazocompound to an alkene, electron rich as well as electron poor, is to dissolve the metal complex in the alkene as solvent. The alkene is thus present in a large excess.



2.19 X = H, Cl
R = CH_3, C_6H_5

4.22

Scheme 4.14 Attempted addition of ethyl α-diazoacetate to acetals **2.19**

The reaction of 2-alkenyl acetals **2.19** with a metal complex and α-diazo ethylacetate suffers from inherent difficulties, which could not be solved in such a way to make a good reaction possible (Scheme 4.14). Making a solution of a metal-complex in a pure 2-alkenyl acetal **2.19** is a problem because magnetic stirring is very difficult due to the viscosity of the oily acetal. Subsequent slow addition of α-diazoacetate in dichloromethane as solvent gave no addition reaction at all. The reason for this failure must be the poor to no mixing of the diazoacetate in solution with the alkenyl acetal **2.19**. Only carbene dimer and unchanged acetals **2.19** were obtained. To overcome this problem the 2-alkenyl acetal was dissolved in a solvent. $Rh_2(OAc)_4$ or $Mo(CO)_6$ were added (2-5 mole %) and α-diazoethyl acetate was added over 6 hours, dissolved in the same solvent. As solvents were used benzene, diethyl ether, and dichloromethane. The solutions were kept very concentrated, three to five mmoles of acetal **2.19** in 1-1.5 ml solvent. Two to three equivalents of α-diazoacetate were added in the same amount of solvent. In all attempts only carbene dimer and acetal **2.19** were isolated. No addition product **4.21** could be identified.

Because the reaction between an alkene and a diazo compound is a very general one, the negative result with our 2-alkenyl acetals was very disappointing. Several explanations may be given. A large excess of alkene is indeed necessary, and our solutions were still too dilute. Low reactivity of the alkene moiety may be a problem as a result of steric hindrance by the 1,3-dioxane ring. The electron density of the carbon-carbon double bond is probably enhanced by the ethereal oxygens. So $Rh_2(OAc)_4$ is likely to be the best suited complex to catalyze the reaction. To be sure $Mo(CO)_6$ was also used as a catalyst, with the same negative result. No further investigations were undertaken.

4.8 CONCLUDING REMARKS

In this chapter the cyclopropanation reactions of unsaturated acetals **2.19** have been described. The modern Simmons-Smith procedure, which uses Et_2Zn/CH_2I_2 to generate the zinc- carbenoid, gave good chemcial yields. The diastereoselectivities in these reactions, however, were only moderate. Deprotection of the cyclopropane acetals **4.19** could be achieved by oxidation with ozone, followed by hydrolysis in basic media,

resulting in the synthesis of cyclopropanecarboxylic acids in moderate enantiomeric excess. We have proposed a transition state in the methylene transfer from the zinc-carbenoid to the carbon-carbon double bond which explains the formation of enantiomers of the cyclopropanecarboxylic acid that we have found in excess. However, flexibility in the transition state prevents a high diastereoselectivity in the cyclopropanation.

The use of α,β-unsaturated acetals **2.19** derived from cyclic α,β-unsaturated ketones could perhaps reduce this flexibility. Unfortunately, the synthesis of such acetals is not feasible (see Chapter 2), probably because of unavoidable steric hindrance caused by large axial and equatorial substituents on the acetal carbon atom. We have found no obvious differences in the effectiveness as chiral auxiliary between 1-phenyl- and 1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol in the stereoselective Simmons-Smith reaction of acetal **2.19**.

The cyclopropanation of 2-alkenyl acetals **2.19** by ethyl diazoacetate, catalyzed by $Rh_2(OAc)_4$ or $Mo(CO)_6$ was not succesful. Probably, a large excess of alkene is necessary for these type of conversions. However, to use a diastereomerically pure alkene (i.e. acetals **2.19**) for this purpose is not meaningful.

4.9 EXPERIMENTAL SECTION

General remarks: For general remarks see also the Experimental Sections of the preceeding chapters.

The cyclopropanation reactions were performed under a dry nitrogen atmosphere. Diethylzinc was purchased as a 1.1M solution in toluene (Aldrich) and was used as such. Diiodomethane (Aldrich) was stored on molecular sieves and was kept in the dark. $Rh_2(OAc)_4$ and $Mo(CO)_6$ (Strem-Chemicals and Aldrich) were used as such. Toluene was distilled twice from sodium/benzophenone, the second time under a dry nitrogen atmosphere prior to use in the Simmons-Smith reaction. Ozone was generated by leading a stream of oxygen (50 l/hr) through a Fisher ozone generator model 501. Approximately 15.8 mmoles/hr were generated when 0.1A was applied. A Saga Instruments syring pump model 352 was used for controlled additions of fluids to a reaction mixture over a prolonged period of time.

Cyclopropanation: general procedure

These reactions were performed in a dry nitrogen atmosphere. Toluene was distilled from sodium/benzophenone in a dry nitrogen atmosphere immediately before use. In 5 ml of toluene was dissolved 2mmoles of an unsaturated acetal **2.19**. This solution was magnetically stirred and cooled to -30°C. Diethylzinc (3-5 equivalents) was added as a 1.1M solution in toluene, followed by the careful addition of diiiodomethane (6-10 equivalents). The temperature was kept below -20°C during this operation. The resulting solution was stirred at -20 °C for 3h. At 0°C, ether was added and subsequently

water to hydrolyze the excess diethylzinc. This mixture was stirred for 5-10 min. HCl (6M) was then added to dissolve the zinc salts. The organic layer was washed twice with a 10% $NaHSO_3$ and once with a saturated brine solution. After drying over $NaSO_4$ and concentration in vacuo, the resulting oil was purified by column chromatography (silica gel hexane/dichloromethane), or by bulb-to-bulb distillation.

(2R,4S)-(+)-2-(2'-E-Phenylcyclopropane)-4-phenyl-5,5-dimethyl-1,3-dioxane 4.13a

387 mg (1.32 mmoles) of (+) acetal **2.19a** was dissoved in 7 ml toluene. It was allowed to react with 6.6 mmoles of Et_2Zn and 13.2 mmoles of CH_2Cl_2. After work-up 261 mg (0.85 mmoles; 64%) of **4.13a** was obtained.
^{1}H-NMR ($CDCl_3$, TMS): δ 0.80 (s, 3H); 1.10 (s, 3H); 1.12 (m, 1H); 1.40 (m, 1H); 1.75 (m, 1H); 2.30 (m, 1H); 3.82 (dd, 2H, ^2J = 11Hz); 4.55 (s, 1H); 4.85 (t, 1H); 7.2-7.6 (m, 10H).
^{13}C-NMR ($CDCl_3$): δ 11.6 (t); 18.4 (t); 19.0 (q); 21.7 (q); 25.6 (t); 33.9 (s); 78.1 (t); 86.5 (d); 101.9 (d); 125.4 (d); 125.9 (d); 126.0 (d); 127.3 (d); 128.1 (d); 137.9 (d); 142.3 (s).
$[\alpha]_{578}$ +3.57° ($CHCl_3$, c 0.51)
Integration of the ^{1}H-NMR gave an estimated d.e of 25-28%.

(2S,4S)-(-)-2-(2'-E-Phenylcyclopropane)-4-(2-chlorophenyl)-5,5-dimethyl-1,3-dioxane 4.13b

Acetal **2.19b** (545mg, 1.66mmoles) was dissolved in 7 ml of toluene and was allowed to react with 8.3 mmoles of Et_2Zn and 16.6 mmoles of CH_2I_2. After work-up 550 mg (1.61 mmoles, 97%) of **4.13b** was obtained.
^{1}H-NMR ($CDCl_3$, TMS): δ 0.70 (s, 3H); 0.85 (m, 1H); 0.95 (s, 3H); 1.15 (m, 1H); 1.45 (m, 1H); 2.05 (m, 1H); 3.55 (m, 2H); 4.60 (d, 1H, ^3J= 4.5Hz); 4.95 (s, 1H); 7.05-7.50 (m, 9H).
^{13}C-NMR ($CDCl_3$): δ 11.7 (t); 19.0 (d); 19.2 (q); 21.7 (q); 25.6 (d); 35.3 (s); 78.4 (t); 81.6 (d); 102.3 (d); 125.4 (d); 126.0 (d); 128.1 (d); 128.3 (d); 128.5 (d); 128.9 (d); 130.3 (d); 132.6 (s); 138.9 (s); 142.2 (s).
$[\alpha]_{578}$ +7.27° ($CHCl_3$, c 0.33)

(2R,4S)-(+)-2-(2'-E-Methylcyclopropane)-4-phenyl-5,5-dimethyl-1,3-dioxane 4.13c

Acetal **2.19c** (1.03g, 4.44mmoles) was dissolved in 7 ml of toluene and was allowed to react with 22.2mmoles Et_2Zn and 44.4 mmoles CH_2I_2. After work-up 895 mg (3.64 mmoles, 82%) of **4.13c** was obtained.
^{1}H-NMR ($CDCl_3$, TMS): δ 0.25 (m, 1H); 0.70 (s, 3H); 0.90 (s, 3H); 0.95 (m, 1H); 0.97 (m, 2H); 1.15 (d, 3H); 3.50 (d, 1H, ^2J= 12.8Hz); 3.65 (d, 1H, ^2J= 12.8Hz); 4.30 (s, 1H); 4.36 (m, 1H); 7.12 (m, 5H).
^{13}C-NMR ($CDCl_3$): δ 9.15 (d); 9.24 (t); 18.4 (q); 18.5 (q); 21.7 (q); 33.8 (s); 78.3 (t, major diastereoisomer); 78.6 (t, minor diasteroisomer); 86.6 (d, major diastereoisomer); 86.9 (d, minor diastereoisomer); 103.7 (d); 126.6 (d); 127.2 (d); 138.1 (s).
$[\alpha]_{578}$ +67.5° ($CHCl_3$, c 0.69)
Exact mass: calc. 246.161; exp. 246.162
Diastereomeric excess estimated from ^{13}C-NMR is 75-78%.

2S,4S)-(-)-2-(2'-E-Methylcyclopropane)-4-(2-chlorophenyl)-5,5-dimethyl-1,3-dioxane 4.13d

Acetal **2.19d** (710 mg, 2.66 mmoles) was dissolved in 7 ml toluene and was allowed

to react with 13.3 mmoles Et_2Zn and 26.6 mmoles CH_2I_2. After work-up 484 mg (1.72 mmoles, 65%) of **4.13d** was obtained.
^{1}H-NMR ($CDCl_3$, TMS): δ 0.11 (m, 1H); 0.55 (m, 1H); 0.70 (s, 3H); 0.90 (m, 2H); 0.95 (s, 3H); 1.00 (d, 3H); 3.60 (m, 2H); 4.35 (dd, 1H); 4.90 (s, 1H); 7.05-715 (m, 3H); 7.45 (m, 1H).
^{13}C-NMR ($CDCl_3$): δ 9.23 (t); 9.29 (d); 18.3 (d); 19.2 (q); 21.7 (q); 23.0 (q); 35.2 (s); 78.5 (t, minor diastereoisomer); 78.8 (t, major diastereoisomer); 81.6 (d, major diastereoisomer); 81.9 (d, minor diastereoisomer); 103.8 (d); 128.5 (d); 130.4 (d); 132.7 (d); 136.1 (s).
$[\alpha]_{578}$ -39.8° ($CHCl_3$, c 1.08)
The diastereomeric excess estimated from ^{13}C-NMR was 75%.

(2R,4S)-(+)-2-(2'-E-n-Propylcyclopropane)-4-phenyl-5,5-dimethyl-1,3-dioxane 4.13e

Acetal **2.19e** (1.32 g, 5.08 mmoles) was dissolved in 7 ml toluene and was allowed to react with 25.4mmoles Et_2Zn and 59.8 mmoles CH_2I_2. After work-up 1.36 g (4.96 mmoles, 97%) of **4.13e** was obtained.
^{1}H-NMR ($CDCl_3$, TMS): δ 0.15 (m, 1H); 0.70 (s, 3H); 0.85 (s, 3H); 0.60-1.00 (s+m, 6H); 3.55 (m, 2H); 4.25 (s, 1H); 4.30 (d, 1H); 7.20 (s, 5H).
^{13}C-NMR ($CDCl_3$): δ 8.05 (t); 8.15 (t); 13.8 (d); 14.8 (q); 18.5 (q); 21.6 (d); 21.9 (q); 22.4 (t); 35.5 (s); 78.2 (t); 86.4 (d, major diastereoisomer); 86.8 (d, minor diastereoisomer); 103.3 (d, minor diastereoisomer); 103.6 (d, major diastereoisomer); 127.1 (d); 127.2 (d); 127.3 (d); 127.7 (d); 138.2 (s).
$[\alpha]_{578}$ +48.7° ($CHCl_3$, c 0.46)
Exact mass: calc. 274.193, exp. 274.192
The diastereomeric excess estimated from ^{13}C-NMR was 56-60%.

(2S,4S)-(-)-2-(2'-E-n-Propylcyclopropane)-4-(2-chlorophenyl)-5,5-dimethyl-1,3-dioxane 4.13f

Acetal **2.19f** (952 mg, 3.23 mmoles) was dissolved in 7 ml toluene and was allowed to react with 16.2 mmoles Et_2Zn and 32.2 mmoles CH_2I_2. After work-up 882 mg (2.85 mmoles, 88%) **4.13f** was obtained.
^{1}H-NMR ($CDCl_3$, TMS): δ 015 (m, 1H); 0.65 (m, 1H); 0.75 (s, 3H); 0.80-0.95 (s+m, 5H); 1.00 (s, 3H); 1.05-1.40 (m, 4H); 3.60 (m, 2H); 4.45 (d, 1H); 4.95 (s, 1H); 7.15-7.35 (m, 3H); 7.50 (m, 1H).
^{13}C-NMR ($CDCl_3$): δ 8.05 (t); 8.25 (t); 13.7 (d); 14.8 (d); 19.1 (q); 19.2 (q); 21.8 (q); 22.3 (t); 35.5 (s); 78.4 (t); 81.5 (d); 103.5 (d); 126.1 (d); 128.4 (d); 128.9 (d); 130.2 (d); 132.6 (s); 136.1 (s).
$[\alpha]_{578}$ -33.3° ($CHCl_3$, c 0.39)
Exact mass: calc. 308.847, exp. 308.849

(2R,4S)-(+)-2-(2'-E-Phenyl-1'-methylcyclopropane)-4-phenyl-5,5-dimethyl-1,3-dioxane 4.13g

Acetal **2.19g** (1.10 g, 3.57 mmoles) was dissolved in 7 ml toluene and was allowed to react with 17.9 mmoles Et_2Zn and 35.7 mmoles CH_2I_2. After work-up 760 mg (2.36 mmoles, 66%) **4.13g** was obtained.
^{1}H-NMR ($CDCl_3$, TMS): δ 0.63 (s, 3H); 0.75 (m, 1H); 0.85 (s, 3H); 0.90 (s, 3H); 1.10 (m, 1H); 2.15 (m, 1H); 3.60 (m, 2H); 3.60 (m, 1H); 4.35 (s, 1H); 4.40 (s, 1H); 7.00-7.30 (m, 10H).

^{13}C-NMR ($CDCl_3$): δ 13.9 (d); 14.0 (t); 18.5 (q); 21.7 (q); 25.1 (q); 25.6 (s); 33.9 (s); 78.2 (t); 85.8 (d, minor diastereoisomer) 86.3 (d, major diastereoisomer); 104.2 (d, minor diastereoisomer); 105.9 (d, major diastereoisomer); 125.7 (d); 125.8 (d); 126.6 (d); 127.0 (d); 127.2 (d); 127.3 (d); 127.4 (d); 127.5 (d); 127.7 (d); 129.2 (d); 129.9 (d); 138.4 (s); 138.7 (s).
$[\alpha]_{578}$ +29.1° ($CHCl_3$, c 0.51)

(2S,4S)-(-)-2-(2'-E-Phenyl-1'-methylcyclopropane)-4-(2-chlorophenyl)-5,5-dimethyl-1,3-dioxane 4.13h

Acetal **2.19h** (1.05 g, 3.06 mmoles) was dissolved in 10 ml toluene and was allowed to react with 15.3 mmoles Et_2Zn and 30.6 mmoles CH_2I_2. After work-up 836 mg (2.34 mmoles, 76%) **4.13h** was obtained.
^{1}H-NMR ($CDCl_3$, TMS): δ 0.80 (s, 3H); 0.90 (m, 1H); 0.95 (s, 3H); 1.10 (s, 3H); 1.20 (m, 1H); 2.35 (m, 1H); 3.75 (m, 2H); 4.40 (s, 1H, major diastereoisomer); 4.55 (s, 1H, minor diastereoisomer); 5.05 (s, 1H, minor diastereoisomer), 5.20 (s, 1H, major diastereoisomer); 7.10-7.40 (m, 8H); 7.55 (m, 1H).
^{13}C-NMR ($CDCl_3$): δ 13.8 (d); 13.9 (t); 19.1 (q); 21.7 (q); 25.0 (q); 25.5 (s); 35.2 (s); 78.3 (t); 81.4 (d); 105.9 (d); 125.6 (d); 126.0 (d); 127.7 (d); 128.4 (d); 128.9 (d); 129.2 (d); 130.3 (d); 132.6 (s); 136.3 (s); 138.6 (s).
$[\alpha]_{578}$ -2.19° ($CHCl_3$, c 0.55).
Exact mass: calc. 380.125; exp. 380.125

Ozonolysis and subsequent ester hydrolysis: general procedure

A cyclopropyl acetal **4.13** (1.0-1.5 mmole) was dissolved in 15 ml ethyl acetate. This solution was cooled to 0°C by means of an ice/salt bath. Ozone was bubbled through the solution (15.8 mmoles/h) The progress of the reaction was monitored by tlc (silicagel hexane/ethyl acetate 2:1). After 3-4 h no starting material was detected. the solution was then concentrated in vacuo in order to remove all traces of ethyl acetate thoroughly. The crude product was dissolved in 5-7 ml 1M KOH solution in ethanol/water 1:1 (v/v), and was stirred for 10 h the solution was then acidified by addition of 6n HCl. Extraction with CH_2Cl_2, drying over $MgSO_4$, filtration, and concentration in vacuo gave the cyclopropanecarboxylic acid **4.12**. This product could be putified by bulb-to-bulb distillation or by column chromatography.

(1R,2R)-(-)-Trans-2-phenylcyclopropanecarboxylic acid 4.12a

Acetal **4.13a** (373 mg, 1.09 mmoles) with $[\alpha]_{578}$ 3.57° was ozonolyzed and hydrolyzed according to the general procedure. After column chromatography (sillica gel/ ethyl acetate) 109 mg (0.70 mmole, 67%) **4.12a** was obtained. The NMR and IR matched literature data.
$[\alpha]_D$ -98.3°, (abs. ethanol, c 0.59). Lit. $[\alpha]_D$ -311°, ee 32%.

(1S,2S)-(+)-Trans-2-phenylcyclopropanecarboxylic acid 4.12b

Acetal **4.13b** (550 mg, 1.61 mmoles) with $[\alpha]_{578}$ +7.27° was ozonolyzed and hydrolyzed according to the general procedure. After column chromatography (sillicagel/ethyl acetate) 99mg (0.61 mmole, 39%) **4.12b** was obtained. The NMR and IR matched literature data.
$[\alpha]_D$ +64.1° (abs. ethanol, c 0.99). Lit. $[\alpha]_D$ +311°, ee 20.5%

(1R,2R)-(-)-Trans-2-methylcyclopropanecarboxylic acid 4.12c

Acetal **4.13c** (694mg, 2.85mmoles) with $[\alpha]_{578}$ +67.5° was ozonolyzed and hydrolyzed according to the general procedure. Bulb-to-bulb distillation (90°C, 15mm Hg) gave 94 mg (0.95 mmole, 34%) of **4.12c**. The NMR and IR matched the literature data. $[\alpha]_D$ -57.4° (abs. ethanol, c 0.61). Lit $[\alpha]_D$ -77.8°, ee 73%.

(2S,4S)-(+)-Trans-2-methylcyclopropanecarboxylic acid 4.12d

Acetal **4.13d** (484 mg, 1.58 mmoles) with $[\alpha]_{578}$ -39.8° was ozonolyzed and hydrolyzed according to the general procedure. Bulb-to-bulb distillation (90°C, 15-20mm Hg) gave 64 mg (0.64 mmole, 41%) of **4.12d**. The NMR and IR matched literature data. $[\alpha]_D$ +63.9° (abs. ethanol, c 0.34). Lit. $[\alpha]$ +77.8° (abs. ethanol), ee 78%.

Trans-(-)-2-n-Propylcyclopropanecarboxylic acid 4.12e

Acetal **4.13e** (658 mg, 2.40 mmoles) with $[\alpha]_{578}$ =48.7°, was ozonolyzed and hydrolyzed according to the genral procedure. Bulb-to-bulb distillation (110°C, 15mm Hg) gave 132 mg (1.03 mmoles, 43%) of **4.12e**.
^{1}H-NMR ($CDCl_3$/TMS): δ 0.8- 2.0 (m, 11H); 11.5 (br, 1H).
$[\alpha\}_{578}$ -48.1° (abs. ethanol, c 1.13)

Trans-(+)-2-n-Propylcycloproanecarboxylic acid 4.12f

Acetal **4.13f** (490mg, 1.59mmoles) with $[\alpha]_{578}$ -33.3°, was ozonolyzed and hydrolyzed according to the general procedure. Bulb-to-bulb distillation (110° C, 15mm Hg) gave 107 mg (0.84 mmole, 53%) of **4.12f**.
^{1}H-NMR data are the same as described for **4.12e**.
$[\alpha]_{578}$ +50.0° (abs. ethanol, c 1.07).

(-)-2-E-Phenyl-1-methylcyclopropanecarboxylic acid 4.12g

Acetal **4.13g** (347 mg, 1.08 mmoles) with $[\alpha]_{578}$ +29.1°, was ozonolyzed and hydrolyzed according to the general procedure. Column chromatography (silica gel/ethyl acetate) gave 86 mg (0.49 mmole, 46%) of **4.12g**.
^{1}H-NMR ($CDCl_3$, TMS): δ 0.95 (s, 3H); 1.2 (m, 2H); 1.8 (s, 1H); 7.1 (br, 5H).
IR ($CHCl_3$) 3600 (OH); 1710 (C=O).
$[\alpha]_{578}$ -63.0° (abs. ethanol c 0.86).

(+)-2-E-Phenyl-1-methylcyclopropanecarboxylic acid 4.12h

Acetal **4.13h** (781 mg, 2.19 mmoles) with $[\alpha]_{578}$ -2.19°, was ozonolyzed and hydrolyzed according to the general procedure. Column chromatography (silica gel/ethyl acetate) gave 192mg (1.09 mmoles, 50%) of **4.12h**.
^{1}H-NMR and IR data are the same as described for **4.12g**.
$[\alpha]_{578}$ +103° (abs ethanol, c 0.42).

Esterification of trans-cyclopropanecarboxylic acids: general procedure:

The cyclopropanecarboxylic acid **4.12** (0.5-1.0 mmol) was dissolved in 3 ml p.a methanol. Cs_2CO_3 (0.5 equivalents) was added and the mixture was stirred for 15 minutes. The solution was then concentrated in vacuo to complete dryness. DMF (3-5 ml) was added together with 2.0 equivalents of methyliodide. The resulting clear solution was stirred at 50°C for 6 hours. Ether was added and this solution was washed successively

with water (2x) and a saturated brine solution. After drying (Na_2SO_4), filtration and evaporation of the solvent, the methyl ester was purified by bulb to bulb distillation.

Trans-2-phenylcyclopropanecarboxylic acid methyl eters 4.14a

(+)-Trans-2-phenylcyclopropanecarboxylic acid **4.12b** (68 mg; 0.42 mmole) with $[\alpha]_D^{20}$ = +64.1° (abs EtOH) was esterified with 68.5 mg Cs_2CO_3 (0.2 mmole) and 110 mg CH_3I (0.77 mmole) according to the general procedure. After bulb to bulb distillation 49 mg of methyl ester were obtained (0.27 mmole; 64%).
^{1}H-NMR ($CDCl_3$/TMS): δ 1.1-2.0 (m, 3H); 2.3-2.8 (m, 1H); 3.70 (s, 3H); 7.3-7.7 (m, 5H);

$[\alpha]_D^{20}$ = +71.2° (c = 0.68; $CHCl_3$).

(+)-Trans-2-n-propylcyclopropanecarboxylic acid methyl ester 4.14c

(+)-Trans-2-propylcyclopropanecarboxylic acid **4.12f** (105 mg; 0.82 mmole) with $[\alpha]_{578}^{20}$ = +50.0 (c = 1.07, abs ethanol) was esterified according to the general procedure with 134 mg Cs_2CO_3 (0.41 mmole) and 175 mg CH_3I (1.23 mmole). After bulb to bulb distillation (70°C; 50 mmHg) 63 mg methyl ester were obtained (0.44 mmole; 54%);
^{1}H-NMR ($CDCl_3$/TMS): δ 0.50-1.75 (m, 11H); 3.75 (s, 3H); $[\alpha]_{578}$ = +54.3 (c 0.63; $CHCl_3$).

Reduction of cyclopropanecarboxylic acids with lithium aluminum hydride: General procedure

The cyclopropanecarboxylic acid **4.12** was dissolved in 5 ml THF (dried over sodium/benzophenone). This solution was added to a stirred suspension of LAH/THF, under a dry nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 hr. The mixture was now refluxed for 1.5-2 hrs to ensure complete reduction. The excess LAH was destroyed by carefful addition of sodium hydroxide solution. Then ether and water were added. The water layer was extracted twice with ether and the combined ether layers were washed twice with a saturated brine solution. After drying ($MgSO_4$), filtration and evaporation of the ether; the resulting oil was purified by bulb to bulb distillation.

(-)-Trans-2-n-propylcyclopropylmethyl alcohol 4.15e

(-)-2-(n-Propyl)cyclopropanecarboxylic acid **4.12e** (122 mg; 0.95 mmole) with $[\alpha]_{578}$ = -48.1° (c 0.46; abs. ethanol) wad reduced by 75 mg LAH to yield 56.5 mg (0.50 mmole; 52%) **4.19a**;
$[\alpha]_{578}$ = -12.9° (c 0.57; $CHCl_3$);
^{1}H-NMR ($CDCl_3$/TMS): δ 0.3 (m, 2H); 0.50 (m, 1H); 0.8 (m, 1H); 0.85 (t, 3H); 0.9-1.3 (m, 4H); 3.35 (2xd, 2H); IR ($CHCl_3$): 3300 (br, OH).

(+)-E-2-Phenyl-1-methylcyclopropylmethylalcohol 4.15h

(+)-E-2-Phenyl-1-methylcyclopropanecarboxylic acid **4.12h** (192 mg; 1.09 mmole) with $[\alpha]_{578}$ = +103 (c 0.42; abs. EtOH) was reduced with 85 mg LAH to yield 121 mg (0.75 mmole; 69%) cyclopropylmethyl alcohol **4.19h** after bulb to bulb distillation (120°C; 0.1 mmHg);
$[\alpha]_{578}$ = +1.03 ($CHCl_3$; c 1.21);
^{1}H-NMR ($CDCl_3$/TMS); δ 0.80 (s, 3H); 0.90 (m, 2H); 1.95 (m, 1H); 3.45 (s, 2H); 7.1-7.3

(m, 5H).

α-Diazo ethylacetate[74]

Ethylglycinate hydrochloric acid salt (14.0 g, 0.10 mmole) was dissolved in 25 ml water. Dichloromethane (60 ml) was added. The stirred mixture was cooled to -5°C and flushed with nitrogen. $NaNO_2$ (8.3 g, 0.12 mmole) in 25 ml water was added. This mixture was now cooled to -9°C and 5% v/v H_2SO_4 (9.5 g) was added dropwise. The temperature was not allowed to rise above 1°C. Stirring was maintained for another 10 min. The layers were separated and the water layer was washed with CH_2Cl_2. The combined green yellow CH_2Cl_2 layers were washed with a cold 5% $NaHCO_3$ solution and thereafter with a dilute $NaHCO_3$ solution until acid was no longer present. After drying over Na_2SO_4 and evaporation of CH_2Cl_2 in vacuo (waterbath temperature below 35°C!) 11.5 g (81 mmole; 81%) of a yellow fluid remained. This product was used without further purification, and was stored at 3°C in the dark;
^{1}H-NMR ($CDCl_3$/TMS): δ 1.25 (t, 3H); 4.20 (q, 2H); 4.80 (s, 1H).

Attempted transition metal catalyzed cyclopropanation of acetals 2.19 with α-diazo ethylacetate

An acetal **2.19** (1.0-1.2 mmole) was dissolved in 3 ml benzene or diethyl ether. $Rh_2(OAc)_4$ or $Mo(CO)_6$ (3-5 mole %) was added. Stirring at room temperature was maintained until complete dissolution. $Rh_2(OAc)_4$ resulted in a blue solution and $Mo(CO)_6$ gave a colourless solution. The solution was then protected from light by aluminum foil. Two equivalents of α-diazo ethylacetate in 2 ml of benzene or diethyl ether were added through a syringe and by an injection apparatu in 4-6 hrs. The α-diazo ethyl acetate solution was also protected from light by aluminum foil.
After addition the solution was stirred for another hour. Extra solvent was added and the solution was washed with 10% $NaHCO_3$ solution and with a saturated brine solution. The organic layer was dried over $MgSO_4$. After filtration and concentration in vacuo an oil remained that consisted of acetal **2.19** and carbene dimer. Cyclopropane formation was not observed. In case of $Mo(CO)_6$ most of the α-diazo ethyl acetate was recovered unchanged.

4.10 REFERENCES

1. E. Vogel; Angew. Chemie **72**, 4 (1960).
2. M.Y. Lukina; Russ. Chem. Rev. **31**, 419 (1962).
3. S. Danishevsky; Acc. Chem. Res. **12**, 66 (1979).
4. J. Salaun; Chem. Rev. **83**, 619 (1983).
5. H.N.C. Wong; M.Y. Hon; C.W. Tse; Y.C. Yip; J. Tanka; T. Hudlicky; Chem. Rev. **89**, 165 (1989).
6. A. Greenberg; J.F. Liebman; Strained Organic Molecules; Academic Press, New York (N.Y.) 1978.
7. C.A. Coulson; W.E. Moffit; J. Chem. Phys. **15**, 151 (1947).
8. a. A.D. Walsh; Trans Faraday Soc. **45**, 179 (1949).
   b. H. Basch; M.B. Robin; N.A. Kuebler; C. Baker; D.W. Turner; J. Chem. Phys. **51**, 52 (1969).
9. M.J.S. Dewar; J. Am. Chem. Soc. **106**, 669 (1984).
10. D. Cremer; J. Gause; J. Am. Chem. Soc. **108**, 7467 (1986).

11. J.D. Cox; G. Pilcher; Thermochemistry of Organic and Organometallic Compounds, Academic Press, London, 1970.
12. R.G. Snyder; J.H. Schachtschneider; Spectrochim. Acta. **21**, 169 (1965).
13. K. Nishimura; N. Shinoda; Y. Hirose; Tetrahedron 7 (1969).
14. D. Robinson; C. West; Biochemistry **14**, 1921 (1975).
15. J.E. McMurry; G.K. Bosch; J. Org. Chem. **52**, 4885 (1987).
16. T. Norin; Acta Chem. Scand. **15**, 1676 (1961).
17. a. R.E. Moore; J.A. Pettus; M.J. Doty; Tetrahedron Letters 4787 (1968).
b. R.E. Moore; J.A. Pettus; J. Mistysyn; J. Org. Chem. **39**, 2201 (1974).
18. H. Staudinger; L. Radzicka; Helv. Chim. Acta **7**, 177 (1924).
19. E. Wenkert; D.A. Berges; J. Am. Chem. Soc. **89**, 2507 (1967).
20. S. Danishevsky; J. Regan; R. Doehner; J. Org. Chem. **46**, 5255 (1981).
21. H.E. Simmons; T.L. Cairns; S.A. Vladuchick; Organic Reactions **20**, 1 (1973).
22. H.E. Simmons; R.D. Smith; J. Am. Chem. Soc. **81**, 4256 (1959).
23. Vogel; "Textbook of Practial Organic Chemistry", Longman, London 4th ed. p. 318.
24. J. Furukawa; N. Kawabata; J. Nishimura; Tetrahedron **24**, 53 (1968).
25. J. Nishimura; N. Kawabata; J. Furukawa; Tetrahedron **25**, 2647 (1969).
26. E.C. Friedrich; S.E. Lunetta; E.J. Lewis; J. Org. Chem. **54**, 2388 (1989).
27. W. Carruthers in: Comprehensive Organometallic Chemistry; G. Wilkinson (Ed.), Pergamon Press, 1982, vol. 7, 666-669.
28. I.T. Harrison; R.J. Rawson; R.J. Turnbull; J.H. Fried; J. Org. Chem. **36**, 3515 (1971).
29. a. S. Winstein; J. Sonnenberg; L. de Vries; J. Am. Chem. Soc. **81**, 6523 (1959).
b. S. Winstein; J. Sonnenberg; J. Am. Chem. Soc. **83**, 3235 (1961).
30. a. J.H.H. Chan; B. Rickborn; J. Am. Chem. Soc. **90**, 6406 (1968).
b. J.A. Staroscik; B. Rickborn; J. Org. Chem. **37**, 738 (1972).
31. a. S. Sawada; T. Takehana; Y. Inoue; J. Org. Chem. **33**, 1767 (1968).
b. S. Sawada; J. Oda; Y. Inoue; J. Org. Chem. **33**, 2141 (1968).
32. C.R. Johnson; M.R. Barbachyn; J. Am. Chem. Soc. **104**, 4290 (1982).
33. a. T. Sugimura; T. Futagawa; A. Tai; Tetrahedron Lett. **29**, 5775 (1988).
b. T. Sugimura; T. Futagawa; M. Yoshikawa; A. Tai; Tetrahedron Lett. **30**, 3807 (1989).
34. a. E.A. Mash; K.A. Nelson; P.C. Heidt; Tetrahedron Lett. **28**, 1865 (1987).
b. E.A. Mash; K.A. Nelson; Tetrahedron **43**, 679 (1987).
c. E.A. Mash; S.K. Math; J.B. Arterburn; J. Org. Chem. **54**, 4951 (1989).
d. E.A. Mash; S.B. Hamperly; K.A. Nelson; P.C. Heidt; S. v. Deusen; J. Org. Chem. **55**, 2045 (1990).
e. E.A. Mash; S.B. Hamperly; J. Org. Chem. **55**, 2055 (1990).
35. E.A. Mash; S.K. Math; C.J. Flann; Tetrahedron **45**, 4945 (1989).
36. A. Mori; I. Arai; H. Yamamoto; H. Nakai; Y. Arai; Tetrahedron **42**, 6447 (1986).
37. A. Mori; K. Ishihara; H. Yamamoto; Tetrahedron Lett. **27**, 987 (1986).
38. J.D. Eliot; J. Steele; W.S. Johnson; Tetrahedron Lett. **26**, 2535 (1985).
39. a. G.R. Sullivan in Topics in Stereochemistry **10**, 287 (1977); E.L. Eliel and N.L. Allinger (Eds.).
b. D. Parker; Chem. Rev. **91**, 1441 (1991).
40. J.A. Dale; D.L. Dull; H.S. Mosher; J. Org. Chem. **34**, 2543 (1969).

41. H. Hiemstra; Dissertation 1980.
42. B.L. Feringa; A.A. Smaardijk; H. Wynberg; J. Am. Chem. Soc. **107**, 4598 (1985).
43. B. Strijtveen; Dissertation 1987.
44. W.H. Kruizinga; J. Bolster; R.M. Kellogg; J. Kamphuis; W.H.J. Boesten; E.M. Meijer; H.E. Schoemaker; J. Org. Chem. **53**, 1826 (1988).
45. J. March; Advanced Organic Chemistry 3th edition Wiley, Chapter 10.
46. T.G. Bonner; N.M. Saville; J. Chem. Soc. 2851 (1960).
47. Ozonation in Organic Chemistry, Vol I and II, P.S. Bailey, Academic Press, New York, 1982.
48. C.F. Schönbein; C.R. Hebel Seances Acad. Sci. **10**, 706 (1840).
49. Homer; "Iliad" **8**, 135; **14**, 415; "Odyssey" **12**, 417; **14**, 307. The Complete Works of Homer; Modern Library Edition, Random House, New York, 1950.
50. P. Deslongchamps; C. Moreau; Can. J. Chem. **49**, 2465 (1971).
51. P. Deslongchamps; P. Atlani; D. Fréhel; A. Malaval; C. Moreau; Can. J. Chem. **52**, 3651 (1974).
52. T. Veysoglu; L.A. Mitscher; J.K. Swayze; Synthesis 807 (1980).
53. Y. Inoue; T. Sugita; H.M. Walborsky; Tetrahedron **20**, 1695 (1964).
54. T. Sugita; Y. Inoue; Bull. Chem. Soc. Jpn. **35**, 1075 (1966).
55. W. von E. Doering; W. Kirmse; Tetrahedron **11**, 272 (1960).
56. T.L. Ho; "Hard and Soft Acids and Bases Principle in Organic Chemistry": Academic Press (NY) 1977.
57. S.D. Kahn; W.J. Hehre; J. Am. Chem. Soc. **109**, 666 (1987).
58. a. J.H. Brewster in: Topics in Stereochemistry, Vol. 2; N.L. Allinger and E.L. Eliel (Eds.), Interscience Publisher, 1967, New York.
b. J.H. Brewster; J. Am. Chem. Soc. **81**, 5475, 5483 (1959).
59. M.P. Doyle; Chem. Rev. **86**, 919 (1986).
60. M.P. Doyle; Acc. Chem. Res. **19**, 348 (1986).
61. P.Y. Yates, J. Am. Chem. Soc. **74**, 5356 (1952).
62. A.J. Anciaux; A.J. Hubert; A.F. Noels; N. Petinot; P. Teyssié; J. Org. Chem. **45**, 695 (1980).
63. C.P. Casey; S.W. Polichnowski; A.J. Shusterman; C.R. Jones; J. Am. Chem. Soc. **101**, 7282 (1979).
64. a. M.P. Doyle; J.H. Griffin; J. da Conceicao; J. Chem. Soc., Chem. Commun. 328 (1985).
b. M.P. Doyle; J.H. Griffin; V. Bagheri; R.L. Dorow; Organometallics **3**, 53 (1984).
65. H. Nozaki; H. Takaya; S. Moriuti; R. Noyori; Tetrahedron **24**, 3655 (1968).
66. a. W.R. Moser; J. Am. Chem. Soc. **91**, 1135 (1969).
b. W.R. Moser; J. Am. Chem. Soc. **91**, 1141 (1969).
67. T. Aratani; Y. Yoneyoshi; T. Nagase; Tetrahedron Lett. 1707 (1975).
68. T. Aratani; Y. Yoneyoshi; T. Nagase; Tetrahedron Lett. 2599 (1975).
69. T. Aratani; Y. Yoneyoshi; T. Nagase; Tetrahedron Lett. **23**, 685 (1982).
70. A. Nakamura; A. Konishi; R. Tsujitani; M. Kudo; S. Otsuka; J. Am. Chem. Soc. **100**, 3449 (1978).
71. a. A. Nakamura; A. Konishi; Y. Tatsuno; S. Otsuka; J. Am. Chem. Soc. **100**, 3443 (1978).
b. ibid; **100**, 6544 (1978).

72. M.P. Doyle; R.L. Dorow; J.W. Terpstra, R.A. Rodenhouse; J. Org. Chem. **50**, 1663 (1985).
73. R. Huisgen; Pure & Appl. Chem.; 53, 171 (1981).
74. Organic Synthesis coll. vol 4,424 (19630, Ed. N. Rabjohn