Stereoselective Synthesis of Cyclopropanols

P. Garcia, D. Diez*, A. B. Antón, N. M. Garrido, I. S. Marcos, P. Basabe and J. G. Urones

Departamento de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain

Abstract: Cyclopropanols have found an increasing number of uses as synthetic intermediates and as functional groups in the design of enzyme inhibitors. This mini-review will discuss some of the most recent and successful methodologies for the synthesis of these entities, focusing mainly on the stereoselective transformations. The new procedure developed in our group for the preparation of cyclopropanols in chiral form is also reviewed.

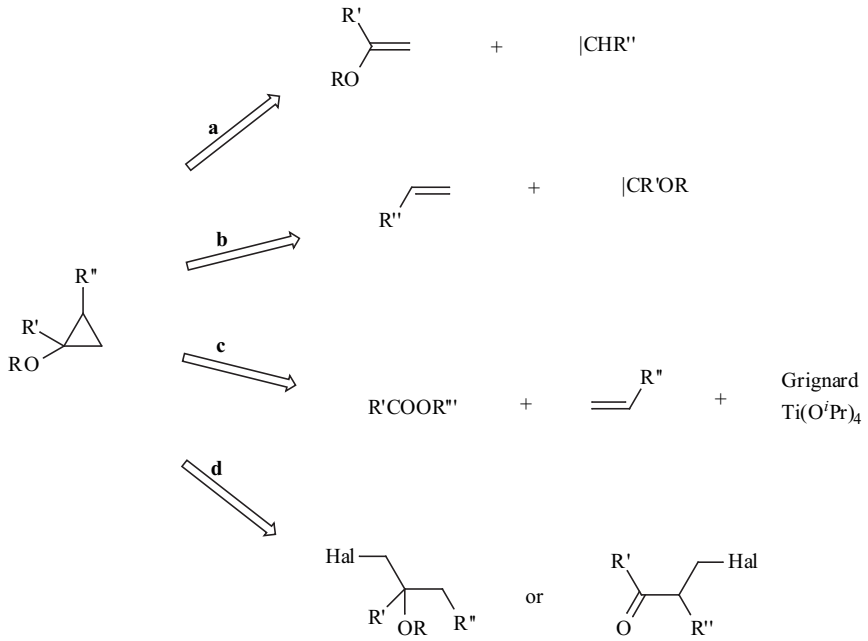
Keywords: Cyclopropanols, stereoselective synthesis.

INTRODUCTION

Cyclopropane derivatives are frequently employed as versatile building blocks in organic synthesis [1]. Moreover, natural and synthetic cylopropanes bearing simple functionalities, such as hydroxy, amino, carboxylic acid groups, nucleic bases and so on, are endowed with a large spectrum of biological properties [2]. The rigidity of the three membered ring allows the preparation of molecules with a well defined orientation of functional groups. That's why, many cyclopropane containing unnatural products have been prepared to study enzyme mechanism or inhibition [3].

Because all of these reasons, there has been a huge interest in the synthesis of cyclopropanes and their derivatives in a enantio and diastereoselective fashion [4]. Much effort has been dedicated, for instance, to the preparation of cyclopropane-containing natural products [5].

In particular, substituted cyclopropanols have been widely obtained in the last twenty years, and its reactivity studied thoroughly [6]. In 2003, there was published a special issue, *103*, for pertinent reviews on cyclopropane chemistry in Chemical Reviews, and this report will review different methodologies that permit the preparation of cyclopropanols focusing mainly on the stereoselective transformations.

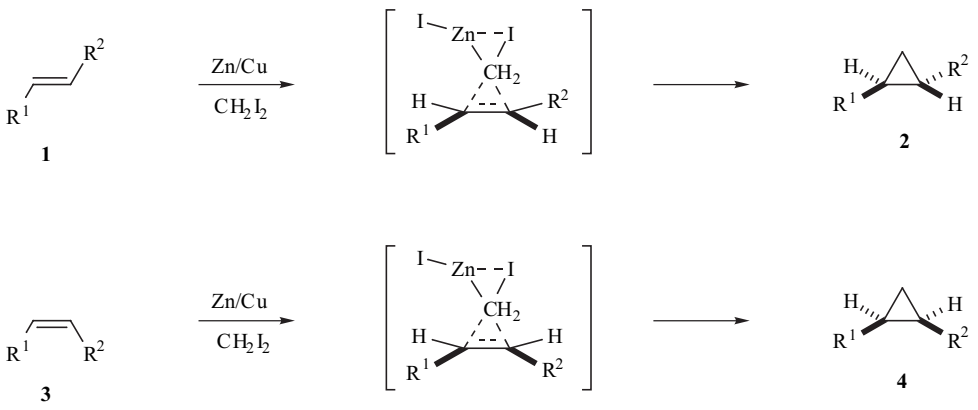


Scheme 1. Retrosynthetic analyses of cyclopropanols.

Scheme **1** shows four possible pathways for the synthesis of cyclopropanols. The three membered ring is most frequently prepared by reaction of carbenes or their equivalents with alkenes. This is also true for cyclopropanols, which are accessible by addition of a carbene to an enol ether (pathway a). There are different reactions depending on the carbenoid used, such as Simmons-Smith reaction, cyclopropanation with dihalocarbenes,

*Address correspondence to this author at the Departamento de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain; E-mail: ddm@usal.es

1570-193X/06 $50.00+.00



Scheme 2. Transition state involved in Simmons-Smith cyclopropanation of olefins.

diazomethane or diazoesters. The complementary approach (pathway b) combines a hydroxy/alcoxy-substituted carbene with any alkene, which are called Fischer carbene complexes. The hydroxyl group in the cyclopropanol can come from an ester (pathway c) in the reaction with an alkene in the presence of titanium isopropoxide and a Grignard reagent, what is named Kulinkovich reaction [7]. These rather straightforward (formal) [2+1] cycloadditions are supplemented by some other methods such as intramolecular cyclizations.

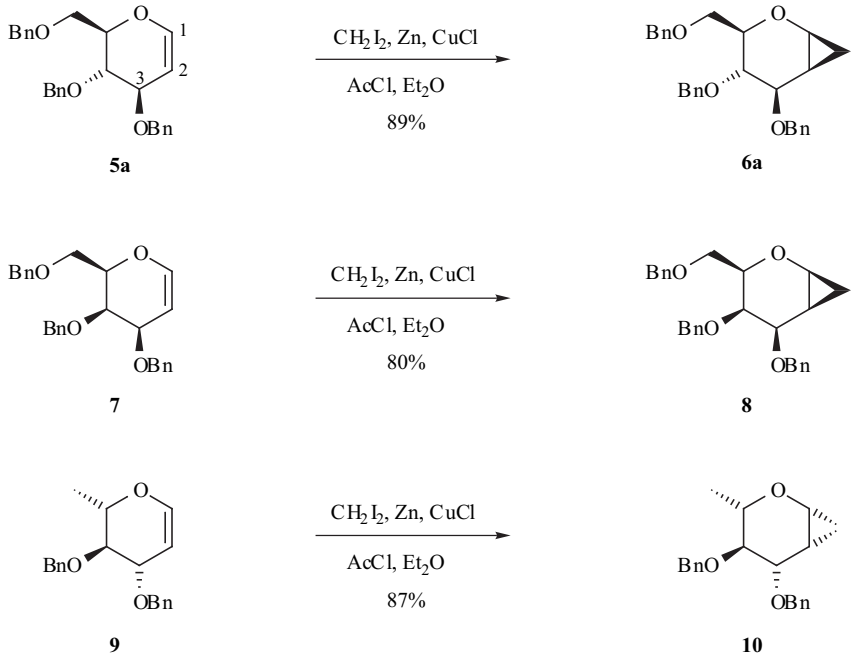
Some of these reactions have been well-known for many years and only new, synthetically useful developments such as efficient intramolecular and highly enantioselective versions as well as the use of Fischer carbene complexes and the Kulinkovich reaction will be described in this account.

1. SIMMONS-SMITH CYCLOPROPANATION

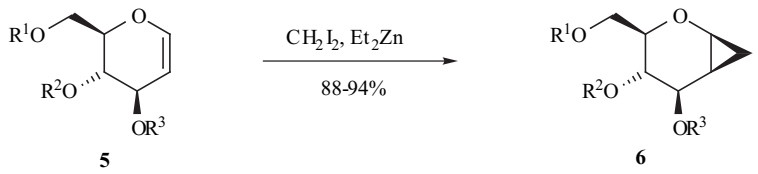
The classic Simmons-Smith reaction [8], that employs diiodomethane in the presence of activated zinc to carry out the cyclopropanation of alkenes, is an efficient method that has also been used in the selective conversion of enol ethers to cyclopropanols. The reaction is stereospecific proceeding through a "butterfly-type" transition structure [9] (Scheme **2**), that involves partial delivery of methylene group between the $IZnCH_2I$ (the reactive intermediate specie) and the double bond.

The principal characteristic is that, in cyclic and acyclic systems, cyclopropanation diastereoselectivity is strongly directed by allylic hydroxyl substituents due to the chelating effect of that allylic oxygen to the organozinc reagent, yielding mainly *syn* addition products as can be seen in Scheme **3**, for the preparation of cyclopropanated sugars.

Despite the strong synthetic potential of cyclopropanated carbohydrates, the area remained unexplored until recent decades. The group of Nagarajan [10] presents some of the early Simmons-Smith glycal cyclopropanation in 1995. In that study (Scheme **3**), benzyl protected glycals **5a**, **7** and **9** were transformed to the cyclopropanated derivatives under treatment with CH_2I_2/Zn/CuCl activated by acetyl chloride.



Scheme 3. Simmons-Smith cyclopropanation of glycals.



5 **6**

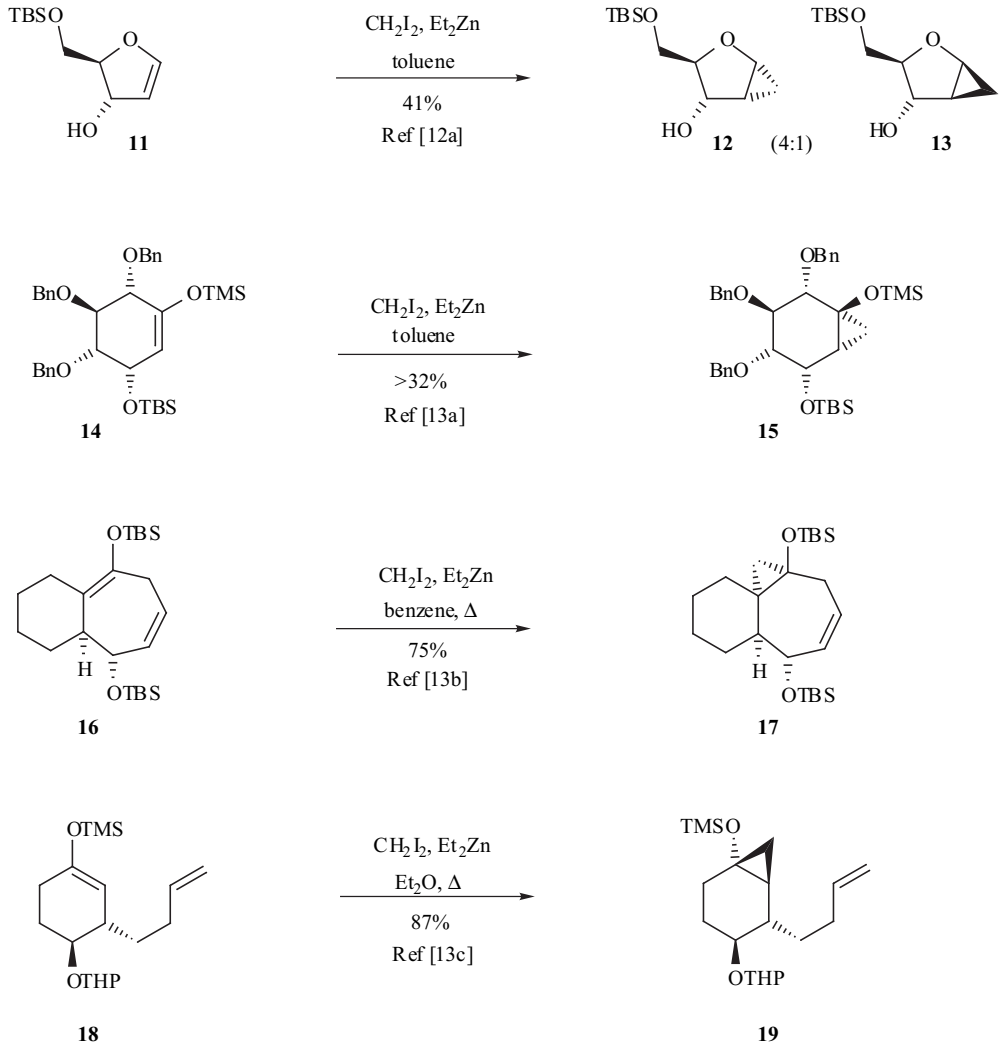
Scheme 4. Furukawa's modified Simmons-Smith cyclopropanation of glycals.

In the examples reported, the C(3) substituent appeared responsible for complete control over facial selectivity to provide exclusively the *syn* diastereoisomer.

The Furukawa's modification [11] of the Simmons-Smith reaction employs diethylzinc instead of the pair Zn-Cu, which results in more reproducible results under milder reaction conditions. The facial selectivity is the same: *syn* products are obtained (Scheme **4**). Cyclopropanated sugars [12] were prepared in high yield (88-94%), which is strongly affected by steric factors, decreasing to 33% or even 0% when using bulky protecting groups, such as the *tert*-butyldimethylsilyl group.

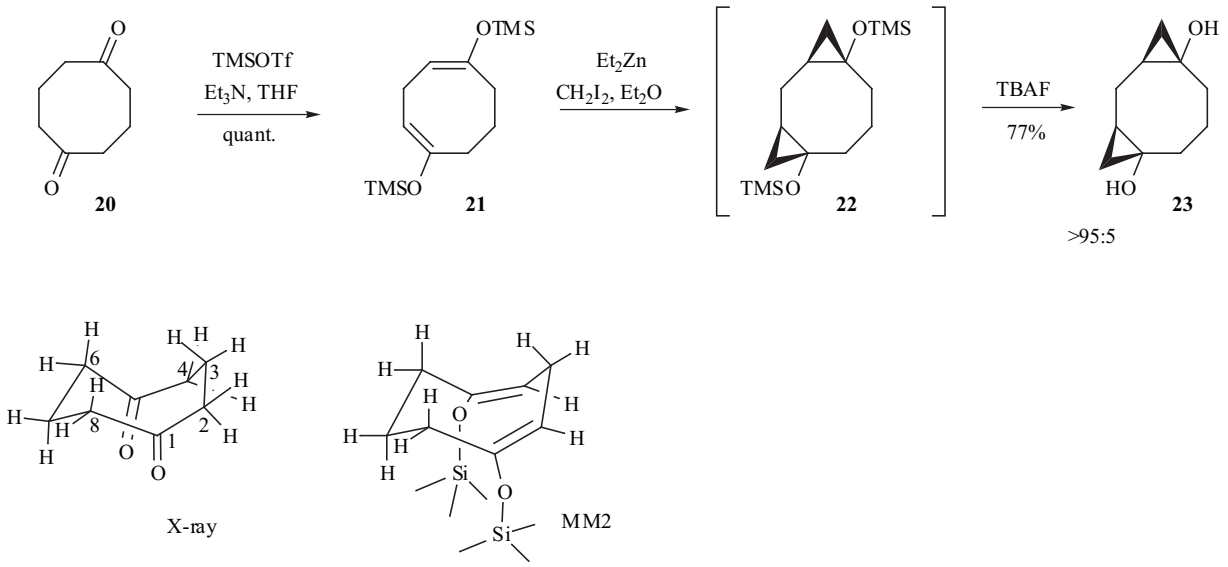
Recent additional examples [13] of stereocontrol in the cyclopropanation of functionalized cycloalkenol derivatives are presented in Scheme **5**. This collection of examples shows the compatibility of a variety of functional groups under the cyclopropanation conditions, especially when an alcohol or a basic group is present to direct the methylenation.

When there are no directing groups, the cyclopropanation diastereoselectivity of cyclic alkenes is affected by steric factors. The level of stereochemical induction is usually very high, and the direction can be predicted on the basis of the prevailing ground-state conformation of the starting olefin. In this manner, dicyclopropanol **23** [14] (Scheme **6**) is the only product isolated in the reaction of the bis-(trimethylsilyl)enol ether **21** with Furukawa's reagent, with excellent yield and stereocontrol (>15:1). The authors predicted a boat-chair conformation for the *bis*-(silyl enol) ether **21**, what explains the almost exclusive formation of



14 **15** **16** **17** **18** **19**

Scheme 5. Selected examples of diastereoselective cyclopropanation of cyclic alkenes.



Scheme 6. Schreiber's *bis*-cyclopropanation.

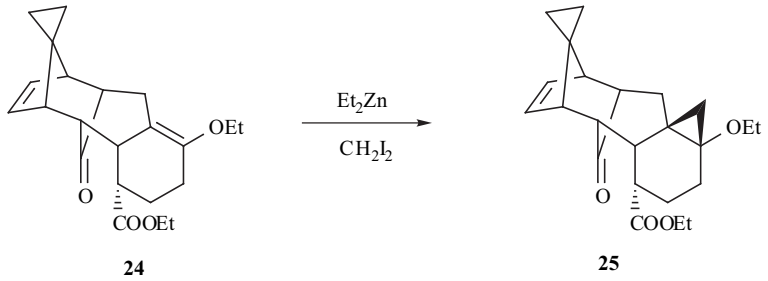
the *syn* isomer **23** as the approach of the organozinc reagents is effected through the less hindered direction, opposite to the TMS-group.

Note also the regioselectivity of enol silyl ether formation. The X-ray crystal structure of 1,5-cyclooctanedione, **20**, shows that in the solid state, the molecule exists in a boat-chair conformation. If the bis(enolization) of **20** were to occur from the same conformation, high diastereoselectivity to produce a *E,E*-1,4 *bis*-(enolate) **21** would be expected, due to the fact that the most acidic protons are those which have the highest overlap of the C-H σ-bond with the carbonyl π-system, i.e. those nearly perpendicular to the plane of the C-O bond of the carbonyl at carbons 2, 4, 6 and 8; and enolization at positions 6 and 8 was considered unlikely since the strain involved with formation of a *trans* olefin in an eight-membered ring is on the order of 11 kcal/mol.

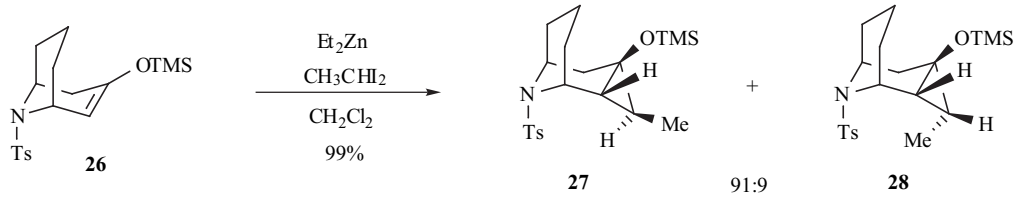
The cyclopropanation of **24** leads to only one diastereomer, **25**, [15] in which the cyclopropane ring is *trans* to the ketone and the ester group (Scheme **7**).

In the same way a high diastereoselectivity is achieved in the cyclopropanation of silyl enol ether **26** [16] with the reagent derived from 1,1-diiodoethane and diethylzinc (Scheme **8**). The level of induction was highly dependent on the nature of the nitrogen protecting group. Momose *et al*. have employed the main diastereomer, **27**, in the preparation of (-)-pinidine [16].

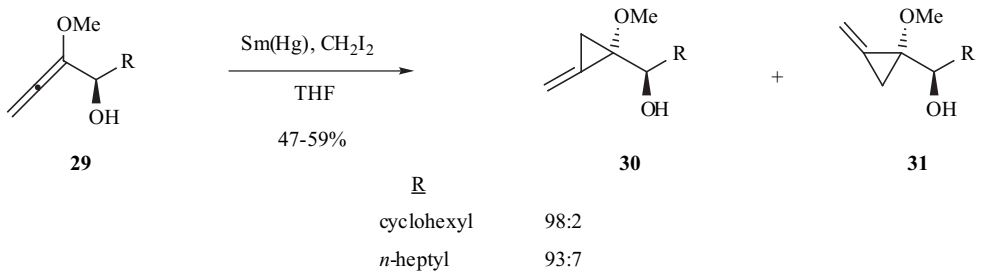
Acyclic alkenes have been extensively used in Simmons-Smith cyclopropanations, especially allylic alcohols due to the possible diastereoselectivity induction by the allylic hydroxyl substituent. However, only a few examples are reported about Simmons-Smith cyclopropanation of acyclic enol ethers. Lautens and Delanghe [17] have reported a



Scheme 7. Example of a chemoselective cyclopropanation of a cyclic alkene.



Scheme 8. Example of a diastereoselective cyclopropanation of a cyclic alkene.



29 **30** **31**

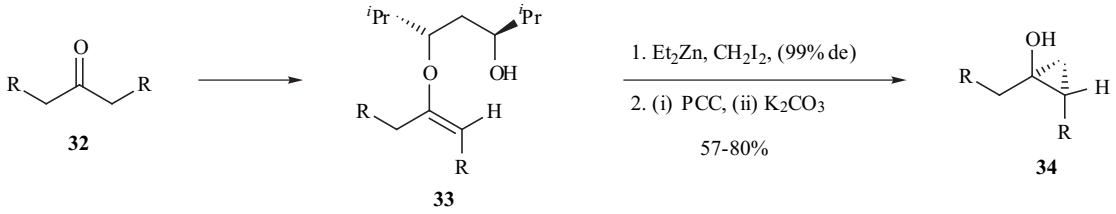
R	
cyclohexyl	98:2
n-heptyl	93:7

Scheme 9. Diastereoselective cyclopropanation of allenic alcohols.

highly regioselective cyclopropanation of α-allenic alcohols **29** using a samarium carbenoid that provided the methylenecyclopropane carbinol in good yield (Scheme **9**). Diastereoselectiviy is high for the methoxyallenes. The use of the samarium reagent was essential to optimize the regioselectivity of this process and to minimize the formation of spiropentane carbinols.

cyclopropanated under the Simmons-Smith conditions yielding with outstanding diastereoselectivity, the corresponding cyclopropyl ethers [18]. The destructive cleavage of the auxiliary (i. PCC; ii. K_2CO_3) produced cyclopropanols **34**.

Very little work has been reported on the use of more complex diiodoalkane as precursors to more substituted

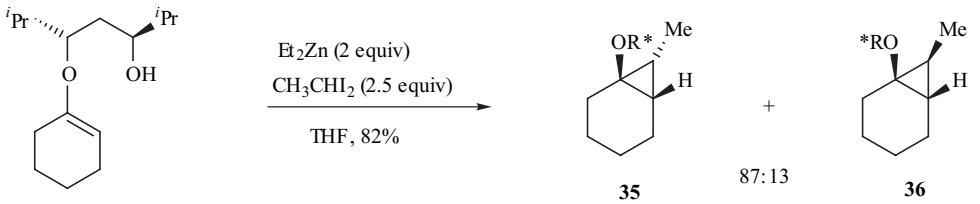


32 **33** **34**

Scheme 10. Tai's chiral auxiliary in halomethylzinc-mediated cyclopropanation.

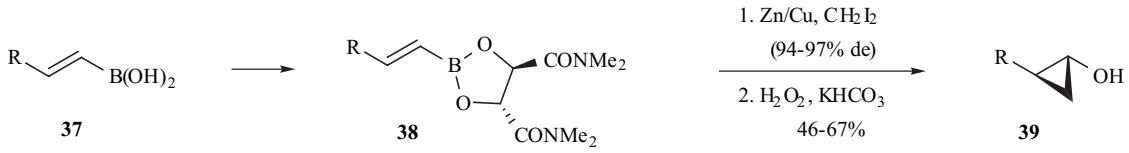
The field of chiral auxiliaries has been more studied and good results have been achieved in the preparation of enantioenriched cyclopropanols after auxiliary cleavage. Enol ether **33** (Scheme **10**) that has a chiral diol as auxiliar is

haloalkylzinc reagents. Sugimura [19] has reported that his chiral auxiliary was effective at producing one major diastereomer from this reaction (Scheme **11**).

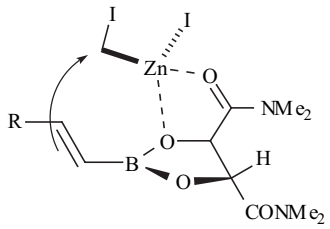


33a **35** **36**

Scheme 11. Tai and Sugimura's chiral auxiliary in haloethylzinc-mediated cyclopropanation.



37 **38** **39**



Scheme 12. Imai's chiral auxiliary in halomethylzinc-mediated cyclopropanation.

Imai and coworkers [20] have employed as chiral auxiliar boronic esters bearing the tetramethyltartramide group (Scheme **12**). Again the reaction proceeds with high diastereoselectivity, allowing the asymmetric synthesis of 2-substituted cyclopropanols **39** after oxidation (H_2O_2, $KHCO_3$). The high degree of diastereoselectivity is rationalized on the basis of a transition state (Scheme **12**) in which the zinc reagent $IZnCH_2I$ is coordinated to both oxygens, the one in the boronic ester and that one in the adjacent amide carbonyl group.

This methodology that uses boronic esters has been widely developed by the group of Pietruszka [21]. They have designed different diols as chiral auxiliaries (Fig. **1**), achieving the best results with 2*R*,3*R*-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol **40**.

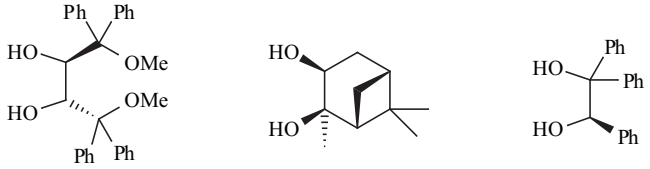


Fig. (1). Pietruszka's chiral auxiliaries for diastereoselective Simmons-Smith cyclopropanation.

In this manner, highly stable cyclopropylboronic esters **44a** and **45a** have been conveniently synthesized under the modified Simmons-Smith conditions (Scheme **13**), but with low selectivity (**44a**/**45a**, 36:64). It was also observed a matched/mismatched interaction when a chiral ligand **46** or *ent*-**46** [22] was added, Table **1**. Indeed, when performing the cyclopropanation as described by Denmark *et al*. [23], products **44a** and **45a** are obtained in good yield (90%) with

Table 1.

Additives	Yield (%) (44a+45a)	dr (44a:45a)
none	94	36:64
46	90	20:80
ent-**46**	91	60:40

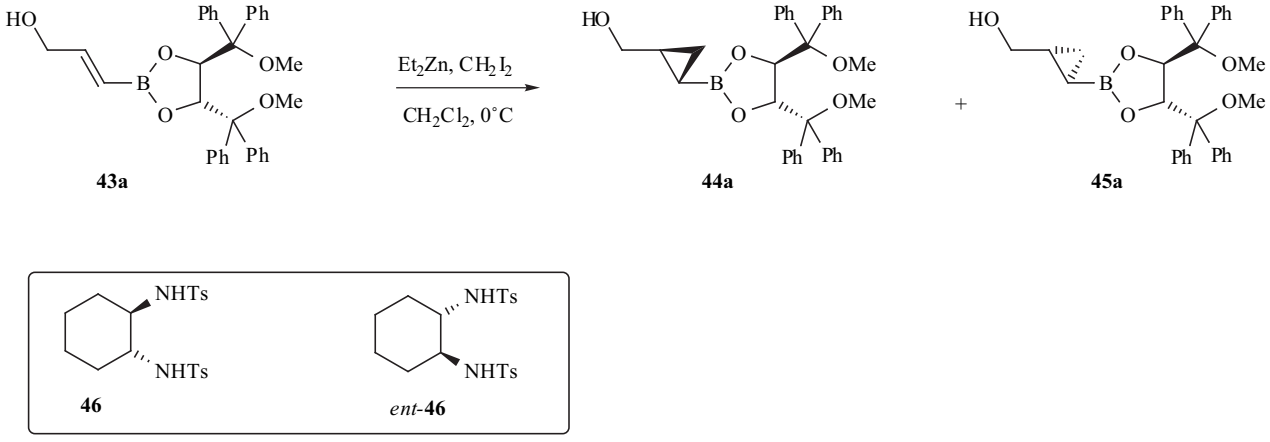
bissulfonamide **46** in a 20:80 ratio and with the enantiomeric ligand *ent*-**46** as a 60:40 mixture. Both diastereoisomers **44a** and **45a**, can be separated, so the cyclopropanols could be obtained in a enantiomerically pure form, after separation and oxidation.

The possibilities of obtaining not only 1,2-disubstituted cyclopropanes but higher substituted derivatives (Schemes **14** and **15**) were also investigated [24]. For this purpose 2,2-diiodopropane and 1,1-diiodoethane has been employed together with diethylzinc to effect the cyclopropanation of the alkenylboronic esters. The sterically demanding auxiliary hampered the successful transformation (Scheme **14**) when using 2,2-diiodopropane achieving low conversion of the starting material.

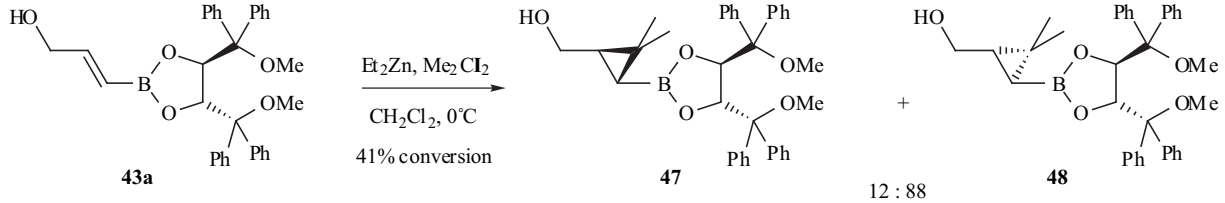
The four possible diastereoisomers were formed in 89% yield when using the zinc reagent obtained from 1,1-diiodoethane and diethylzinc (Scheme **15**).

2. DIHALOCARBENE CYCLOPROPANATION

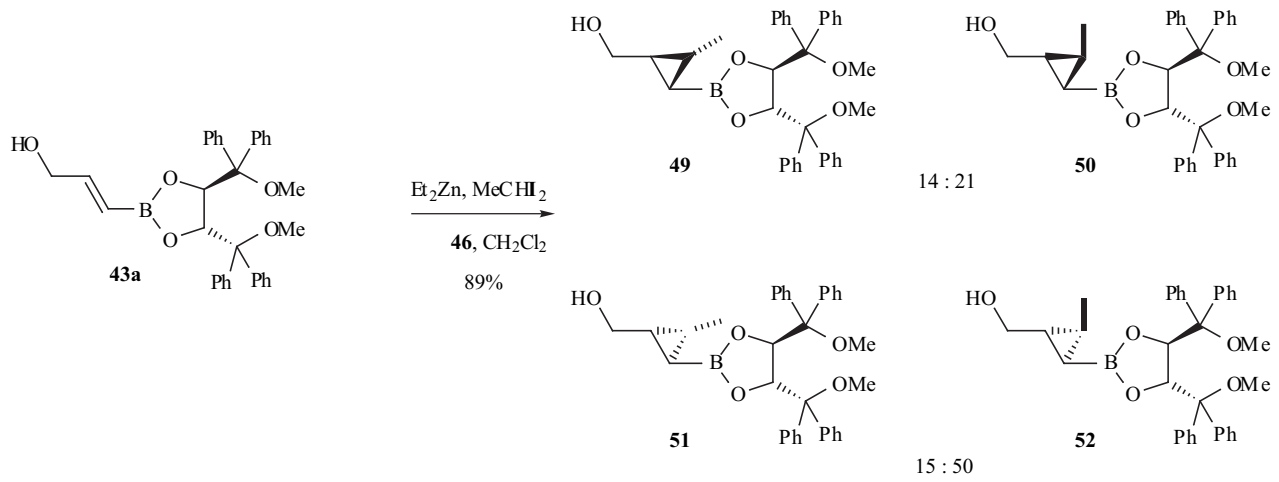
A different type of carbenes are dihalocarbenes. They are formed under treatment of chloroform or analogues with a base such as sodium hydroxyde and have also been used in the cyclopropanation of enol ethers. The dihalocarbene



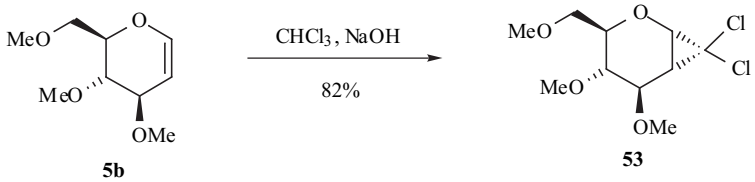
Scheme 13. Pietruszka's chiral auxiliary in halomethylzinc-mediated cyclopropanation.



Scheme 14. Pietruszka's chiral auxiliary in halo-1-methylethylzinc-mediated cyclopropanation.

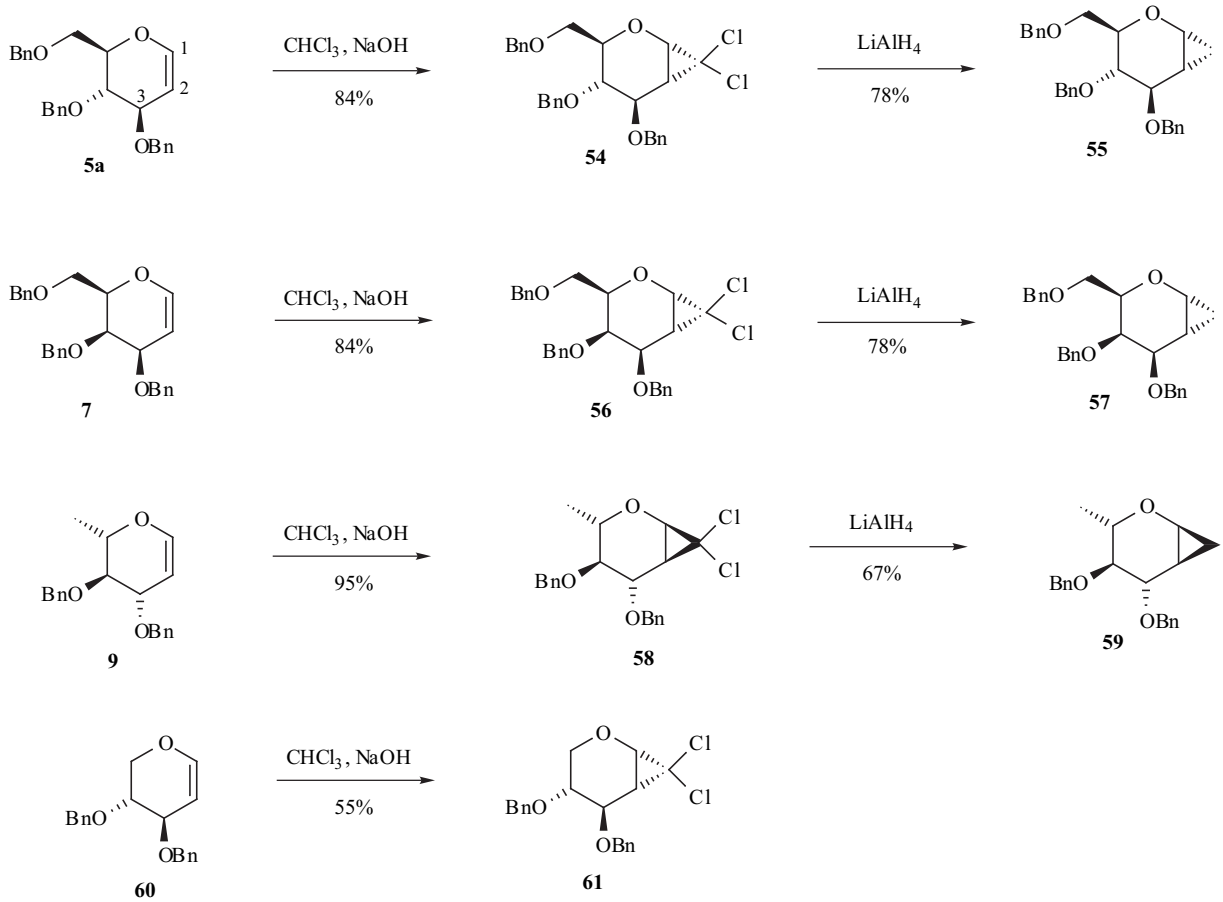


Scheme 15. Pietruszka's chiral auxiliary in haloethylzinc-mediated cyclopropanation.



Scheme 16. Glycal cyclopropanation using a dihalocarbene.

cycloaddition allows *trans* cyclopropanation of allylic hydroxyl/alkoxyl substituted carbohydrates. In 1967, Brimacombe and co-workers [25] reported the first glycal cyclopropanation through dichlorocarbene addition (Scheme **16**).



Scheme 17. Glycals cyclopropanation using dihalocarbenes.

However, only recently, a general methodology has been developed by Nagarajan [10, 26] for cyclopropanation of a series of protected glycals as illustrated in Scheme **17**. The stereochemistry in this process is governed by steric approach control, with the substituent at C(3) being of primary importance. This result is quite interesting because subsequent reductive dehalogenation affords products with stereochemistry complementary to that obtained in the Simmons-Smith reaction.

3. CYCLOPROPANATION WITH DIAZOMETHANE/ PALLADIUM ACETATE

The cyclopropanation of olefins with excess diazomethane is possible using $Pd(OAc)_2$ as catalyst. In general, the reaction for acyclic olefins proceeds with low diastereoselectivity, however Pietruszka [21] has reported good results (Scheme **18**, Table **2**) when using his chiral auxiliary **40** in the boronic ester. The diastereoisomeric cyclopropylboronic esters have been obtained in high yield (89-99%) and with good to excelent diastereomeric ratios (up to 95:5). Both diastereoisomers were separated by means of MPLC, and transformed to the cyclopropanols [27] by an oxidation step (H_2O_2, $KHCO_3$).

Notably, the direction of diastereoselectivity is opposite to that observed in the Simmons-Smith reaction. The approach of the Pd-carbene species is effected through the less hindered direction (Scheme **18**), without any complexation to the bulky boronic ester groups.

4. DIAZOESTERS CYCLOPROPANATION

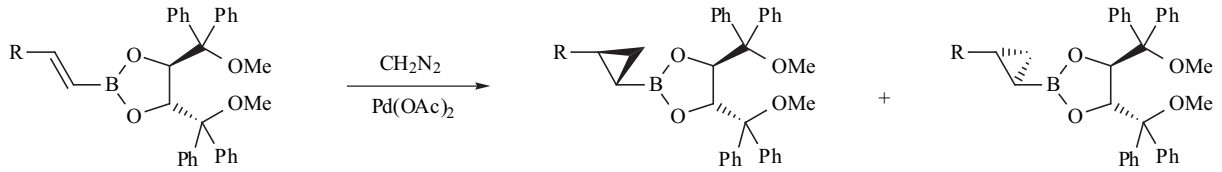
The preparation of cyclopropanecarboxylates using the transition metal-catalyzed decomposition of diazoacetates is one of the most extensively studied reactions of the organic chemistry. Many transition metal complexes (derived from Cu, Rh, Ru, Co, Fe, Os, Pd, Pt, Cr and others) are known to catalyze this reaction, and the associated problems of diastereoselectivity (i.e. *trans vs. cis*) and enantioselectivity may be addressed by varying the metal-ligand system, as well as the steric bulk of the ester group.

When using diazoesters in the cyclopropanation of enol ethers (Scheme **19**), the obtained three membered rings have electron donating and withdrawing substituents. These products, **64**, have been named by Reissig [28] as donor-acceptor (DA) cyclopropanes and are particularly suitable for synthetic applications, since electronic effects of the substituents guarantee activation of the system and provide products after ring cleavage, not easily available by alternative methods.

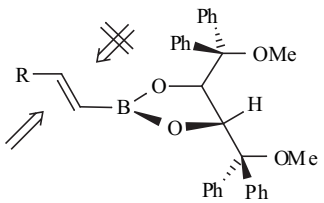
The reaction of ethyl diazoacetate with a chiral cyclic alkene usually proceeds well in terms of yield and diastereoselectivity. Unsaturated sugars give the cyclopropanated derivatives in high yield. Several catalyst

Table 2.

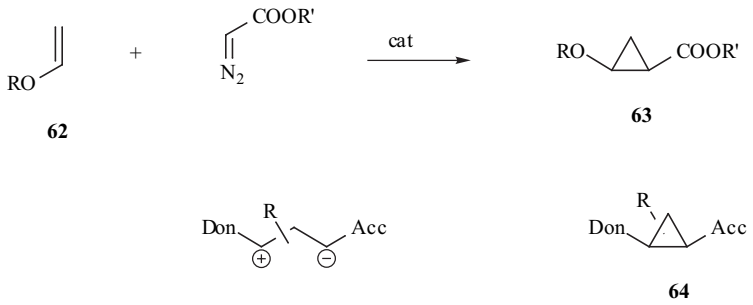
R	(%)	dr
n-pentyl	99	93:7
n-Bu	98	89:11
^{t}Bu	95	87:13
Ph	93	86:14
$TIPSO(CH_2)_3$	89	95:5
$TBSOCH_2$	90	70:30



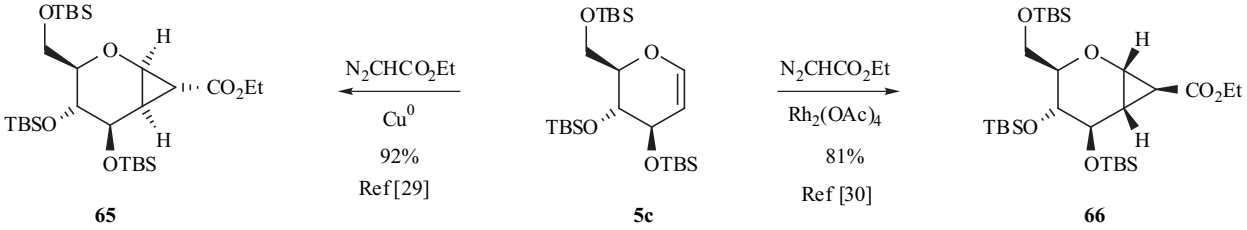
43 **44** **45**



Scheme 18. Pietruszka's chiral auxiliary in pd(ii)acetate catalyzed cyclopropanation with diazomethane.



Scheme 19. Diazoesters cyclopropanation of enol ethers.



Scheme 20. Glycal cyclopropanation using a diazoester.

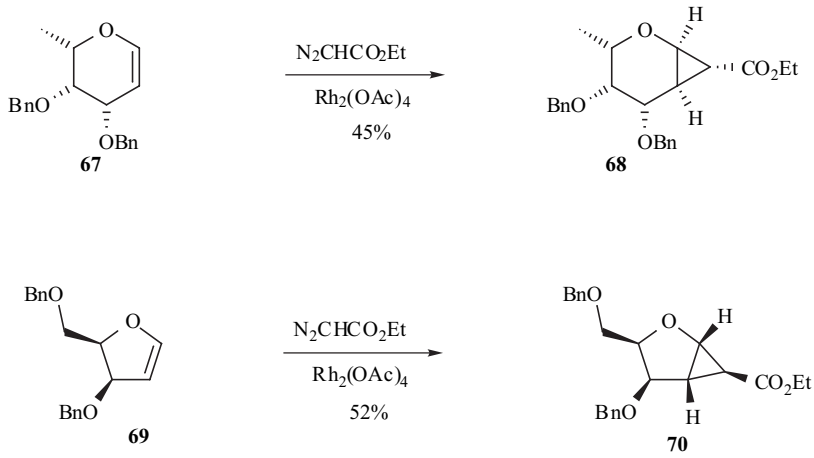
can be used to effect the decomposition of the diazoacetate. Henry and Fraser-Reid [29] found that the cyclopropanation of tri-*O-tert*-butyldimethylsilyl-D-glucal **5c** (Scheme **20**) with copper powder provided exclusive β facial selectivity giving the cyclopropane **65** in 92% yield.

Hoberg and Claffey [30] reported their results from an independent investigation of this reaction employing other carbohydrate substrates and transition metal catalysts. As illustrated in Scheme **20**, unlike Fraser-Reid's results, α diastereomers **66** were obtained in this case when using rhodium acetate as catalyst. Judicious employment of either $Rh_2(OAc)_4$ or Cu(0) catalysts in the cyclopropanation of glycals with ethyl diazoacetate provides convenient access to products with complementary stereochemistry.

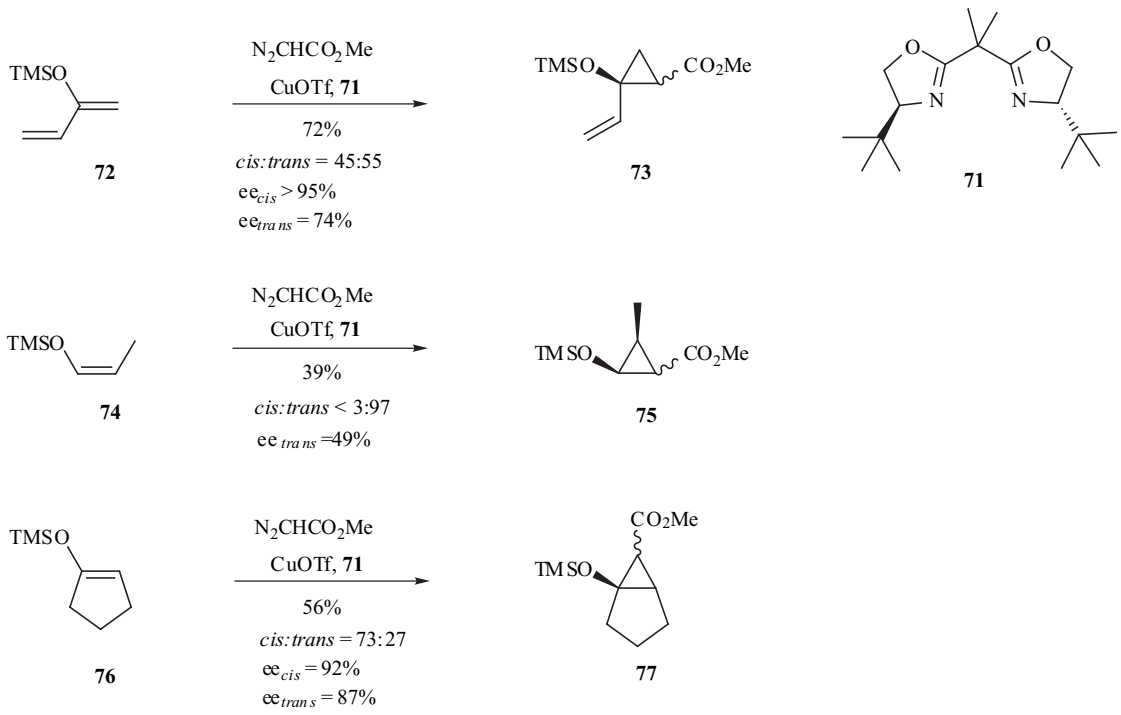
These studies and the work by van Boom and co-workers [31] on the cyclopropanation of furanose and pyranose ring systems (Scheme **21**) revealed that among the homogeneous catalyst examined $Rh_2(OAc)_4$ resulted in the highest efficiency. Substrates **67** and **69** were transformed stereoselectively in an acceptable yield into the respective *exo*-adducts **68** and **70**.

Chiral catalysts can be employed to carry out the process asymmetrically. This reaction has been studied extensively. Lots of different chiral catalysts have been tested, but still there is not a satisfactory general solution in terms of enantio and diastereoselectivity. Scheme **22**, presents typical examples where good enantioselectivities were recorded. Evans's bisoxazoline ligand **71** [32] is used in these transformations. Donor-acceptor cyclopropane **75** were formed [33] with high *trans*-selectivity, but the ee was only 49%. On the other hand, Pfaltz [34] obtained both diastereomers of bicyclic product **77** with high ee values, but the diastereoselectivity was only in the range of 3:1.

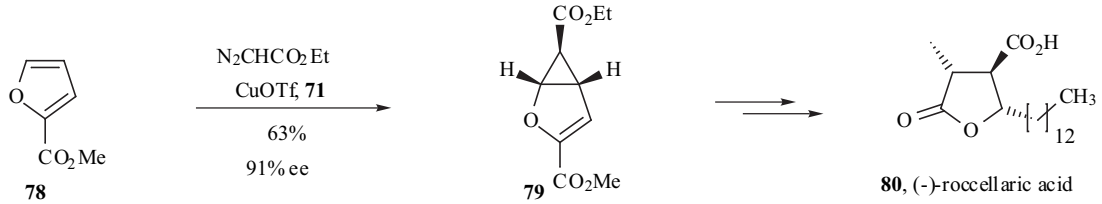
Excelent results have been achieved by Reiser and Böhm [35] in the reactions of furan derivatives with diazoacetates in the presence of Evans' bisoxazoline copper catalyst and similar complexes obtaining the bicyclic DA cyclopropanes in good yield, excellent diastereoselectivity, and good to



Scheme 21. Glycals cyclopropanation using diazoesters.



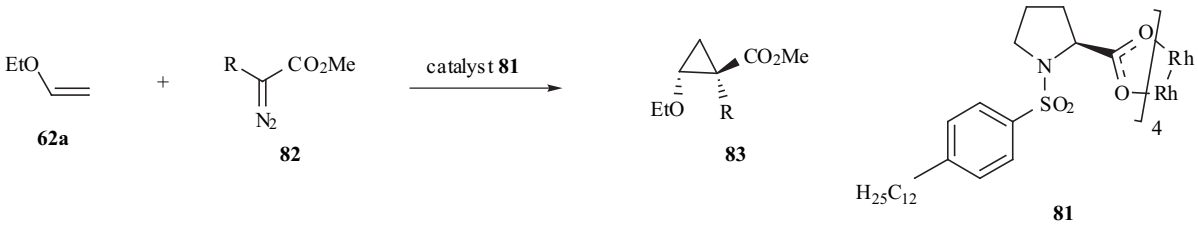
Scheme 22. Selected examples of enol ethers enantioselective cyclopropanation with diazoacetates catalyzed by Cu (i)-**71**.



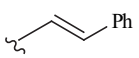
Scheme 23. Reiser's enantioselective cyclopropanation of furan derivatives.

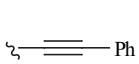
very good enantioselectivity. In the example depicted in Scheme **23**, methyl furan 2-carboxylate 7**8** yields compound **79**, and the ee is as high as 91% but it can be raised to 99% in one recrystalization. With a related aza(bisoxazoline) copper catalyst, a slightly higher ee was recorded; however, the yields with this type of catalyst were inferior. Derivatives of type **79** are valuable starting materials for further synthetic applications, such as the preparation of roccellaric acid [35].

Rhodium catalyst are also effective in these cyclopropanations with diazocompounds. As an example, rhodium (II) prolinate derivative **81** has been shown to act as very good catalyst as illustrated in Scheme **24** [36], for enantioselective cyclopropanation of enol ethers with diazoacetates **82** bearing unsaturated substituents. The achieved enantioselectivities are good for some of the substrates (up to 94% ee).

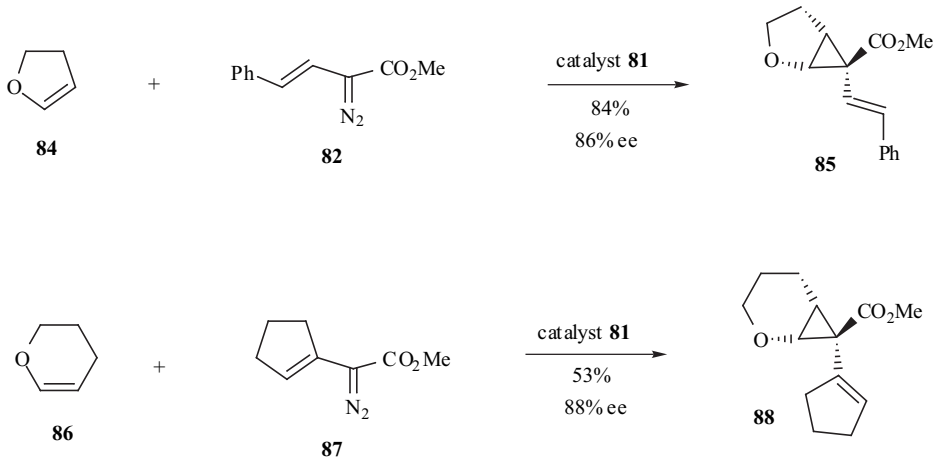


R = Ph — 88% (*trans:cis* = 97:3) — ee_{trans} = 66%

R =  — 71% (only *trans*) — ee = 94%

R =  — 66% (only *trans*) — ee = 87%

Scheme 24. Ethyl enol ether enantioselective cyclopropanation with diazoesters catalyzed by **81**.

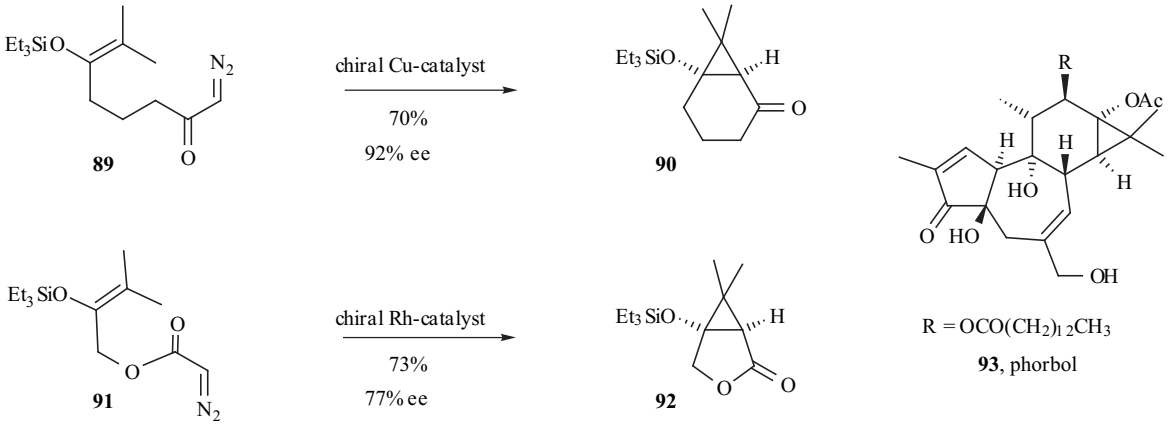


Scheme 25. Enol ethers enantioselective cyclopropanation with diazoesters catalyzed by **81**.

Cyclic enol ethers such as 2,3-dihydrofuran, **84**, and dihydropyran, **86**, have also been employed as suitable starting materials for highly enantioselective reactions with diazoacetates **82** and **87** in the presence of the chiral catalyst **81** (Scheme **25**) [37]. The enantiomeric excesses were close to 90% while the diastereoselectivities were exceptional. Products **85** and **88** have been used in a vinylcyclopropane-cyclopentene rearrangement to afford enantioenriched cyclopentene derivatives.

5. CYCLOPROPANATION WITH FISCHER CARBENE COMPLEXES

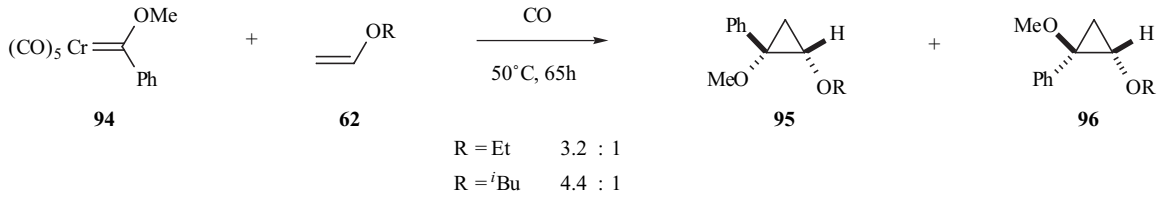
The cyclopropanation of olefins with heteroatom-stabilized pentacarbonyl complexes of the group 6 metals is one of the most studied reactions in Fischer-type carbene chemistry. These cyclopropanations with Fischer carbenes have a few limitations like formation of C-H insertion products and modest diastereoselectivity, as frequently equal amounts of *cis* and *trans* isomers are obtained. However,



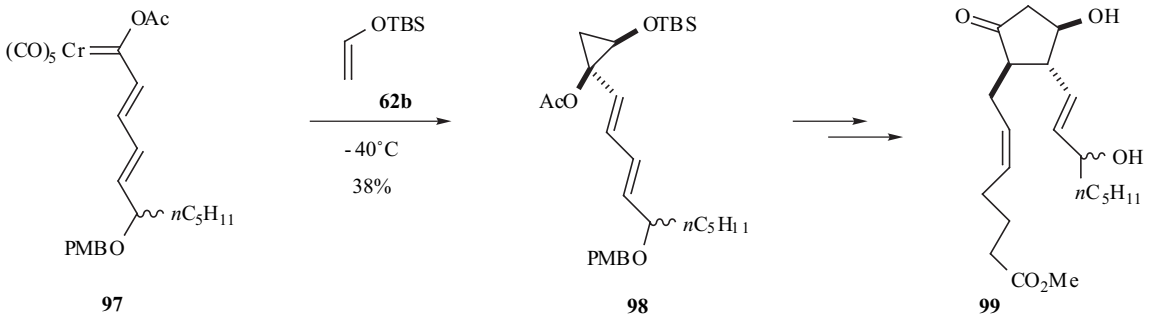
Scheme 26. Intramolecular enantioselective cyclopropanation with diazoesters.

The enantioselective cyclopropanation reaction has also been conducted intramolecularly, giving bicyclic compounds (Scheme **26**) [38]. In this case only one diastereoisomer is formed due to geometric constraints. Both products **90** and **92** were required for an approach to the phorbol CD-ring skeleton.

much higher stereoselectivities are attained when these carbene transfer reactions involve a conjugated system either in the alkene or in the carbene ligand. The success of this cyclopropanation reaction is not only highly dependent on the electronic nature of the alkene but is also influenced by the intra- or intermolecular nature of the process and the

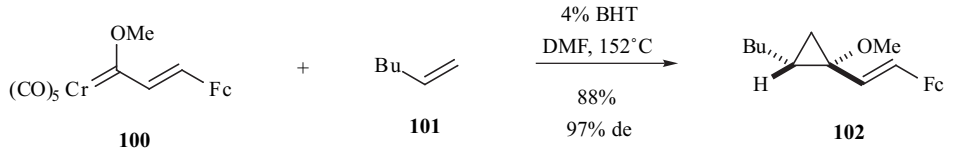


Scheme 27. Enol ethers cyclopropanation with Fischer carbene complex **94**.



97 **98** **99**

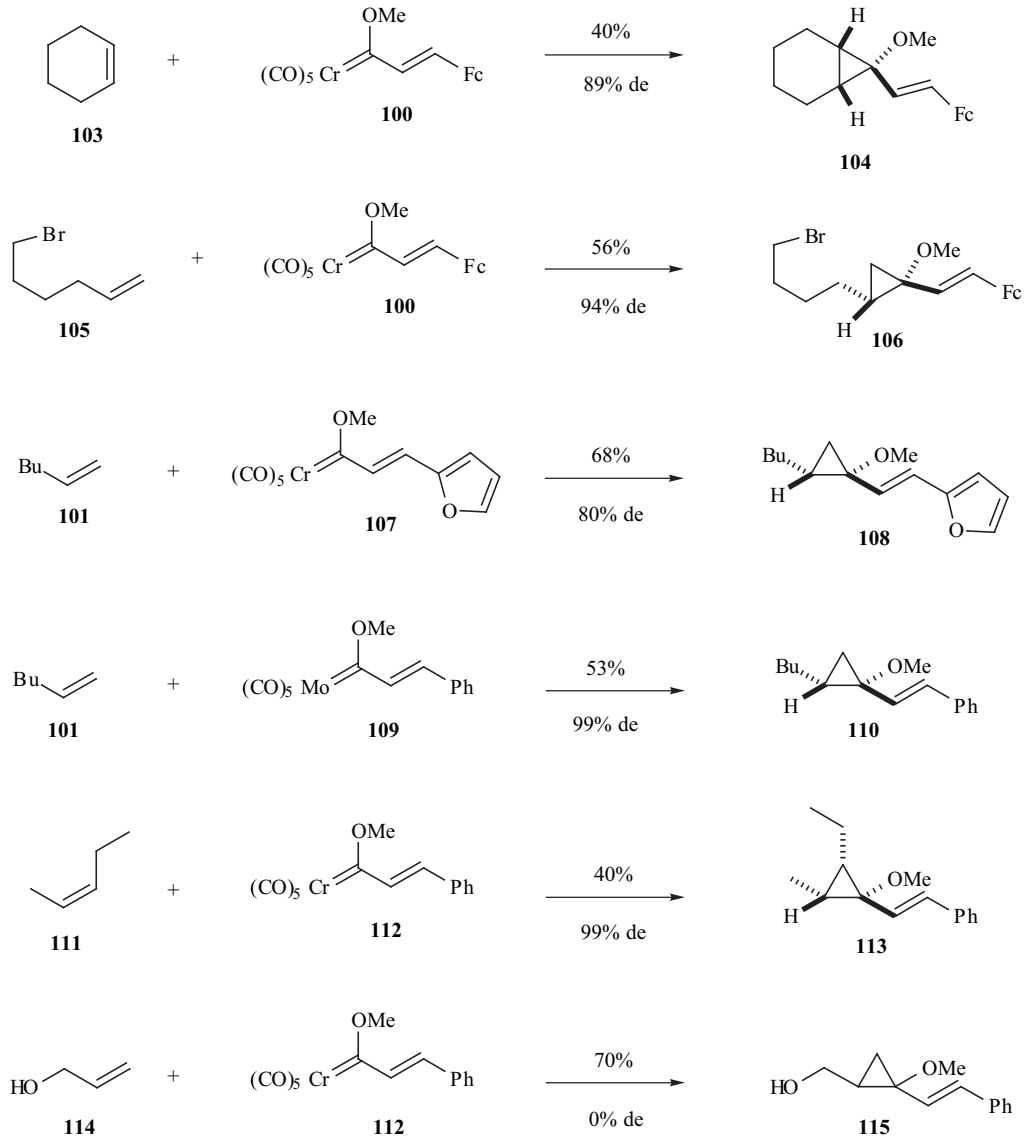
Scheme 28. Wulff's synthesis of prostaglandin E_2.



100 **101** **102**

Fc = ferrocenyl

Scheme 29. Diastereoselective cyclopropanation of **101** with Fischer carbene complex **100**.



Scheme 30. Selected examples of cyclopropanation of electronically neutral alkenes with Fischer carbene complexes.

nature of the heteroatom directly bonded to the carbene carbon. The reaction with electron rich olefins (Scheme **27**) must be carried out under high pressure of carbon monoxide in order to avoid the corresponding olefin metathesis. This is precisely, one of the first cyclopropanations studied by Fischer and Dötz [39].

Wulff and coworkers [40] however, don't use carbon monoxide pressure to carry out the cyclopropanation in the *tert*-butyldimethylsilyl enol ether (Scheme **28**), but employ an acyloxycarbene complex, **97**. Because of the enhanced reactivity on the carbene, the reaction can be accomplish for the synthesis of prostaglandin E_2, **99**.

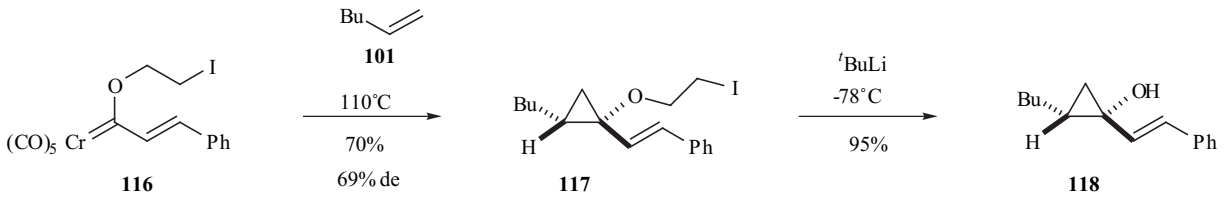
The cyclopropanation of simple olefins (alkyl substituted) has also been carried out by means of Fischer carbene complexes. These unactivated alkenes can be easily cyclopropanated if the carbene transfer reaction is carried out in an intramolecular fashion. The intermolecular version has been recently developed by the group of Barluenga [41]. Their methodology consist on the treatment of carbene complex **100** with a high 20-fold molar excess of the olefin (Scheme **29**) and a substoichiometric amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) in dimethylformamide (DMF) at reflux.

Under these conditions several olefins have been cyclopropanated [42]. Different functional groups in the alkene are compatible with this methodology and it has also been developed with success for other carbene complexes. Some of the most representative examples are shown in Scheme **30**.

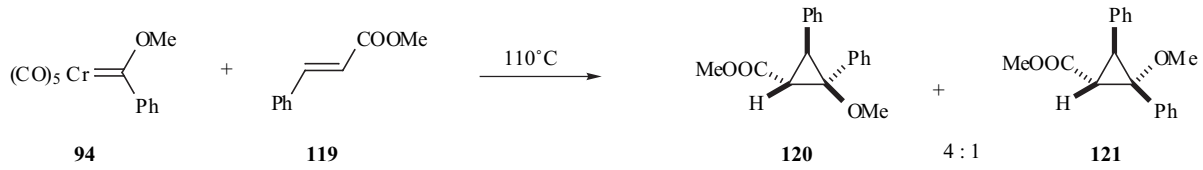
The same group has achieved the preparation of deprotected cyclopropanols (Scheme **31**) [43] when using carbene complexes presenting a 2-iodoethoxy group instead of the methoxy group, that is more difficult to cleavage. In this manner, once the cyclopropanation is achieved, treatment with *tert*-BuLi allows a quick exchange iodo-lithium forming a unstable intermediate that yields the cyclopropanol through a β-elimination. Moreover, this hydroxycyclo-propanation of alkenes can be performed in a one-pot procedure.

The process of cyclopropanation of electron deficient olefins by means of Fischer carbene complexes is another methodology for the preparation of donor-acceptor cyclopropanes (Scheme **32**) [44].

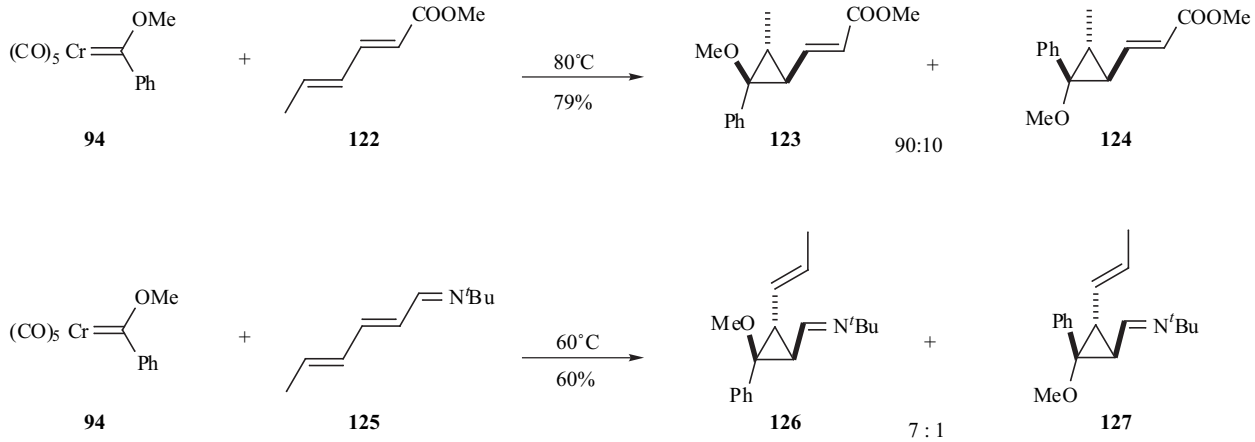
Alkenyl-substituted DA cyclopropanes **123**-**127**, have been prepared in thermal reactions of Fischer carbene complexes with electron-deficient 1,3-dienes. The transformation proceeds with high regioselectivity. The three membered-ring is formed at the remote carbon-carbon double bond when the electron-accepting group is an ester (Scheme **33**) [45]. The observed chemoselectivity is opposite in the case of an analogue imine, **125**. When the latter is treated with the same carbene complex, the cyclopropanation is produced in the double bond next to the imine functionality (Scheme **33**) [46]. In both cases, the attained diastereoselectivity is high.



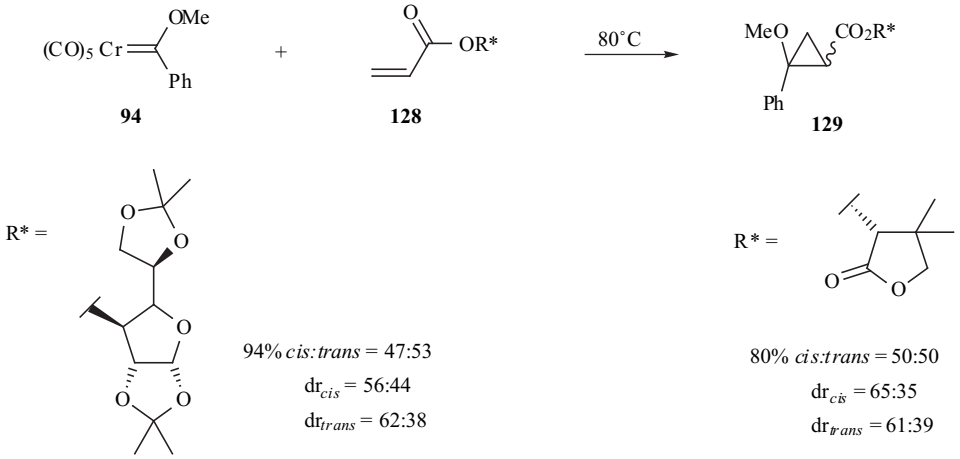
Scheme 31. Hydroxycyclopropanation of **101** with Fischer carbene complex **116**.



Scheme 32. Cyclopropanation of electron deficient alkenes with Fischer carbene complex **94**.



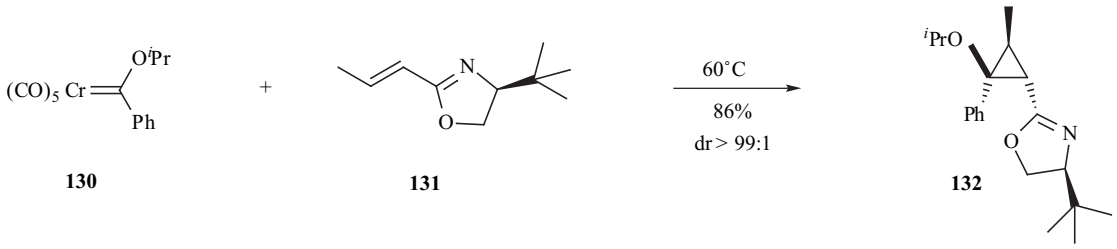
Scheme 33. Cyclopropanation of electron deficient alkenes with Fischer carbene complex **94**.



Scheme 34. Chiral auxiliaries mediated cyclopropanation with Fischer carbene complex **94**.

The principal drawback in these transformations with Fischer carbene complexes is that there is still no asymmetric version. Only a few attempts have been made using chiral auxiliaries. Moderate diastereoselectivities were observed by the group of Reissig [28], when using auxiliaries (di-acetone glucose or *R*-pantolactone) esterificating acrylic acid as it is shown in Scheme **34**.

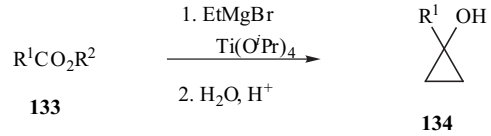
Promising results have been obtained by Barluenga and coworkers [47] that employ a chiral oxazoline, as illustrated in Scheme **35**. Treatment of the alkenyl-substituted oxazoline **131** with the chromium carbene complex in THF at 60ºC afford the *trans* cycloadduct **132** with exceptional facial selectivity. The diastereomeric excess for major *trans*-isomers of **132** is superior to 98%. Once the cyclopropane was formed it was not possible to remove the auxiliar without ring opening.



Scheme 35. Chiral auxiliary mediated cyclopropanation with Fischer carbene complex **130**.

6. KULINKOVICH REACTION

In 1989, the group of Kulinkovich found that treatment of a carboxylic acid ester with a mixture of titanium tetraisopropoxide and an excess of ethylmagnesium bromide at -78 to -40ºC affords 1-substituted cyclopropanols in good to excelent yields.



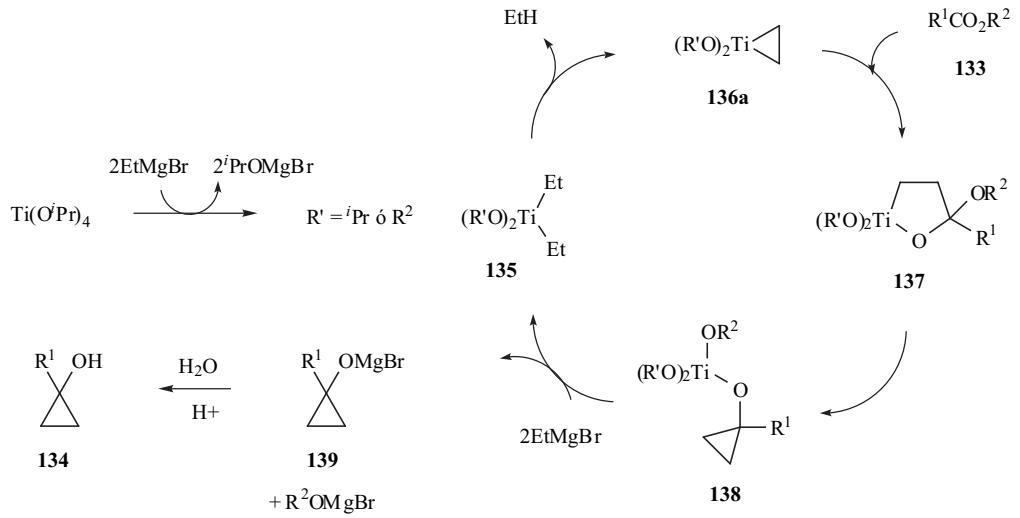
Scheme 36. Kulinkovich reaction.

This transformation can also be carried out with substoichiometric amounts of $Ti(O^iPr)_4$ (5-10 mol%). In this case, the reaction is conducted at room temperature. Mechanistically, the reaction can be rationalized as shown in Scheme **37** [48]. It is thought that two equivalents of the Grignard reagent reacts with the $Ti(O^iPr)_4$ forming an unstable diethyltitanium intermediate **135** which rapidly undergoes β-hydride elimination to yield ethane and the reactive intermediate titanacyclopropane **136a**. This latter acts as a double alkylation agent in front of the ester. This probably happens by insertion of the carbonyl group into one of the Ti-C bonds to give an oxatitanacyclopentane and subsequent ring contraction. The titaniumcyclopropanolate **138** reacts with one or two molecules of the Grignard reagent to reform the unstable diethyl titanium intermediate **135**, completing then a catalytic cycle, and give the magnesium cyclopropanolate **139** that is eventually hydrolyzed to the cyclopropanol **134**.

Several cyclopropanols [49] have been prepared under these conditions. Different functional groups are well tolerated [50-55] and also lactones [54] are good starting materials in this transformations. Some examples are illustrated in Table **3**.

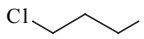
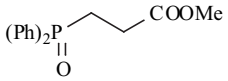
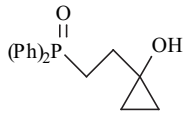
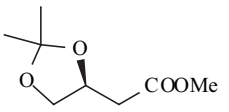
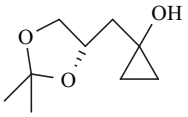
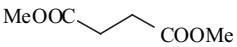
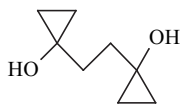
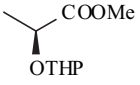
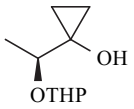
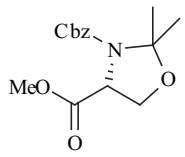
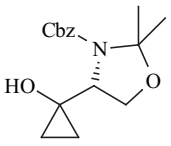
1,2-disubstituted cyclopropanols **140** can be prepared from esters and 2-substituted ethylmagnesium halides in the presence of $Ti(O^iPr)_4$ or $ClTi(O^iPr)_3$ (Scheme **38**).

Several examples [56-59] can be seen in Table **4**. In the absence of any chelating substituents in the substrate, the products **140** are formed with high diastereoselectivity, i.e., the two substituents on the 1,2-disubstituted cyclopropanol preferentially end up in a *cis* relationship with one another. There have been two recent studies [60] on the mechanism of Kulinkovich reaction to rationalize the observed diastereoselectivity.

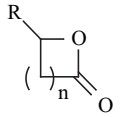
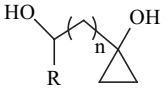
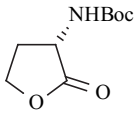
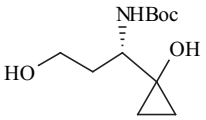


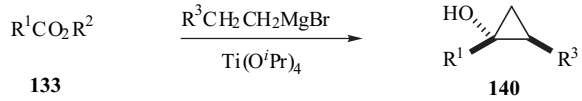
Scheme 37. Kulinkovich reaction mechanism.

Table 3. 1-Alkylcyclopropanols 134 from Esters and Ethylmagnesium Bromide in the Presence of Titanium Tetraisopropoxide

Starting Ester, 133	Product, 134	Yield	Ref.
$BuCO_2Me$		90	[48]
		99	[50]
$PhCO_2Me$		93	[49]
		85	[51]
		64	[52]
		85	[53]
		80	[49]
		60	[54]
		64	[55]

(Table 3)contd.....

Starting Ester, 133	Product, 134	Yield	Ref.
	n = 1, 2, 3 R = H, Me 	70-80	[54]
		65	[54]



133 **140**

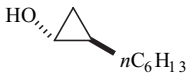
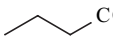
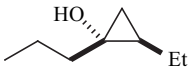
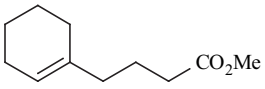
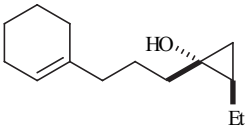
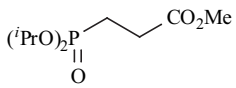
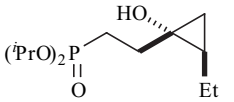
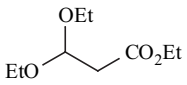
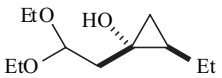
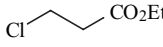
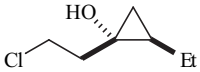
Scheme 38. Kulinkovich reaction using 2-substituted ethyl magnesium bromides.

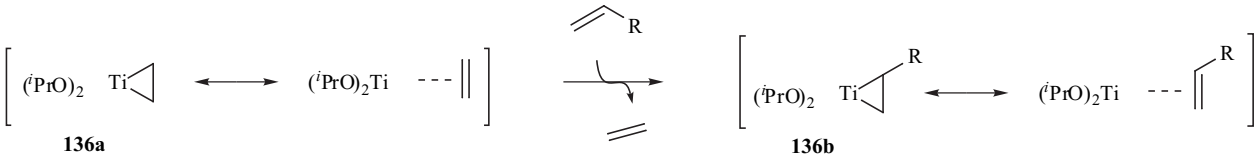
This cyclopropanol preparation methodology is very versatile, in particular if we take on account the increased potential of titanacyclopropane species generated by ligand exchange. As depicted in Scheme **39**, a titanacyclopropane is just the dominating resonance structure of an alkenetitanium complex, so that it is quite understandable that such titanacyclopropanes **136a** (Scheme **37**) formed from dialkyltitanium diisopropoxides **135** can undergo ligand exchange.

This approach is favored by using cyclohexyl, cyclopentyl and isopropyl magnesium halides as Grignard reagents, and has been establish as an efficient method for the hydroxyclycloprapanation of monosubstituted olefins. With the exception of norbornene [61], only terminal alkenes have been hydroxycyclopropanated in this way (Scheme **40**) and the presence of remote other functional groups [61-63] is tolerated.

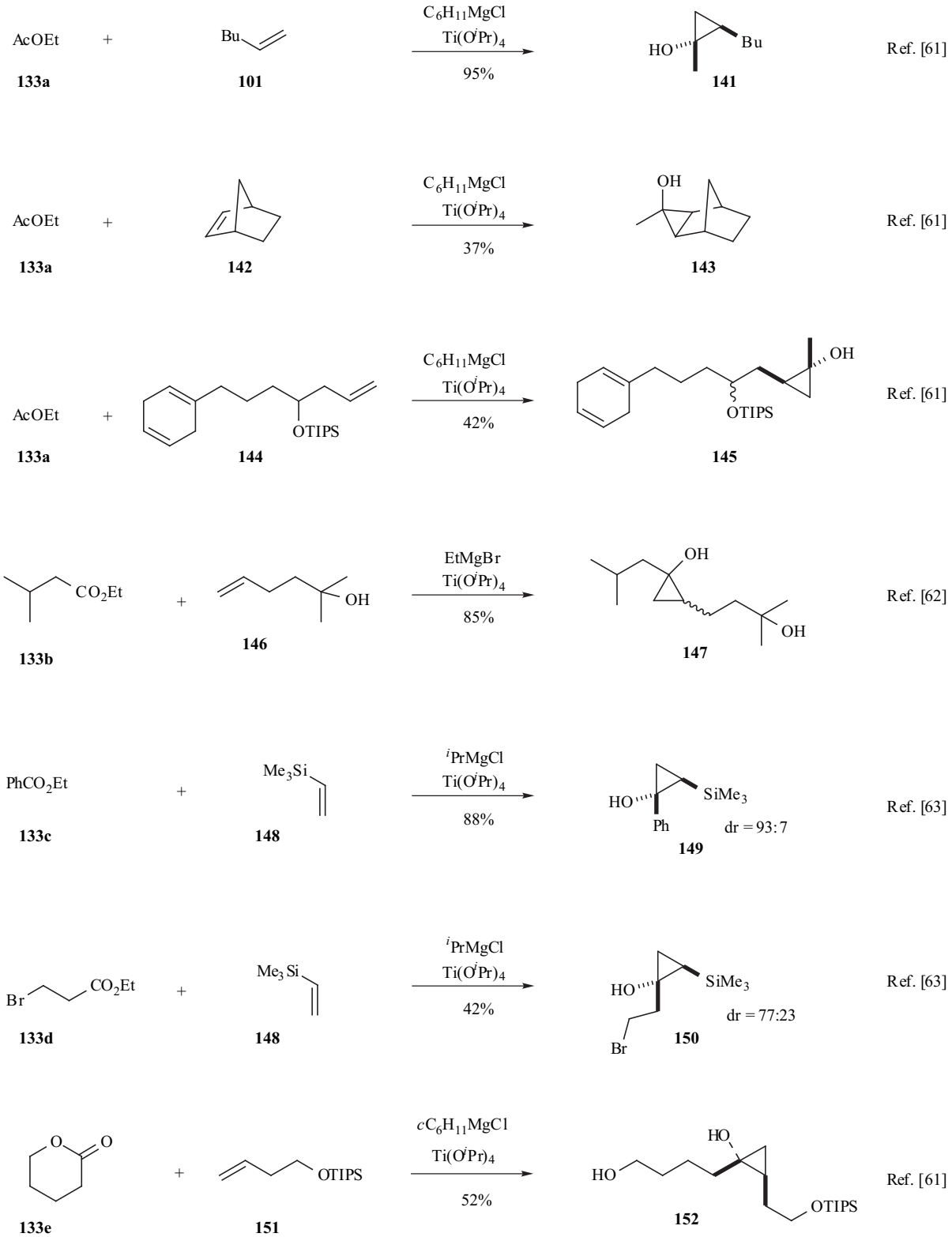
The hydroxycyclopropanation of a terminal double bond also works perfectly well intramolecularly with terminally alkenyl-substituted esters. In this way, starting with ω-vinylcarboxylates (Scheme **41**) the corresponding bicyclic cyclopropanols are form either with carbo- [57] or heterocyclic [64] skeleton.

Table 4. 1,2-Disubstituted Cyclopropanols 140 from Esters and 2-Substituted Ethylmagnesium Halides in the Presence of Titanium Tetraisopropoxide

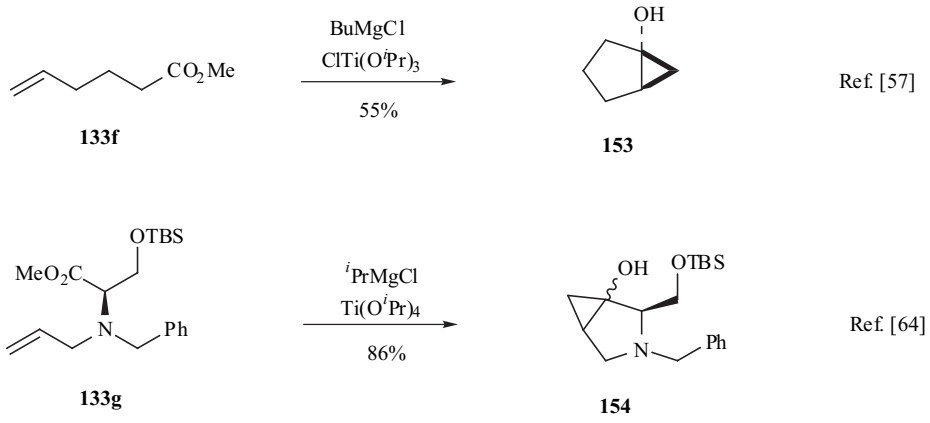
Starting Ester, 133	Grignard	Product, 140	%	Ref.
HCO_2Me	$nC_6H_{13}CH_2CH_2MgBr$		72	[56]
	BuMgBr		79	[56]
CH_3CO_2Me	$PhCH_2CH_2MgBr$		83	[56]
	BuMgBr		good	[57]
	BuMgBr		71	[52]
	BuMgBr		92	[58]
	BuMgBr		65	[59]



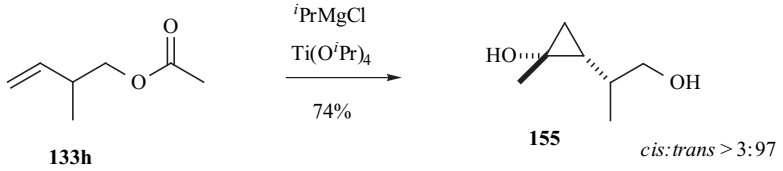
Scheme 39. Ligand exchange in titanacyclopropane species.



Scheme 40. Substituted cyclopropanols from esters and titanium reagents generated by ligand exchange.



Scheme 41. Intramolecular Kulinkovich reaction.



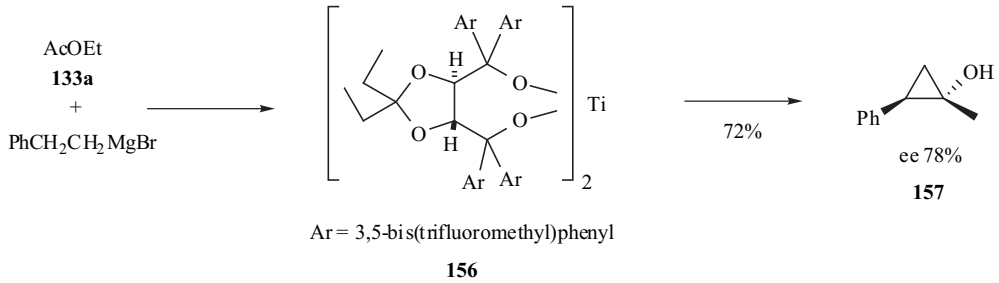
Scheme 42. Kulinkovich cyclopropanation of homoallyl esters.

When the intramolecular hydroxycyclopropanation is effected on homoallyl esters (Scheme **42**) [57,65] the corresponding 1,2-disubstituted cyclopropanols are prepared, but with much higher preference for the *trans*-diastereoisomer. This stereochemical outcome complements the *cis*-stereochemistry of the intermolecular Kulinkovich reaction.

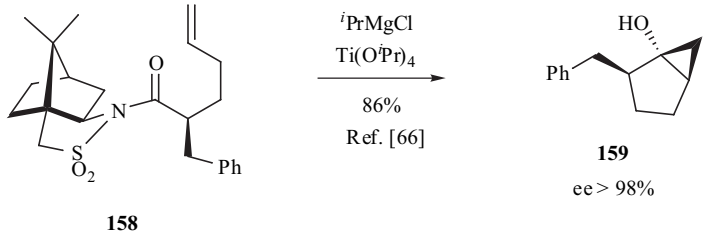
The possibilities of enantioselective transformations are being studied. Corey and coworkers [56] have used chiral titanium catalyst **156** (0.3-1 equivalents) obtaining the cyclopropanol **157** (Scheme **43**) with a enantioselectivity of 89:11.

Sato [66] described the use of chiral auxiliaries in the enantioselective synthesis of bicyclic cyclopropanols from *N*-acylcamphorsultame derivatives (Scheme **44**). Enantiomeric excesses in the products were up to >98%. No success was attained however, in intermolecular transformations [63] when employing the same chiral auxiliar.

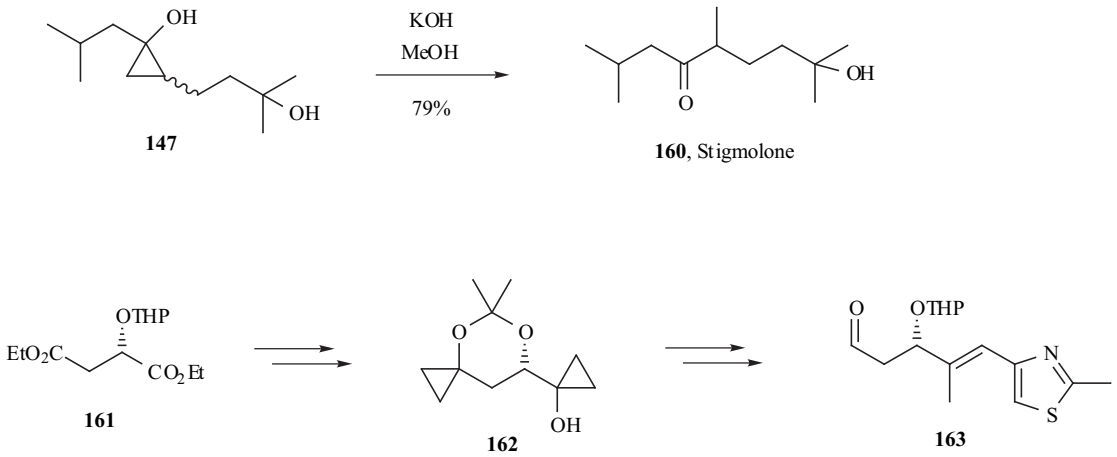
The Kulinkovich hydroxycyclopropanation reaction is being used extensively in the synthesis of natural products [62, 67]. For instance, Stigmolone **160**, has been prepared [62] in a two-step synthesis (Scheme **40** and **45**). The fragment C13-C21 of epothilones, **163**, [67a-b] has also



Scheme 43. Enantioselective Kulinkovich cyclopropanation.



Scheme 44. Sato's chiral auxiliary in enantioselective Kulinkovich cyclopropanation.



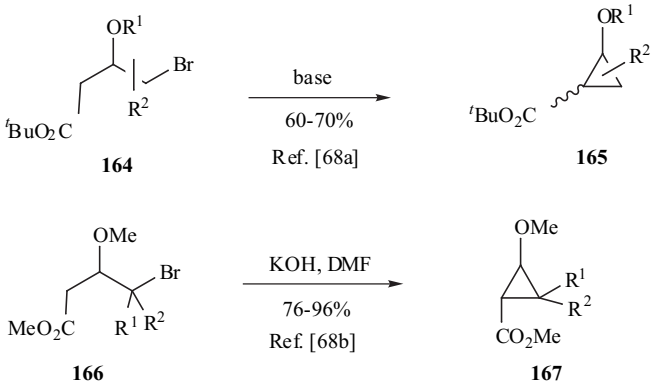
Scheme 45. Kulinkovich reaction in natural products synthesis.

been obtained by means of this strategy of hydroxy-cyclopropanation-ring cleavage (Scheme **45**).

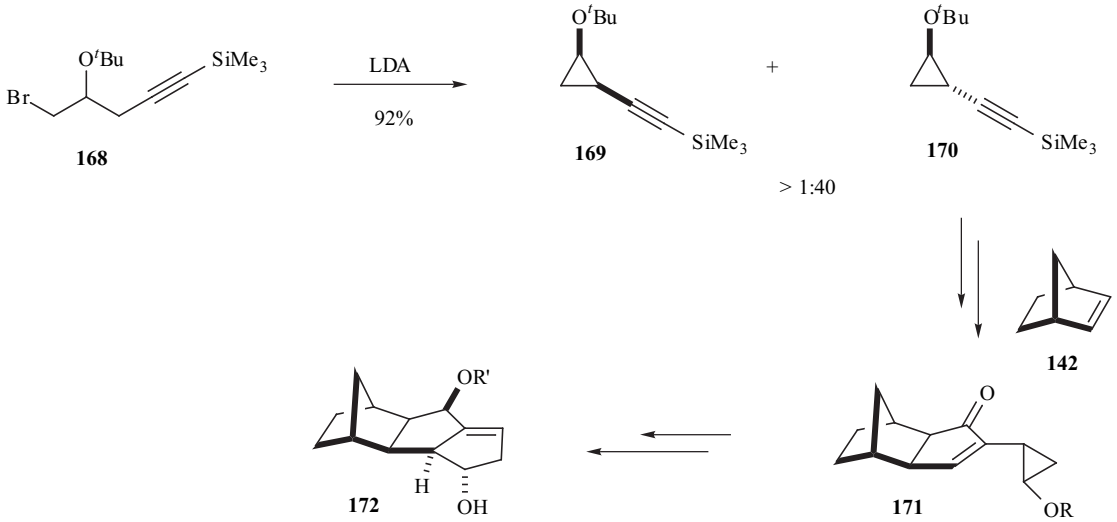
7. INTRAMOLECULAR CYCLIZATIONS

Although less commonly, cyclopropanols have also been synthetised by means of intramolecular cyclization reactions. The transformation can be carried out in a nucleophilic or radical manner. Treatment with base of γ-halo-β-alcoxycarboxylates (Scheme **46**) [68] yields the corresponding alcoxycyclopropanes in high yield and *trans* selectivity.

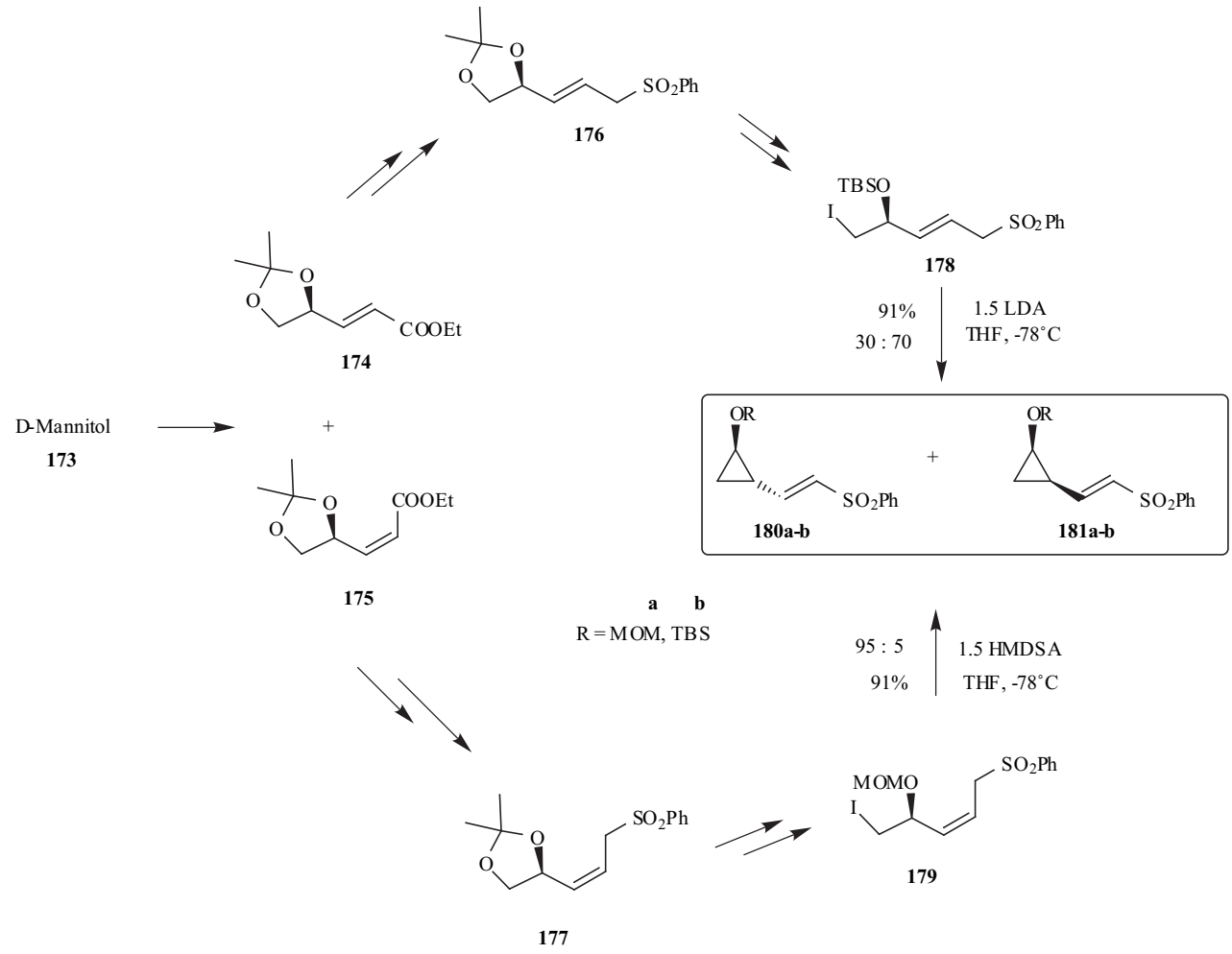
de Meijere [69] has obtained in a similar manner (S_N2 intramolecular reaction) 2-alkoxy-ethynyl cyclopropanes that have been used in a Pausond-Khand reaction (Scheme **47**) with norbornene. Subsequent vinylcyclopropane-cyclopen-



Scheme 46. Intramolecular nucleophilic substitution in alcoxycyclopropane formation.



Scheme 47. Intramolecular nucleophilic substitution in alcoxycyclopropane formation.



Scheme 48. Intramolecular nucleophilic substitution in alcoxycyclopropane formation.

tene rearrangement allows the preparation of policyclic systems.

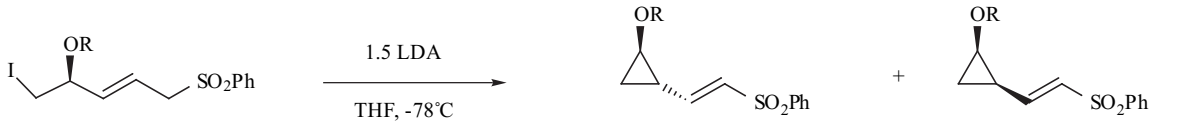
In our research group, chiral cyclopropanols have been prepared from allylic sulfones (previously obtained from D-Mannitol) [70] by means of an intramolecular nucleophilic substitution. Base treatment of the corresponding iodo derivatives **178** and **179** [71] afford the protected *trans* and *cis* vinylcyclopropanols **180** and **181** (Scheme **48**).

A study of this cyclopropanation reaction was made varying double bond configuration, protecting group, leaving group and base. It was found a high diastereoselection *trans*:*cis* of 95:5 (independent of the protecting group and the cation) when HMDSA (A = Na, K, Li) was employed as base and the starting material **179** have a *Z* configuration [71c] (Scheme **49**).

When *E* allylic sulfones **178** were used [71b], diastereoselectivity of the cyclopropanation reaction was strongly dependent on the protecting group (Scheme **50**). The highest *cis* ratio was achieved with the TBS compound **178b** when treatment with LDA.

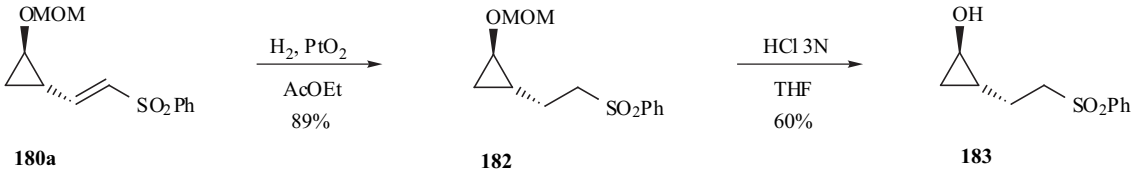
	R				R
179a	MOM	91%,	**180a**	95 : 5	**181a** MOM
179b	TBS	91%,	**180b**	95 : 5	**181b** TBS
179c	THP	91%,	**180c**	95 : 5	**181c** THP

Scheme 49. Cyclization using *Z*-allylsulfones **179**.

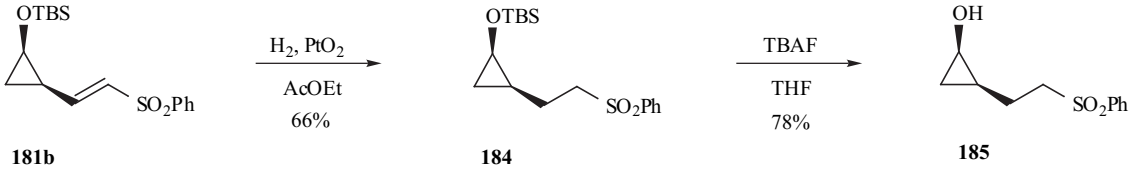


	R				R
178a	MOM	91%,	**180a**	70 : 30	**181a** MOM
178b	TBS	91%,	**180b**	30 : 70	**181b** TBS
178c	THP	94%,	**180c**	70 : 30	**181c** THP
178d	PMB	68%,	**180d**	50 : 50	**181d** PMB
178e	$C(CH_3)_2(OCH_3)$	100%,	**180e**	40 : 60	**181e** $C(CH_3)_2(OCH_3)$

Scheme 50. Cyclization using *E*-allylsulfones **178**.

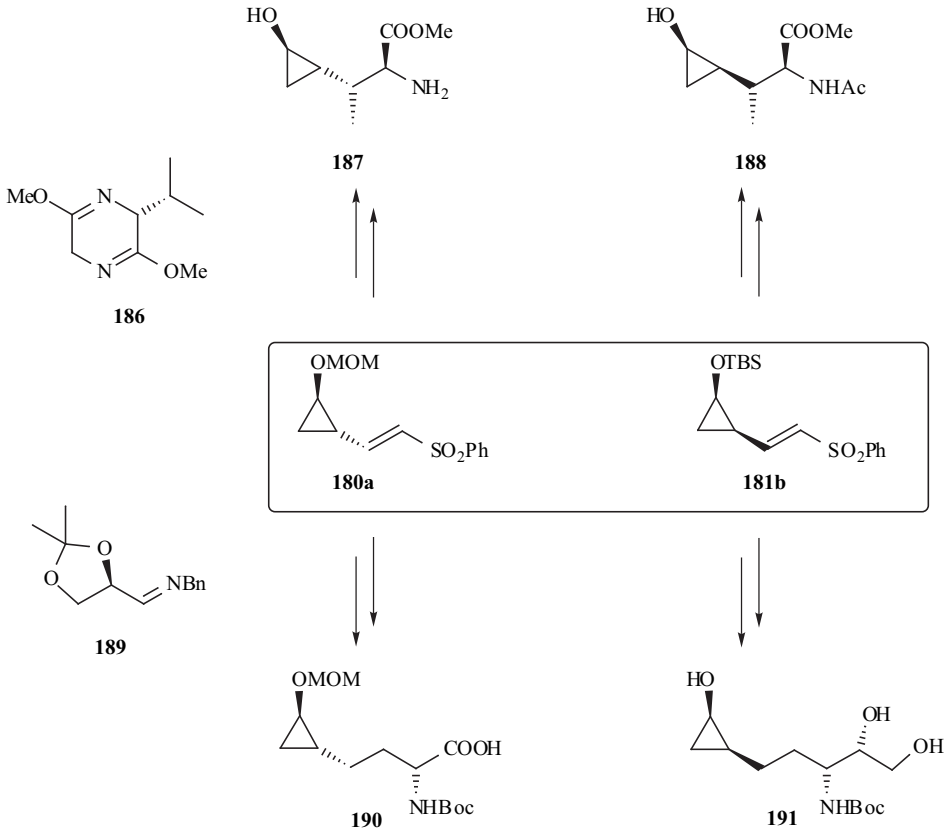


180a **182** **183**

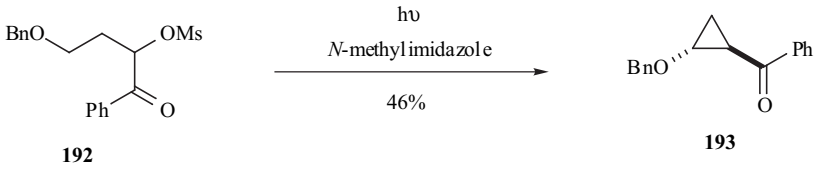


181b **184** **185**

Scheme 51. Synthesis of chiral cyclopropanols **183** and **185**.

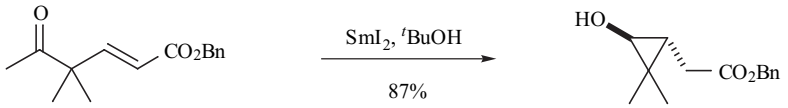


Scheme 52. Synthesis of conformationally restricted amino acids using vinylcyclopropanols.



192 **193**

Scheme 53. Light-mediated radical intramolecular cyclization in alcoxycyclopropane formation.

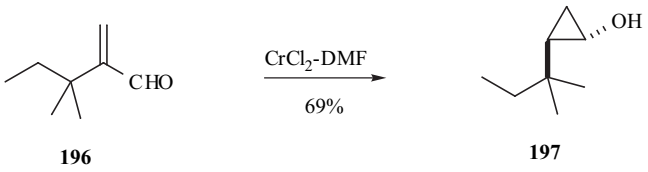


194 **195**

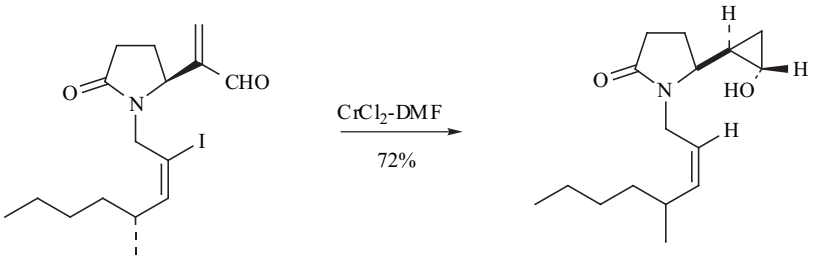
Scheme 54. SmI_2-mediated radical intramolecular cyclization in cyclopropanol formation.

Deprotected cyclopropanols **183** and **185**, could only be obtained [71b] by previous hydrogenation of the double bond and subsequent hydrolysis of the protecting group under the corresponding usual conditions (Scheme **51**). imine **189**, several other precursors **190** and **191** [73] of conformationally restricted amino acids were synthetised.

Radical pathways also allows the preparation of cyclopropanols. As depicted in Scheme **53** [74], dia-



196 **197**



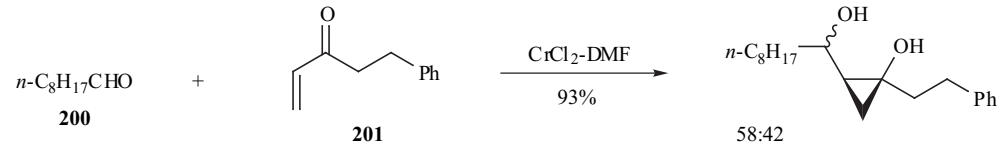
198 **199**

Scheme 55. $CrCl_2$-mediated radical intramolecular cyclization in cyclopropanols formation.

Results were analogous for both *trans* and *cis* cyclopropanes.

Protected vinylcyclopropanols **180a** and **181b** have been used by our group for the synthesis of conformationally restricted amino acids. In this manner, compouds **187** [71c] and **188** [72], precursors of analogues of glutamic acid have been prepared (Scheme **52**), being the key step a Michael addition of Schöllkopf´s bislactim ether **186** to the vinylsulfone. On the other hand, exploiting the α-carbanion stabilization to the phenylsulfonyl group in the addition to stereoselective photochemical cyclization of **192** lead to the product **193**.

Samarium diiodide, widely employed in cyclization reactions for the preparation of five and six membered rings, is also useful for the diastereoselective cyclopropanol formation. In this manner, δ-oxo-α,β-unsaturated esters (Scheme **54**) in the presence of samarium diiodide and a proton source (^{t}BuOH) afford exclusively *anti* cyclopropanols [75], independently of the double bond configuration *E* or *Z* of the starting olefin.



200 **201** 58:42 **202**

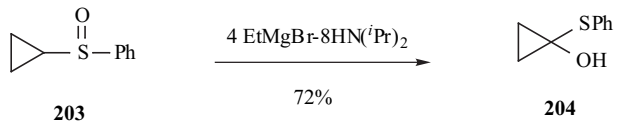
Scheme 56. $CrCl_2$-mediated radical intramolecular cyclization in cyclopropanols formation.

α,β-Unsaturated aldehydes or ketones are converted to the corresponding cyclopropanols in the presence of $CrCl_2$ (Scheme **55**) [76].

The latter cyclopropanol formation has been accomplished with an aldol condensation by the group of Takai [77]. The mixture of enone **201** with an aldehyde (nonanal, **200**) in the presence of $CrCl_2$ produce the cyclopropanediol **202** with a 93% yield (Scheme **56**).

8. OTHER METHODS

Some other methodologies have been employed in the preparation of cyclopropanols. Kobayashi [78] has reported a very interesting Pummerer type reaction of cyclopropyl phenyl sulfoxide **203**, leading to 1-phenylthiocyclopropanol **204** in good yield (Sheme **57**).



203 **204**

Scheme 57. Pummerer-type reaction in cyclopropanol formation.

CONCLUSIONS

This mini review pretends to present like a catalogue of the available methods in the preparation of cyclopropanols. As it can be seen, a great effort it is being made nowadays, what states the huge interest of these structures. It has also been included only a few examples in which cyclopropanols are involved as synthetic intermediates, demonstrating its versatility.

Although most of the methodologies have long been known (Simmons-Smith, dihalocarbene, diazomethane, diazoesters and intramolecular cyclopropanations), quite a number of new modifications and variations were developed directed to obtain high levels of stereoselectivity and especially leading to cyclopropanols in enantioenriched or enantiomerically pure form.

New procedures (Fischer carbene complexes mediated cyclopropanation and Kulinkovich reaction) are emerging as powerful tools in the preparation of these entities. It can be envisaged the great potencial of these reactions that are demanding further development.

Although methods for synthesis of cyclopropanols are very versatile and usually efficient, a general solution for enantioselective preparation of this class of small-ring compounds is still missing.

ACKNOWLEDGEMENTS

The authors are gratefully acknowledged to Dr. A. Lithgow and Dr. C. Raposo, from the NMR and Mass Spectrometry Services, respectively, of Universidad de Salamanca and to the CICYT (CTQ2005-06813/BQU) for financial support.

REFERENCES

[1] (a) Reissig, H.-U. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 1987; Chapter 8, pp. 375-443. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev*. **1989**, *89*, 165-198. (c) de Meijere, A.; Kozhushkov, S. I.; Khlebnivow, A. F. *Top. Curr. Chem*. **2000**, *207*, 89-147. (d) de Meijere, A.; Kozhushkov, S. I.; Hadjiarapoglou, L. P. *Top. Curr. Chem*. **2000**, *207*, 149-227. (e) Bekish, A. V.; Prokhorevich, K. N.; Prityts kaya, T. S.; Kulinkovich, O. G. *Polish J. Chem*. **2006**, *80*, 549-558. (f) Lysenko, I. L.; Lee, H. G.; Cha, J. K. *Org. Lett*. **2006**, *8*, 2671-2673.

[2] Salaün, J. *Top. Curr. Chem*. **2000**, *207*, 1-67.

[3] Suckling, C. J. *Angew. Chem. Int. Ed.* **1988**, *27*, 537-552.

[4] (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev*. **2003**, *103*, 977-1050. (b) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc*. **2005**, *127*, 18014-18015.

[5] (a) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams. D. J. *J. Am. Chem. Soc*. **1997**, *119*, 8608-8615. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589-8627.

[6] Gibson, D. H.; DePuy, C. H.; *Chem. Rev*. **1974**, *74*, 605-623.

[7] Kulinkovich, O. G. *Polish J. Chem*. **1997**, *71*, 849-882.

[8] Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc*. **1958**, *80*, 5323-5324. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc*. **1959**, *81*, 4256-4264.

[9] (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307-1370. (b) Marsh, J. *Adv. Org. Chem*., 4th ed.; Wiley: New York, **1992**. (c) Hermann, H.; Lohrenz, J. C. W.; Kühn, A.; Boche, G. *Tetrahedron* **2000**, *56*, 4109-4115.

[10] Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc. Chem. Commun*. **1995**, 217-218.

[11] (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353-3354. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53-58.

[12] (a) Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831-6834. (b) Hoberg, J. O. *J. Org. Chem*. **1997**, *62*, 6615-6618.

[13] (a) Boyer, F.-D.; Lallemand, J.-Y. *Synlett* **1992**, 969-971. (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1995**, *117*, 9919-9920. (c) Iwasawa, N.; Funahashi, M.; Narasaka, K. *Chem. Lett*. **1994**, 1697-1700.

[14] Schreiber, S. L.; Smith, D. B.; Schulte, G. *J. Org. Chem*. **1989**, *54*, 5994-5996.

[15] Oh, J.; Cha, J. K. *Synlett* **1994**, 967-968.

[16] Momose, T.; Nishio, T.; Kirihara, M. *Tetrahedron Lett*. **1996**, *37*, 4987-4990.

[17] (a) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem*. **1993**, *58*, 5037-5039. (b) Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc*. **1994**, *116*, 8526-8535.

[18] (a) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807-3810. (b) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett*. **1988**, *29*, 5775-5778. (c) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955-5966.

[19] Sugimura, T.; Katagiri, T.; Tai, A. *Tetrahedron Lett.* **1992**, *33*, 367-368.

[20] Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem*. **1990**, *55*, 4986-4988.

[21] Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem*. **1999**, *64*, 8287-8297.

[22] Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691-5700.

[23] Denmark, S. E.; O'Connor, S. P. *J. Org. Chem*. **1997**, *62*, 584-594.

[24] García García, P.; Hohn, E.; Pietruszka, J. *J. Organomet. Chem*. **2003**, *680*, 281-285.

[25] Brimacombe, J. S.; Evans, M. E.; Forbes, E. J.; Foster, A. B.; Webber, J. M. *Carbohydr. Res*. **1967**, *4*, 239-243.

[26] Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694-7703.

[27] Pietruszka, J.; Widenmeyer, M. *Synlett* **1997**, 977-979.

[28] Reissig, H.-U.; Zimmer, R. *Chem. Rev*. **2003**, *103*, 1151-1196.

[29] Henry, K. J.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 8901-8904.

[30] Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett*. **1996**, *37*, 2533-2536.

[31] Timmers, C. M.; Leeuwenburgh, M. A.; Verheijen, J. C.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Asymmetry* **1996**, *7*, 49-52.

[32] (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc*. **1991**, *113*, 726-729. (b) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem. Int. Ed*. **1992**, *31*, 430-432.
[33] Schumacher, R.; Dammast, F.; Reissig, H.-U. *Chem. Eur. J.* **1997**, *3*, 614-619.
[34] Ebinger, A.; Heinz, T.; Umbricht, G.; Pfaltz, A. *Tetrahedron* **1998**, *54*, 10469-10480.
[35] Böhm, C.; Reiser, O. *Org. Lett*. **2001**, *3*, 1315-1318.
[36] (a) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett*. **1996**, *37*, 4133-4136. (b) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc*. **1996**, *118*, 6897-6907. (c) Davies, H. M. L.; Boebel, T. A. *Tetrahedron Lett*. **2000**, *41*, 8189-8192.
[37] Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem*. **1998**, *63*, 2641-2645.
[38] (a) Tokunoh, R.; Tomiyama, H.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett*. **1996**, *37*, 2449-2452. (b) Sato, H., Kim. Y. S.; Shibasaki, M. *Tetrahedron Lett*. **1999**, *40*, 2973-2976.
[39] Fischer, E. O.; Dötz, K. H. *Chem. Ber.* **1972**, *105*, 3966-3973.
[40] Murray, C.; Yang, D.C.; Wulff, W. D. *J. Am. Chem. Soc*. **1990**, *112*, 5660-5662.
[41] Barluenga, J.; Fernández-Acebes, A.; Trabanco, A. A.; Flórez, J. *J. Am. Chem. Soc*. **1997**, *119*, 7591-7592.
[42] Barluenga, J.; López, S.; Trabanco, A. A.; Fernández-Acebes, A.; Flórez, J. *J. Am. Chem. Soc*. **2000**, *122*, 8145-8154.
[43] Barluenga, J.; López, S.; Trabanco, A. A.; Flórez, J. *Chem. Eur. J.* **2001**, *7*, 4723-4729.
[44] Dötz, K. H.; Fischer, E. O. *Chem. Ber*. **1972**, *105*, 1356-1367.
[45] Buchert, M.; Reissig, H.-U. *Tetrahedron Lett.* **1988**, *29*, 2319-2320.
[46] Barluenga, J.; Tomás, M.; López-Pelegrín, J. A.; Rubio, E. *J. Chem. Soc. Chem. Commun*. **1995**, 665-666.
[47] Barluenga, J.; Suárez-Sobrino, A. L.; Tomás, M.; García-Granda, S.; Santiago-García, R. *J. Am. Chem. Soc.* **2001**, *123*, 10494-10501.
[48] Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234.
[49] Kulinkovich, O. G.; de Meijere, A. *Chem. Rev*. **2000**, *100*, 2789-2834.
[50] de Meijere, A.; Kozhushkov, S.; Spaeth, T.; Zefirov, N. S. *J. Org. Chem*. **1993**, *58*, 502-505.
[51] Kulinkovich, O. G.; Masalov, N. V.; Tyvorskii, V. I.; De Kimpe, N.; Keppens, M. *Tetrahedron Lett*. **1996**, *37*, 1095-1096.
[52] Winsel, H.; Gazizova, V.; Kulinkovich, O.; Pavlov, V.; de Meijere, A. *Synlett* **1999,** 1999-2003.
[53] Achmatowiz, B.; Jankowski, P.; Wicha, J. *Tetrahedron Lett.* **1996**, *37*, 5589-5592.
[54] Esposito, A.; Taddei, M. *J. Org. Chem*. **2000**, *65*, 9245-9248.
[55] Esposito, A.; Piras, P. P.; Ramazzotti, D.; Taddei, M. *Org. Lett*. **2001**, *3*, 3273-3275.
[56] Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc*. **1994**, *116*, 9345-9346.
[57] Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996,** *118*, 291-292.
[58] Kozyrkov, Y. Y.; Pukin, A.; Kulinkovich, O. G.; Ollivier, J.; Salaün, J. *Tetrahedron Lett.* **2000**, *41*, 6399-6402.
[59] Racouchot, S.; Sylvestre, I.; Ollivier, J.; Kozyrkov, Y. Y.; Pukin, A.; Kulinkovich, O. G.; Salaün, J. *Eur. J. Org. Chem.* **2002**, 2160-2176.
[60] (a) Wu, Y.-D.; Yu, Z.-X. *J. Am. Chem. Soc*. **2001**, *123*, 5777-5786. (b) Casey, C. P.; Strotman, N. A. *J. Am. Chem. Soc.* **2004**, *126*, 1699-1704.
[61] Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1996**, *118*, 4198-4199.
[62] Epstein, O. L.; Kulinkovich, O. G. *Tetrahedron Lett*. **2001**, *42*, 3757-3758.
[63] Mizojiri, R.; Urabe, H.; Sato, F. *J. Org. Chem*. **2000**, *65*, 6217-6222.
[64] Shirai, M.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 5331-5332.
[65] Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079-6082.
[66] Mizojiri, R.; Urabe, H.; Sato, F. *Angew. Chem. Int. Ed*. **1998**, *37*, 2666-2668.
[67] (a) Bekish, A. V.; Kulinkovich, O. G. *Tetrahedron Lett*. **2005**, *46,* 6975-6978. (b) Bekish, A. V.; Isakov, V. E.; Kulinkovich, O. G. *Tetrahedron Lett*. **2005**, *46*, 6979-6981. (c) Bekish, A. V.; Prokhorevich, K. N.; Prityskaya, T. S.; Kulinkovich, O. G. *Polish J. Chem*. **2006**, *80*, 549-558.
[68] (a) Henniges, H.; Militzer, H.-C.; de Meijere, A. *Synlett* **1992**, 735-737. (b) Rasmussen, P. B.; Bøwadt, S. *Synthesis* **1989**, 114-117.
[69] Militzer, H.-C.; Schömenauer, S.; Otte, C.; Puls, C.; Hain, J. Bräse, S.; de Meijere, A. *Synthesis* **1993**, 998-1012.
[70] Diez Martín, D.; San Feliciano, S. G.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Urones, J. G. *Synthesis* **2001**, 1069-1075.
[71] (a) Díez, D.; García, P.; Pacheco, M. P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synlett* **2002**, 355-357. (b) Díez, D.; García, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synthesis* **2003**, 53-62. (c) Díez, D.; García, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Org. Lett*. **2003**, *5*, 3687-3690.
[72] Diez, D.; García, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2005**, *61*, 699-707.
[73] Diez, D.; García, P.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G. *Synthesis* **2005**, 3327-3334.
[74] Wessig, P.; Mühling, O. *Angew. Chem. Int. Ed*. **2001**, *40*, 1064-1065.
[75] (a) Villar, H.; Guibé, F. *Tetrahedron Lett*. **2002**, *43*, 9517-9520. (b) Bezzenine-Lafollée, S.; Guibé, F.; Villar, H.; Zriba, R.; *Tetrahedron* **2004**, *60*, 6931-6944. (c) Zriba, R.; Bezzenine-Lafollée, S.; Guibé, F.; Guillerez, M.-G. *Synlett* **2005**, 2362-2366.
[76] Montgomery, D.; Reynolds, K.; Stevenson, P. *J. Chem. Soc. Chem. Commun*. **1993**, 363-364.
[77] Toratsu, C.; Fujii, T.; Suzuki, T.; Takai, K. *Angew. Chem. Int. Ed*. **2000**, *39*, 2725-2727.
[78] Kobayashi, K.; Horita, M.; Irisawa, S.; Matsunaga, A.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn*. **2002**, *75*, 1367-1369.

Received: April 05, 2006 **Revised: June 15, 2006** **Accepted: July 17, 2006**