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Faculté des Sciences
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Molecular Chemistry, Materials and Catalysis

Divergent and Selective Rearrangements of Vinylcyclopropanes into 1,4-Dienes and Cyclopentenes

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« Je remercie .....de..... »

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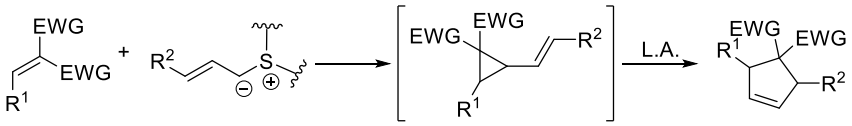
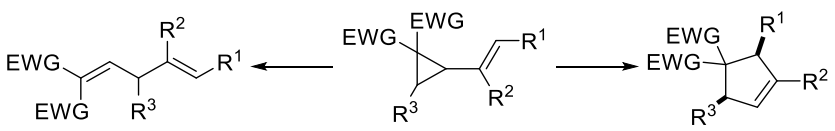
Abstract

The formation of five-membered carbocycles is a fundamental and important issue in organic synthesis, this scaffold being part of a large amount of biologically active compounds. Cycloaddition or annulation strategies have been described but these reactions requires very specific reactants and thereby are restrictive. Accordingly, we propose to develop a general and effective (3+2) annulation strategy toward five-membered carbocycles by investigating the reaction between activated olefins and sulfonium ylides. Preliminary results showed the feasibility of this methodology *via* a (2+1) annulation followed by a rearrangement.



First, we focused on the optimization of the reaction conditions. Then, we concentered on the extension of the scope of this process by synthesizing new substituted olefins leading to more functionalized cyclopentenes. Interestingly, we discovered that it was also possible to obtain functionalized 1,4-dienes from synthesized vinylcyclopropanes. This scaffold is also very important because it is part of many biologically active compounds and its synthesis is still a challenge in organic chemistry. We thus investigated the mechanism of the vinylcyclopropane rearrangements and the link existing between cyclopentene and 1,4-diene, both being obtained using the same reagents. Presently, this methodology allows forming selectively the 1,4-diene or the cyclopentene just, by changing the reaction conditions, and therefore provides an efficient synthetic tool for this kind of scaffolds.



Foreword

This Ph.D. thesis is part of a long term research program carried out in our laboratory. The reader may also be interested by the following references:

- O. Rousseau, T. Delaunay, G. Dequirez T. Trieu-Van, K. Robeyns, R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899-12902

- S. Clergue, O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, S. El Aakchioui, G. Barozzino-Consiglio, R. Robiette, *Chem. Eur. J.* **2018**, *24*, 11417-11425

Besides that, this Ph.D. led to the publication of the following article:

- M. Richald, A. Delbrassinne, R. Robiette, *Eur. J. Org. Chem.* **2019**, *23*, 3779-3782

Abbreviation list

^{13}C NMR: Carbon-13 nuclear magnetic resonance

^{1}H NMR: Proton nuclear magnetic resonance

ACN: Acetonitrile

AcOEt: Ethyl acetate

AcOH: Acetic acid

AE: Activation Energy

Alk: Alkyl

COD: Cycloocta-1,5-diene

Comp.: Complex

CP: Cyclopentene

CPsec: Secondary cyclopentene

d.r.: Diastereoisomeric ratio

DABCO: 1,4-Diazabicyclo[2.2.2]octane

DCE: Dichloroethane

diVCP: Divinylcylopropane

DMF: *N,N*-Dimethylformamide

DMT: Dimethyl Terephtalate

dppp: 1,3-Bis(diphenylphosphino)propane

e.e.: Enantiomeric excess

EDG: Electron donating group

EWG: Electron withdrawing group

HMDS: Hexamethyldisilazane

HPLC: High performance liquid chromatography

HRMS: High resolution mass spectroscopy

i-Bu: Isobutyl

i-Pr: Isopropyl

IR: Infrared

Kcal/Mol: Kilo calory per mole

L.A.: Lewis acid

LDA: Lithium diisopropylamide

LiHMDS: Lithium bis(trimethylsilyl)amide

Me: Methyl

MeOH: Methanol

MS: Molecular sieves

n-BuLi: *n*-Butyllithium

RT: Room temperature

TBAF: Tetrabutyl ammonium fluoride

TBAT: Tetrabutylammonium difluorotriphenylsilicate

^{t}Bu: Tertiobutyl

TEA: Transversely Excited Atmospheric

TEAB: Tetraethylammonium bromide

TEMPO: 2,2,6,6-Tetramethyl-1-piperidinyloxy

THF: Tetrahydrofurane

THT: Tetrahydrothiphene

TMSCl: trimethylsilyl chloride

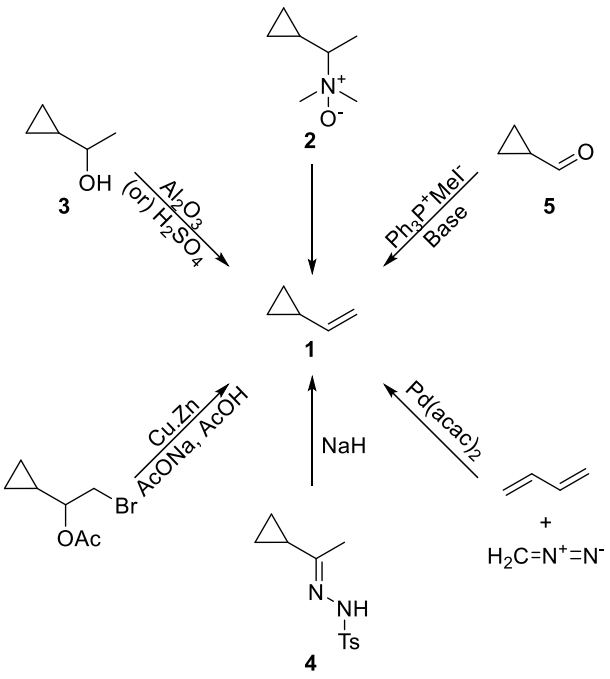
TMSOTf: Trimethylsilyl trifluoromethanesulfonate

VCP: Vinylcyclopropane

Chapter 1 General introduction

1.1 Synthesis of vinylcyclopropanes

Cyclopropane has been discovered by the Austrian chemist August Freund in 1882 who has cleverly proposed the right structure the same year.[1] A few years later, in 1896, the first vinylcyclopropane (VCP) has been synthesized as a side product by Gustavson.[2] However, it is only in 1922 that Demjanov and Dojarenko have described the first synthesis to access VCP **(1)** as the main product from methylated oxime **(2)** (Scheme 1).[3] Later, Boord and Slabey have demonstrated that 1-cyclopropylethanol **(3)** can be dehydrated into **1**. Other studies showed that VCP derivatives can also be obtained from a tosyl hydrazone species **(4)** or from an aldehyde **(5)** via a Wittig reaction. Reactions such as copper-zinc mediated elimination and palladium catalyzed cyclopropanation were also described as being efficient synthetic pathways for obtaining VCPs.[4]



Scheme 1

Over the last decades, the synthesis of vinylcyclopropane derivatives has been further studied and many different routes leading to the formation of polysubstituted vinylcyclopropanes are now available. At the present day, there are two main synthetic pathways allowing the formation of three-membered cycles. The first one is based on carbene compounds whereas the second use ylides.[5] Depending on the strategy, carbene or ylide, different types of three-membered cycles can be formed as depicted on the Scheme 2.

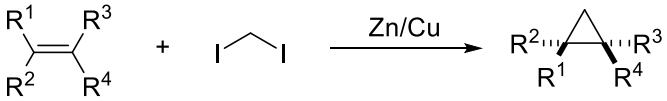
Scheme 2

However, this work will only focus on cyclopropane and especially on VCP synthesis. Therefore, the two major synthetic routes toward VCP are discussed in the following sections.

1.1.1 The use of transition metals and carbenoid species

Most of the reported routes toward VCPs using transition metals are based on metal carbenoids and cycloaddition of polyunsaturated compounds. Metal carbenoids are efficient intermediates for accessing cyclopropanes in a limited number of steps. One of the most famous example is the Simmons-Smith cyclopropanation reaction.[4]

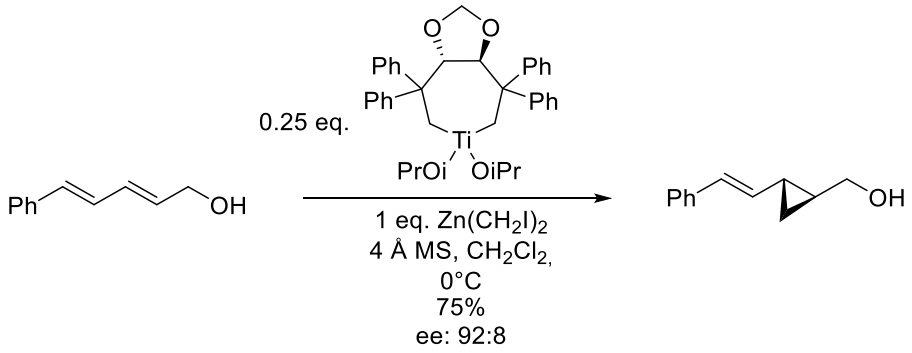
The procedure of the Simmons-Smith reaction originally employed diiodomethane in the presence of copper-zinc and an alkene.[6] The cyclopropane ring is obtained as a methylene transfer product as depicted on Scheme 3.[7]



Scheme 3

Over the years, many modifications of the Simmons-Smith reaction have been made and some of them directly on developing other metal reagents than Zn/Cu which are not easily prepared.[7] Other versions of the Simmons-Smith reaction allow to replace diiodomethane by brominated compounds.[8] However, the major drawback of the Simmons-Smith methodology is the poor substitution allowed on the carbenoid species.[6a] Indeed, excepted a few examples of ethylidene and benzylidene transfers, the methodology is restricted to methylene transfer.[9] The scope for the alkene partner is wider with many functional groups, such as non-protected alcohols, being tolerated. Allylic alcohols have even been showed to enhance diastereoselectivity.[9-10]

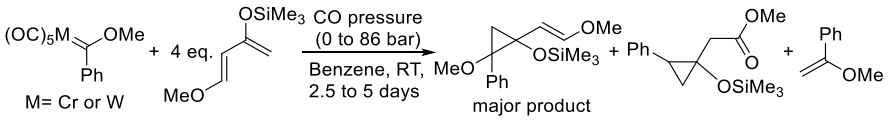
Asymmetric versions of this reaction have been developed. For example, Charette and co-workers have reported an asymmetric cyclopropanation methodology based on the Simmons-Smith procedure and mediated by titanium-TADDOL-ate complex (Scheme 4).[11]



Scheme 4

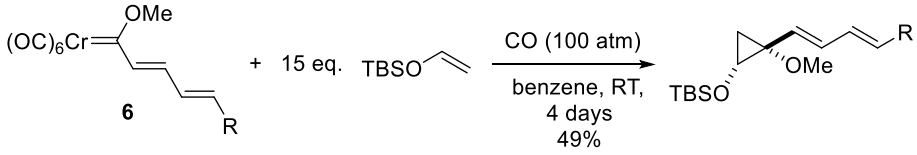
Using this chiral catalyst, Charette and co-workers were able to obtain good enantiomeric ratios (up to 92:8) for vinylcyclopropane formation.

Fisher carbenes are another possibility to perform methylene transfer in order to synthesize VCPs. The first cyclopropanation reaction with a Fisher carbene was reported by Wulff in 1988 (Scheme 5).[12] However, he obtained a mixture of several products with variable yields.



Scheme 5

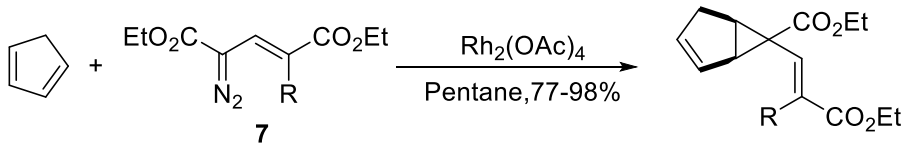
Two years later, Wulff and co-workers showed that different metal carbenes (**6**) can be used for the cyclopropanation reaction and demonstrated also that the reaction works with other types of alkenes (Scheme 6).[13]



Scheme 6

Different groups have studied this methodology and various metal carbenoids were proposed. Harvey and Lund reported that Mo(0) and Cr(0) based carbenes react with a large variety of 1,3-dienes leading to the corresponding VCPs. However, high temperatures and CO pressure are often required and constitute a real handicap for these processes. Moreover, this methodology suffers from additional drawbacks such as uncontrolled rearrangement, self-dimerization[4], difficult manipulations and some structural requirements in terms of metal-carbene partner which limits the scope of these methodologies.[14]

However, the use of diazo compounds enables milder reaction conditions. Indeed, Davies and co-workers worked on a strategy based on diazo compounds (**7**) and demonstrated that rhodium acetate dimer is an efficient catalyst to trigger the decomposition of the diazo species under mild reaction conditions (Scheme 7).[15]



Scheme 7[1]

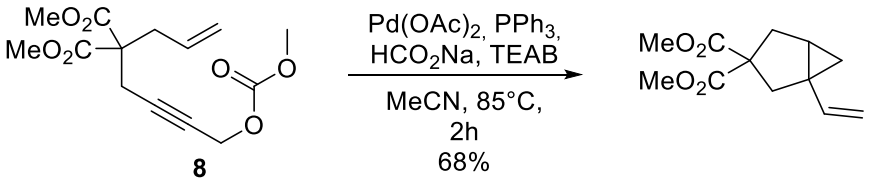
The methodology explored by Davies group's requires an electron-withdrawing group on the carbene center to ensure the stabilization of this latter and avoid side reactions.[15a] In 2007, Davies showed that even with

[1] Reaction time is not provided in the litterature

another metal such as silver, the electron withdrawing groups are still required in order to stabilize the carbene species.[16]

Because the synthesis of diazo-compounds without functional group was challenging, this field has been investigated and a series of methods starting from tosyl hydrazone and other ruthenium catalysts were reported to be efficient.[17]

Besides that, the preparation of vinylcyclopropanes via a metal-mediated cycloaddition on poly-unsaturated compounds (**8**) was reported by de Meijere with palladium catalysis (Scheme 8).[18]



Scheme 8

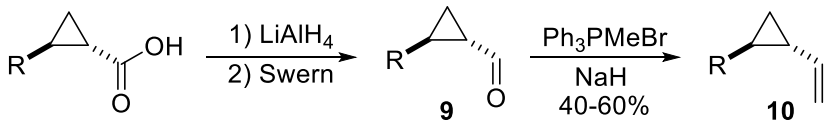
Numerous methods based on the catalysis by a transition metal such as Ir, Pt, Rh(I), Pd, Ru, were reported by different groups. However the preparation of diazo compounds remains tricky and these compounds are more difficult to handle than their diazo-carbonyl equivalents. Other methods based on metal catalysts and consisting of C-H activation or allylic substitution were also investigated but because of their different reactivity, they will not be discussed in this work.[4]

1.1.2 Ylides chemistry as a tool for VCPs synthesis

"An ylide is defined as a neutral dipolar molecule containing a negatively charged atom directly attached to a positively charged heteroatom, in which the negatively charged atom is a nucleophilic center and the onium group is usually a good leaving group." [19]

For almost 70 years since Wittig discovered the usefulness of ylides for chemistry, this family of compounds has been deeply studied and developed under their different forms (phosphonium, ammonium, tellurium, sulfonium, etc.).[20]

It is well known that phosphonium ylides are mostly used in olefination reaction especially for late stage introduction of an alkene group.[21] Gajewski and co-workers exploited this strategy to synthesize vinylcyclopropanes (**9**) from the corresponding cyclopropane carbaldehyde (**10**) as shown in Scheme 9.[22]

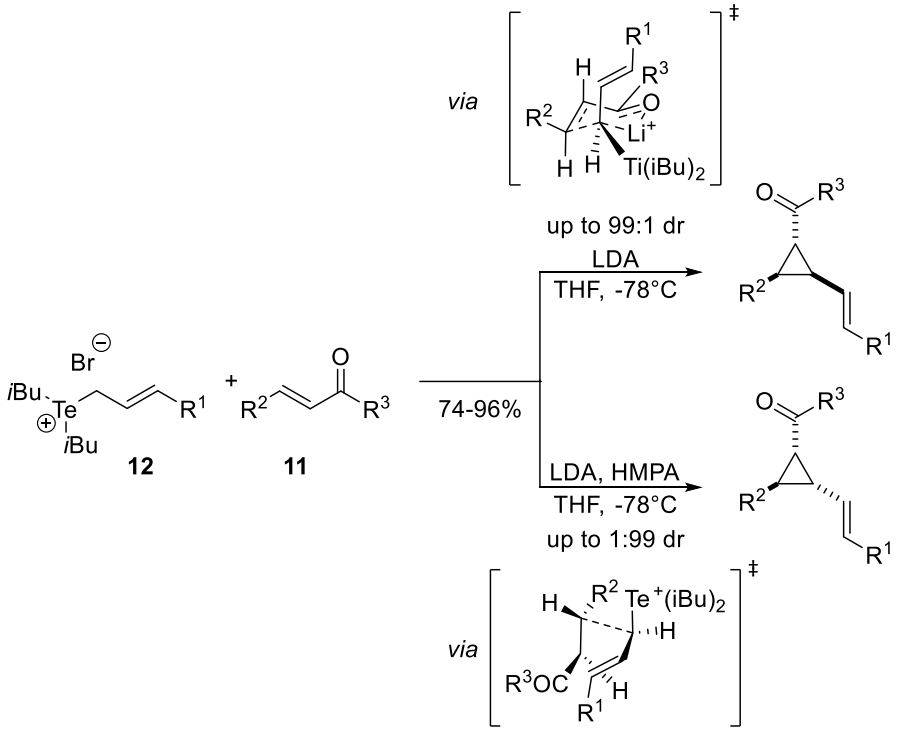


Scheme 9

However, this methodology remains a classical olefination reaction and requires first to build the cyclopropane skeleton.

Because phosphonium ylides do not react with C=C bonds, research groups have investigated other ylides to form the VCP skeleton in a minimum number of steps. Nowadays, tellurium[23], ammonium[24] and sulfonium ylides,[25] are the most developed, and used, onium ylides for cyclopropanation reactions. However, one has to note that a myriad of other ylides[26] exist and can be used for different applications in organic synthesis including cyclopropanation reactions.[27]

Regarding tellurium ylides, they are more versatile than their phosphonium equivalent but remain more reactive and unstable than their corresponding sulfonium analogs.[28] Tang and co-workers reported nonetheless an efficient route from α,β-unsaturated carbonyl (**11**) and tellurium ylide (**12**) leading to VCPs in a single step (Scheme 10).[23]



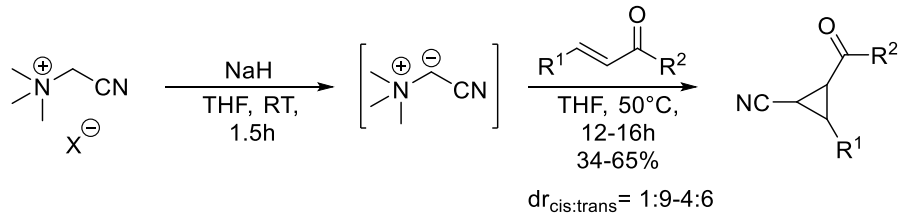
Scheme 10

As depicted in Scheme 10, the Tang team was able to change the nature of the diastereomer formed in the presence of HMPA which complex the cation. An enantio- and diastereoselective version of this methodology based on a chiral auxiliary has been tested. They obtained moderate yields from 74 to 96% with reasonable diastereoisomeric ratios for racemic products and a range of enantiomeric excess between 80:20 and 99:1 for asymmetric version.

Despite the efficient cyclopropanation of telluric ylides, the utilization of such compounds suffers from considerable drawbacks. Indeed, tellurides have an especially pungent odor and generate highly toxic tellurium side products.[29] In addition, the availability of telluric compounds is restricted and they are much more expensive than their sulfurated equivalents.

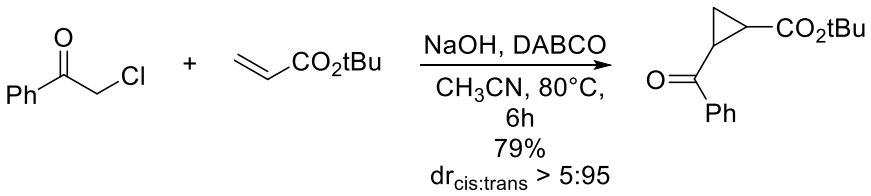
Alternatives to these ylides to carry a cyclopropanation reaction would be sulfonium and ammonium ylides. The later are more nucleophilic than the former because the negative charge is less stabilized. This difference in stabilization of the negative charge between S- and N-ylides is due to the polarizability and hyperconjugation effects.[30] Accordingly, N-ylides are generally generated *in situ*, under basic conditions, and further stabilized by a withdrawing group.

The first example of cyclopropanation with an N (sp_3) based ammonium ylide was reported by Bhattacharjee and co-workers in 1982 (Scheme 11).[31]



Scheme 11

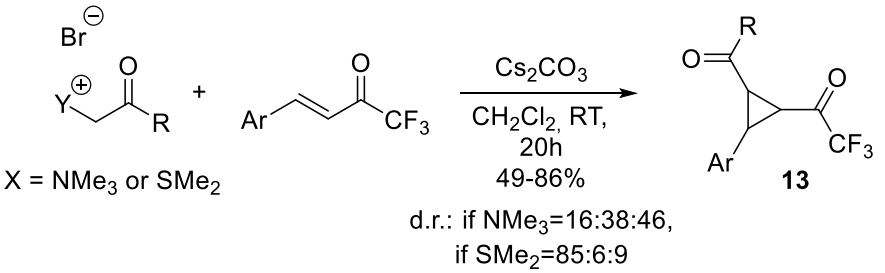
In this example, Bhattacharjee obtained the cyclopropane with a moderated yield and a low diastereoselectivity. This type of ylide has been left behind for several years until Jonczyk developed a two-phase system based on ammonium ylides leading to moderate yields.[32] Later, Gaunt and co-workers developed a method using tertiary amine DABCO in a catalytic amount to form cyclopropane (Scheme 12).[33]).[33] However, the scope of the reaction remains limited to the formation of cyclopropane without additional C=C bond external to the ring.



Scheme 12

Moreover, a higher temperature than in the case of Te- or S-ylide is required to afford the corresponding cyclopropane with moderate yield. This is mainly due to the lower nucleofugacity of the ammonium group, as compared to sulfonium and tellurium ones, which induces a higher energy barrier for the cyclization step (see further for the mechanism).

Among the groups whose pursued the study on N-ylide based cyclopropanation, the group of Waser has developed a route affording fluorinated VCPs (**13**) at room temperature with moderate diastereoselectivity (Scheme 13).[24]

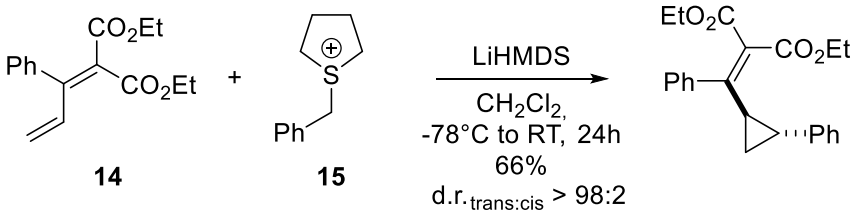


Scheme 13

However this methodology is limited to the synthesis of arylcyclopropanes. Given the difficulty to access real vinylcyclopropanes with double bonds not included in an aromatic ring from N-ylides, scientists have turned their attention to sulfonium ylides.

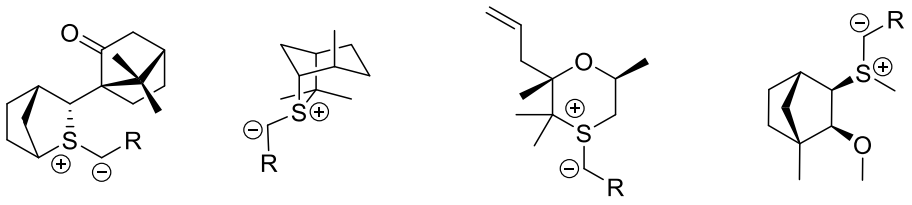
One of the first example of cyclopropane formation based on sulfur ylide was reported by Corey and Chaykovsky in 1965.[34] Since their discovery, sulfur ylides have been widely studied as key intermediates in organic chemistry.[35]

In 2015 our group reported an efficient synthesis of VCP by reacting 1,1-bisactivated 1,3-dienes (**14**) with a benzylic sulfonium ylides (**15**) under mild reaction conditions (Scheme 14).[36]



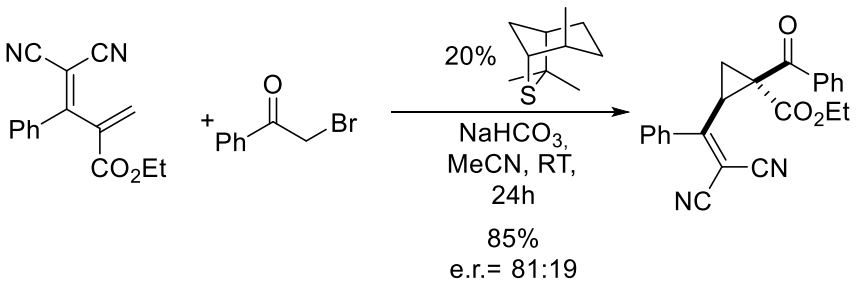
Scheme 14

Aggarwal has strongly contributed to the development of asymmetric cyclopropanation reactions using chiral sulfonium ylides.[37] With his co-workers, he has synthesized different chiral auxiliaries that induce asymmetry when they are included in a sulfonium ylide (Scheme 15).[38] It is important to note that all these auxiliaries can be synthesized in a few steps and are therefore readily available.



Scheme 15

Plenty of elegant methodologies have been developed using these chiral sulfur ylides. To mention just one of these, Qing-Zhu Li and co-workers reduced the amount of chiral sulfide needed to 20% for the process exposed in Scheme 16.[39]

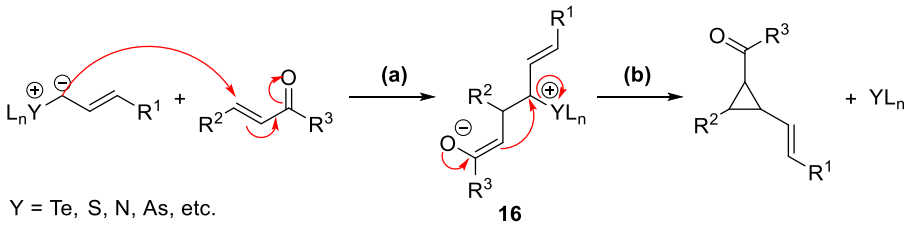


Scheme 16

Nowadays, the synthesis of vinylcyclopropane compounds has been widely studied and developed and show a wide range of application in agrochemical [40], pharmaceutical drugs[41] and as a versatile synthon in organic synthesis.[4]

1.1.3 Mechanism

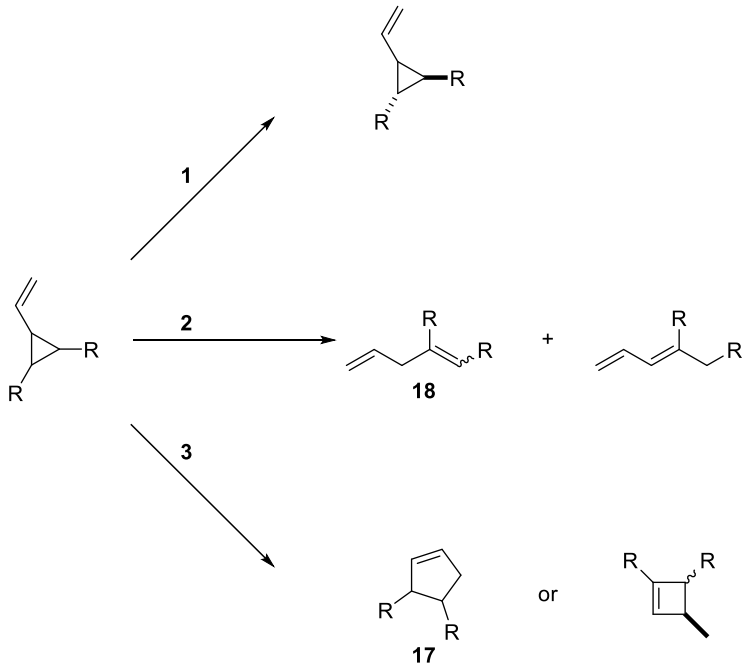
Concerning the mechanism of vinylcyclopropane formation using an ylide, it is largely accepted that it proceeds via two consecutive steps: **(a)** addition to form a betaine intermediate (**16**), **(b)** the ring closure with concomitant departure of the onium group (Scheme 17).



Scheme 17

1.2 Reactivity of vinylcyclopropane

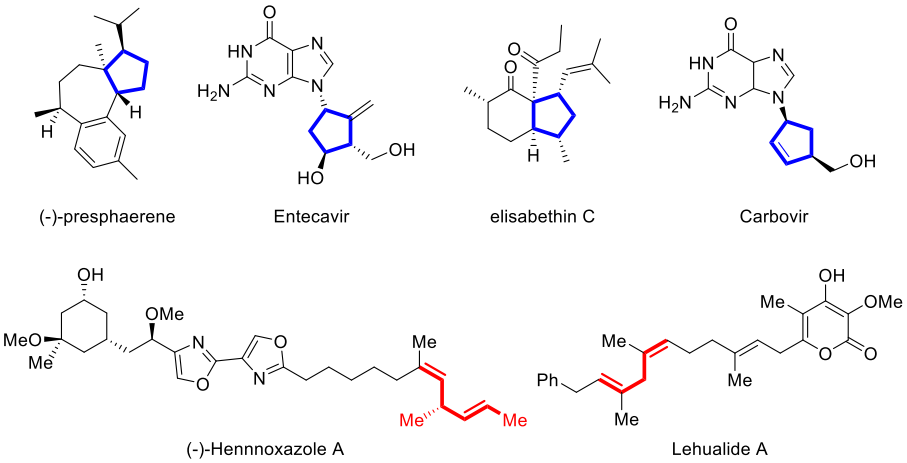
Vinylcyclopropanes are versatile building blocks in organic synthesis showing a wide range of applications in the synthesis of important targets. Indeed, VCPs easily undergo ring-opening reactions (releasing ring strain) to generate reactive species that can be used in a range of important reactions. Their use in (3+2) or (5+2) cycloadditon for instance has been well studied.[42] However, this reactivity requires an additional species and therefore will not be discussed in this work which focuses on rearrangements. VCPs can undergo three major rearrangements: *cis-trans* isomerization **(process 1)**, rearrangement into dienes **(process 2)**, and finally, rearrangement into cyclopentene (CP) or, in more specific cases, to cyclobutene **(process 3)** (Scheme 18).[43]



Scheme 18

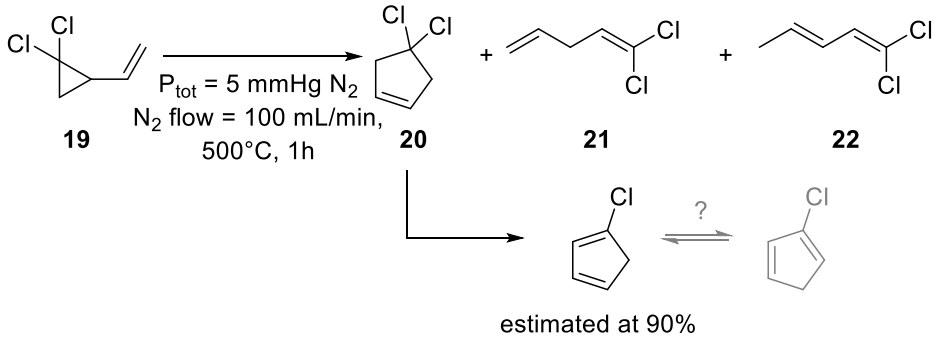
Among these products, cyclopentenes (**17**) and non-conjugated dienes (1,4-dienes also called skipped dienes) (**18**) are very interesting because they

are present in many biologically active compounds including natural products (Scheme 19).[44]



Scheme 19

Concerning the rearrangements of VCPs, even if they were involved in reactions developed early in the 20th century, they have not been reported until the study of Neureiter in 1959.[45] He was the first to report the rearrangement of a vinylcyclopropane by heating it up to 500°C (Scheme 20)[46].



Scheme 20

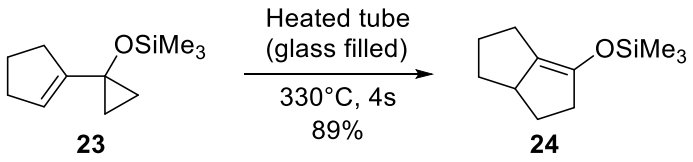
The pyrolysis of (**19**) leads to the formation of three main products: A cyclopentene (**20**), a skipped diene (**21**) and a 1,3-diene (**22**). Neureiter

postulated that **19** undergoes a ring opening affording a stabilized diradical which subsequently reacts to form the three different observed compounds. After the discovery of Neureiter and until the early 1960s, many studies on the VCP-CP rearrangement and its possible mechanisms have been achieved.[45] Since 1970 sufficient information has been gathered about the VCP-CP rearrangement allowing its widespread application in organic synthesis. Nowadays, multiple methods enabling the rearrangement of VCPs are reported: thermally or photochemically triggered, or even catalyzed by Lewis acids or organometallic species.[45]

1.2.1 Thermal rearrangement

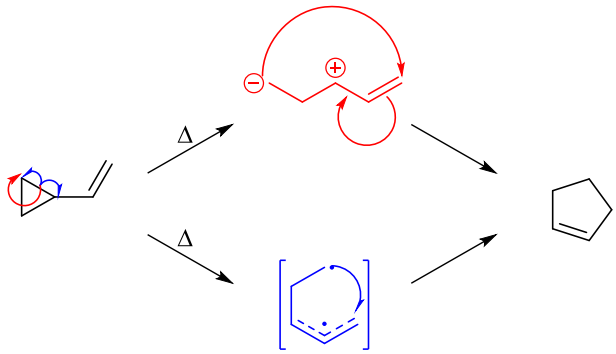
As described in the previous paragraph, the first example of VCP-CP rearrangement was reported by Neureiter. However, the harsh reaction conditions required (500°C) have undoubtedly reduced its potential use in organic synthesis.

The first methods using lower temperatures than Neureiter process were reported by Simpson in 1973. He showed that functionalizing the cyclopropyl groups with phenyl or methoxy groups allows to perform the VCP-CP rearrangement at "only" 220°C.[47] The same year, Trost observed the same temperature lowering effect using siloxy-substituted VCPs (**23**) affording the cyclopentene (**24**) in good yields (Scheme 21)[48].



Scheme 21

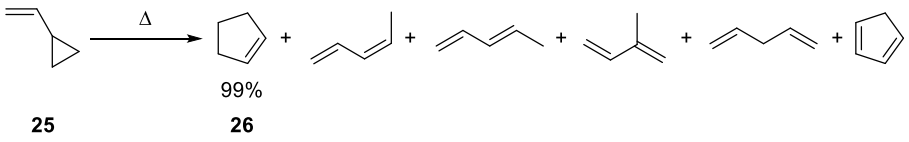
Regarding the mechanism of the thermal rearrangement of VCPs into CP, Frey and co-workers proposed the following mechanisms (Scheme 22).[43, 49]



Scheme 22

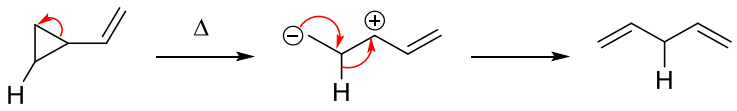
Formaly, these mechanisms are a 1,3-sigmatropic shift leading to the cyclopentene via either hetero- or homolytic cleavage of one σ C-C bond of the cyclopropane ring followed by a ring closure. It was showed that both zwitterionic and diradical pathways are accessible and the nature of the mechanism at play depends mainly on the substitution pattern.[3, 50] Computational studies have also indicated that the mechanism can in some cases be concerted.[50b, c]

Furthermore, Frey and co-workers have shown that the thermolysis of VCP (**25**) affords predominantly cyclopentene (**26**) but other minor products were also isolated (Scheme 23). However, the mechanism followed to form these side products remains unkown at this time.[43, 49b]



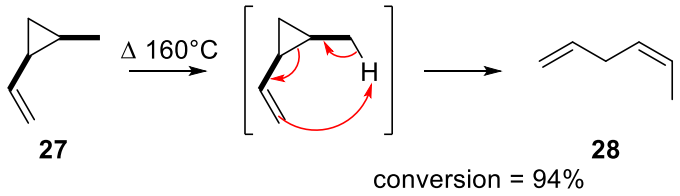
Scheme 23

To explain the formation of the 1,4-diene, Frey's group proposed a mechanism based on the heterolytic cleavage of one σ C-C bond of the cyclopropane ring followed by a H-migration to yield a 1,4-diene (Scheme 24).



Scheme 24

Later, they reported that certain VCPs like *cis*-2-methylvinylcyclopropane (**27**) rearrange upon heating to the corresponding 1,4-diene (**28**) as the only product (Scheme 25).[49a] It is important to note that the *cis* configuration of the VCP is mandatory to permit the formation of the 1,4-diene.



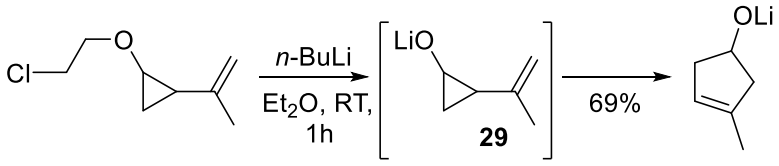
Scheme 25

Regarding the mechanism for the 1,4-diene formation, it probably involves a six membered ring transition state. Furthermore, Frey and co-workers reported that no *trans* isomer of the VCP was formed during the reaction.

These data are the first showing that a vinylcyclopropane rearrangement can lead either to cyclopentene or to 1,4-diene.[51] However, almost no publications report specific thermal rearrangement leading to 1,4-diene as the main product. Only one more recent paper from Turos reports an enhancement of the rearrangement selectivity toward 1,4-diene when the VCP bears a silyl group.[52]

In 1973, Simpson has also shown that when the VCP is substituted by a methoxy group, the reaction occurs more readily and at a lower temperature than in the case of VCPs substituted by alkyl groups.[47] However, the required temperature was still too high to enhance the interest for this

reaction as a tool in organic synthesis. Because of the lack of applicability of reported thermal VCP-CP rearrangement and the necessity to find milder reaction conditions in term of temperature, Danheiser has demonstrated in 1980 a VCP-CP rearrangement occurring at room temperature for the lithium salt of 2-vinyl-1-cyclopropanol (**29**) (Scheme 26).[53]



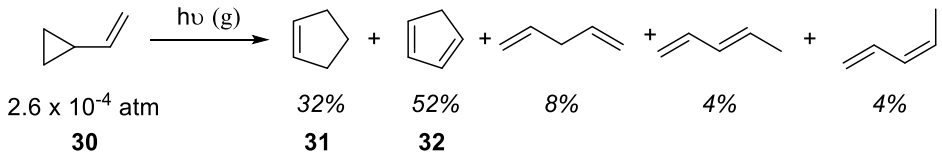
Scheme 26

The system developed by Danheiser requires an excess of *n*-BuLi to trigger the transformation but this methodology has opened a new kind of VCP-CP rearrangement which is not thermally triggered.[53-54]

1.2.2 Photo-rearrangement of vinylcyclopropanes

Cyclopropane rings act as a moderately powerful auxochrome in vinylcyclopropane inducing a bathochromic shift of 8 to 15 nm in the absorption band of the olefin.[55] However, the maximum absorption wavelength of the VCPs for the $\pi \rightarrow \pi^*$ band remains included between 175 and 200 nm. It thus explains why most of the VCP rearrangement promoted by light use VCPs bearing chromophoric substituents.[43]

Farneth *et al.* reported a rearrangement of a simple gaseous VCP (**30**) induced by a CO_2-TEA laser emitting in the infrared (940.6 cm^{-1}) and leading to a mixture of cyclopentene (**31**) and cyclopentadiene (**32**) as major products (Scheme 27).[56] Three different dienes were also reported as side products.



Scheme 27

In reported examples, VCPs undergo a photo-rearrangement leading to mixtures of different isomers when they are not subjected to the entire fragmentation of the starting compound.[43, 57] Some experiments working with naphthalene or toluene as photo-sensitizers have been carried out but they also led to a mixture of various VCP isomers.

Despite the various examples reported for photo-rearrangement of VCPs, this approach remains inefficient to obtain selectively cyclopentene or 1,4-diene and it is mostly used in polymerization processes of VCPs.[43, 58] Additionally, many of these examples give only poor yields and/or require harsh reaction conditions in term of wavelength, vacuum, and temperature.[59] Even when metal catalysis is used in combination with photochemistry[60], scientists evolved the method to avoid the photo-activation process because of observed side reactions.[61]

1.2.3 Catalyzed processes

Reactions of VCPs involving a metal-catalyzed process have been widely studied and significant progresses has been achieved in this field. A myriad of metals and Lewis acids have been used to trigger the transformation of the VCP into another product. As compared to thermal- and photo-rearrangements, metal-catalyzed processes are much more controlled and lead more selectively to cyclopentene and even to dienes.[50a, 62]

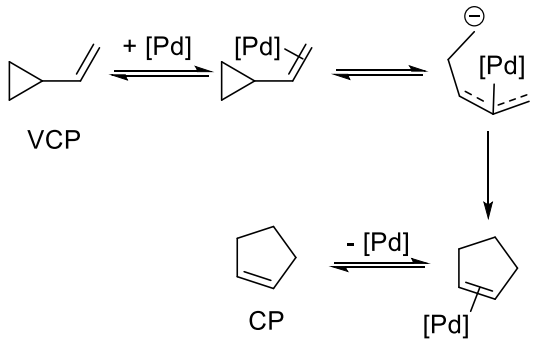
1.2.3.1 Rearrangement to cyclopentenes

1.2.3.1.1 Via transition metal catalysis

Aris and Huldicky were the first to report a VCP-CP rearrangement via metal catalysis.[63] Nowadays, countless metals have been used to promote this transformation but palladium, rhodium and nickel remain the most important metals used in VCP rearrangement. [60a, 64]

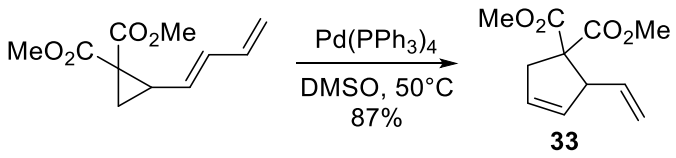
Using Pd catalyst

Palladium is widely used to trigger the rearrangement of VCP into CP. Mechanistically, Pd-catalyzed rearangements follows a pathway in which three main intermediates can be enlighted (Scheme 28).[50a, 65] First, after complexation of the double bond, the palladium promotes an heterolytic cleavage of the vinylcyclopropane ring to provide a stabilized anion. Then, a ring closing step followed by a decomplexation provide the cyclopentene.



Scheme 28

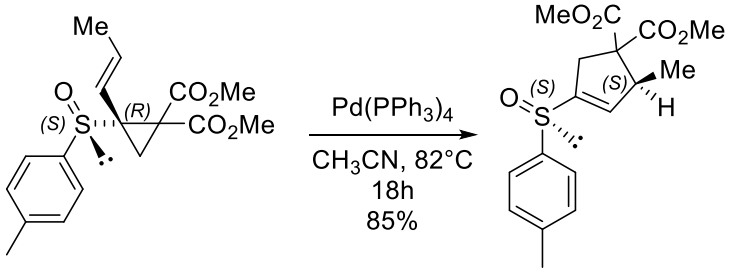
Regarding examples of VCP-CP rearrangement, one can point the work of Oshima and co-workers who reported an efficient process using $Pd(PPh_3)_4$ and affording cyclopentene **33** in a good yield (Scheme 29).[66]



Scheme 29

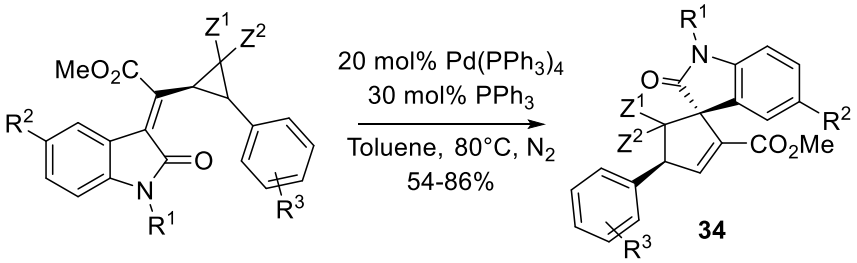
Oshima and co-workers concluded that the diene part and the two electron-withdrawing groups on the VCP are prerequisite conditions for a successful rearrangement.[66] Indeed, these chemical function play an important role in the stabilization of the intermediates.

Later, Hiroi showed that is was possible to perform the reaction with retention of configuration by introducing an asymmetric sulfoxide group and via palladium-catalysis (Scheme 30).[67] In this case, a simple alkene group on the VCP was sufficient to observe the rearrangement.



Scheme 30

Later, in 2013, Shanmugam and co-workers showed the usefulness of palladium-catalyzed VCP rearrangement to synthesize hindered cyclopentene as 3-spiro-2-oxindoles (**34**) (Scheme 31).[68]

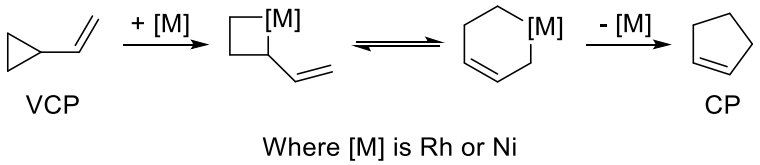


R^1= Me, Allyl; R^2= H, Br, Me; R^3= 2-Me, 4-Me, 3-NO_2, 2-Br, 3-OMe, 4-F, 4-Cl;
Z^1= Z^2= CN (or) CO_2Et

Scheme 31

<u>Using Rh and Ni catalyst</u>

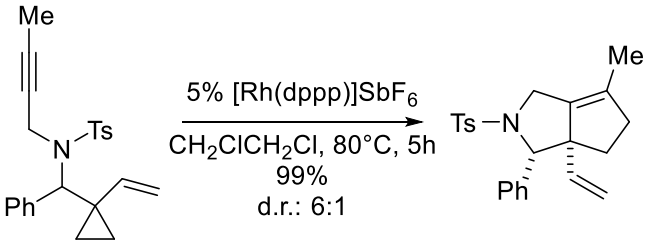
Other metals have also been used for the VCP-CP rearrangement. Since 1971, it has been shown that triggering a VCP-CP rearrangement with an Rh-catalyst enables the reaction at lower temperature (-50°C to 50°C).[69] In the case of nickel and rhodium catalysts, the mechanistic pathway followed is different than with palladium.[50a] Indeed, the mechanism involves formation of a metallacyclobutane which is then isomerized into a metallacyclohexene providing the desired cyclopentene after reductive elimination and release of the metal center (Scheme 32).



Scheme 32: in some cases, additional intermediates are reported.

It has to be mentionned that most of the time, many side reactions are observed and in some cases they predominate over the VCP-CP rearrangement.[63b, 69-70]

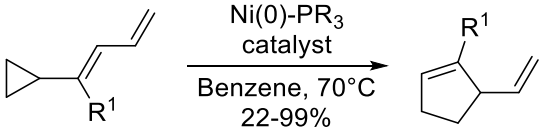
A good example of efficient VCP-CP rearrangement under Rh catalysis has been reported by Yu and co-workers who described an efficient intramolecular cycloaddition of VCPs (Scheme 33).[71]



Scheme 33

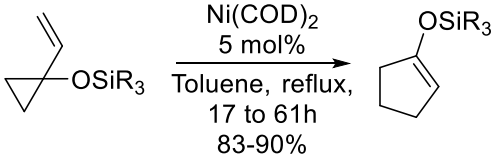
Although high selectivity for five-membered carbocycles could be achieved, the methodology developed by Yu remains quite restricted by the structural requirements on the VCP: additional alkene, alkyne and N-tosyl group must be included in the starting compound.

Some VCP-CP transformations under Ni-catalysis have also been described.[72] Murakami reported for instance a method in which only VCPs with extended π-systems such as diene or styrene groups led to the desire cyclopentene (Scheme 34).[72a]



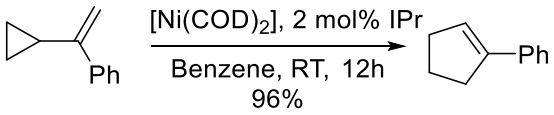
Scheme 34

Later, Ryu considered VCPs bearing siloxy group for a Ni-catalyzed process.[72b] He has shown that using a low catalyst loading it was possible to afford cyclopentene in good yield (Scheme 35).



Scheme 35

In the same study, Ryu reported a lower conversion and isomerization of starting material to 1,3 and 1,4-dienes when Pd, Pt, or Rh-catalysts are used in place of Ni-catalyst. Regarding non-activated alkyl VCPs, they have been rearranged to their corresponding CP under Ni-catalysis with high yields and good selectivity by Louie (Scheme 36).[72c]

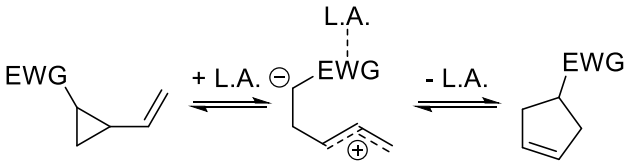


Scheme 36

Therefore, even if metals such as Pd, Rh and Ni allow rearranging VCPs into CPs, these strategies remain limited by the structural requirements on the VCP and by undesired reactions occurring in the media.

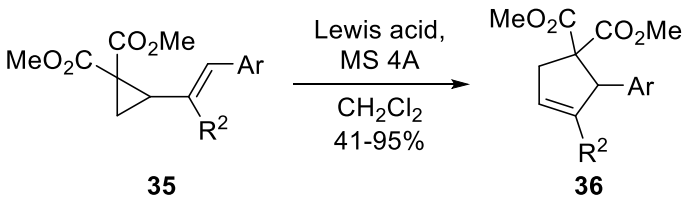
1.2.3.1.2 Via Lewis acids catalysis

VCP can also be rearranged into CP under Lewis acid conditions. The mechanism in this case involves the heterolytic opening of the cyclopropane ring followed by a ring closing step to give the cyclopentene (Scheme 37).[73]



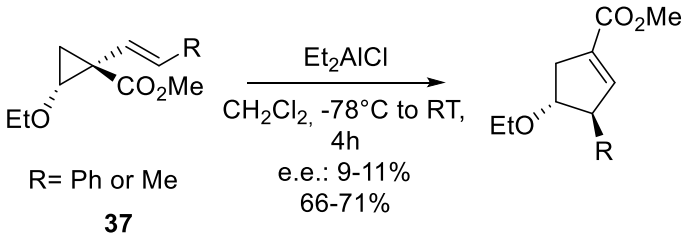
Scheme 37

One of the most recent examples of VCP-CP rearrangement involving a Lewis acid and following the previously exposed mechanistic path has been reported by Ivanova and co-workers in 2018 (Scheme 38)[73b]. In their work, they used different Lewis acids such as $GaCl_3$, $TiCl_4$ or $Sc(OTf)_3$ to rearrange donor-acceptor VCPs (**35**) into the corresponding cyclopentenes (**36**).



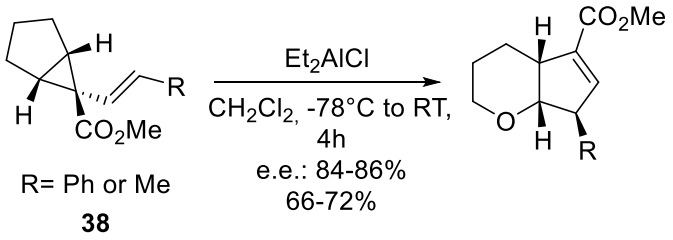
Scheme 38

Depending on the substituent borne by the styryle group, they used different Lewis acids of different strength. However, most of the examples require to use $GaCl_3$, a Lewis acid which is very difficult to handle. According to Ivanova, the mechanism involved in the cyclopentene formation is complex and would proceed via ring opening to form a zwitterionic intermediate. In order to develop an enantio-specific version of the VCP-CP rearrangement, Davies considered highly substituted VCPs (**37**) and diethyl aluminum chloride to trigger the reaction (Scheme 39).[74]



Scheme 39

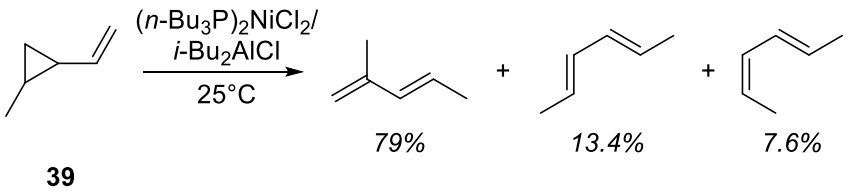
Despite the use of a more common Lewis acid, the nature of the starting VCPs restrains the scope of the reaction. Indeed, only some examples in which the substituent is a phenyl or a methyl group have been reported. Furthermore, the enantiomeric excesses remain between 9 and 11%. Only a few examples of cyclopentenes have been obtained with moderate enantiomeric excess and requiring each time to use fused VCPs (**38**) (Scheme 40).



Scheme 40

1.2.3.2 Rearrangement to dienes

VCPs can lead to two different types of dienes: 1,3- and 1,4-dienes, these later being also called skipped dienes because the two double bonds are not conjugated. As briefly explained in the previous section *(see 1.2.3.1)*, dienes are mostly obtained as side products of VCP-CP rearrangement.[43, 46, 57, 72a] Only a few publications have reported the formation of 1,3- or 1,4-dienes as the main product. For instance, Miller *et al.* described the formation of three conjugated dienes using Ni- and Al- catalysts starting from VCP (**39**) (Scheme 41).[75]

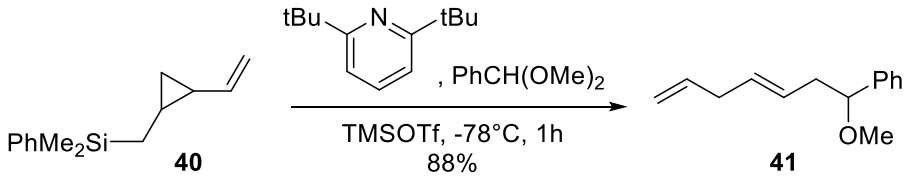


Scheme 41

In contrast to previously developed thermal isomerization, Miller started from a mixture of *cis* and *trans* isomers of the VCP and showed that both isomers were leading to conjugated dienes.

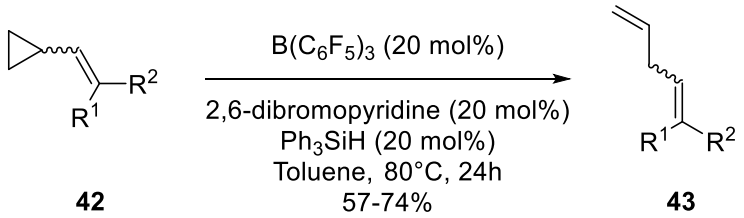
1.2.3.2.1 Diene formation using Lewis acids

Braddock reported a VCP - 1,4-diene rearrangement of silylated VCPs (**40**) triggered by TMSOTf under mild reaction conditions and with excellent yields (Scheme 42).[76] However, these methods do not allow to substitute the central sp^3 carbon in the skipped diene (**41**).



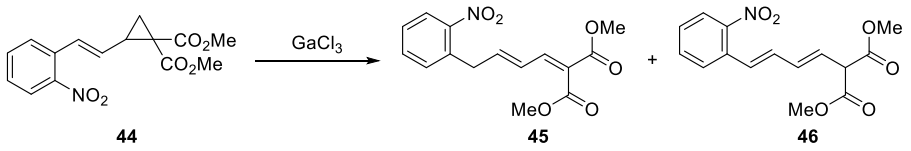
Scheme 42

Recent work made by Zhang and co-workers provides another efficient way to access 1,4-dienes from unactivated VCPs (**42**) (Scheme 43).[77] However, as in the previous methodology, the central sp^3 carbon of the 1,4-diene (**43**) remains unsubstituted. Moreover, one of the alkenes function is always terminal and does not bear any substituent.



Scheme 43

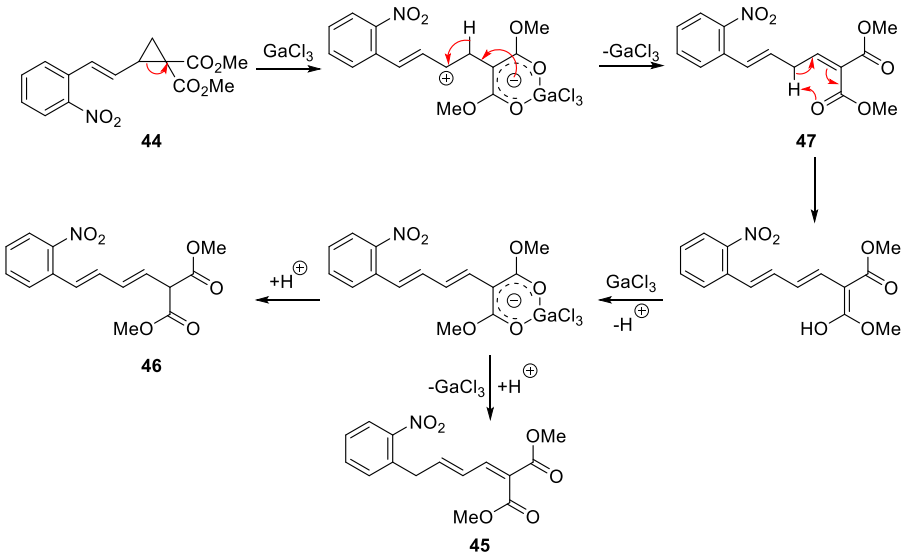
Concerning 1,3-dienes, Ivanova and co-workers developed a controlled 1,3-dienes formation from VCPs using Lewis acids such as $GaCl_3$, $TiCl_4$ and $Ni(ClO_4)_2$.[73b] This group has worked with VCPs (**44**) activated by two electron withdrawing groups and has shown that they could be rearranged selectively into the corresponding 1,3-dienes (**45**) and (**46**) by introducing a strong EWG such as a nitro group on the aromatic substituting the vinyl function (Scheme 44).



44 45 46

Scheme 44

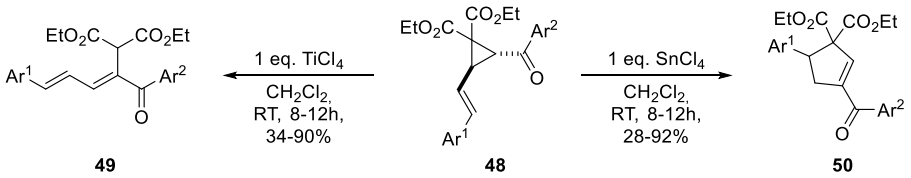
Furthermore, they have proved that these 1,3-dienes **45** and **46** are coming from the rearrangement of the 1,4-diene (**47**) which cannot be isolated in their process (Scheme 45).



44 47 46 45

Scheme 45

Another recent example of selective formation of 1,3-dienes or cyclopentenes has been developed by Srinivasan and Thangamani (Scheme 46).[78] Starting from different donor-acceptor VCPs (**48**) and by using either $TiCl_4$ or $SnCl_4$ they can afford the corresponding 1,3-diene (**49**) or the cyclopentene (**50**) selectively.



49 **48** **50**

Scheme 46

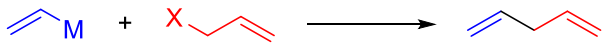
In conclusion, despite the numerous VCP rearrangements reported, most of them afford cyclopentenes or conjugated dienes. Regarding 1,3-dienes, many different synthetic pathways which do not involve VCPs have been developed and remain highly effective for the synthesis of this kind of compounds.[50a, 79] Referring to cyclopentene, the VCP-CP rearrangement is a really attractive strategy for accessing this class of structures. For 1,4-dienes synthesis via VCP rearrangement, only a few limited examples have been reported. However, as it will be exposed in the next section (see 1.3), 1,4-dienes remain very attractive targets in organic synthesis and various methods not involving vinylcyclopropane have been developed for their preparation. Furthermore, thanks to all research that has been reported, one we can clearly understand that 1,3-diene, 1,4-diene, and cyclopentene species are strongly interlinked in the rearrangement of VCPs.

1.3 Preparation of 1,4-dienes

1,4-Dienes are present in a vast array of natural products showing pharmacological interests[80] or flavour[81] propreties (see section 1.2). The importance of 1,4-dienes and the challenges associated with their preparation have spurred the development of numerous methods for their synthesis. These methodologies can be classified into four main strategies.

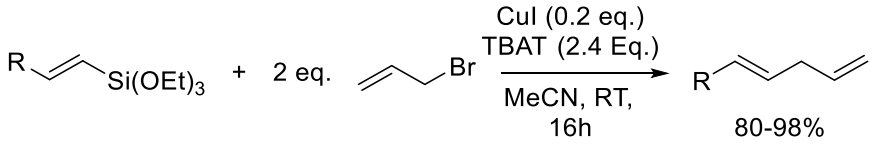
1.3.1 Cross-coupling reaction of alkenyl organometallic reagents

The first strategy for accessing 1,4-dienes is based on cross coupling reaction of alkenyl organometallic reagents with allylic electrophiles using transition metals catalysts such as copper[82], iridium[83] or rhodium[84] (Scheme 47).



Scheme 47

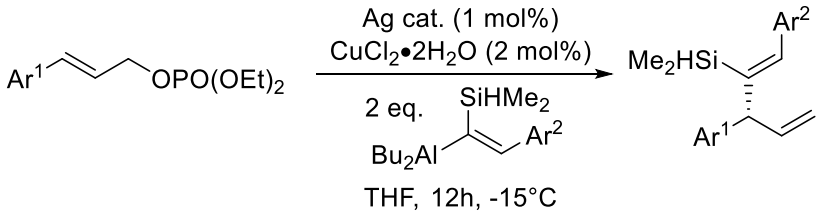
Many different groups have used this methodogy to acces 1,4-dienes with high efficiency.[82-85] For instance, the group of Prof. O. Riant has developed a copper-catalyzed vinylsilane allylation allowing to synthesize 1,4-dienes with great efficiency and using mild reaction conditions (Scheme 48).[82a]



Scheme 48

However, despite the numerous reports available most of these methodologies lead to terminal dienes and only a few reports can be found on the formation of sp^3 substituted 1,4-dienes. And even when it is the case,

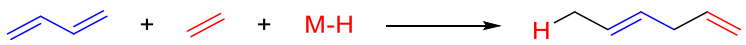
the scope remains quite restricted to only a few substituents such as methyl[85a] or phenyl group.[82, 85c] In some cases, the possibility to reach a good control of the absolute configuration of the carbon C_3 was demonstrated. For example, Hoveyda was able to set a phenyl group on the central carbon with an enantiomeric ratio better than 95:5 (Scheme 49).[82b]



Scheme 49

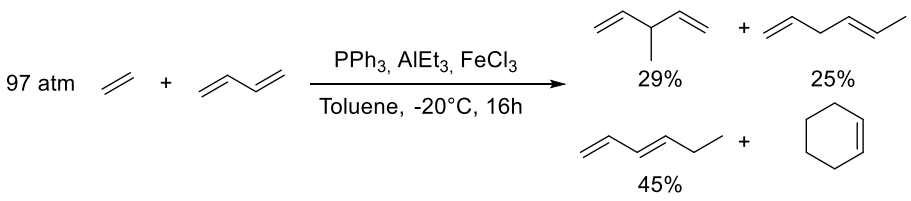
1.3.2 Hydroalkenylation of 1,3-dienes

Another strategy for accessing 1,4-dienes consists in synthesizing them via hydroalkenylation of 1,3-dienes (Scheme 50).[86]



Scheme 50

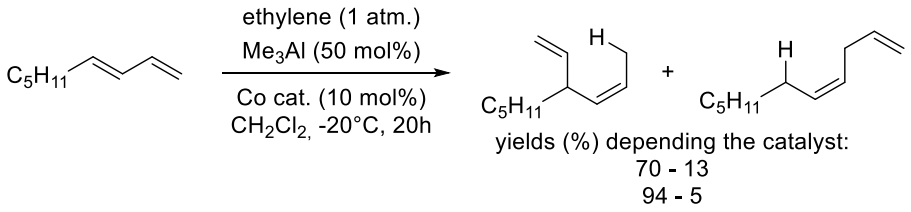
One of the first examples leading to 1,4-diene from an olefin was reported by Yuguchi and Iwamoto using butadiene and ethylene under cobalt, iron and aluminium catalysis for the obtention of 3-methyl-1,4-pentadiene in a complex mixture (Scheme 51).[87] However, this procedure involves a high pressure of ethylene and provide a poor selectivity.



Scheme 51

Other examples using a catalyst based on nickel[88], iron[89], rhodium[90] and cobalt[91] have been reported and allow accessing 1,4-dienes in high yields and great selectivity. Even private companies have focused on this strategy for accessing 1,4-hexadiene.[92] A great advantage of this methodology versus the cross coupling strategy, is that the substrate do not need to be pre-functionalized. However most of these procedures remain limited by their scopes and require harsh reactions conditions or highly toxic catalysts.

However, among the examples using this strategy to give rise to 1,4-dienes [86, 93], one we can mention the work of Babu and co-workers who developed a methodology starting from a 1,3-diene and a low pressure of ethylene gas (Scheme 52).[86] A strength of this work is the possibility to modify the selectivity toward the C_3 substituted or unsubstituted 1,4-diene. However, this methodology do not allow substitution on the carbon C_3 and lead to terminal alkenes as most of the others available procedures.

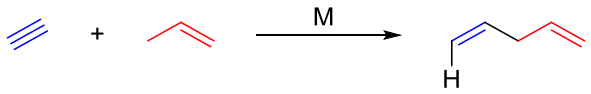


Scheme 52

Other researchers demonstrated the possibility to replace the ethylene gas by an olefin such as styrene[89] or other olefins bearing other substituents.[94]

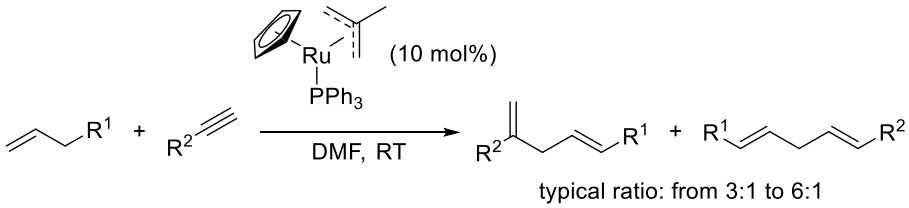
1.3.3 Hydroallylation of alkynes

The third main strategy toward the formation of 1,4-diene is the hydroallylation of alkynes (Scheme 53).[95]



Scheme 53

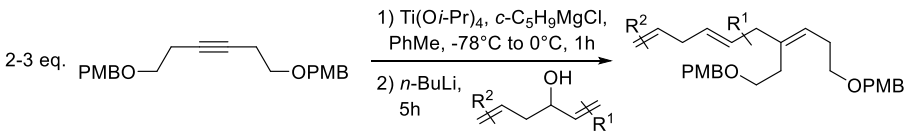
One of the probably most famous example is the Ru-catalyzed addition developed by Trost (Scheme 54).[96]



Scheme 54

Even if this reaction benefits from a great substrate scope and good functional group compatibility, it suffers from the necessity to use terminal alkyne and lead to a mixture of branched and linear product.

Among the examples reported for this strategy, one can point the work of Micalizo and co-workers (Scheme 55).[95a] They demonstrated the possibility of accessing 1,4-dienes starting from a 1,5-diene with a high control of the site selectivity. Furthermore, their procedure allows the use of a non-terminal alkyne and can even lead to non-conjugated triene without using highly toxic or expensive metal catalyst.



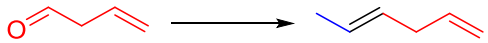
Scheme 55

Many other research groups have investigated the field of 1,4-diene with this methodology and some of them even developed procedure to access these skeleton with a very high yield and selectivity toward the linear

product.[95c] Some of them used hydroallylation of alkyne as a tool for natural polyene synthesis.[97]

1.3.4 Olefination of β,γ-unsaturated aldehyde

The last main strategy for the synthesis of 1,4-diene is the olefination of β,γ-unsaturated aldehyde (Scheme 56).



Scheme 56

This strategy is probably the less general one to access 1,4-dienes. Indeed, the starting aldehyde can be reacted through many different reaction to lead finally to the targeted 1,4-dienes. For example, Marko *et al.* have used a double olefination (a 1st Julia olefination followed by a 2nd Julia-Kociensky olefination) to reach the targeted Jerandolid molecule.[98] Other groups have preferred to work with organo magnesium compound and make them react on the aldehyde to provide the first double C=C bond of the 1,4-diene prior to form the second C=C bond via a coupling reaction using titanium catalyst and an alkyne[99]. The major difficulties in this strategies are the control of the *E/Z* selectivity associated with the unstable β,γ-unsaturated system. This methodology thus suffers from a lack of generality and is usually used for specific applications

1.3.5 Conslusion about the 1,4-diene synthesis

Existing methodologies for accessing 1,4-dienes can be classified in four main strategies:

- Cross coupling reaction of alkenyl organometallic reagents
- Hydro alkenylation of 1,3-dienes
- Hydroallylation of alkynes
- Olefination of β,γ-unsaturated aldehydes

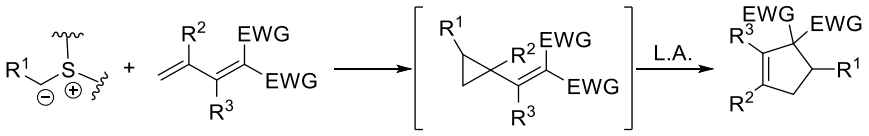
All these methodologies have their specificity but they have some common points. Indeed, in almost all of these reactions, some atoms are lost during the processs and therefore tarnish these methodologies from a moderate or poor atom economy. Some of these developed reactions benefit however from a satisfactory atom economy but then they involve toxic metals or/and expensive metals as catalyst with sometimes ligands requiring fastidious multisteps synthesis.

Regarding obtained 1,4-dienes, only a few versions of these reactions allows to substitute the central carbon on the diene and the scope of the possible substitution in this position is limited. Furthermore, most of the reported examples lead to the formation of terminal 1,4-dienes which are not the most present in natural compounds.

Therefore, at this time, the synthesis of 1,4-dienes benefits from several possibilities of synthesis but suffers from a real lack of generality.

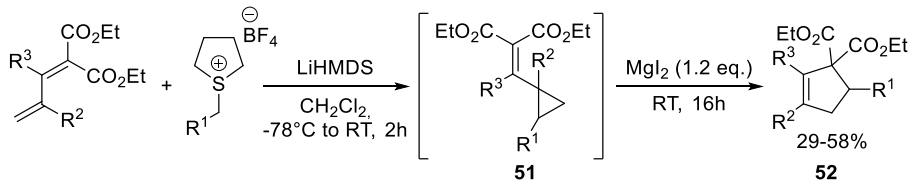
Chapter 2 Preliminary results of the laboratory

As described in the introduction, VCPs are well known to rearrange into cyclopentenes via different processes, from thermal activation to Lewis acid triggered rearrangement.[43, 45] Cognizant of this, Prof. R. Robiette envisaged the possibility to synthesize cyclopentenes from sulfonium ylides and activated olefins in a one-pot stategy, via a VCP intermediate (Scheme 57).



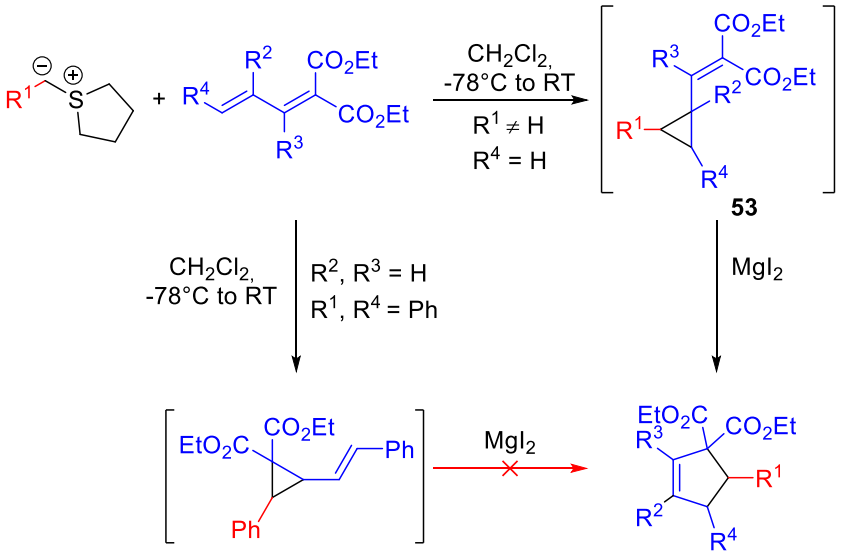
Scheme 57

During his Ph.D. thesis, Dr. O . Rousseau developed a formal one-pot (4+1) annulation based on the reaction of a benzylic sulfonium ylide and a bis-activated 1,3-diene. This reaction leads to a VCP (**51**) which is directly rearranged into a cyclopentene (**52**) in the presence of MgI2 (Scheme 58).[25, 100] Dr. O. Rousseau tested various substituents for the R^1 position and showed that a broad range of substituants was tolerated, from alkyl to aryl groups bearing EWG and EDG. Later Dr. S. Clergue, pursued the development of this methodology and introduced new possibilities regarding the nature of the EWG and the substituents on the 1,3-diene. It has to be noted that, in the many cases, the synthesis of the 1,3-diene turned out to be tricky and some 1,3-dienes were found to be unstable[101].



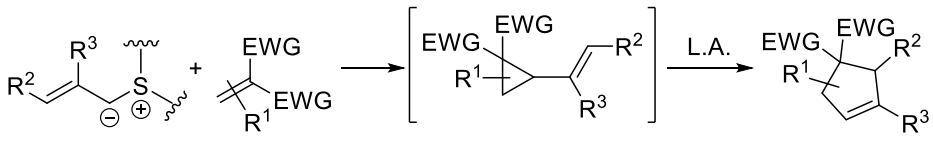
Scheme 58

Furthermore, it has been shown that when R^2 and R^3 are hydrogen atom, a different VCP is formed which does not undergo a rearrangement in the presence of magnesium iodide (Scheme 59). Indeed, Dr. O. Rousseau reported that a group on R^1 position was required in order to constrain the ylide to regioselectively add onto the terminal carbon atom of the 1,3-diene moiety (1,6-addition) and lead to the VCP (**53**) which can undergo the rearrangement into the desired CP.



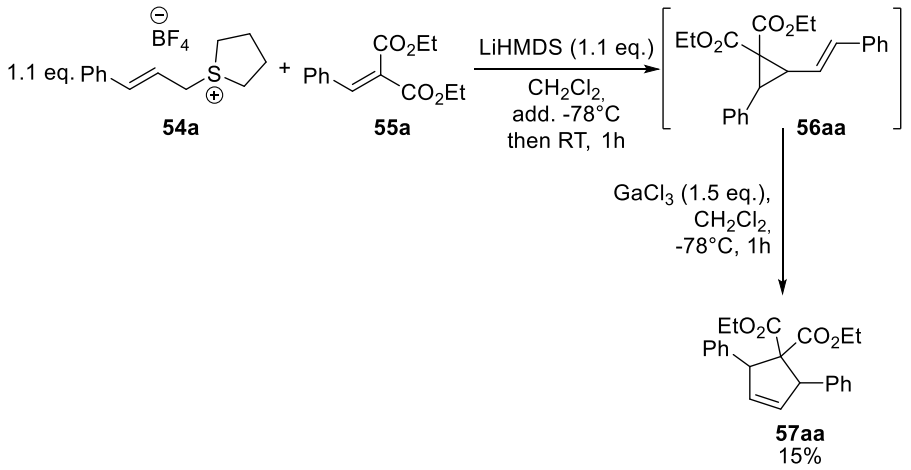
Scheme 59

In order to avoid the tedious synthesis of 1,3-dienes and regioselectivity issues for the ylide addition, our research group considered a strategy based on an allylic sulfonium ylide and an activated olefin (Scheme 60).



Scheme 60

During his postdoctoral stay, Dr. G. Dequirrez showed that the reaction of allylic ylides (**54a**) with a bis-activated olefin (**55a**) leads to the corresponding VCP (**56aa**) and that this latter can be rearranged into the corresponding CP (**57aa**) upon Lewis acid catalysis (Scheme 61). However, some important differences with the previously developed (4+1) anulation have to be noted. Indeed, in this case, the EWG are directly on the cyclopropane ring, and not on the vinylic part of the VCP. Also, MgI_2 does not trigger the rearrangement of the VCP in this case. An excess of the Lewis acid $GaCl_3$ has to be used to provide the CP.



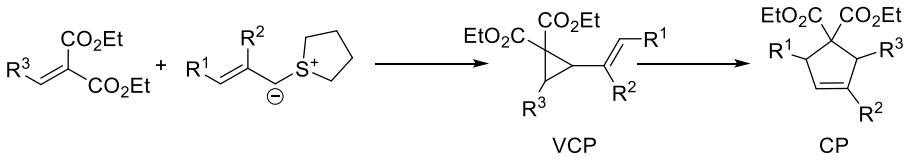
Scheme 61

Despite many attempts to improve it, this methodology suffered from a lack of reproducibility and different unidentified side products were obtained depending on reaction parameters. Futhermore, other Lewis acids

than $GaCl_3$ have been tested but none of them led to the desired product, only unidentified side products or poor conversions were obtained.

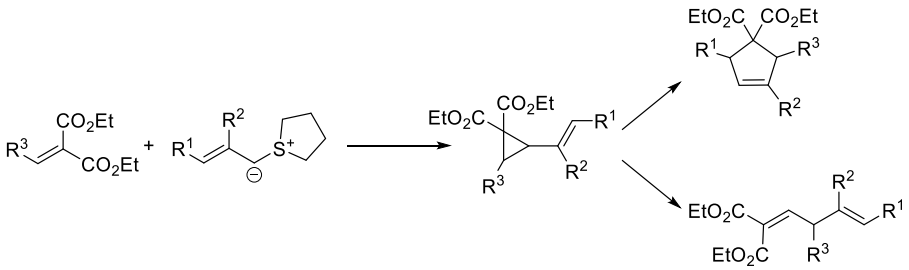
Chapter 3 Objectives and strategy

At the time of starting this thesis, the ultimate objective was the development of a (3+2) annulation strategy from sulfonium ylides and activated olefins via a vinylcyclopropane intermediate (Scheme 62).



Scheme 62

However, in the course of our studies to establish the optimal reaction conditions for the VCP-CP rearrangement, we discovered the possibility to access 1,4-dienes from our VCPs. As explained in the previous section, 1,4-dienes are important motifs found in numerous biologically active compounds but their synthesis remains a significant challenge in organic chemistry. We thus decided to develop divergent methodologies leading selectively either to cyclopentenes or 1,4-dienes from activated olefins and allylic sulfur ylides via rearrangements of a common vinylcyclopropane intermediate (Scheme 63).



Scheme 63

In order to simplify the accomplishment of our main goal, we divided this later into two sub-categories of objectives: The first part is devoted to the

rearrangement toward cyclopentenes and the second one to the formation of 1,4-dienes.

Accordingly, based on the previously acquired knowledge of the laboratory our sub-objectives for the synthesis of cyclopentenes are:

1. Our first targeted goal is to find the optimal reaction conditions for an efficient cyclopentene formation in terms of Lewis acid, temperature, solvent, etc. In addition, a one-pot version of our methodology will be considered.

2. The second point that we will investigate when the reaction conditions will be determined is the exploration of the scope of reaction in order to identify the limits of our proposed methodology.

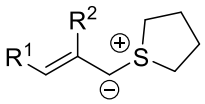
3. Next, we propose to develop an asymmetric version of our methodology to form enantiomerically enriched CPs.

4. Finally, our last goal is to derivatize obtained CPs in order to demonstrate the usefulness of our methodology through several examples.

Regarding the rearrangement toward 1,4-dienes, we defined the following sub-obectives:

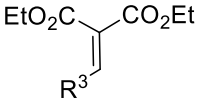
A. We will investigate the formation of the 1,4-diene vs. cyclopentene and try to find the best reaction conditions to obtain this compound

B. Next, the exploration of the reaction scope will be investigated. First, the nature of ylide and olefin substituents will be varied (Figure 1).



R^1 = Ph, *p*-MeOPh, *p*-CO_2MePh, Alkyl

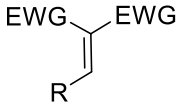
R^2 = EWG, Alkyl



R^3 = Ph, *p*-MeOPh, *p*-CO_2MePh, Alkyl

Figure 1

C. Next, the impact of changing the activating EWG group borne by the olefin will be studied (Figure 2).



EWG = CO_2Et, CN

Figure 2

D. Finally, our last goal is to get a global understanding of the different mechanisms leading to all observed products (*cis* and *trans*-VCP, 1,4-diene, CP, CPsec).

Because we observed the unexpected formation of 1,4-diene and that it prompted us to reconsider our targeted objectives, the goals related to the 1,4-diene formation and the ones for the CP formation were pursued in parallel.

Chapter 4 Substrates synthesis

This chapter is dedicated to the formation of the required substrates: Sulfonium salts and activated olefins. These latter were our cornerstone reagents in view of synthesizing the required VCPs, which will subsequently be rearranged into desired cyclopentenes and 1,4-dienes.

4.1 Synthesis of sulfonium salts

As it has been explained in the introduction, sulfonium ylides are great candidates for the synthesis of VCPs. These ylides are formed *in situ* via deprotonation of their corresponding sulfonium salt. Therefore, in order to synthesize different VCPs bearing diverse substituents on their double C=C bond, various allylic sulfonium salts have been synthesized according to the methodology reported by Aggarwal and co-workers[102].

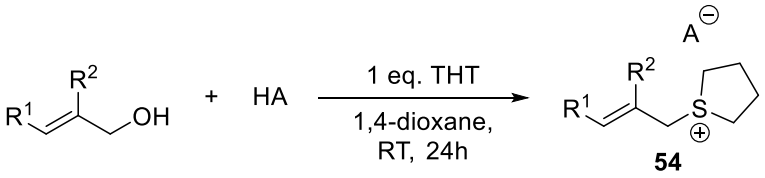
Two types of sulfonium salts were prepared: non-chiral ones for which the sulfide used is the tetrahydrothiophene (THT) and a chiral-salt bearing a chiral auxiliary reported by Aggarwal[103].

4.1.1 Non-chiral sulfonium salts

The methodology of Aggarwal[104] has been used for most of the salts synthesized during this thesis. However, particular salts have required to modify this procedure to successfully form the desired compound.

In the presence of tetrafluoroboric acid (HBF_4) or hexafluorophosphoric acid (HPF6) and THT, cinnamyl alcohol or one of its derivatives affords the corresponding sulfonium salt (Table 1). The acid HBF_4 has been used in order to set BF_4^- as a counter ion. Indeed, tetrafluoroborate salts are less hygroscopic and more soluble in organic solvants than corresponding chloride or bromide salts. However, in some cases, the reaction with this acid and some cinnamyl derivatives afforded very complicated mixtures which were very difficult to purify through a recrystallization process. In

these cases, HPF_6 was utilized to take advantage of the crystallization ability of PF_6^- salts.



Salt	R^1	R^2	Counterion(A^-)	Yield (%)
54a	Ph	H	BF_4^-	75
54b	*p*-CO_2MePh	H	BF_4^-	73
54c	Ph	Me	BF_4^-	55
54d	*p*-MePh	H	PF_6^-	60
54e	$CH(CH_3)_2$	H	BF_4^-	44
54f	H	H	BF_4^-	51
54g	Ph	CO_2Me	PF_6^-	51

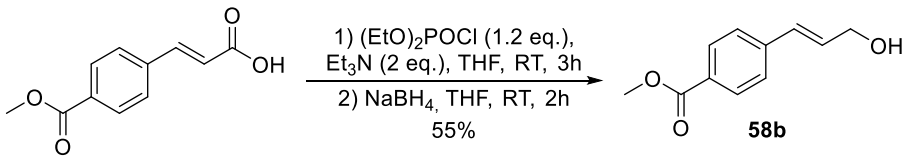
*Table 1: Sulfonium salts synthesized. **54e** has turned out to be in a liquid state at room temperature.*

It has to be noted that the purification via recrystallization turned out to be tricky for all salts and therefore this fact could rationalize the observed loss of yield.

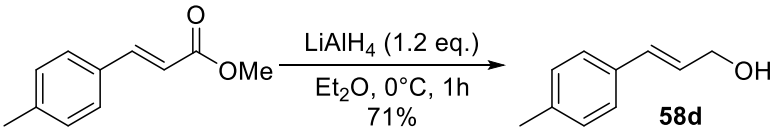
All synthesized sulfonium salts were found to be bench stable for months.

4.1.2 Intermediates synthesis

The starting alcohols for synthesizing the salts (**54b**) and (**54d**) are commercially available but quite expensive. Therefore, we synthesized these compounds via the following reactions (Scheme 64, Scheme 65).

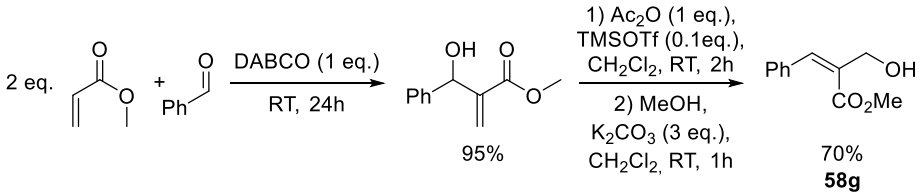


Scheme 64[105]



Scheme 65

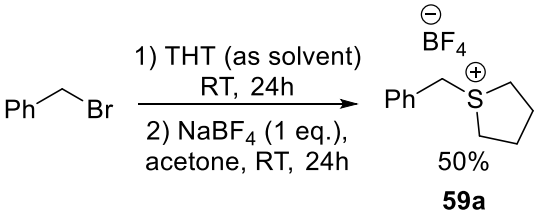
Regarding the allylic sulfonium salt (**54g**) the corresponding alcohol is not commercially available. Accordingly, we have synthesized this alcohol in two steps via procedures reported by Nicponski[106] and Basavaiah[107] (Scheme 66).



Scheme 66

4.1.3 Benzylic sulfonium salts

Beside the allylic sulfonium salts, one benzylic sulfonium salt has been used in order to access special VCPs which were not easily attainable via the cyclopropanation with allylic ylides. Our reference benzilic sulfonium salt (**59a**) was already available in the laboratory and has been synthesized according to the procedure described by Aggarwal (Scheme 67)[104].



Scheme 67

4.1.4 Chiral sulfonium salt

As mentioned in the chapter about the objectives, one part of our work is dedicated to the development of an enantioselective version of our methodology. In order to induce enantioselectivity in the cyclopropanation step, several options are available. In this work, as it will be explained in the next chapter, we decided to proceed via a chiral ylide. Our choice fell on chiral sulfides reported by Aggarwal. Indeed these ylides are readily available and already showed good results for the synthesis of three-membered rings (Figure 3)[38].

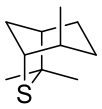
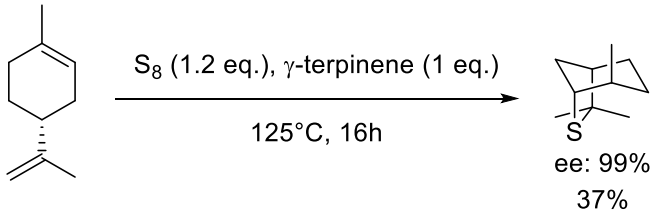


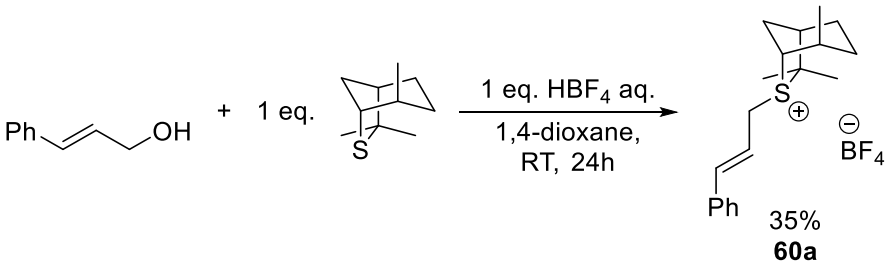
Figure 3

Moreover, this sulfide has been already widely used in our laboratory by Dr. Sébastien Clergue[108] and Dr. Olivier Rouseau[100] during their Ph.D. thesis. This chiral sulfide called isothiocineol present a relatively complex structure. However, despite his apparent sophistication, this auxiliary is obtained in one step by the reaction between γ-terpinene, (+)-limonene and elemental sulfur. A reasonable yield is obtained but the enantiomeric excess is very high (Scheme 68)[103]. It is important to mention that we never tried to recover the chiral auxiliary because it is readily available and cheap. However, in his work, Aggarwal has shown the possibility to recover the chiral auxiliary with great efficiency[103-104].



Scheme 68

The chiral sulfonium salt **(60a)** has been synthesized using the method described for allylic non-chiral salts (Scheme 69).

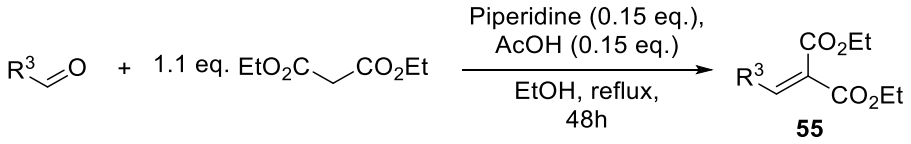


Scheme 69

4.2 Synthesis of activated olefins

In order to extend the scope of the reaction, we synthesized various activated olefins to introduce different groups directly attached on the cyclopropane ring. Three different types of olefinic scaffolds have been obtained: aromatic, hetero-aromatic and non-aromatic. Fortunately, these activated olefins were readily accessible from a synthetic point of view; one of them (**55a**) was even commercially available. Furthermore, these compounds are characterized by a high stability allowing to stock them for months at room temperature without special requirements.

For this purpose, we have synthesized these compounds via a simple Knoevenagel condensation reaction between the corresponding aldehyde and diethyl malonate (Table 2). Products were purified by distillation and obtained as the residue of the distillation process.

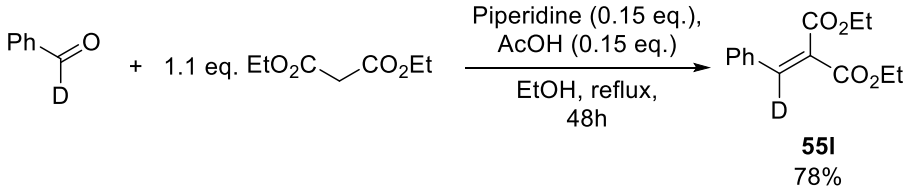


	R³	Yield (%)
55a	Ph	commercial
55b	*p*-MePh	77
55c	*p*-MeOPh	82
55d	*p*-CO_2MePh	75
55e	*p*-FPh	98
55f	*p*-BrPh	86
55g	*m*-BrPh	95
55h	2-furyl	98
55i	1-Me-pyrol-2-yl	77
55j	*i*-Bu	31
55k	*i*-Pr	92

Table 2: activated olefins synthesized

4.2.1 Deuterated labeled olefin

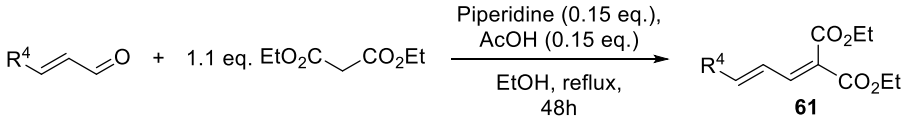
In order to provide a better understanding of the mechanism of 1,4-dienes formation, we have synthesized a labeled olefin (**55l**) using deuterated benzaldehyde (Scheme 70). The same reaction conditions as for the other olefins were used.



Scheme 70

4.2.2 *Synthesis of activated 1,3-dienes*

In order to access di-vinylcyclopropanes, three 1,3-dienes have been synthesized via the same Knoevenagel condensation reaction but starting from the corresponding conjugated aldehydes (Table 3).



	R⁴	Yield (%)
61m	Ph	89
61n	*p*-MeOPh	95
61o	2-furyl	74

Table 3: 1,3-dienes synthesized

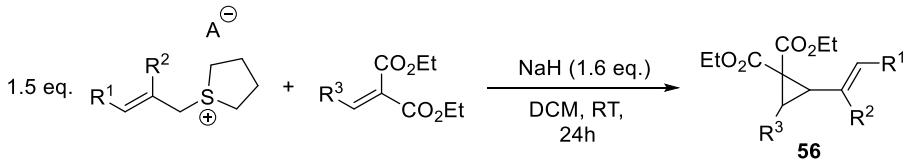
4.3 Synthesis of vinylcyclopropanes

VCPs were our cornerstone intermediates in order to access 1,4-dienes and cyclopentenes as it will be explained further in this document.

4.3.1 *From allylic sulfonium ylides and activated olefins*

With the aim of synthesizing VCPs, an activated olefin was reacted with a sulfonium ylide formed in situ by deprotonation of the corresponding sulfonium salt. Because this chemistry has been studied for a long time in our laboratory, we first attempted to transpose to our system the procedure used by Dr. S. Clergue and Dr. O. Rousseau for the development of a (4+1) annulation between a 1,3-diene and benzylic ylides (see Chapter 2). However, the use of LiHMDS led to a low conversion and a complicated mixture of products. We thus searched for better reaction conditions and found that employing NaH as a base allows obtaining the VCP in good yield and better purity (Table 4). Different ratios between the *cis* and *trans* isomers were obtained depending on the nature of the VCP.

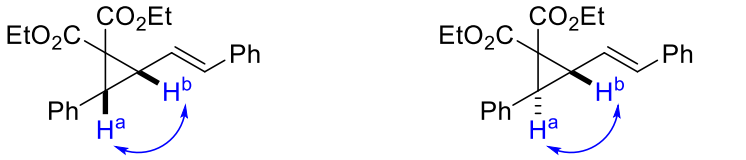
Despite, the improvement of reaction conditions, the separation of the remaining olefin and the formed VCP (as two diastereoisomers) by flash column chromatography was complex because of the similar polarity.



	R¹	R²	R³	Yield (%)	*Cis/Trans*[b]
56aa	Ph	H	Ph	90	*4/6*
56ab	Ph	H	*p*-MePh	42	*4/6*
56ac	Ph	H	*p*-MeOPh	61	*4/6*
56ad	Ph	H	*p*-CO_2Me	53	*4/6*
56ae	Ph	H	*p*-FPh	67	*4/6*
56af	Ph	H	*p*-BrPh	74	*4/6*
56ag	Ph	H	*m*-BrPh	53	*4/6*
56ah	Ph	H	2-furyl	95	*4/6*
56ai	Ph	H	1-Me-pyrol-2-yl	5	*4/6*
56aj	Ph	H	$CH_2CH(CH_3)_2$	28	*0/10*[c]
56ak	Ph	H	$(CH_3)_2CH$	31	*0/10*[c]
56ba	*p*-CO_2MePh	H	Ph	55	*0/10*[d]
56ca	Ph	Me	Ph	19	*4/6*
56da	*p*-MePh	H	Ph	32	*4/6*
56ea	$(CH_3)_2CH$	H	Ph	97	*3/7*
56fa	H	H	Ph	11 (90)[a]	*5/5*
56ga	Ph	CO_2Me	Ph	0	/

Table 4: VCPs coming from allylic sulfonium salts and activated olefins. [a] NMR calculated yield using DMT as internal standard. [b] diasteromeric ratios were measured by ^{1}H NMR on the crude mixture [c] The modification of the ratio between cis and trans isomers is rationalized by assuming the intervention of a steric hindrance effect as already reported by Aggarwal[37] [d] the modification of the ratio between cis and trans isomer could be explained by a enhanced acidity of the cyclopropane proton in α position of the styryl group.

The two VCP-diastereoisomers *cis* and *trans* are identified through the difference of coupling constant of the hydrogen atoms on the cyclopropane ring. The *cis* isomer exhibits a higer coupling constant value than the *trans* isomer as shown on the example **56aa** (Figure 4).



J_{ab}^{cis} = 9.7 Hz

Typical J_{ab}^{cis} range: 7 - 10 Hz

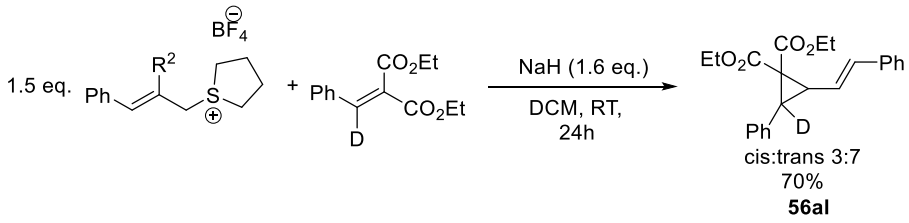
J_{ab}^{trans} = 7.9 Hz

Typical J_{ab}^{trans} range: 2 - 6 Hz

Figure 4[109]

4.3.1.1 Deuterium-labeled VCP for mechanistic experiments

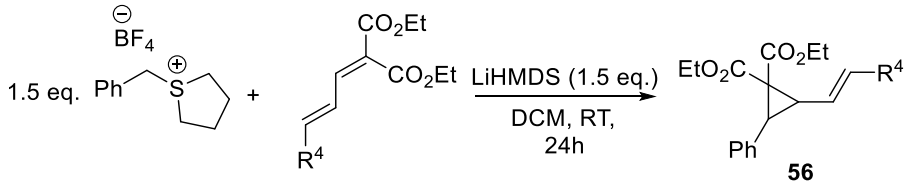
A VCP bearing a deuterium atom on the cycle has been prepared in order to better understand how the 1,4-diene is formed from the VCP (Scheme 71) as it will be explained later in this work (see 5.2.2).



Scheme 71

4.3.2 From benzylic ylides and 1,3-dienes

Because some VCPs are not accessible using an allylic sulfonium ylide, we considered the possibility of proceeding through a methodology based on the reaction of an activated 1,3-diene and a benzylic sulfonium ylide (Table 5). In this case, accordingly to the procedure described by Dr. S. Clergue and Dr. O. Rousseau, LiHMDS was used as a base.[100-101]

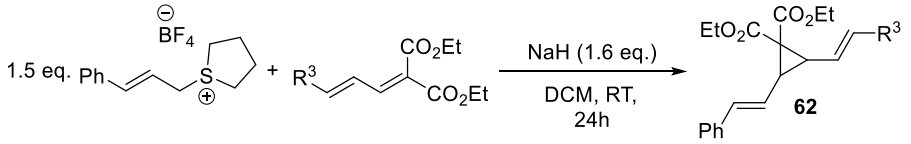


	R⁴	Yield (%)
56an	*p*-MeOPh	62
56ao	2-Furyl	13

Table 5: VCPs synthesized using benzylic sulfonium ylides and activated 1,3-dienes.

4.3.2.1 Di-vinylcyclopropanes formation

Two di-VCPs have been synthesized using the same cyclopropanation conditions of those with allylic ylides and olefins (see 4.3.1). In this case, a 1,3-diene is reacted with an allylic sulfonium ylide and led to a VCP bearing two double bonds (**62**) (Table 6).

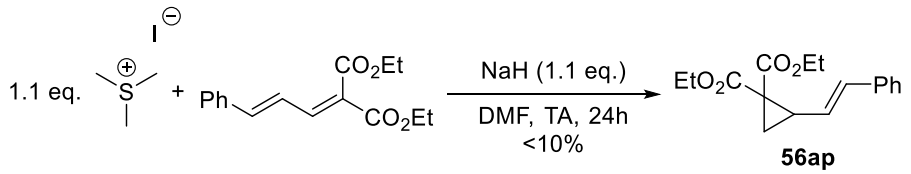


	R³	Yield (%)	*cis/trans*
62am	Ph	32	*3/7*
62an	*p*-MeOPh	26	*3/7*

Table 6: VCPs coming from allylic sulfonium salts and activated 1,3-dienes

4.3.3 Preparation of C_1 unsubstituted VCP

Trimethyl sulfonium iodide has been used for synthesizing a special VCP bearing an additional hydrogen atom on the cyclopropane ring (Scheme 72).



Scheme 72

We used this method instead of the described route in Table 4 because the corresponding olefin was too difficult to produce via the Knoevenagel condensation. Desired VCP was obtained with a poor yield but reaction conditions were not optimized.

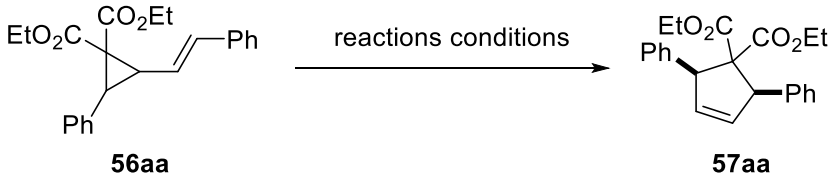
Chapter 5 Rearrangement reactions

This chapter is divided into three distinct parts. The first one is dedicated to the understanding of the formation of cyclopentenes. In the next part we will try to clarify the links existing between 1,4-dienes and cyclopentenes. Finally, the last part is devoted to the synthesis of 1,4-dienes.

5.1 (3+2) annulation reaction

5.1.1 Determination of reaction conditions

The VCP-CP rearrangement of **56aa** has already been observed by Dr. G. Dequirez in 2015 using $GaCl_3$ for triggering the rearrangement (see Chapter 2). However, this reaction was suffering from a low reproducibility and the CP (**57aa**) was obtained in a complex mixture. Therefore, we first focused on the development of reaction conditions allowing access to CP in good yield. To do so, we selected **56aa** as a reference VCP (Scheme 73).



56aa **57aa**

Scheme 73

We began our exploration of the optimal reaction conditions by trying to reproduce experiments made by Dr. G. Dequirez using $GaCl_3$ (entry A, Table 7). It is important to note that only the *cis* isomer of the CP has been observed. Because the cyclopropanation step was carried out in dichloromethane we decided to use the same solvent for the rearrangement in view of a future development of a "one-pot" version of our methodology.

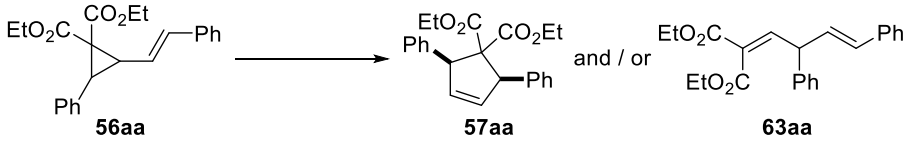
Different Lewis acids have been screened with the aim of finding the most efficient and mild reaction conditions for triggering the rearrangement[2].

Entry	Lewis acid	Equivalents	Temperature & time	Observations
A	$GaCl_3$	1.2 eq.	-78°C 1h, RT 1h	CP and other non-identified products
B		2 eq.	Addition at -78°C then 24h RT	1,4-diene + CP
C		2 eq.	-20°C 2h	1,4-diene + CP
D		1 eq.	-20°C 2h	1,4-diene
E		3 eq.	-78°C 1h, RT 1h	CP
F	$SnCl_4$	1	Add. -78, 24h RT	1.4-diene + degradation
G		0.5	RT, 24h	1,4-diene
H	$FeCl_3 \bullet 6H_2O$	1 eq.	RT, 24h	1,4-diene
I	$TiCl_4$	1.5 eq	RT, 2h	1,4-diene + degradation
J		1 eq.	-78°C 1h, RT 1h	1,4-diene
K		1 eq.	RT 15 min	1,4-diene
L		3 eq.	RT 24h	CP

Table 7: All reactions have been performed in dichloromethane(1mL/10mg of VCP). For most of the tests, yields were not calculated because the obtained mixtures were too complex to purify or to introduce an internal standard

The tests using $GaCl_3$ (entry A to E) showed that it is possible to afford the CP but in most cases it was obtained as a mixture with an unexpected product, that was later found to be the 1,4-diene (Scheme 74).

[2] $GaCl_3$ has been selected because it had already been used in our laboratory by G. Dequirez during his premilinary studies. Concerning $SnCl_4$, $FeCl_3$ and $TiCl_4$ they have been chosen for their ease of use and their availabilities in our laboratory.



Scheme 74

Only when a larger amount of the Lewis acid was used, the CP (**57aa**) was produced as the main product (entry E). However, these reaction conditions are highly sensitive and a large range of yields was obtained using the conditions of entry E. That could be due to the high reactivity of $GaCl_3$ which makes it very difficult to handle. Consequently, the mass of $GaCl_3$ introduced in each experiment could be slightly different and induces a deviation from the expected result. Furthermore, we showed that a slight variation in temperature or time of the reaction can induce major changes in the obtained results (degradation).

Therefore, because of this lack of reproducibility, we started to investigate new Lewis acids. However, many of them including $Zn(OTf)_2$, $CuCl_2$, $SnCl_2$, and aluminum-based Lewis acids did not trigger the rearrangement (no conversion). Even MgI_2 which is the Lewis acid used in the (4+1) annulation developed in our laboratory[100-101, 108] led only to the isomerization of the VCP from the *cis* isomer to the *trans* one. It has to be noted that some metal catalysts (as $Pd(OAc)_2$, $Pd(PPh_3)_4$) have been tested but no conversion was observed. Just a few Lewis acids such as $SnCl_4$ (entry F and G), $FeCl_3$ (entry H) were active and led to the corresponding 1,4-diene (**63aa**), instead of the desired CP. Because only $TiCl_4$ exhibited the possibility to afford CP (**57aa**) selectively (entry L) we choose this Lewis acid to carry out futher studies. In addition, $TiCl_4$ is in a liquid state at room temperature and therefore its handling is easier than $GaCl_3$ and provides a superior reproducibility. In order to ensure that hydrochloric acid formed by the reaction of $TiCl_4$ with moisture was not the active species, we tested the activity of HCl regarding the rearrangement. No modification of the VCP has

been observed in the time scale considered, indicating that it is not some traces of HCl which are the active catalyst.

Knowing the efficiency of $TiCl_4$ to trigger the rearrangement, we investigated how many equivalents of this Lewis acid were actually required in order to produce the desired CP in high yield and selectivity (Chart 1).

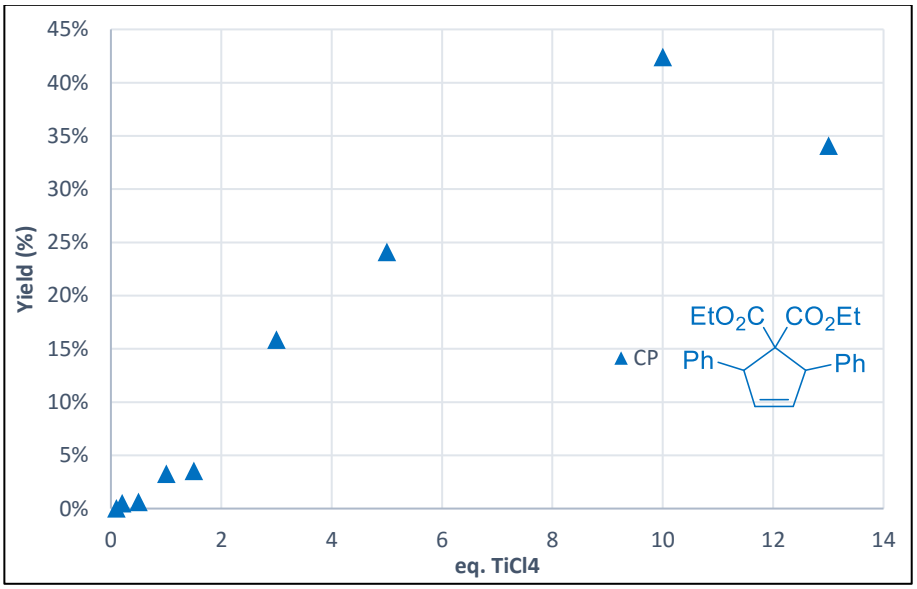
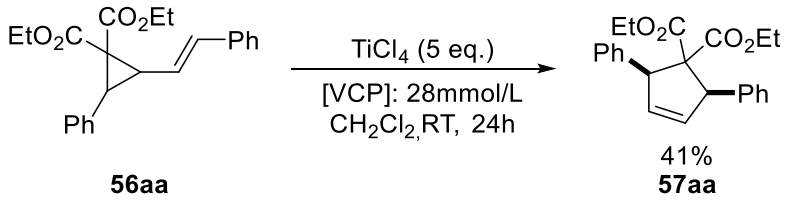


Chart 1: Yield of CP versus the number of $TiCl_4$ equivalent. Reaction conditions: CH_2Cl_2, RT, overnight.

Analyzing the results, we understand that in one hand, working with a large excess of $TiCl_4$ allows increasing the yield in CP, but in the other hand, when the number of the equivalent of Lewis acid is too high (>10 eq.), degradation occurs leading to a decrease of the yield. Furthermore, $TiCl_4$ is a strong Lewis acid and we tried to keep the reaction conditions as mild as possible. Therefore, we concluded that five equivalent of $TiCl_4$ is required to afford the CP as the main product if the reaction was stirred for several hours. We have then screened different solvents: acetonitrile and toluene have been tested but led to very complex mixtures. The influence of the concentration has been investigated as well and it was found that

10 mg VCP/mL of solvent were a good compromise between the volume of solvent providing an easy handling and a reasonable rate of reaction.

To summarize, the following reaction conditions have been chosen as the most effective of those tested (Scheme 75).



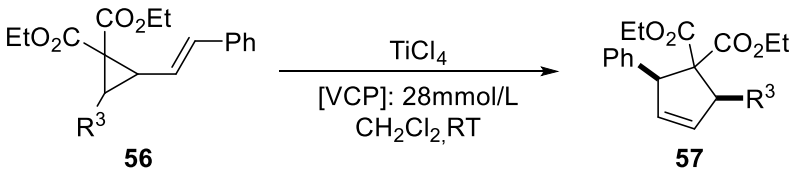
56aa **57aa**

Scheme 75

It has to be noted that despite that more than one equivalent of Lewis acid is used to trigger the reaction, experiments involving a non-stoichiometric amount of $TiCl_4$ proved that this Lewis acid is acting as a catalyst (see Table 13, section 5.3.3.2).

5.1.2 Extending the scope of the reaction

The rearrangement of different decorated VCPs was tested and new CPs have been obtained (Table 8). We first focused on the substitution of the R^1 group directly attached to the cyclopropane ring.



56 **57**

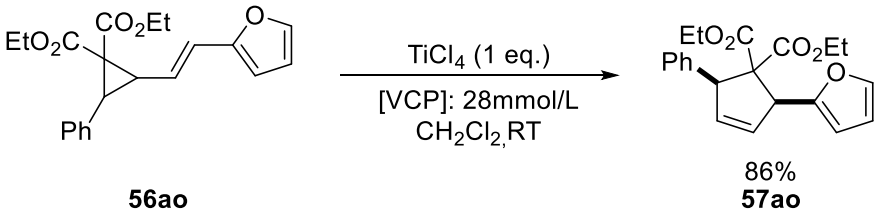
	R^3	Eq. $TiCl_4$	Time	Yield (%)
57aa	Ph	5	24 h	41
57ac	*p*-MeOPh	1.5	24 h	0[a]
57ad	*p*-CO_2MePh	1.5	24h	26
57ae	*p*-FPh	1.5	24 h	27
57aj	$CH_2CH(CH_3)_2$	3	20 min	70
57ak	$(CH_3)_2CH$	5	15 min	82
57ap	H	3	1 h	<10

Table 8: [a] A mixture of two side products which are isomers of the desired CP have been obtained (see 7.2.10). The conversion of the reaction was almost total in all cases (^{1}HNMR)

Despite the developed reaction conditions, a number of these VCPs required an adjustment in terms of reaction time and equivalent of Lewis acid, with only the best results being reported in Table 8. Obtained yields remained poor in the case of **56ad** and **56ap**. That can be explained by the difficulties encountered during the purification process. Beside that, we noted a better efficiency with electron poor R^1 groups. This will be discussed in the following subchapter taking into account the mechanism of the rearrangement.

Next, we tried to investigate the effect of the substitution on R^2. A VCP bearing 2-furyl group on R^2 has been rearranged. This rearrangement efficiently led to the selective formation of the desired cyclopentene in good yield using 1 equivalent of $TiCl_4$. If one compare this result with our reference

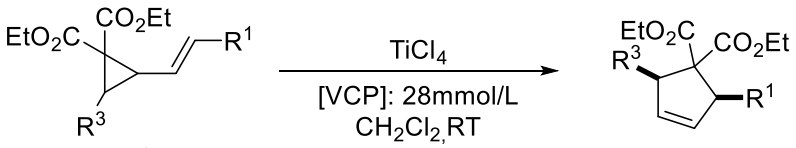
VCP (**56aa**), it suggests that a higher electron density on R^2 favors the efficient formation of the corresponding CP (Scheme 76).



56ao **57ao**

Scheme 76

However, in many cases, VCPs do not afford CPs and only a side product that will be discussed further in this work has been observed (Table 9).



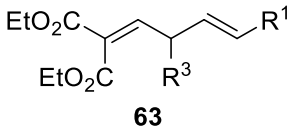
56 **57**

	R^3	R^1	Eq. $TiCl_4$	Yield (%)
57ab	Ph	*p*-MePh	1.5	20
57ac	*p*-MeOPh	Ph	5	22
57ad	Ph	*p*-CO_2MePh	5	0[a]
57ae	*p*-FPh	Ph	5	<10
57ah	2-furyl	Ph	5	0[a]
57ap	H	Ph	3	<10

Table 9: [a] only a side product in high amount has been observed.

When the group linked directly to the cyclopropane ring is electron rich, the reaction is characterized by a lower efficiency toward the CP. In the case of **5ad**, the group R^2 is electron poor and the formation of the side product is favored versus CP formation as it will be explained further (see 5.2.2).

Ensuing to the gathered results, when the R^1 group is electron deficient, the formation of the CP is favored versus the formation of the side product. Conversly, when R^2 group is an electron rich substituent the formation of the desired CP is favored versus the formation of the side product. Concerning the nature of the side product, further structural analysis reveled that it was a 1,4-diene (Figure 5).

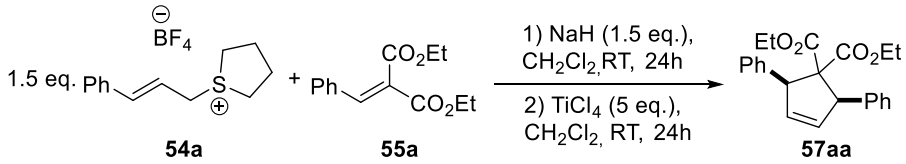


63

Figure 5

5.1.3 Development of a one-pot version

We considered the development of a one-pot version by performing the two steps, the cyclopropanation and the rearrangement, in one synthetic step (Scheme 77). This would allow obtaining polysubstituted CPs directely from readily available reactants, an activated olefin and a sulfonium salt. Favorably, our reaction conditions for the rearrangement have been set to work with the same solvent as the prior cyclopropanation.

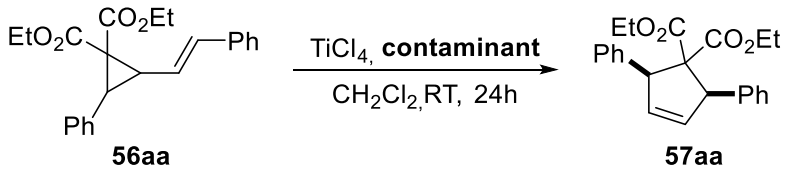


54a **55a** **57aa**

Scheme 77

However, when attempted, the one-pot process did not lead to the CP. Therefore, in order to determine the factors influencing the yield of CP, we designed an experiment plan (*JMP program*) for the following parameters: temperature, equivalents of $TiCl_4$ and amount of sulfonium salt and base have been investigated. The ratio between the different products was

calculated by ^{1}H NMR analysis of the crude mixture. Despite the different reaction conditions tested, only small amounts of CP have been observed (less than 10%) and did not allow us to conclude about the explored parameters.[3] In order to investigate which factor is responsible for these disappointing results, we have tested the VCP rearrangement step in the presence of various potential contaminants (Scheme 78).



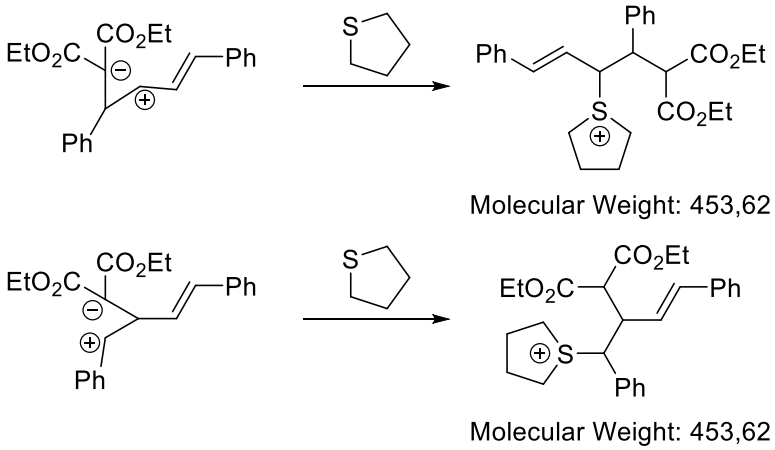
56aa **57aa**

Scheme 78

Sulfonium salt, base, and the sulfide auxiliary (from 0.5 to 2 eq.) have been tested as potential contaminants. When the sulfide (1 eq.) was introduced into the media, with the VCP and the Lewis acid, no CP could be observed.[3] Different hypotheses can be proposed to explain the problem faced.

One possibility is the quenching of the opened intermediate of the VCP by the sulfide auxiliary, followed by a protonation during the work-up (Scheme 79).

[3] 1,4-diene in a complex mixture was observed in almost all cases



Scheme 79

We thus are not able to conclude regarding the poisoning effect due to the THT. However, thanks to all experiments that we performed to improve the understanding of the inefficient one-pot process, we know that THT is not compatible with a one-pot procedure

5.1.4 Conclusion

During the course of our investigation toward the formation of CP we reported that the 1,4-diene was in many cases observed as the main product instead of the cyclopentene. Therefore, since these two species seem to be strongly interlinked, as it has been previously reported by other scientists[43, 46, 57, 72a], we decided to investigate the origin of this 1,4-diene formation and try to understand how one could control the CP/1,4-diene selectivity. Moreover, after reviewing the literature, we understood that these 1,4-diene scaffolds are interesting in organic chemistry because they are part of many biologically active and natural compounds[44a, b].

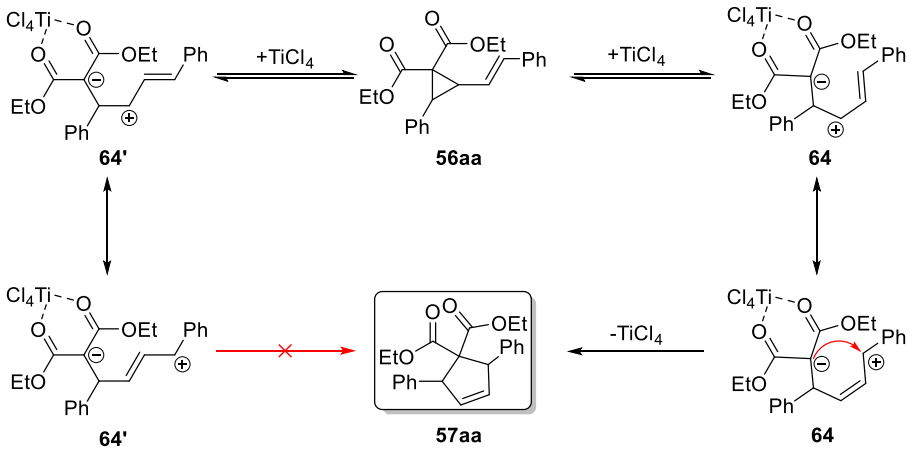
5.2 Mechanism of 1,4-diene and cyclopentene formation

From the first time that we observed the 1,4-diene in this project, we wondered how this compound could be formed and how it could be in competition with the formation of CP. Therefore, we have investigated the mechanism of the rearrangement, by performing a kinetic study, theoretical calculations (performed by Prof. R. Robiette and A. Delbrassinne) and study of the rearrangement of different VCPs bearing EWGs and EDGs.

In this section, we first expose the proposed mechanism involved in the formation of the CP and the 1,4-diene. Next, a comparison of the proposed mechanisms will permit to understand how they are linked and how the selectivity toward CP or 1,4-diene is determined. Finally, an additional side product called secondary cyclopentene (CPsec) will be introduced and discussed regarding the global mechanism.

5.2.1 Proposed mechanism for the CP formation

Based on the experience of our laboratory in VCP rearrangements, we propose the following mechanism for the formation of CP: when the VCP react with the Lewis acid, it undergoes a ring opening process leading to a zwitterionic intermediate (**64**) (Scheme 80). Then, a mesomeric effect followed by the ring closure gives the CP. This intermediate can then ring-close to give the CP.

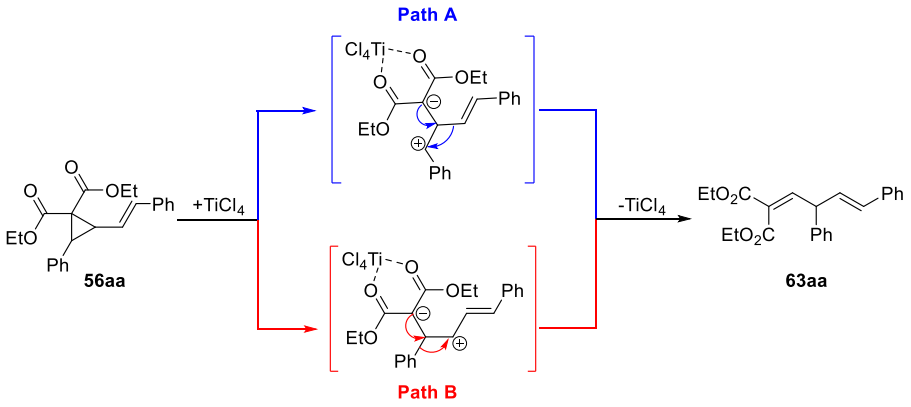


Scheme 80

It is important to note that the zwiterrionic intermediate can be formed as two isomers (**64** and **64'**). However the *trans* isomers (**64'**) cannot afford the CP due to geometric reasons, the impossibility in that case to bring the two reactive centers in close proximity.

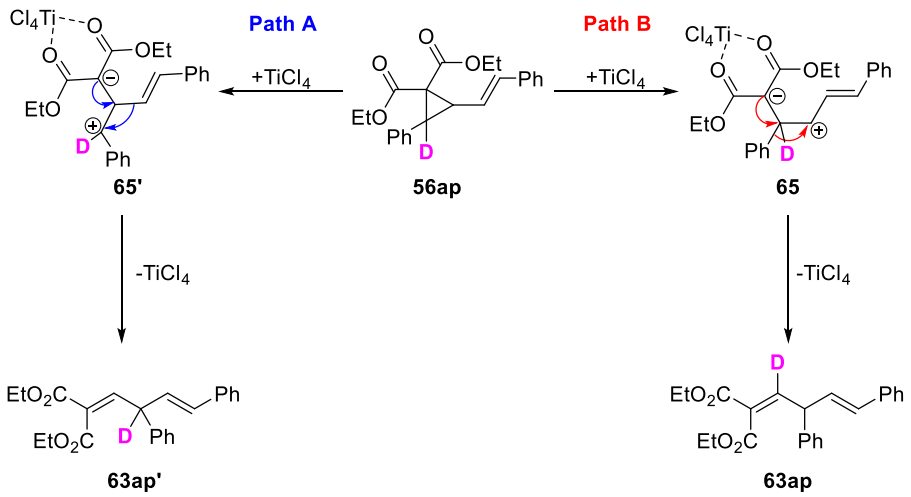
5.2.2 Proposed mechanism for the 1,4-diene formation

Regarding the formation of the unexpected 1,4-diene, we proposed two different mechanisms (Scheme 81). In both cases, the final product is the same and formed via a ring-opening step followed by a 1,2-migration but the two mechanisms differ by the nature of the bond of the VCP which will be broken and the group which will migrate.



Scheme 81

In order to discriminate these two mechanistic pathways, we used labelled VCP. Indeed, using deuterated VCP allows to distinguish products **63ap** and **63ap'** by NMR (Scheme 82).



Scheme 82

Hence, we carried out this experiment and we observed the presence of 1,4-diene (**63ap**) as the unique product. Hence, we conclude that only pathway B, where a phenyl group migrates, is taken by the VCP to afford the 1,4-diene.

5.2.1 Interconnection between the formation of the cyclopentene and the 1,4-diene

In order to get a better and more global understanding of the rearrangement of the VCP, we first performed a kinetic study by monitoring, by ^{1}H NMR analysis, the formation of the different species as a function of time (Chart 2).

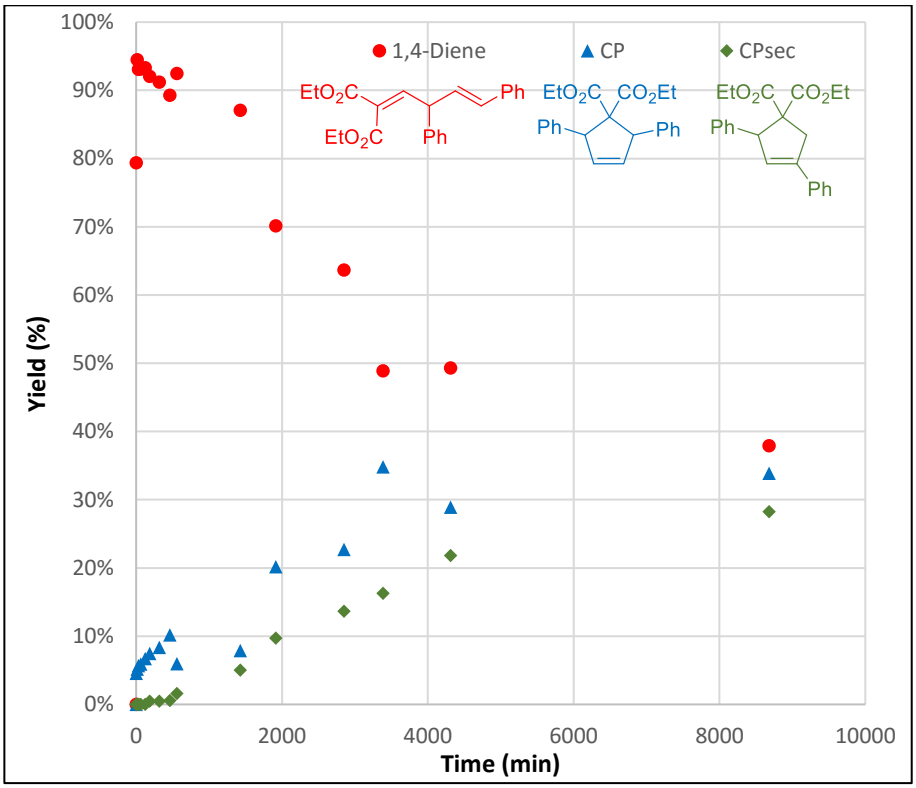
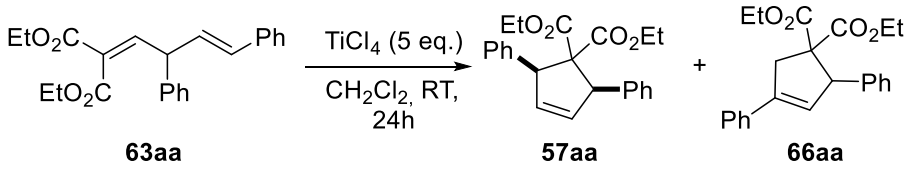


Chart 2: Kinetic study of VCP rearrangement toward 1,4-diene, CP and CPsec. Data have been obtained by ^{1}H NMR using DMT as an internal standard.

Interestingly, after 15 min, the conversion of VCP is already very high and the yield in 1,4-diene is close to 95%, whereas the yield of CP remains below 10%. Then, the yield in 1,4-diene is progressively decreasing in favor of CP and CPsec. We concluded that 1,4-diene formation is the fastest rearrangement reaction occurring in the media.

In order to decrease the rate and allow a more accurate analysis of the beginning of the transformation, we performed further experiments with fewer equivalents of $TiCl_4$. These experiments showed that the first and the fastest reaction occurring is, in fact, the VCP isomerization of the *cis*-isomer into the *trans*-isomer. Indeed, it has been shown that a quantitative isomerization of the *cis* isomer to the *trans* isomer can be obtained in less than one minute. These results are in good agreement with obtained computational results (see in the next subchapter).

Furthermore, an interesting fact is the decline of the 1,4-diene yield while the CP and CPsec yields are raising. This observation suggests that these two latter species are formed from 1,4-diene. This hypothesis was confirmed by an experiment where isolated 1,4-diene (**63aa**) is reacted with $TiCl_4$ and lead to CP (**57aa)** and CPsec (**66aa**) (Scheme 83).



63aa **57aa** **66aa**

Scheme 83

Besides that, we studied the obtained yield of 1,4-diene versus cyclopentene as a function of the number of $TiCl_4$ equivalents (Chart 3). One can see that for a low loading of $TiCl_4$ the yield of 1,4-diene is high whereas in order to rise the CP yield, it is necessary to increase the number of $TiCl_4$ equivalents. We understand that the formation of the CP is slower than the 1,4-diene formation and a higher concentration of Lewis acid is necessary to allow a sufficient rate for CP formation.

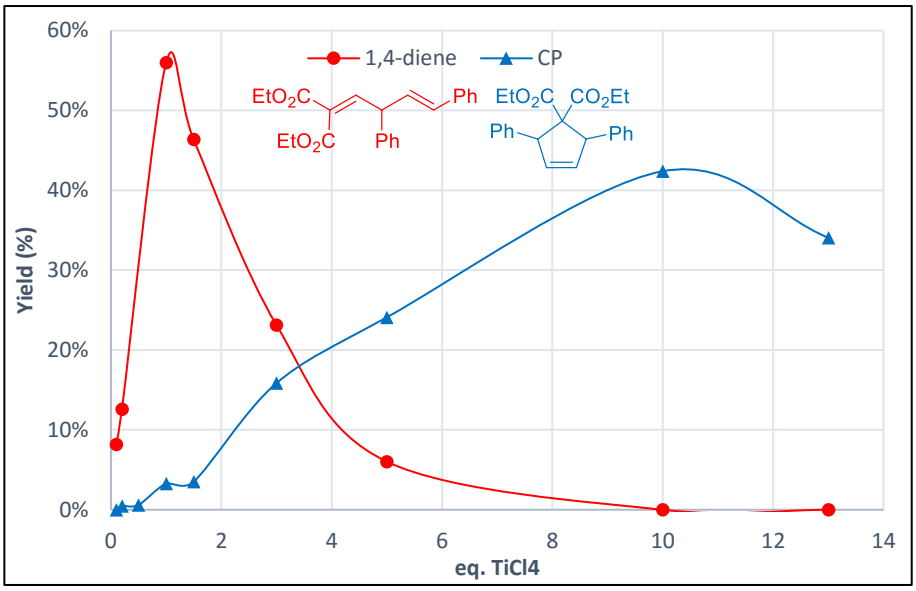
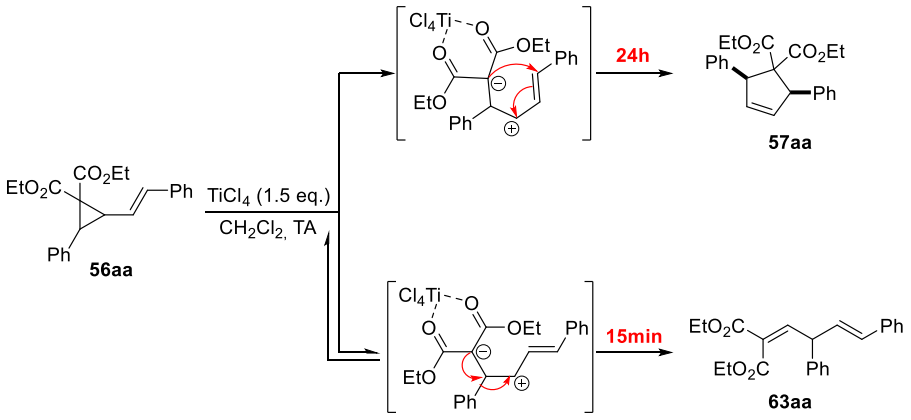


Chart 3: Yield of 1,4-diene and CP versus the number of $TiCl_4$ equivalent. Reaction conditions: CH_2Cl_2, RT, overnight. Data obtained by ^1H NMR with DMT as an internal standard.

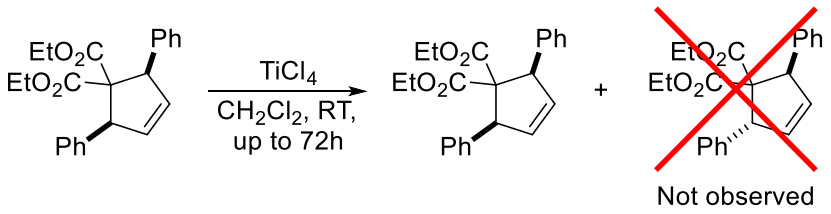
Based on these observations, we proposed the global mechanism depicted in Scheme 84. In this mechanism, the 1,4-diene would be the kinetic product and the CP and/or CPsec the thermodynamic product(s).



Scheme 84

Interestingly, we never observed the formation of the *trans* isomer of the CP. This could be explained either by the faster non-reversible formation of

the *cis*-isomer or the quick conversion of the *trans* isomer into the *cis* (kinetic or thermodynamic selectivity). Fortunately, thanks to theoretical calculation performed by Prof. R. Robiette, we concluded that the CP *cis*-isomer is both the kinetic and the thermodynamic product (Scheme 85). Therefore, the stability of this CP has been tested using $TiCl_4$ and it has been shown that no transformation or modification of the isomer ratio are observed in these reaction conditions and at this time scale.



Scheme 85

5.2.1 Proposed mechanism for the formation of the secondary cyclopentene (CPsec)

Beside the 1,4-diene and the desired CP, we were able to identify another side product which was actually formed during all our VCP rearrangements towards the CP (Figure 6).

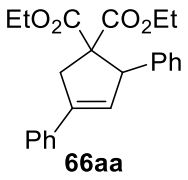
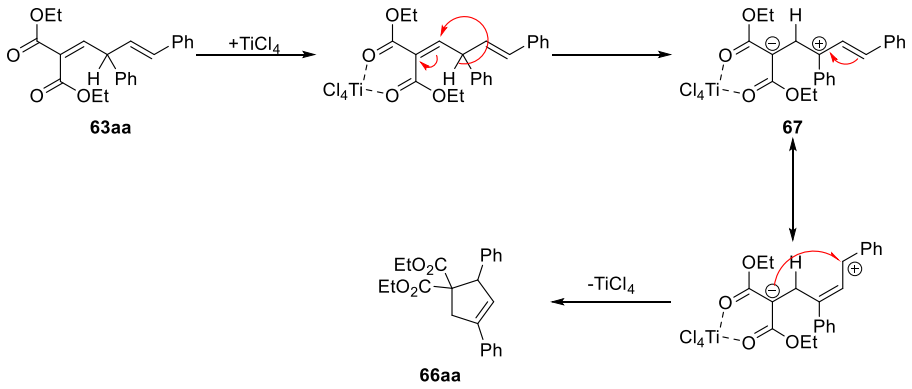


Figure 6: Observed secondary cyclopentene (CPsec) side product

We proposed a mechanism for the formation of this CPsec starting from the previously described 1,4-diene (Scheme 86). By reaction with the Lewis acid, the 1,4-diene can undergo a 1,2-migration of a hydrogen atom - and not a phenyl group - as it was the case heretofore for the CP formation.

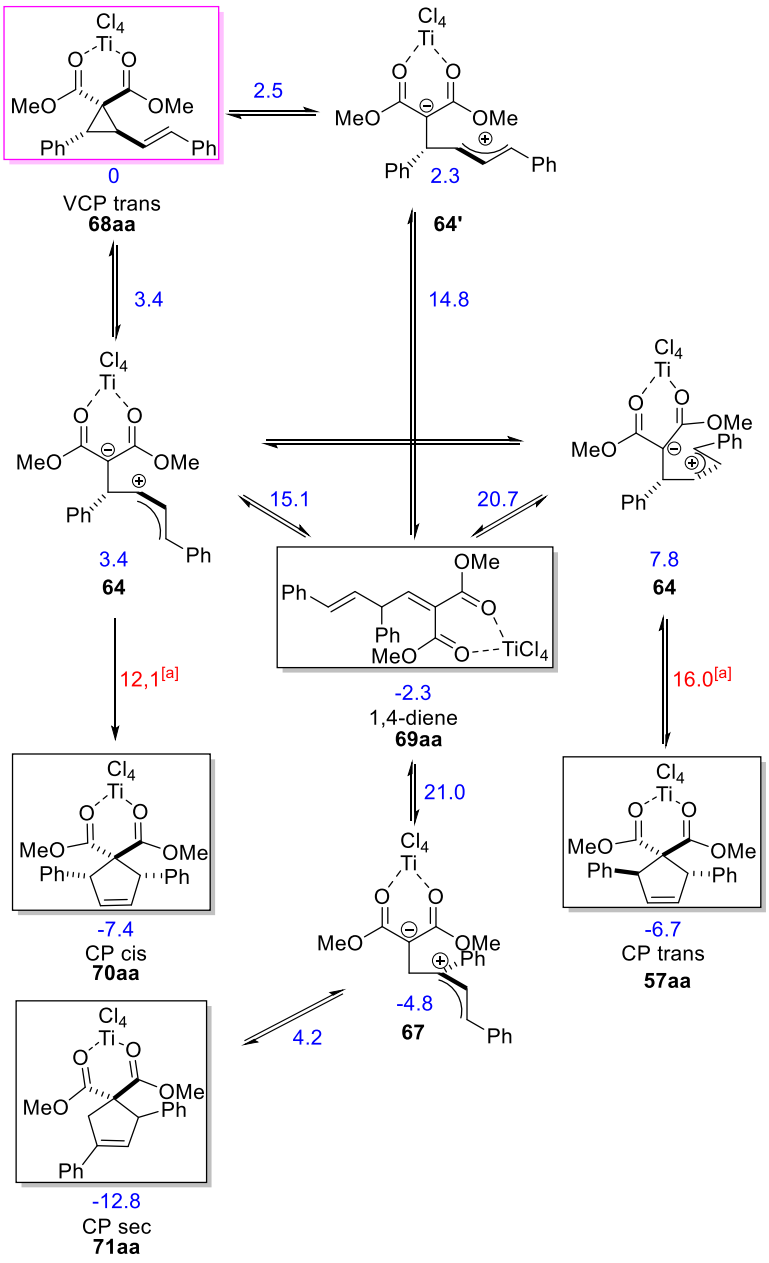


Scheme 86

A newly opened VCP intermediate is formed (**67**) and can ring close toward CPsec (**66aa**).

5.2.2 Theoretical calculations

In order to get a fundamental understanding of the considered system, a detailed computational study of the rearrangement of VCPs has been carried out by A. Delbrassinne (UCLouvain, Master thesis 2018). The different reaction pathways and corresponding computed free energies are repoted in Scheme 87.[110]



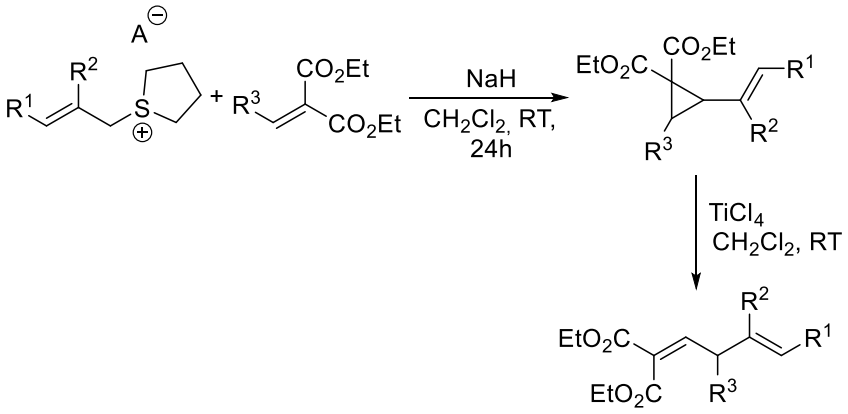
*Scheme 87 Proposed general mechanism with relative free energy (kcal/mol) values obtained at the B3LYP-D3/6-311+G**(CH_2Cl_2)//B3LYP-D3/6-31+G*(CH_2Cl_2) level of theory. (The full calculated mechanism is available in the appendix.) [a]: Benchmark calculations showed that these values are highly underestimated by the method used (by at least 8 kcal/mol). However, the difference between these two values can be interpreted since the errors are expected to cancel out.*

Computational results are in good agreement with our experimental observations and provide support to our proposed mechanism. Furthermore, these results show that the 1,4-diene is the kinetic product (barriers in red are underestimated). Indeed, it is formed rapidly through an overall barrier of 15.1 kcal/mol. And, as we hypothesized in the previous section, there is indeed a pathway from the diene to CPs which are more stable (thermodynamic products)

Finally, these calculations indicate that CP*cis* is formed faster (kinetic) and more stable (thermodynamic) than CP*trans*. However, CPsec is the most stable product (probably due to conjugation and less steric hindrance). Selectivity between the different CP must thus be kinetically controlled

5.3 Formation of 1,4-dienes

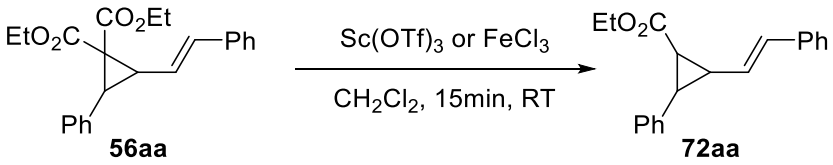
In the course of our work, we discovered the ability of VCPs to rearrange with a great efficiency into 1,4-diene bearing a substituent on the central carbon. Accordingly, we reviewed the literature and we understood that these 1,4-dienes constitute a great challenge in organic synthesis. Indeed 1,4-diene structures are part of many natural products exhibiting biological activities[44b, 98, 111]. However, only a few synthetic strategies toward this kind of structure are reported, especially when the central sp^3 carbon atom of the 1,4-diene is substituted[82a, 112]. Thus, we decided to develop a short and efficient methodology toward 1,4-dienes using our new rearrangement of VCP (Scheme 88).



Scheme 88

5.3.1 Development of the reaction conditions

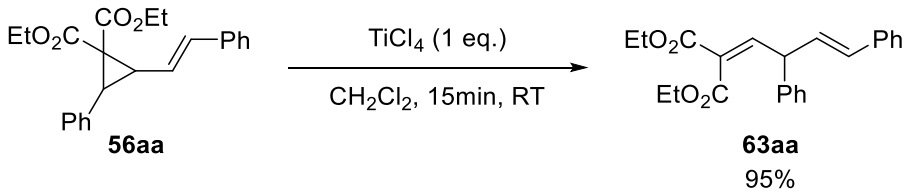
Thanks to the results previously obtained (see section 5.2), we quickly found optimal reaction conditions towards the formation of our reference 1,4-diene. Indeed, the kinetic study performed for the purpose of mechanism understanding showed us that the formation of 1,4-diene was completed after 15 min minutes. Furthermore, other tests allowed us to conclude that only one equivalent of $TiCl_4$ is required to form the desired product without any contamination by CP or CPsec. Other weaker Lewis acids such as $Sc(OTf)_3$, $FeCl_3$ have nonetheless been tested as potential milder substitutes of $TiCl_4$. However, only decarboxylated VCP (**72aa**) could be observed in these cases (Scheme 89).



Scheme 89

At this time, we do not have any convincing explanation for the formation of this side product as it will be discussed further in this work (see

5.3.2.3). Therefore, we kept the developed conditions reactions depicted in Scheme 90.



Scheme 90

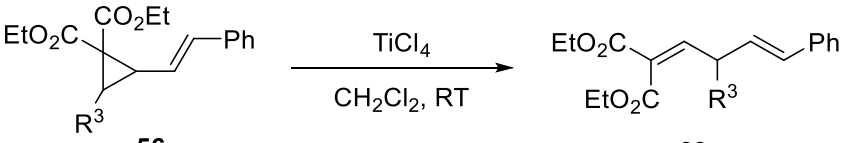
Because this mild methodology has shown considerable efficiency for the synthesis of our reference 1,4-diene, we envisaged the exploration of the scope of this methodology in order to allow the migration of various aryl, heteroaromatic and alkyl groups.

5.3.2 Exploration of the scope

In order to explore the scope of our methodology toward 1,4-dienes, we used various ylides and olefins to synthesize different decorated VCPs (Table 10). Then, these VCPs have been reacted with $TiCl_4$ to trigger the rearrangement and try to access the targeted 1,4-diene. Furthermore, with the aim of improving the efficiency of the reaction, some VCPs have been rearranged with reaction conditions that have been modified in terms of time, Lewis acid equivalents or both. The following subchapter is therefore split into four parts, each explaining the reactivity of a kind of substituted VCP.

5.3.2.1 Substitution of the olefin

This part gathers all the results obtained for the rearrangement of substituted VCPs synthesized from different olefins. The reaction of VCPs containing chlorine or bromine atoms will be discussed in a separate subchapter. Seven VCPs have been tested for the rearrangement into 1,4-dienes. The obtained results are reported in Table 10.

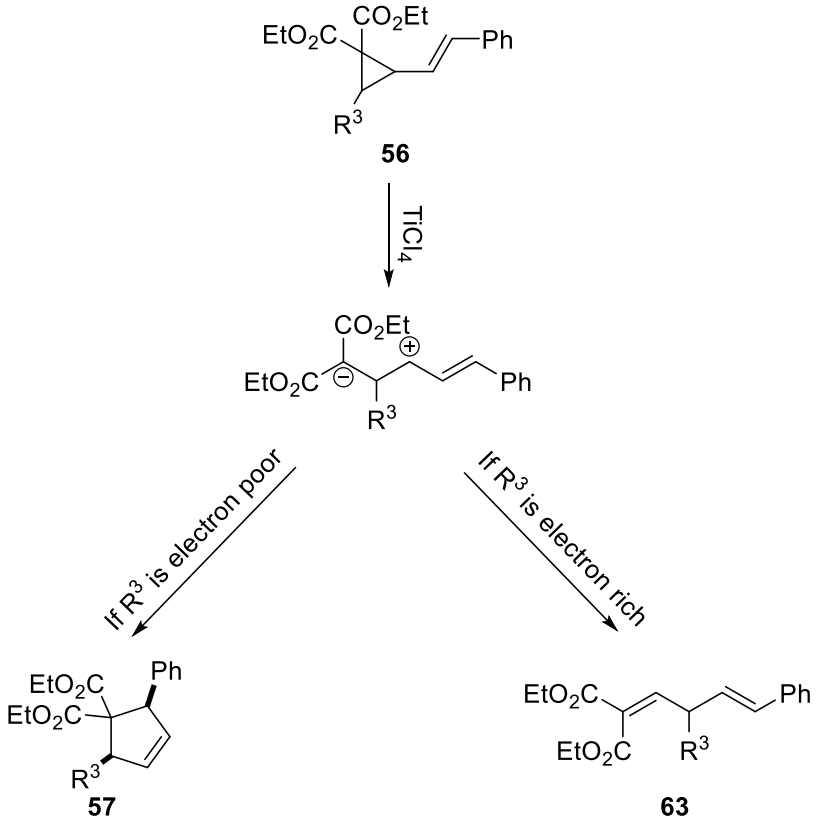


56 **63**

	R^3	Eq. $TiCl_4$	Yield (%)
63aa	Ph	1	95
63ab	*p*-MePh	1	95
63ac	*p*-MeOPh	0.4	Quant.
63ad	*p*-CO_2MePh	1	0[a]
63ae	*p*-FPh	1	71
63ah	2-Furyl	1	Quant.
63ai	1-Me-pyrol-2-yl	1	0 (degradation)
63ak	$(CH_3)_2CH$	1	0[a]

Table 10: [a] Only CPs have been observed (see 5.1.2). Reaction time depends on the substrate (see Chapter 7)

Various aryl substituted (R^3 = Ar) VCPs have shown a good efficiency toward the formation of 1,4-diene, especially when R^3 is an electron-rich group. However, when the aryl group bears strong electron withdrawing substituent, the yield decreases considerably for the benefit of CP formation. The electronic density of the aryl substituent thus has an influence on the nature of the preferred pathway (Scheme 91).



Scheme 91

If the migrating group is electron-rich one could expect a ring opening process occurring on the other side of the cyclopropane and observe the migration of the styryl group. However, a computational study led by A. Delbrassinne showed that even if the electron density is higher on R^3, the migration of this group remains more probable than the styryl group.[110] Indeed, as observed in pinacol and Wagner-Meerwein rearrangements, electron-rich aryl groups shows increased migratory aptitude as compared to electron-poor ones.[113]

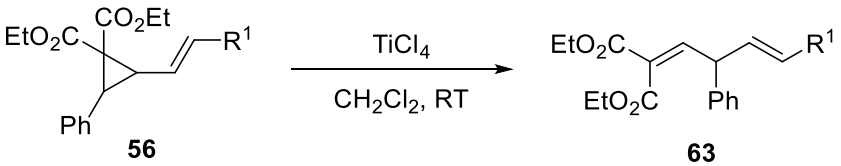
In the case of an electron-poor aryl substituent (R^3), the rate of the migration will be decreased (due to low migratory aptitude, *vide supra*) and therefore the cyclization reaction becomes competitive. In the case of a

strongly electron-withdrawing substituent on the aryl group such as p-CO_2Me, that is the cyclopentene which is exclusively formed.

The same reasoning holds for the attempts with the isopropyl derivatives. Indeed, alkyl groups are generally poorer migrating groups than aryl ones.

5.3.2.2 Substitution of the ylide

Various ylides have been used to synthesize VCPs bearing different substituents on their vinylic part. These VCPs were rearranged into their corresponding 1,4-dienes. Obtained results are summarized in Table 11.

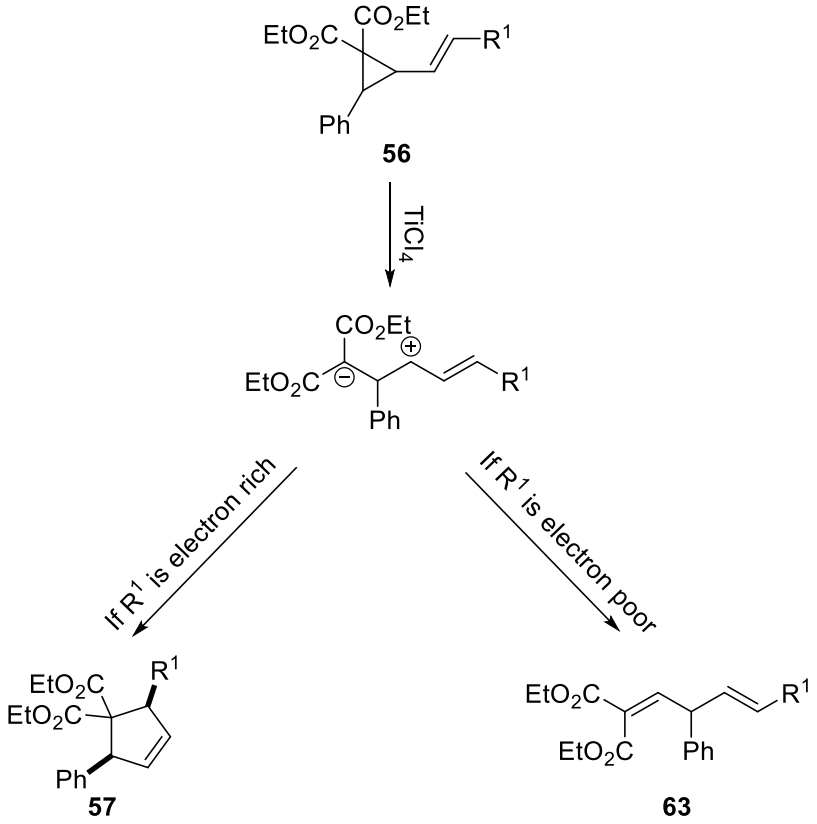


56 **63**

	R¹	Eq. $TiCl_4$	Yield (%)
63an	*p*-MeOPh	1	0[a]
63ao	2-Furyl	1	0[a]
63aq	*p*-CO_2MePh	1.5	Quant.
63da	*p*-MePh	1.5	40
63ea	$(CH_3)_2CH$	1.5	15 (90[b])
63fa	H	1.5	41[b]

Table 11: Obtained 1,4-diene via the rearrangement of VCP bearing substituents on the vinyl group R¹. [a] Only CP has been obtained. [b] Yield determined on the crude mixture by ¹H NMR, using DMT as an internal standard. Reaction time depends on the substrate (see Chapter 7)

Conversly to the previous subchapter (see 5.3.2), in this case, if the substituent R¹ is an electron-rich aryl group, the formation of the desired 1,4-diene is disadvantaged while the rearrangement toward the CP is favored (Scheme 92). These observations are in agreement with the mechanism proposed and can be explained by the fact that an electron-donating substituent decreases the rate of the migration step while the cyclisation is not significatively affected.

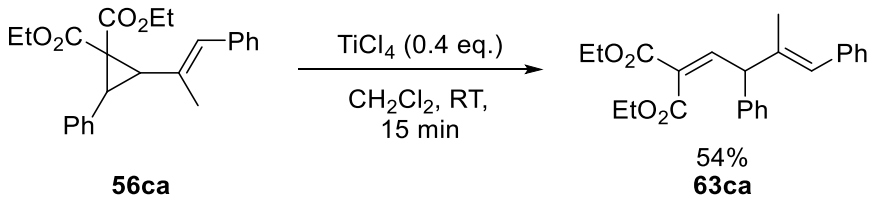


Scheme 92

In summary, regarding the electron density of the substituents, one can conclude that the accessible scope of the 1,4-diene synthesis is a function of the substituents borne by the VCP. Regarding substituents on the olefin (R^3), the more electron rich is the group, the faster the 1,2-migration will be. For the vinyl group, coming from the ylide, the poorer is the electron density of the substituent, the faster the formation of the 1,4-diene will be. However, a combination of these effects would impact the 1,2-migration in a much more complex manner and it would be probably the strongest effect that will control the rearrangement.

Besides the use of substituents with EDG or EWG, a more hindered VCP, bearing a methyl on the vinyl group, has been synthesized and rearranged into the corresponding 1,4-diene (Scheme 93). The success of this

rearrangement shows that it is possible to bring an additional substituent on the formed 1,4-diene in another position.

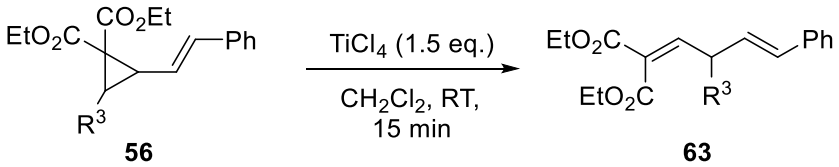


56ca **63ca**

Scheme 93

5.3.2.3 Rearrangement of halogenated VCPs

Halogen atoms have been introduced in VCPs in order to reach 1,4-dienes that would be good candidates for further derivatization reactions such as Suzuki cross-coupling or Heck reaction (Table 12).

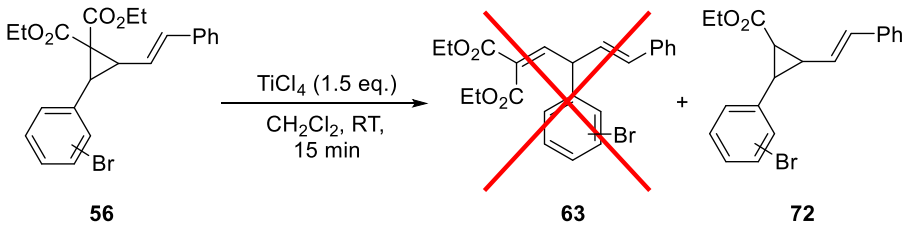


56 **63**

	R³	Yield (%)
63af	*p*-BrPh	20[a]
63ag	*m*-BrPh	27[a,b]

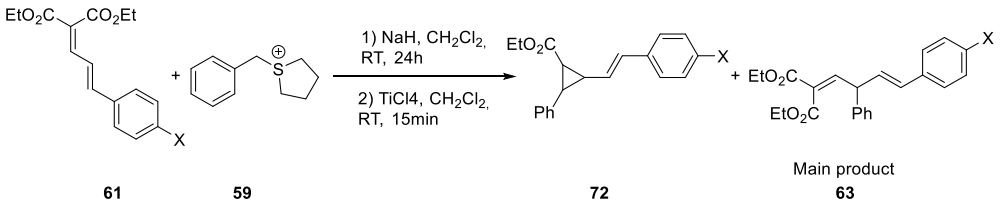
Table 12: [a] Yields have been estimated by ^{1}H NMR with DMT as an internal standard. [b] the product as been obtained in a mixture containing the corresponding CP

However, despite the different reaction conditions tested, yields in 1,4-dienes remained very poor. Actually, in VCP rearrangements where a halogen atom was included in the VCP, a complex mixture was obtained in which the main product was the corresponding decarboxylated VCP (**72**) (Scheme 94).



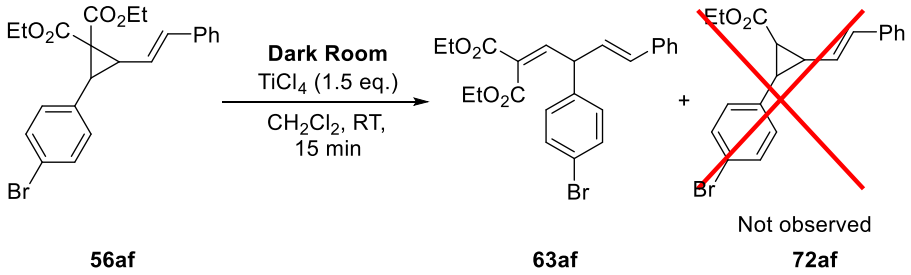
Scheme 94

Similar observations were made by A. Delbrassinne during his master thesis when he tried to form 1,4-dienes in a one-pot fashion from 1,3-diene and benzylic ylide (Scheme 95).



Scheme 95

Later, we tried to perform a VCP rearrangement in the absence of light in order to investigate if the decarboxylation process could be triggered by light (Scheme 96).



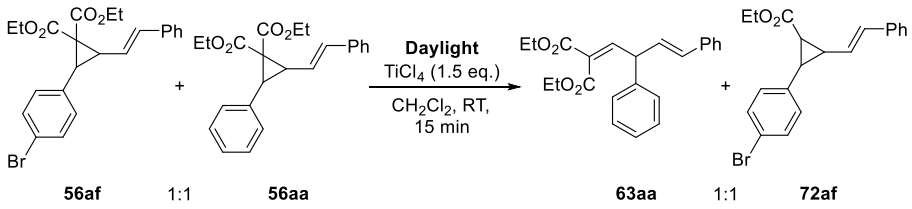
Scheme 96

Interestingly, when the rearrangement is performed in the dark, no decarboxylated VCP (**72af**) is observed and the major product is the desired

1,4-diene (**63af**). However, another undescribed product was also present in the reaction mixture.

Because carbon-halogen bond are well-known to be subject to homolytic cleavage upon photoactivation, we decided to investigate the possibility of forming a bromine radical. To do so, we performed the reaction under the daylight but in the presence of one equivalent of TEMPO as a radical scavenger. We observed that the presence of this radical scavenger favored the formation of 1,4-diene, even if the reaction was carried out in the daylight.

In order to test further our hypothesis, we rearranged a 1/1 mixture of reference VCP (**56aa**) and brominated VCP (**56af**) under daylight and without any radical scavenger (Scheme 97).



Scheme 97

We were surprised to observe that only the brominated VCP afforded the decarboxylated VCP while the reference VCP gave exclusively the 1,4-diene. This last experiment suggests that potential traces of Br• are not responsible for the observed formation of decarboxylated product.

Moreover, as previously mentioned (see section 5.3.1), the formation of decarboxylated VCP has also been observed on non-halogenated VCP when using other Lewis acids than $TiCl_4$, such as $Sc(OTf)_3$ or $FeCl_3$. Taking a look to the literature teached us that $Sc(OTf)_3$ has already been reported to be involved in photo-induced electron transfert and $FeCl_3$ can photo-trigger the decarboxylation of alkyl carboxylate[114]. Another interesting article reports the photo-decarboxylation of aryl carboxylic acids under visible light[115].

These reports do not constitute an effective explanation of our phenomena but remain a line of approach in order to improve the understanding of this phenomena.

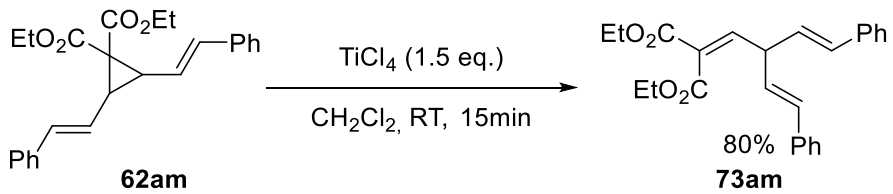
Despite the various tests performed and our review of the litterature, we remain unable to conclude regarding the mechanism involved in the decarboxylation process of halogenated VCPs. We did not try to go further in the investigations of this phenomena due to lack of time and in view of keeping focused on our targeted objectives. However, these observations remain intriguing and it would be interesting to pursue the investigation of this phenomena in the future.

5.3.3 Complementary methodology from 1,3-dienes

5.3.3.1 Synthesis of non-conjugated trienes

Because the rearrangement of VCPs turned out to be an efficient synthetic tool for accessing 1,4-dienes, we considered the extension of the reaction scope to the formation of non-conjugated trienes. Indeed, triene derivatives have been reported as potential antifungal, antibacterial and anti-tuberculosis compounds [116]. In addition, trienes compounds have been investigated by industrials[117] and found application in polymer science and as color dyes[118].

In order to produce the trienes, we started from a di-vinylcyclopropane (diVCP) instead of simple VCP (Scheme 98).

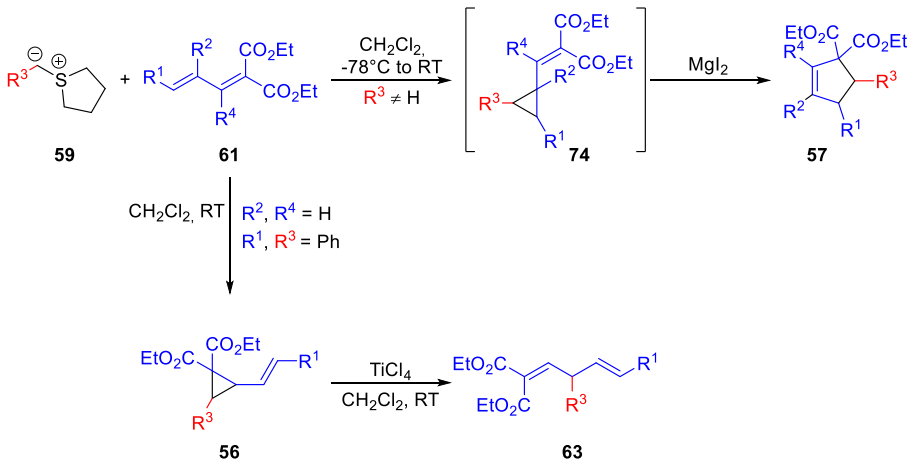


Scheme 98

In this case, the mechanism for accessing the 1,4-diene must involve the migration of a styryl group and therefore proove the possibility to push a styryl group to migrate. We tried to use a *p*-MeOPh group instead of a phenyl group but the obtained structure has not been confirmed yet. Furthermore, if one of the vinyl motif is substituted by a *p*-MeOPh group, one can reasonably think that the styryl group having the highest electron density would migrate. To prove this hypothesis, experiments with a labeled compound would be necessary.

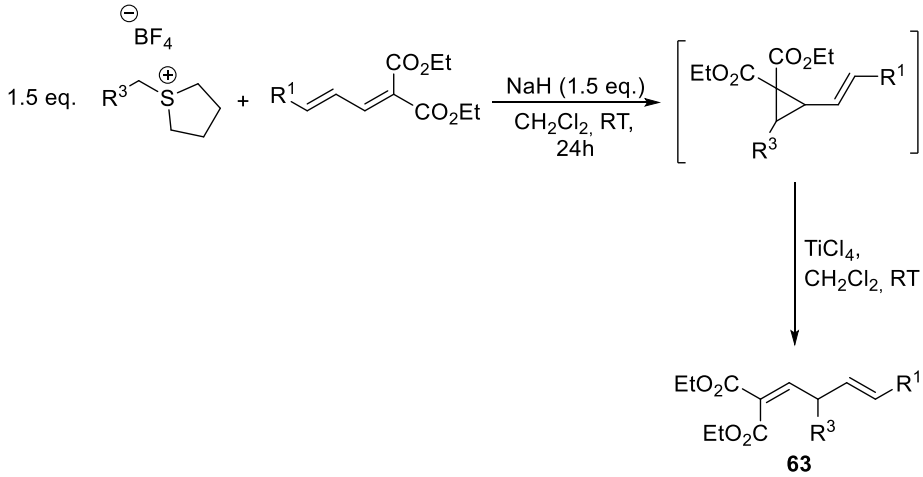
5.3.3.2 Using benzylic ylide

The methodology we have developed so far allows accessing 1,4-dienes (and CP) in two steps from activated olefin and allylic sulfur ylide via a VCP intermediate. We envisioned that this VCP intermediate could also be obtained from a 1,3-diene and a benzylic sulfur ylide. Indeed, in the course of the development of a (4+1) annulation strategy, we discovered that when one engages a less hindered 1,3-diene (R^2, R^4 = H) with a benzylic sulfonium ylide the same VCP intermediate as in our (3+2) methodology is obtained (Scheme 99).[25, 36, 101a]



Scheme 99

Accordingly, Arnaud Delbrassinne synthesized a series of 1,3-dienes and investigated their reaction with benzylic sulfur ylide during his master thesis.[110] In this case, the methodology was developed from the beginning as a one-pot strategy for minimizing the steps required for accessing the 1,4-diene (Table 13). Interestingly, in this case, no strong poisening effect of the $TiCl_4$ were observed.



	R¹	R³	Eq. $TiCl_4$	Time	Yield
63aa	Ph	Ph	1	15 min	90
63ab	*p*-MePh	Ph	1	20 min	95
63ac	*p*-MeOPh	Ph	0.4	15 min	95
63ae	*p*-FPh	Ph	1	75 min	43[b]
63ah	Ph	2-Furyl	1	15 min	0[a,c]
63an	Ph	*p*-MeOPh	0.1.	15 min	0[a]
63aq	Ph	*p*-CO_2Me	1	30 min	0[a]

Table 13: *[a] only the cis isomer of the CP has been identified in a mixture containing another product that we attributed to the trans isomer of the CP. [b] Yield determined on the crude mixture by ^{1}H NMR using an internal standard [c] CP yield is equal to 86%*

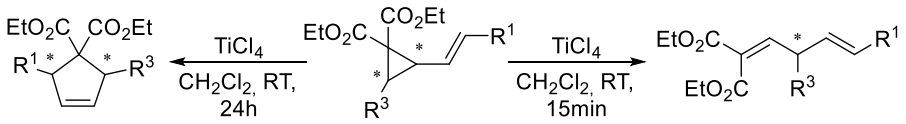
One observes the formation of the desired 1,4-diene with a high yield in our reference case, i.e. with two phenyl groups. However, when a electron-donating substituent is set on the R¹ position, the selective formation of CP

is observed. These results are in agreement with the computational study performed by A. Delbrassinne.

This methodology is complementary to our methodology using allylic ylides. Indeed, this strategy allows to form VCPs which have been reported to be hardly reachable via allylic ylides such as **63ah**.

5.4 Development of an asymmetric version of our methodologies

The rearrangement of a VCP bearing substituents different than hydrogen atoms (R^1, $R^3 \neq H$) can lead either to a CP containing two stereogenic centers included in the carbo-cycle or to a 1,4-diene containing a central asymmetric carbon atom. Accordingly, we became interested in developing an enantioselective version of our methodologies (Scheme 100).



Scheme 100

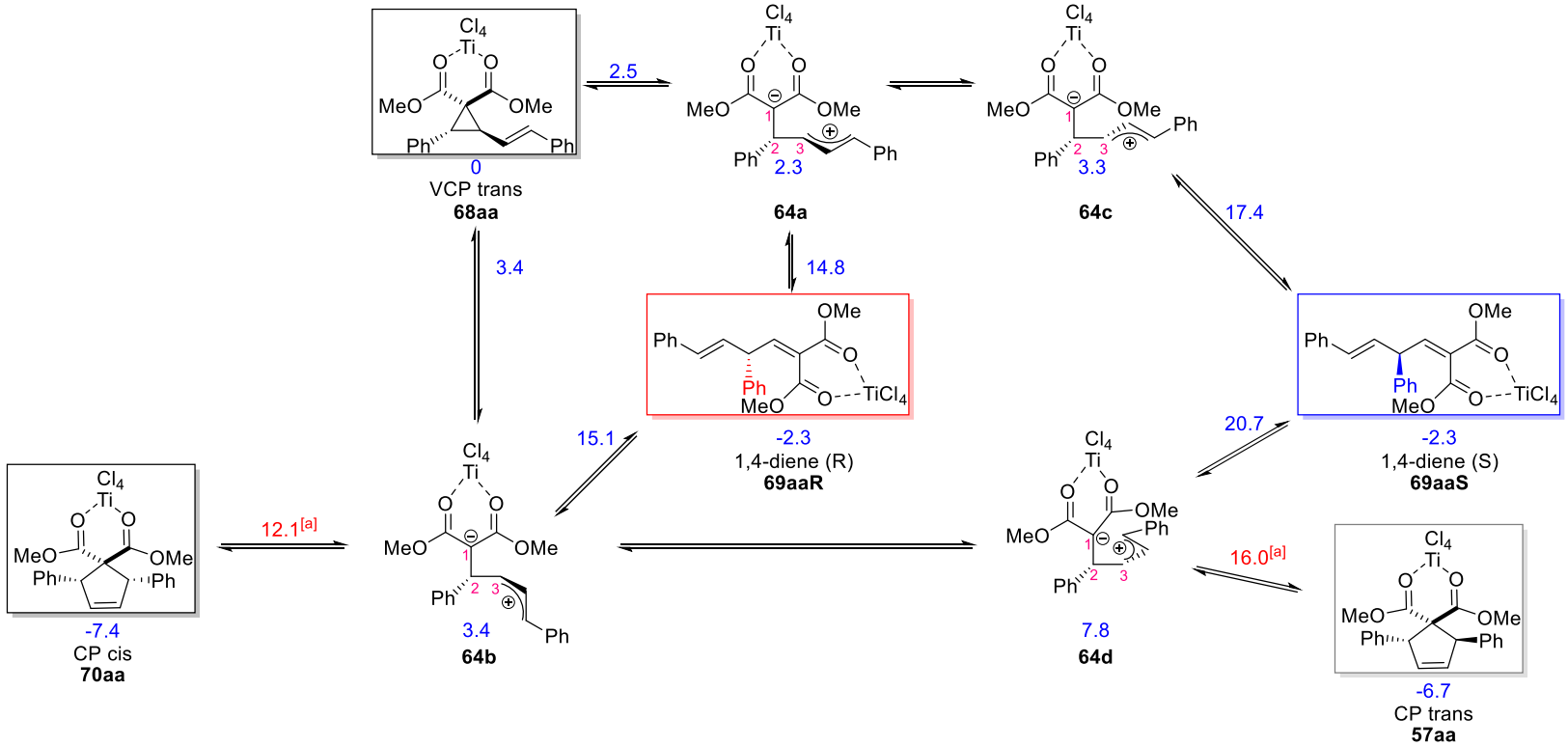
The ideal scenario would be to develop a common asymmetric strategy based on the control of the VCP stereoselectivity. Indeed, Aggarwal has developed chiral sulfonium ylides enabling highly enantioselective formation of three member rings.[37-38, 103] Our research group has already showed that this strategy could be efficiently applied to the synthesis of VCPs.[101a] However, the development of asymmetric methodologies from enantio-enriched VCPs requires a rearrangement step to CP or the 1,4-diene which is stereospecific. Therefore, during his master thesis, A. Delbrassinne has studied this latter aspect via computational studies.

5.4.1 Theoretical study of the rearrangement stereospecificity

We have shown experimentally that the conversion of the *cis* isomer of the VCP to the *trans* isomer is very fast in the presence of $TiCl_4$ and occurs before any rearrangement process (see section 5.2.15.2.2). Hence, in order to simplify the system, we consider that the VCP rearrangement towards 1,4-diene or CP takes place exclusively from the *trans* isomer of the VCP.

Regarding the 1,4-diene, two different enantiomers can potentially be obtained from the enantiomer of the VCP (**68aa**) (Scheme 101). Indeed, zwitterion intermediates directly formed from the opening of the cyclopropane ring **64a** and **64b** will lead to enantiomer *R* of the 1,4-diene (**69aaR**) (after migration of the phenyl group). However, these intermediates can also undergo a conformational equilibrium around the C_2-C_3 carbon bond to yield **64c** and **64d**. The migration of the phenyl group from these conformers would lead the the other enantiomer of the 1,4-diene (**69aaS**). Interestingly, computed free energy barriers indicate that the phenyl migration in **64a** and **64b** should be much faster than the one from **64c** or **64d** ($\Delta G^{\ddagger}$ = 14.8 and 17.4 kcal/mol, respectively), predicting a 99/1 ratio at room temperature. According to these computational results, the rearrangement of VCP into 1,4-diene should thus be highly stereospecific.

Regarding the formation of the CP, a complete diastereoselective rearrangement was observed with exclusive formation of the CP *cis* which comes from intermediate **64b**. The stereochemistry of the stereogenic center C_2 being not affected by the rearrangement, the reaction of one enantiomer of the VCP should thus lead stereospecifically to one CP *cis*.



Scheme 101: [a] Benchmark calculations showed that these values are highly underestimated by the method used (by at least 8 kcal/mol). However, the difference between these two values can be interpreted since the errors are expected to cancel out

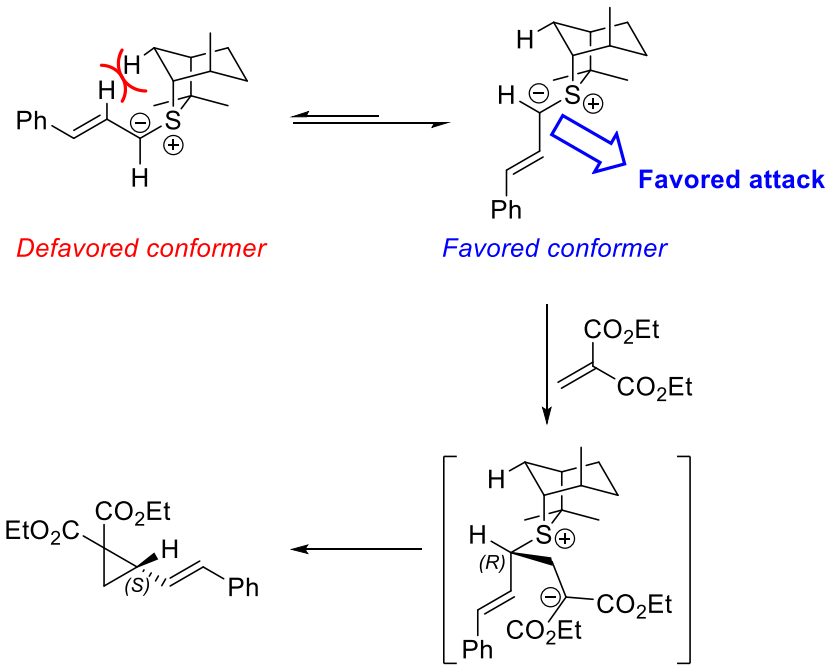
Therefore, in order to take up the challenge of developing a stereoselective version of our methodology we must focus our work on the control of the stereochemistry of the carbon C2.

5.4.2 Utilization of enantiomerically enriched VCPs

In order to produce enantio-enriched VCPs, we used the chiral auxiliary developed by Aggarwal as explained in section 4.1.4 of this document[103]. Two possibilities have been envisaged. First, the use of a chiral allylic sulfur ylide with an activated olefin, and second the reaction of a chiral benzylic sulfonium ylide with a 1,3-diene. In order to allow a comparison of the two methods, the following sections will describe each method before comparing them.

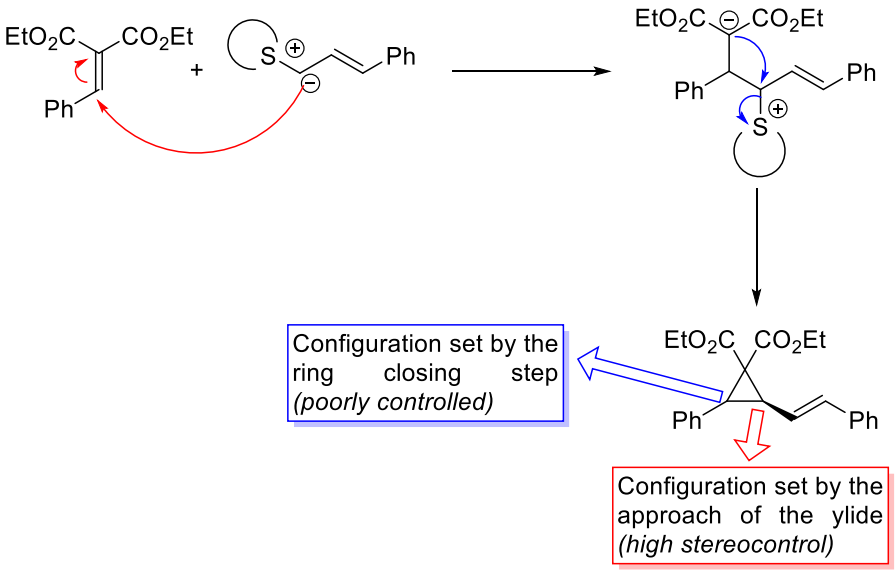
5.4.2.1 From allylic sulfonium ylide and activated olefin

If one looks at the mechanism of the cyclopropanation reaction, one understands that the absolute configuration of the carbon coming from the ylide is set during the addition of the ylide on the olefin. As shown by Aggarwal, when a chiral auxiliary is used, only one face of the ylide is available for an attack on the olefin and the carbon of the ylide becomes defined by a specific absolute configuration (Scheme 102).[103] This is also supported by the very high enantioselectivity observed by our laboratory during the development of a (4+1) annulation strategy (see Chapter 2).[101a, 108]



Scheme 102

The absolute stereochemistry of the other asymmetric carbon of the VCP is determined by the nature of the face of the olefin which is attacked by the ylide (the ring-closure consisting of an intramolecular S_N2 reaction, thus being stereospecific). This step is less controlled as shown by the observation of a mixture of two diastereoisomers (6/4) (Scheme 103).



Scheme 103

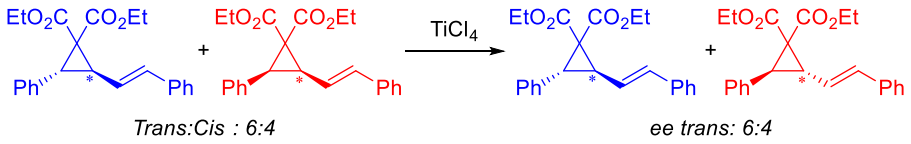
Therefore, this reaction of VCP formation is supposed to provide two diastereoisomers with only one enantiomer for each in the best case (Figure 7).

Trans:Cis : 6:4

Figure 7

However, as previously explained (see section 5.2.1), the fastest reaction occurring during the rearrangement with $TiCl_4$ is an isomerization of the VCP *cis* isomer into the *trans* isomer. Moreover, thanks to the computational studies of A. Delbrassine, we know that isomerisation occurs via breaking of the carbon-carbon bond "b" – and not "a". Therefore, isomerization changes the absolute configuration of the allylic stereogenic carbon center, i.e. the one well-controlled by the stereoselective attack of the ylide (vide supra),

whereas the benzylic asymmetric carbon, whose stereochemistry is poorly controlled during the cyclopropanation, is not affected (Scheme 104).

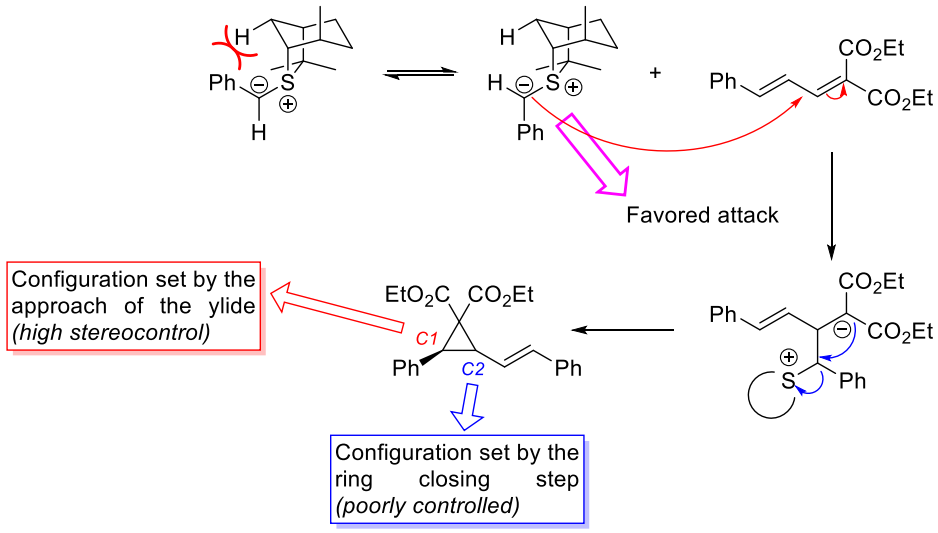


Scheme 104

Consequently, isomerisation will transform the 6:4 mixture of the *trans* and *cis* diastereomers into a 6:4 mixture of the two enantiomers of the *trans* VCP. Thus, even in the case of a highly stereospecific rearrangement reaction, overall a poor enantioselectivity is expected.

5.4.2.2 From benzylic sulfonium ylide and activated 1,3-diene

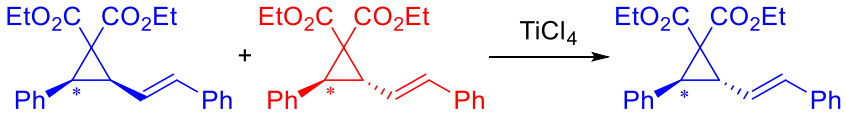
The second cyclopropanation strategy, using a benzylic ylide and a 1,3-diene, allows reversing the setting order of the asymmetric carbons of the VCP as compared to the first strategy discussed in the previous section (Scheme 105).



Scheme 105

In this case, the configuration of carbon C1 which is well controlled whereas the C2 configuration is poorly controlled due to the establishment of this latter by the nature of the face of the diene which is attacked.

Accordingly, in this case, the obtained mixture of diastereomers should isomerizes under the rearrangement conditions into VCP-*trans* without any decrease of the enantioselectivity (Scheme 106).



Scheme 106

5.4.2.3 Comparison between the two pathways for VCP formation

From the analysis made in the two previous sections, it is clear that the strategy from benzylic ylides is more promising for developing an enantioselective version of our methodologies. Indeed, in this method the absolute stereochemistry of the benzylic stereocenter in the VCP should be

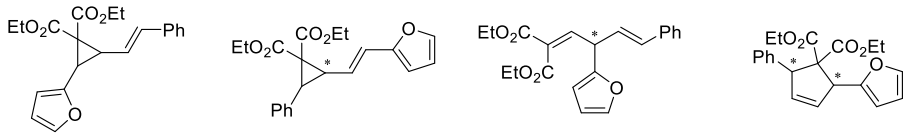
well-controlled and the epimerization of the VCP-*cis* into VCP-*trans* will lead to VCP-*trans* without decrease in enantioselectivity. The stereospecific rearrangement reactions should then lead to CP or 1,4-diene in high enantioselectivity.

In conclusion, the benzylic ylide method should be the most efficient between these two methods for the development of an enantioselective version of our methodologies.

5.4.2.4 Experimental results

In order to measure the enantiomeric excess we considered a method via chiral HPLC. However, despite our hard work on the development of a separation method of the different enantiomers and diastereoisomers of the VCP, we faced many problems for developing an efficient separation method. Indeed, separating enantiomers and diastereoisomers of the classical VCP bearing only phenyl groups have turned out to be very tricky. The separation of 1,4-diene was found to be complex too and we did not succeed in developing a unique and efficient separation method for the reference VCP (**56aa**) and 1,4-diene (**63aa**). Hence, we considered using other VCPs bearing other substituents than just phenyl groups .

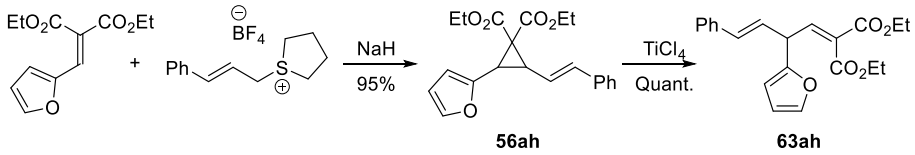
The best candidates we found (yield and clearness of the crude mixture) were the derivatives with a 2-furyl group replacing one of the two phenyl substituents (Scheme 107).



Scheme 107

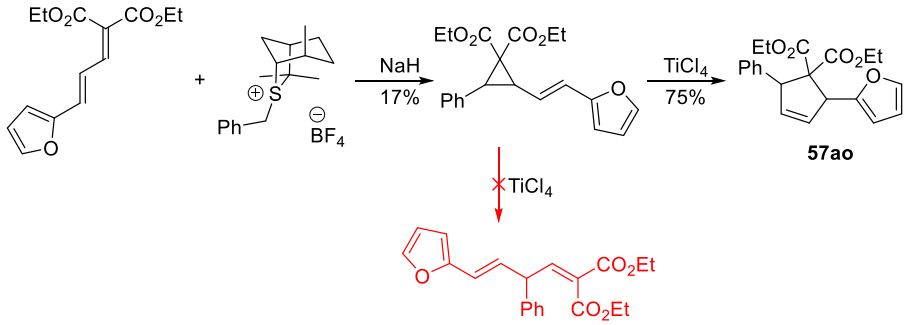
Therefore, we attempted to synthesize these compounds for developing an accurate and reproducible HPLC method. To do so, we first used our

methodology based on allylic sulfonium ylide (Scheme 108). This allowed us to isolate VCP **56ah** and 1,4-diene **63ah**.



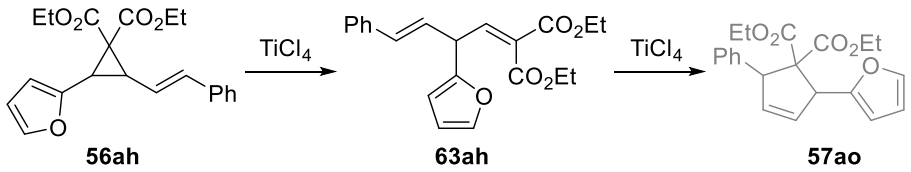
Scheme 108

Later, we used the most promising methodology (see 5.4.1) with benzylic ylide to access the corresponding dienes (Scheme 109). However, when we attempted to rearrange the VCP formed via this benzylic methodology, we observed the exclusive formation of the corresponding cyclopentene **(57ao)**.



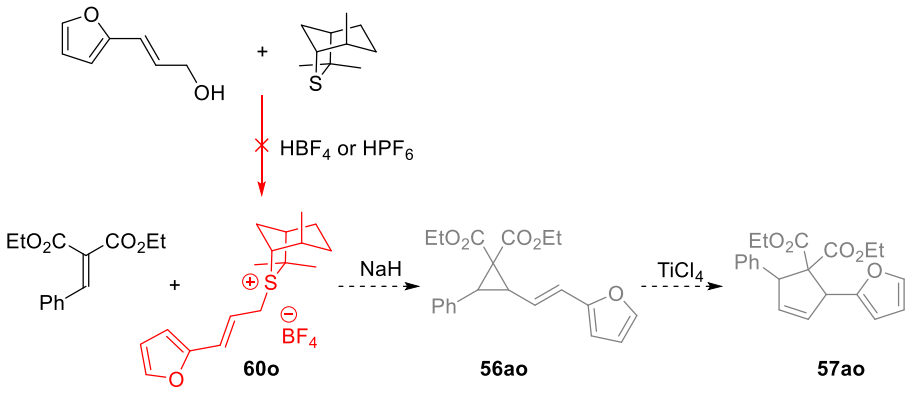
Scheme 109

Therefore, in order to access **57ao** via the methodology involving allylic ylide (Scheme 108) and be able to compare the obtained *e.e.*, we proposed to pursue the rearrangement of the 1,4-diene **(63ah)** to obtain the desired cyclopentene (Scheme 110). However, we did not observed a sufficient conversion of the diene in a reasonable scale of time.



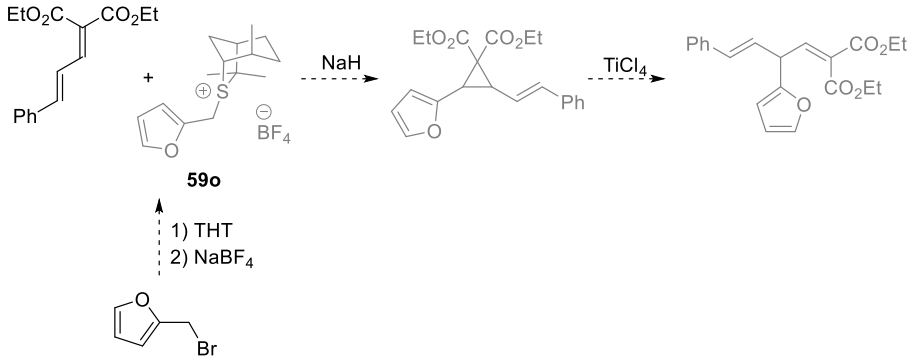
Scheme 110

Thus, we envisioned that it should be possible to get VCP **56ao** and cyclopentene **57ao** using the allylic salt **60o** (Scheme 111). Unfortunately, we never succeeded in forming this salt and therefore to compare the cyclopentene *e.e.* of the two strategies.



Scheme 111

The comparison of the *e.e.* for the formation of a 1,4-diene between the two strategies, was also not possible since only the allylic strategy allowed to acces the desired 1,4-diene (Scheme 108). The only possibility using the benzylic strategy that would lead to the same 1,4-diene **(63ah)** would be to synthesize the corresponding furyl sulfonium salt **(59o)** (Scheme 112). However, due to a lack of time and the availability of the starting product, we did not had the chance to test this possibility.



Scheme 112

In conclusion, the development of an efficient separation method by flash column chromatography and then chiral HPLC took us a long time and turned out to be very complicated in term of product synthesis. Therefore, no conclusive test for measuring *e.e.* on rearranged enantiomerically enriched samples could be performed by the end of this thesis. Despite the numerous problems we faced (high separation dependence to the temperature, similar λ_{max} for all compounds, etc.) an efficient and reproducible method of HPLC analysis has been elaborated for the following compounds:

- Diastereoisomers and enantiomers of the VCP **(56ah)** and **(56ao)** (Figure 8)

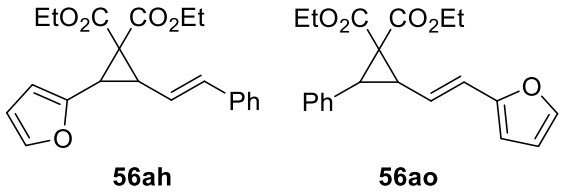
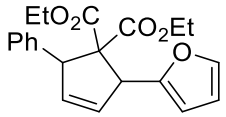


Figure 8

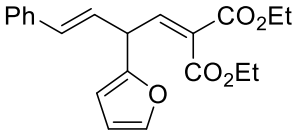
- Enantiomers of the CP **(57ao)** (Figure 9)



57ao

Figure 9

- Enantiomers of the 1,4-diene **(63ah)** (Figure 10)



63ah

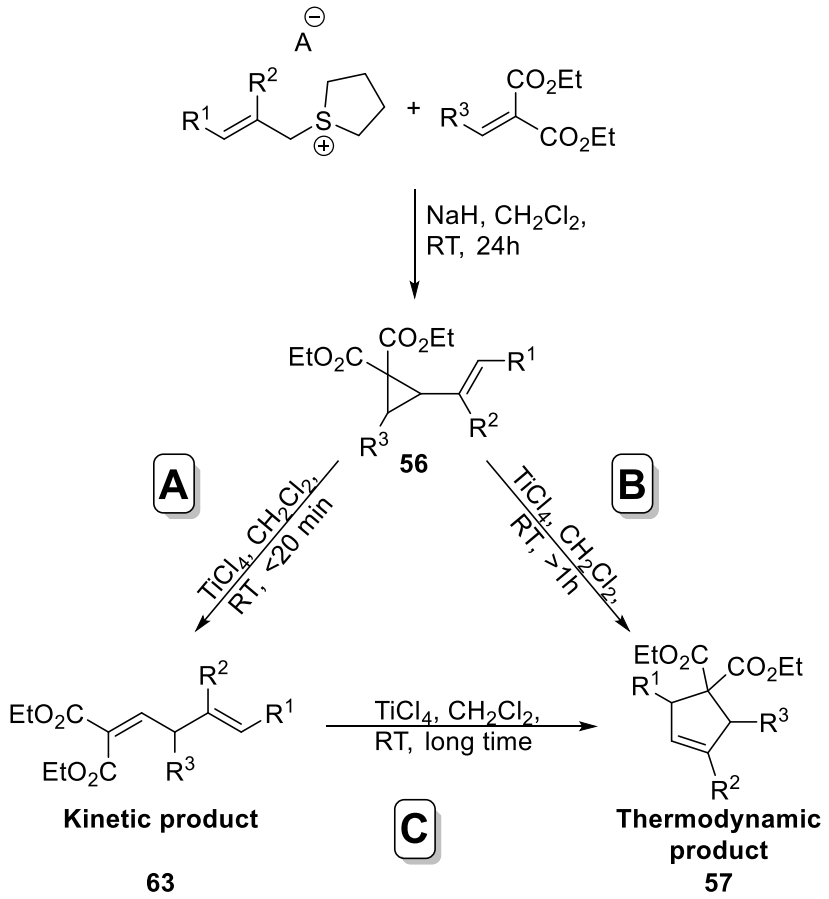
Figure 10

The details of these methods are provided in the experimental section of this work.

DEVELOPMENT OF AN ASYMMETRIC VERSION OF OUR METHODOLOGIES

Chapter 6 Conclusions and perspectives

Following the (4+1) methodology developed these last years by our laboratory, we have successfully developed a divergent and selective methodology for accessing cyclopentenes (Scheme 113, path B) or 1,4-dienes (Scheme 113, path A) through the rearrangement of a common VCP formed from an activated olefin and an allylic sulfonium ylide. A clear understanding of the mechanism of processes involved allowed us to control selectivity by changing reaction conditions (mainly reaction time) and obtain, at will, either the CP or the 1,4-diene.



Scheme 113

Next, we studied the scope and limitations of these methodologies. We produced eight new cyclopentenes and nine new C3-substituted 1,4-dienes. These studies showed that if an EWG is set on the R^1 position of the VCP, the cyclization of the zwitterionic intermediate becomes faster than the migration process, thus leading directly to the CP, even after short reaction time. However, regarding the scope of substituent possibilities for R^3 remains limited toward 1,4-diene. Indeed, at this time only aromatic rings have shown a good efficiency in the migration process. Regarding the formation of the CP, the scope of possibilities for R^3 is broader and alkyl substituents are allowed. Conversly, regarding the rearrangement of halogenated VCPs, we reported an unexpected decarboxylation of the starting compound. Even if many different experiments have been carried out in order to enlight us on what is happening, so far this unexpected reactivity remains misunderstood.

During our investigation, the more we gathered results, the more the system turned out to be complex. Therefore, in order to enhance our understanding of the studied system, we carried out a series of test experiments as well as a computational study (A. Delbrassinne) that allowed us to develop a theoretical model fitting correctly with the experimental observations. We showed that the 1,4-diene is in fact the kinetic product while the CP is the thermodynamic product (Chart 4). Additionally, this model provided insights into the origin of the CPsec product.

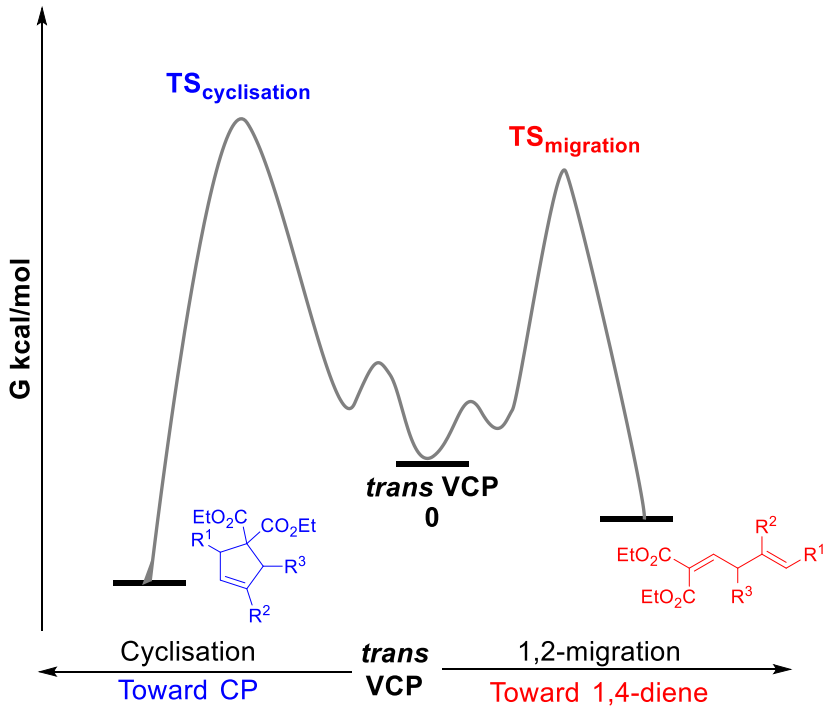
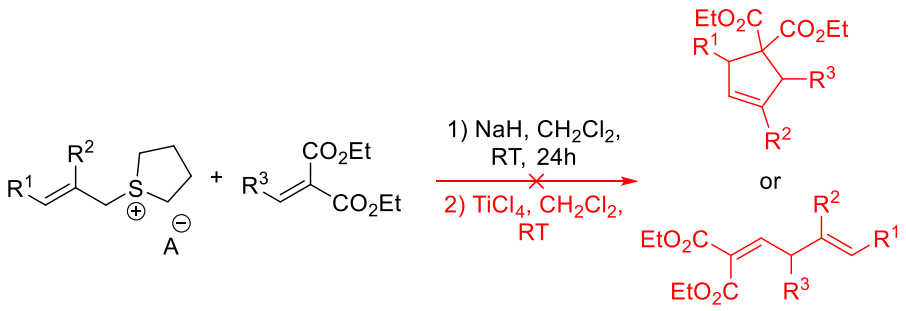


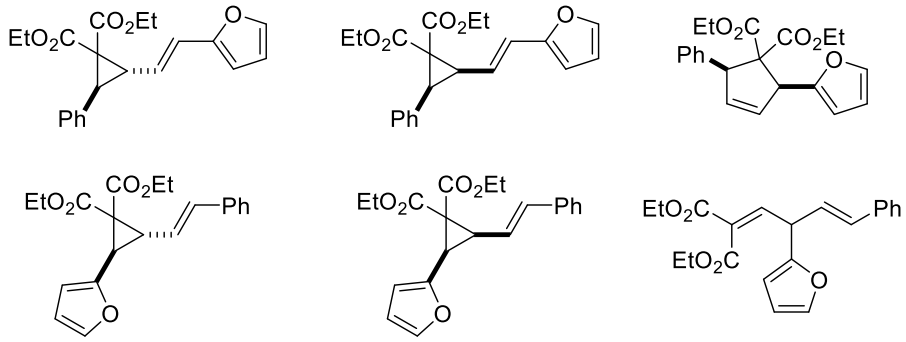
Chart 4

Concerning the development of a one-pot version of our methodology, unfortunately, we did not obtained encouraging results. Indeed, we observed a possible quenching of the zwitterionic intermediate imputed to the released sulfide (Scheme 114). Therefore, this idea of developing a one-pot version has been left aside without further improvement.



Scheme 114

Besides that, we focused on the development of an asymmetric version of our methodologies. We first worked on finding a suitable analytical separation procedure via HPLC enabling *e.e.* measuring. Several tests were performed on various VCP, CP and 1,4-diene derivatives. Despiste our hard work we faced many problems particularly on the synthesis of the required products. Eventually, we successfully determined a separation method for the products bearing a furanyl group (Scheme 115).



Scheme 115

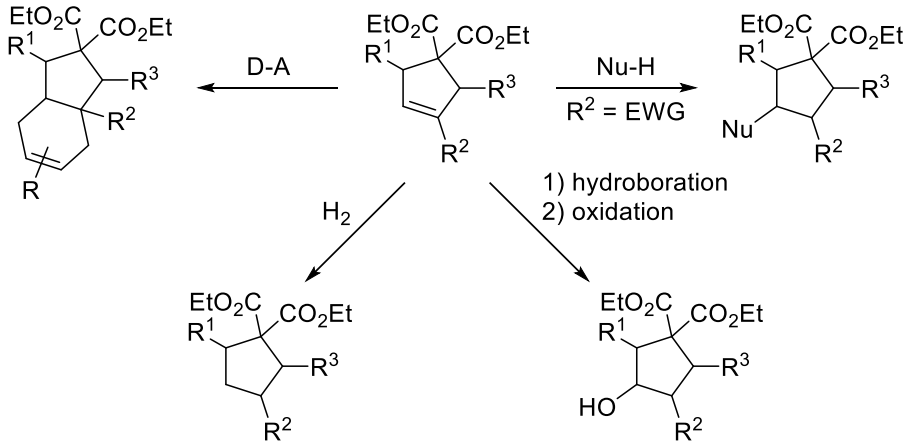
Despite the encouraging results obtained, we did not get enough time to go further in the investigation and development of an enantioselective methodology. However, this point remains very interesting and A. Delbrassinne will continue the development of such a method during his Ph.D. thesis.

In conclusion, our strategy constitue a novel interesting method to synthesize cyclopentenes and especially 1,4-dienes. Indeed, as shown in the section 1.3 of this work, the synthesis of these later compounds remains a real challenge in organic chemistry and frequently involves a toxic or/and expensive catalyst. Furthermore methodologies for accessing 1,4-dienes generally do not show a broad reaction scope and are tarnish by a poor atom economy. Therefore, our methodology constitue a real solution for the synthesis of these non-conguated 1,4-dienes. Indeed our strategy allow accessing C_3 substituted, terminal and non-terminal 1,4-diene with a great

efficiency and in only two steps from readily available reactants. In addition, our rearrangement process benefit from a strong atom economy. Even the cyclopropanation step can spare atoms by recovering and recycling the sulfurated auxiliary as it as been already reported by Aggarwal.[38] Finally the capacity of our system to be divergent add a really valuable asset to our method in these time of acute necessity of material economy.

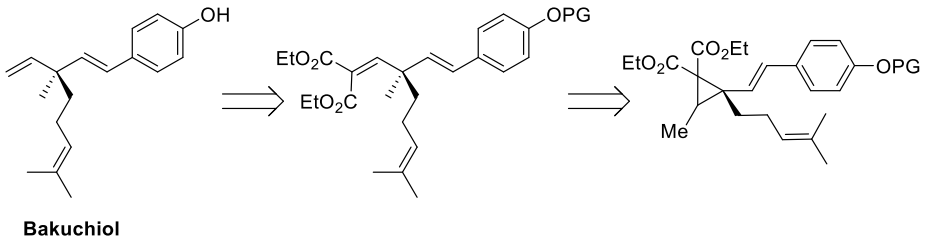
Even if the mechanism of observed rearrangement and the scope of our methodologies is now well understood, There are many investigations which could be done in order to further enhance our understanding of the different processes and the usefulness of the developed strategies:

A. The first point which would be interesting to investigate is the derivatization of formed CPs (Scheme 116). Actually, this point was part of our initial objectives but because of a lack of time and the change in initial goals during our thesis, we did not get the opportunity to pursue this goal. Obviously, as for the CPs, demonstrating the usefulness of the strategy for synthesizing 1,4-diene would also be interesting.



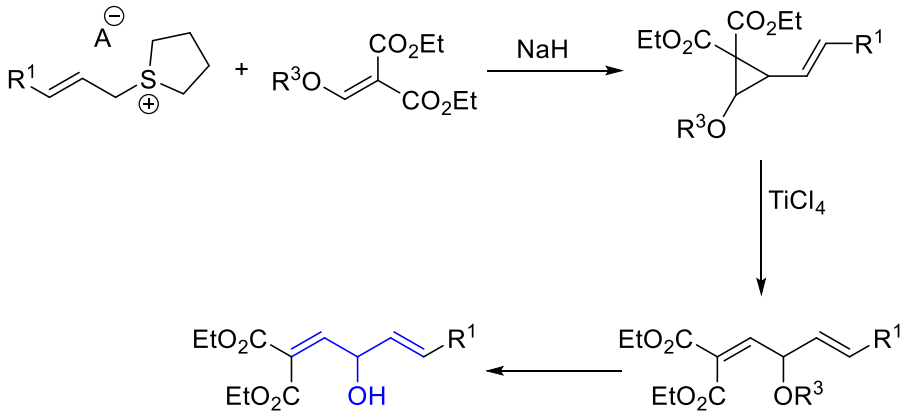
Scheme 116

B. In view of demonstrating the usefulness of our strategy, it would also be interesting to apply it to the synthesis of a natural compound even if this point could be achieved only after further improvement of our methodology. The bakuchiol would be a good candidate for such a synthesis (Scheme 117).[119]



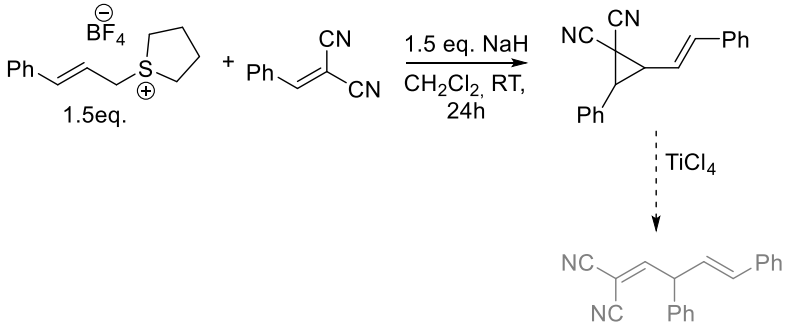
Scheme 117

C. Another interesting idea would be to investigate the possibility of generating a 1,4-diene bearing an alkoxy group (Scheme 118). Indeed, the presence of an alkoxy group on the VCP would have to facilitate the ring opening and the migration of the styryl group. Then, the ether function of the obtained product could be cleaved to provide the corresponding di-allylic alcohol providing a further reactivity.



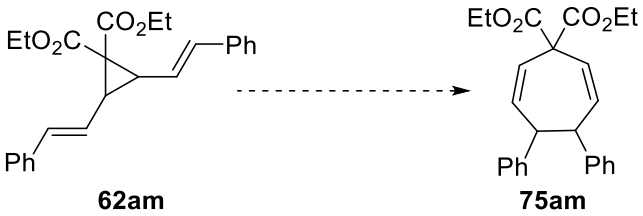
Scheme 118

D. Regarding the activating groups on the VCP, it would be interesting to test other EWGs such as cyano groups. Some promising results have already been obtained and show the possibility to form the VCP and to trigger a ring opening using $TiCl_4$. However, we did not observed the formation of one of our desired products yet (Scheme 119).



Scheme 119

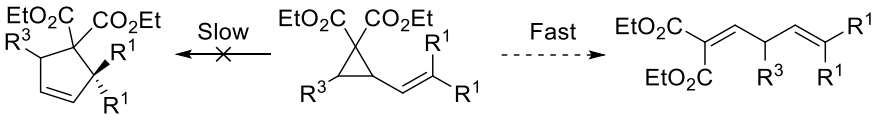
E. In our study, we successfully synthesized di-VCPs (see section 4.3.2.1). It would be interesting to study if one can trigger a rearrangement of these di-VCPs leading to seven membered carbocycles (**75am**) (Scheme 120). Indeed, the synthesis of this kind of skeleton remains a challenge in organic chemistry due to the limited amount of methods available.[120]



Scheme 120

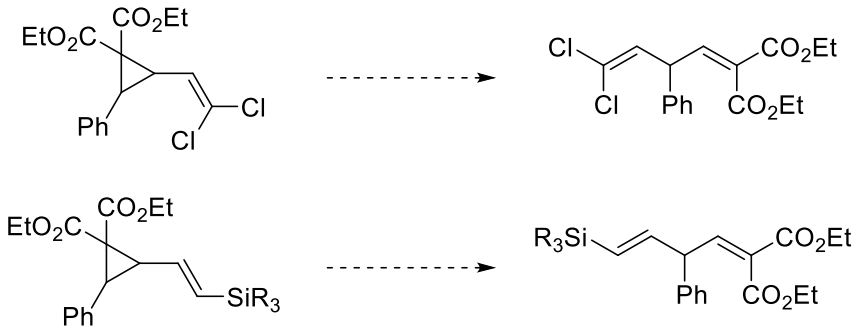
F. So far, we did not succeed in getting an alkyl group or a hydrogen atom to migrate in our methodology toward skipped dienes. It would be interesting to find a solution to this limitation in order to allow access to skipped dienes with no or an alkyl substituent

at the central position. Indeed, most naturally occurring skipped dienes possess an alkyl or no substituent at this position. That could be accomplished by disfavouring the cyclization, for instance, by sterically hindering the terminal position of the vinyl group (Scheme 121).



Scheme 121

Antoher idea that would also disfavor the cyclisation for the benefit of the migration would be to rearrange a VCP bearing two chlorine atoms or a silane group on the π C=C bond (Scheme 122). Additionnaly, setting chlorine atoms of the 1,4-diene skeleton would add a additional reactivity for further derivatization.



Scheme 122

G. For continuing the development of an asymmetric version of our methodologies, we first have synthesized the VCP and the 1,4-diene using the chiral ylide before measuring obtained enantiomeric excess in order to confirm the stereospecificity of the rearrangement step.

H. Finally, an interesting point that would be interesting to investigate is the decarboxylation phenomena observed with halogenated VCPs or with some Lewis acids. Indeed, even if this reactivity is not relevant for the study of the rearrangement of VCP to 1,4-diene or CP, this phenomena could provide a new mild tool for decarboxylation process.

CONCLUSIONS AND PERSPECTIVES

Chapter 7 Experimental part

7.1 General considerations

7.1.1 Equipment

- **NMR analysis:** Spectra were recorded either on a 300 MHZ *Bruker Avance II 300* or on a 500 MHz *Bruker Avance 500* spectrometer in the mentioned solvent. Chemical shifts are given in ppm relative to the internal reference (TMS) or the residual non-deuterated solvent only (for ^{1}H). For some molecules, the ^{1}H and ^{13}C signals attributions required additional analysis such as COSY, HMQC, HMBC, ^{13}C DEPT-Q and NOESY. In the case of NMR calculated yield, the internal standard used is dimethyl terephthalate analytical grade purchased from *Acros Organic company.* The obtained data were processed using MestReNova program version 10.0.2-15465.

- **Mass Spectrometry:** Mass spectra and high-resolution mass spectra were recorded on a *Thermo Orbitrap Exactive* device. The masse values are given in Dalton.

- **High-Performance Liquid Chromatography (HPLC):** Chromatographic analyses were carried out on a quaternary pump *Waters 600* controlled equipped with a *Waters 996 PDA* photodiode array detector and a *Waters 717 plus* autosampler. The columns used (CHIRALPAK IA, IB and IC) were purchased from *Daicel Chemical Industries*. The particles size is 5 µm and the dimensions of the columns are 4.6 mm x 250 mm. The analyses were performed at room temperature without a temperature controller.

- **IR spectrophotometry:** IR spectra were recorded on a *Perkin Elmer FT-IR spectrophotometer UATR Two.* The data were processed using the program *PerkinElmer Spectrum IR* version 10.6.1.

- **Melting points analysis:** Melting point values were recorded on a *Büchi B-540* device.

7.1.2 Laboratory practices

- **Reactions:** All reactions were carried out under magnetic stirring at room temperature unless mentioned.

- **Anhydrous conditions:** Reactions under inert and anhydrous conditions were carried out using glassware preciously heated *via* Bunsen burner under reduced pressure and followed by cooling under argon. atmosphere.

- **Solvents:** All solvents for reactions and purifications were used without further purification unless mentioned. Anhydrous solvent were purchased as anhydrous grade from Merck Sigma-Aldrich company.

- **Reactant and reagents:** Commerial reagents were used as purchased without further purification unless mentioned.

- **Low temperature reactions:** For reaction requiring -78°C, a bath of isopropanol with dry ice was used. Those requiring temperature of 0°C were carried out using an ice bath.

- **High temperature reactions:** Reactions requiring higher temperature were carried out using a silicon bath oil and a magnetic stirrer. The bath was heated by a heating plate equipped with a probe.

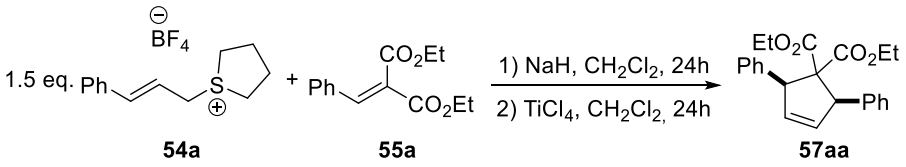
- **Thin layer chromatography (TLCs):** TLCs were carried out on Merck Silica gel 60 F_{254} aluminium backed plates using UV light, potassium permanganate or I_2 for revelation.

- **Flash chromatography:** Purification flash chromatography were performed using Merck Silica gel 60 Å (40-63 µm) with analytical grade solvents.

7.2 Procedures and compounds characterization

7.2.1 Experimental plan

An experimental plan has been designed using *JMP* program in order to determine settings which influence the yield of the one pot strategy.



54a **55a** **57aa**

The following combinations have been tested:

Experiment	Temperature (°C)	Salt eq. / Base	$TiCl_4$ eq.
1	20	1	1.25
2	0	1	2
3	0	2	0.5
4	0	1.5	2
5	20	2	0.5
6	0	2	1.25
7	20	1.5	0.5
8	20	1.5	1.25
9	20	2	1.25
10	0	1.5	0.5
11	20	1.5	1.25
12	0	1	1.25
13	0	1.5	1.25
14	20	1	0.5
15	0	2	2
16	20	1.5	1.25
17	0	1	0.5
18	20	1.5	2

19	20	1	2
20[a]	20	2	2
21[a]	20	1.5	1.25
22[a]	20	2	2
23[a]	20	1	2
24[a]	20	2	10

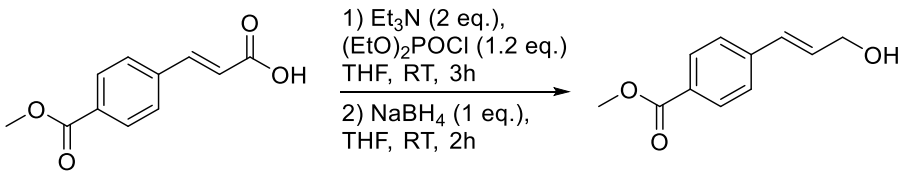
Table 14: [a] these experiements were not part of the initial experimental plan and have been added for trying to add data and being able to draw conclusions from obtained results.

No conclusion could be drawn from obtained data because the results were vitiatied by some errors.

7.2.2 Non chiral sulfonium salts

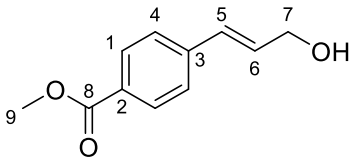
7.2.2.1 Synthesis of the required intermediates

7.2.2.1.1 Methyl-(E)-4-(3-hydroxyprop-1-en-1-yl)benzoate (**58b**)



Procedure: A solution of (*E*)-3-(4-(methoxycarbonyl) phenyl)acrylic acid (35 g, 170 mmol, 1 eq.), Et3N (340 mmol, 2 eq.) and diethyl chlorophosphate (29.4 g, 203 mmol, 1.2 eq.) in THF (340 mL) is stirred at room temperature for 3 hours. The precipitate is filtered off. After concentration of the filtrate under reduced pressure, the residue is dissolved in THF (440 mL). Then, this solution is reacted with a solution of $NaBH_4$ (6.4 g, 170 mmol, 1 eq.) in THF (50 mL) for 2 hours at room temperature.

After 2h, water is added and the aqueous phase is extracted three times with dichloromethane. The organic phases are combined and dried over $MgSO_4$. Finaly, an evaporation of the solvent under reduced pressure afford the desired product (35.5 g).



Chemical Formula: $C_{11}H_{12}O_3$
Molecular Weight: 192.21

CAS: 117390-08-6

Aspect: white solid

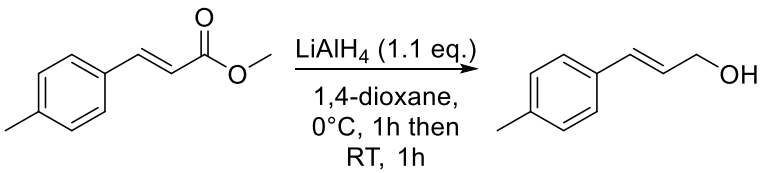
Yield: 77%

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, 2H, *J* = 8.4 Hz, H^1), 7.44 (d, 2H, *J* = 8.4 Hz, H^4), 6.67 (d, 1H, *J* = 15.9 Hz, H^5), 6.48 (dt, 1H, *J* = 15.9, 5.3 Hz, H^6), 4.37 (d, 2H, *J* = 5.3 Hz, H^7), 3.91 (s, 3H, H^9)

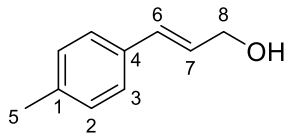
HRMS (ESI): Calculated for $C_{11}H_{13}O_3$: 193.08592, found: 193.08606

Data are in agreement with Y. Nagao, K. Inoue, M. Yamaki, S. Takagi, E. Fujita; *Chemical & Pharmaceutical Bulletin*; **1988**, *36*, 495-508

7.2.2.1.2 (*E*)-3-(p-tolyl)prop-2-en-1-ol (**58d**)



Procedure: In a dry round bottom flask, under argon atmosphere, a solution of methyl (*E*)-3-(p-tolyl)acrylate (9.5 g, 54 mmol, 1 eq.) dissolved in diethyl ether (110 mL) is added dropwise to a solution of $LiAlH_4$ (2.26 g, 60 mmol, 1.1 eq.) in diethyl ether (180 mL) at 0°C. The mixture is stirred for 1h at 0°C and then allowed to warm up to room temperature and stirred for one additional hour before dilution with diethyl ether and washing with brine. The organic layer is dried over $MgSO_4$ and the desired product (5.7 g) is obtained with a after evaporation of the ether under reduced pressure.



Chemical Formula: $C_{10}H_{12}O$
Molecular Weight: 148.21

CAS: 122058-30-4

Aspect: clear liquid

Yield: 71%

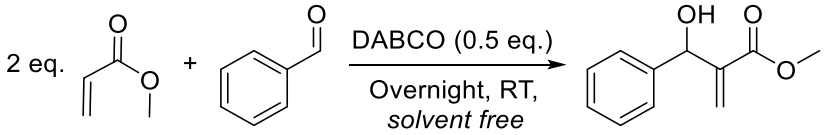
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 2H, H^3), 7.14 (m, 2H, H^2), 6.61 (dt, 1H, *J* = 15.9, 1.5 Hz, H^6), 6.34 (dt, 1H, *J* = 15.9, 5.8 Hz, H^7), 4.33 (dd, 2H, *J* = 5.8, 1.5 Hz, H^8), 2.36 (s, 3H, H^5)

^{13}C NMR (75 MHz, $CDCl_3$): 137.7, 134.0, 131.3, 129.4, 127.5, 126.5, 64.0, 21.3

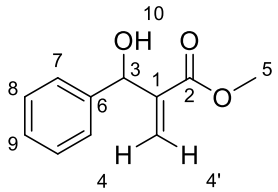
HRMS (ESI): Calculated for $C_{10}H_{13}O$: 149.09609, found: 149.09607

Data are in agreement with Morales-Serna J. A., Garcia-Rios E., Bernal J., Paleo E., Gavino R., Cardenas, J.; *Synthesis*; **2011**, *9*, 1375-1382

7.2.2.1.3 Methyl 2-(hydroxy(phenyl)methyl)acrylate



Procedure: Methylacrylate (35.5 g, 38 mmol, 2 eq.), benzaldehyde (20 g, 19 mmol, 1 eq.) and DABCO (10.6 g, 9.5 mmol, 0.5 eq.) are mixed into a round bottom flask and stirred overnight without any solvent. Then, a purification over chromatography column with silica is performed using an eluent composed of *n*-hexane/AcOEt (8/2) to obtain the desired product.



Chemical Formula: $C_{11}H_{12}O_3$
Molecular Weight: 192.21

CAS: 18020-59-2

Aspect: Colorless oil

Yield: 95%

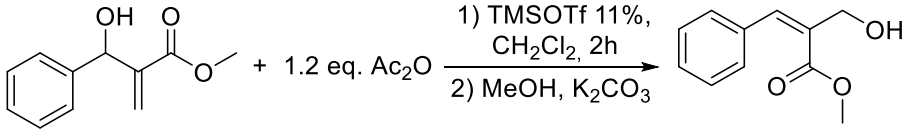
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25-7.41 (m, 5H, H^{arom}), 6.34 (m, 1H, $H^{4 \text{ or } 4'}$), 5.85 (m, 1H, $H^{4' \text{ or } 4}$), 5.58 (m, 1H, H^3), 3.74 (s, 3H, H^5), 2.58 (m, 1H, H^{10})

^{13}C NMR (75 MHz, $CDCl_3$): δ= 166.8, 142.0, 141.3, 128.4, 127.8, 126.6, 126.04, 73.1, 51.9

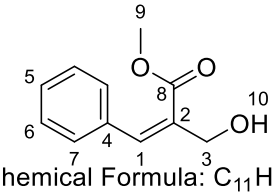
HRMS (ESI): Calculated for $C_{11}H_{13}O_3$: 193.0786, found: 193.0777

Data are in agreement with D. R. Nicponski, *Tetrahedron Letters*, **2014**, *55*, 2075-77

7.2.2.1.4 Methyl-(*Z*)-2-(hydroxymethyl)-3-phenylacrylate (**58g**)



Procedure: TMSOTf (5.26 g, 23.6 mmol, 0.1 eq.) is slowly added, under argon atmosphere, to a solution of methyl 2-(hydroxy(phenyl)methyl) acrylate (41.3 g, 215 mmol, 1eq.) in dichloromethane (400 mL). The mixture is stirred for 2 hours and then transferred into a round bottom flask before evaporating the solvent under reduced pressure. Methanol (500 mL) and K_2CO_3 (89 g, 645 mmol, 3 eq.) are added and the mixture is stirred for one hour a room temperature before passing it through a filter in order to remove the precipitate. Then, the solvent is evaporated under reduced pressure and the desired product is obtained without further purification.



Chemical Formula: $C_{11}H_{12}O_3$
Molecular Weight: 192.21

CAS: 222175-00-0

Aspect: white solid

Yield: 83%

Melting point: 59°C

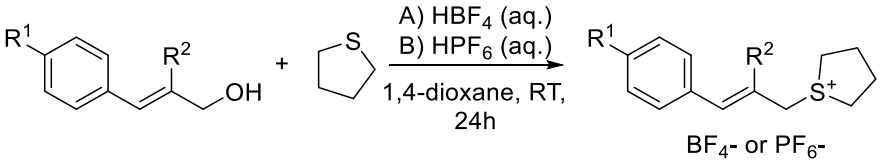
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1H, H^1), 7.48-7.31 (m, 5H, H^{arom}), 4.49 (d, 2H, *J* = 3.9 Hz, H^3), 3.86 (s, 3H, H^9), 2.61 (m, 1H, H^{10})

^{13}C NMR (75 MHz, $CDCl_3$): δ= 168.4, 142.7, 134.5, 130.9, 129.6, 129.3, 128.6, 57.9, 52.2

HRMS (ESI): Calculated for $C_{11}H_{11}O_2$: 175.07536, found: 175.07486 (M^+-OH)

Data are in agreement with Basavaiah; Padmaja; Satyanarayana; *Synthesis*, **2000**, *12*, 1662-64

7.2.2.2 General procedure: Synthesis of allylic sulfonium salts



Scheme 123

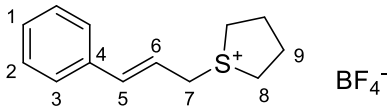
7.2.2.2.1 General procedure Aa: Using HBF_4

Alcohol reagent (1 eq.), tetrahydrothiophene (1 eq.) and 1,4-dioxane (1 mL/mmol of starting alcohol) are introduced in a round-bottom flask. An aqueous solution of tetrafluoroboric acid (1M, 1eq.) is added slowly. After 24 hours of stirring at room temperature, the solvent is evaporated under reduced pressure. The residue is then dissolved in a minimum of methanol and cold diethyl ether is added slowly to trigger the crystallization of the desired product as a white powder.

7.2.2.2.2 General procedure Ab: Using HPF_6

Alcohol reagent (1 eq.), tetrahydrothiophene (1 eq.) and 1,4-dioxane (1 mL/mmol of starting alcohol) are introduced in a round-bottom flask. An aqueous solution of hexafluorophosphoric acid (60% w/w, 1eq.) is then added. After 24 hours of stirring at room temperature, the solvent is evaporated under reduced pressure. The residue is dissolved in a minimum of methanol and cold diethyl ether is added slowly to trigger the crystallization of the desired product as a white powder.

1-[(2E)-3-Phenylprop-2-en-1-yl]thiolan-1-ium tetrafluoroborate[121] (54a)



Chemical Formula: $C_{13}H_{17}SBF_4$
Molecular Weight: 292.14

Procedure: Aa

CAS: 1048694-01-4

Aspect: White powder

Yield: 75%

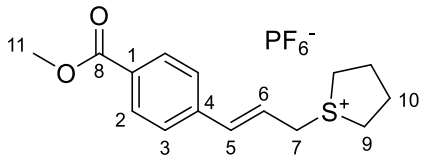
Melting point: 106°C

^{1}H NMR (300 MHz, CD_3CO): δ = 7.46 (m, 2H, $H^{2 \text{ or } 3}$), 7.28 (m, 3H, $H^{3 \text{ or } 2, 7}$), 7.02 (d, 1H, *J* = 15.8 Hz, H^5), 6.38 (dt, 1H, *J* = 15.7, 7.8 Hz, H^6), 4.22 (dd, 2H, *J* = 7.8, 1.1 Hz, 2H, H^7), 3.58 (m, 4H, H^8), 2.32 (m, 4H, H^9)

^{13}C NMR (75 MHz, CD_3CO): δ=141.1, 135.9, 129.2, 129.1, 127.4, 116.1, 44.7, 42.3, 28.9

HRMS (ESI): Calculated for $C_{13}H_{17}{}^{32}S^+$: 205.10455, found: 205.10456

1-[(2E)-3-[4-(Methoxycarbonyl)phenyl]prop-2-en-1-yl]thiolan-1-ium; hexafluoro-lambda5-phosphate (54b)



Chemical Formula: $C_{15}H_{19}O_2SPF_6$
Molecular Weight: 408.33

Procedure: Aa

Yield: 73%

Aspect: White powder

Melting point: 245°C

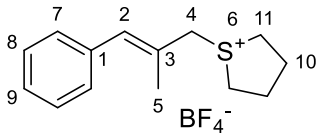
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ = 8.04 (m, 2H, H^2), 7.72 (m, 2H, H^3), 7.23 (d, 1H, *J* = 15.8 Hz, H^5), 6.71 (dt, 1H, *J* = 15.7, 7.7 Hz, H^6), 4.44 (dd, 2H, *J* = 7.7, 1.1 Hz, H^7), 3.92 (s, 3H, H^{11}), 3.80 (m, 4H, H^9), 2.51 (m, 4H, H^{10})

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ= 166.4, 140.4, 140.1, 130.9, 130.3, 127.7, 119.4, 52.1, 44.8, 42.9, one carbon is missing

HRMS (ESI): calculated for $C_{15}H_{19}O_2{}^{32}S^+$: 263.11003, found: 263.10988

IR (cm^{-1}): 2823, 1712, 1679, 1279

1-[(2E)-2-Methyl-phenylprop-2-en-1-yl]thiolan-1-ium tetrafluoroborate (54c)



Chemical Formula: $C_{14}H_{19}SBF_4$
Molecular Weight: 306.17

Procedure: Aa

Yield: 55 %

Aspect: White powder

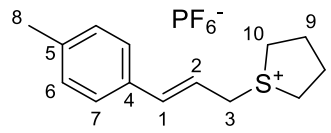
Melting point: 60°C

^{1}H NMR (300 MHz, CD_3CO): δ = 7.36-7.18 (m, 5H, H^{arom}), 6.97 (m, 1H, H^2), 4.34 (d, 2H, *J* = 1 Hz, H^4), 3.75 (m, 4H, H^{11}), 2.53 (m, 4H, H^{10}), 2.15 (d, 3H, *J* = 1.4 Hz, H^5)

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ =136.6, 135.9, 129.6, 128.9, 128.2, 127.4, 53.2, 43.2, 28.9, 17.1

HRMS (ESI): Calculated for $C_{14}H_{19}{}^{32}S^+$: 219.12020, found: 219.12032

1-[(2E)-3-(4-Methylphenyl)prop-2-en-1-yl]thiolan-1-ium; hexafluoro-lambda5-phosphate (54d)



Chemical Formula: $C_{14}H_{19}SPF_6$
Molecular Weight: 364.33

Procedure: Ab

Aspect: White powder

Yield: 60%

Melting point: 116-120°C

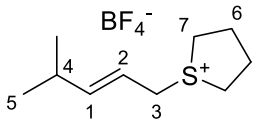
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ= 7.47 (d, 2H, *J* = 8.1 Hz, $H^{6 \text{ or } 7}$), 7.24 (d, 2H, *J* = 7.9 Hz, $H^{6 \text{ or } 7}$), 7.09 (d, 1H, *J* = 15.8 Hz, H^1), 6.46 (dt, 1H, *J* = 15.7, 7.8 Hz, H^2), 4.38 (d, 2H, *J* = 7.8 Hz, H^3), 3.76 (m, 4H, H^{10}), 2.48 (m, 4H, H^9), 2.37 (s, 3H, H^8)

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ = 141.6, 139.7, 133.21, 130.0, 127.6, 114.9, 45.4, 42.7, 20.9, the signal of one carbon is hidden under the solvent signal

HRMS (ESI): calculated for $C_{14}H_{19}{}^{32}S^+$: 219.12020 found: 219.12024

IR (cm^{-1}): 821, 556

1-[(2E)-4-Methylpent-2-en-1-yl]thiolan-1-ium; tetrafluoroborate (54e)



Chemical Formula: $C_{10}H_{19}SBF_4$
Molecular Weight: 258.12

Procedure: Aa

Aspect: white oil *(liquid at room temperature)*

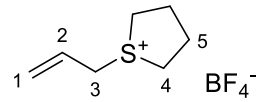
Yield: 44 %

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ = 6.08 (dd, 1H, *J* = 15.4, 6.7 Hz, H^1), 5.42 (ddt, 1H, *J* = 15.3, 7.6, 1.4 Hz, H^2), 3.92 (d, 2H, *J* = 7.7 Hz, H^3), 3.58 (m, 2H, H^7), 3.37 (m, 2H, H^7), 2.35 (m, 5H, $H^{4,6}$), 1.02 (d, 6H, *J* = 6.8 Hz, H^5)

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ= 152.2, 113.0, 44.5, 41.6, 31.5, 28.8, 21.8

HRMS (ESI): calculated for $C_{10}H_{19}{}^{32}S^+$: 171.12020 found: 171.12024

<u>1-(Prop-2-en-1-yl)thiolan-1-ium; tetrafluoroborate (54f)</u>



Chemical Formula: $C_7H_{13}SBF_4$
Molecular Weight: 216.04

Procedure: Aa

CAS: 88926-99-2

Aspect: Brown oil

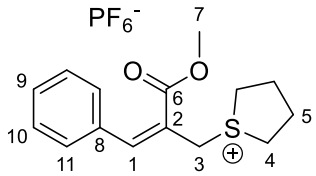
Yield: 51%

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ = 5.96-5.80 (m, 1H, H^2), 5.75-5.62 (m, 2H, H^1), 3.93 (d, 2H, *J* = 7.2 Hz, H^3), 3.65-3.33 (m, 4H, H^4), 2.47-2.24 (m, 4H, H^5)

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ= 128.4, 124.5, 45.2, 42.6, 29.2

HRMS (ESI): calculated for $C_7H_{13}{}^{32}S^+$: 129.07342, found: 129.07325

1-[(2E)-3-Methoxy-3-oxo-2-(phenylmethylidene)propyl]thiolan-1-ium; hexafluoro-lambda5-phosphate (54g)



Chemical Formula: $C_{15}H_{19}O_2SPF_6$
Molecular Weight: 408.33

Procedure: Ab

Yield: 51%

Aspect: white powder

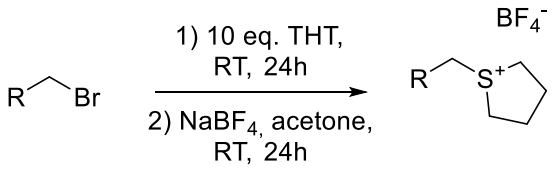
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ = 8.24 (s, 1H, H^1), 7.62-7.51 (m, 5H, H^{arom}), 4.65 (s, 2H, H^3), 3.90 (s, 3H, H^7), 3.80-3.56 (m, 4H, H^4), 2.35-2.19 (m, 4H, H^5)

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ = 166.5, 147.7, 133.5, 130.3, 129.6, 129.3, 52.4, 44.4, 39.6, 28.3, the signal of one carbon is missing

HRMS (ESI): calculated for $C_{15}H_{19}O_2{}^{32}S^+$: 263.11003, found: 263.11000

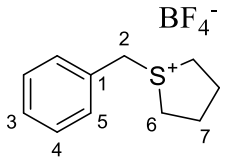
7.2.2.3 General procedure B: Synthesis of benzylic sulfonium salts

Reference: O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-van, K. Robeyns and R. Robiette, *Chem. Eur. J.* **2015**, *21*, 12899-902



In a round-bottom flask are added the bromide derivative (1 eq.) and tetrahydrothiophene (10eq.). After stirring for 24 h at room temperature, the solid is filtrated and washed with cyclohexane in order to remove the excess of tetrahydrothiophene. The crude bromide salt is then diluted with acetone (2mL/mmol of salt), followed by the addition of $NaBF_4$ (1 eq.). After stirring for 24 h at room temperature, the reaction mixture is filtered in order to remove precipitated NaBr. The solution is then concentrated under reduced pressure. The sulfonium salt is purified by precipitation in a $MeOH/Et_2O$ mixture.

7.2.2.3.1 1-Benzylthiolan-1-ium trifluoroborane fluoride (**59a**)



Chemical Formula: $C_{11}H_{15}SBF_4$
Molecular Weight: 266.10

Procedure: B

CAS: 1478-78-0

Aspect: White powder

Melting point: 120 – 121°C

Yield: 48%

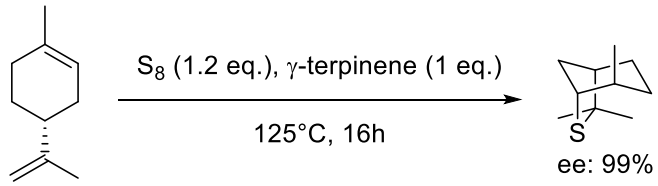
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ= 7.70 (m, 2H, H^{arom}), 7.54 (m, 3H, H^{arom}), 4.81 (s, 2H, H^2), 3.80 to 3.65 (m, 4H, H^6), 2.48 (m, 4H, H^7)

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ= 131.1, 130.4, 130.1, 129.9, 46.2, 43.2, 28.9

HRMS (APCI): Calculated for $C_{11}H_{15}{}^{32}S^+$: 179.08890, found: 179.08889

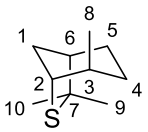
7.2.3 Synthesis of chiral sulfonium salt

7.2.3.1 Synthesis of the precursor: Isothiocineol



ee: 99%
37%

Procedure: In a round-bottom flask are added limonene (60 mmol; 1 eq.), γ-terpinene (60 mmol; 1 eq.), and elemental sulfur (70 mmol; 1.2 eq.). After stirring for 16h at 125°C, pure isothiocineole is isolated by fractional distillation under reduced pressure (45-60°C at 1.5 mbar)



Chemical Formula: $C_{10}H_{18}S$
Molecular Weight: 170.31

CAS: 5718-75-2

Yield: 37%

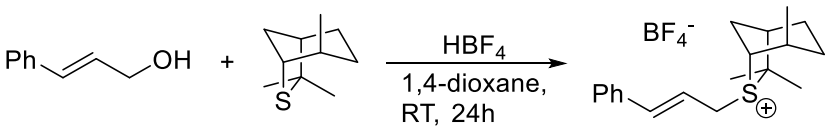
Aspect: colorless liquid

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 3.32 (m, 1H, H^2), 2.32 (m, 1H), 2.11-1.99 (comp, 2H), 1.90 (m, 1H), 1.82 (m, 1H), 1.69-1.55 (comp, 2H), 1.50 (s, 3H, $H^{9 \text{ or } 10}$), 1.38 (s, 3H, $H^{10 \text{ or } 9}$), 1.15 (dd, 1H, *J* = 14.0, 5.3 Hz), 1.06 (d, 3H, *J* = 7.2 Hz, H^8)

HRMS (APCI): Calculated for $C_{10}H_{19}{}^{32}S$: 171.12020, found: 171.12028

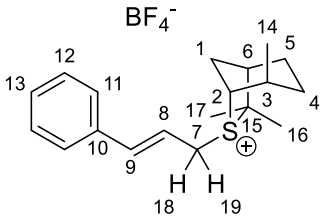
^{1}H and mass spectra are in agreement with the literature, see: O. Illa, O. Arshad, A. Ros, E. M. McGarrigle, V.K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 1828-1830

7.2.3.2 Synthesis of 4,7,7-trimethyl-6-[(2E)-3-phenylprop-2-en-1-yl]-6-thiabicyclo[3.2.1]octan-6-ium trifluoroborane fluoride (60a)



Scheme 124

Procedure: Isothiocineol (1.2 g, 7.4 mmol, 1 eq.), cinamyl alcohol (1 g, 7.45 mmol, 1 eq.) and 10 mL of 1,4-dioxane were introduced in a round-bottom flask. The mixture is cooled to 0°C and 1 mL of aqueous solution of tetrafluoroboric acid (1M) is added. The mixture is stirred for 24 hours at room temperature. The solvent is concentrated under reduced pressure and the obtained mixture is dissolved in a minimum of methanol. The product crystallization is promoted by adding cold diethyl ether. The product is obtained after filtration.



Chemical Formula: $C_{19}H_{27}SBF_4$
Molecular Weight: 374.28

Aspect: white powder

Yield: 37%

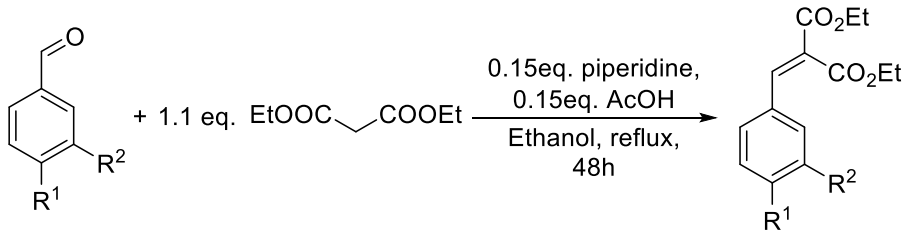
^{1}H NMR (300 MHz, $CDCl_3$) : δ = 7.43 (m, 2H, H^{12}), 7.27 (m, 3H, $H^{11,13}$), 7.09 (d, 1H, *J* = 15.8 Hz, H^9), 6.26 (ddd, 1H, *J*=12.3, 6.3, 1.4 Hz, H^8), 4.36 (ddd, 1H, *J* = 12.3, 6.3, 1.4 Hz, $H^{18 \text{ or } 19}$), 4.07 (dd, 1H, *J* = 12.3, 8.8 Hz, $H^{18 \text{ or } 19}$), 3.94 (m, 1H, H^2), 2.57 (dt, 1H, *J* = 14.5, 4.5 Hz, H^6), 2.36 (d, 2H, *J* = 14.0 Hz, H^1), 2.21 (m, 1H, H^3), 1.77 (s, 4H, $H^{4,5}$), 1.69 (m, 6H, $H^{16,17}$), 1.12 (d, 3H, *J* = 7.1 Hz, H^{14})

^{13}C NMR DEPT-Q (300 MHz, $CDCl_3$): δ= 141.9, 135.5, 129.4, 129.0, 116.1, 72.1, 63.9, 50.4, 41.5, 32.3, 32.1, 25.5, 25.4, 23.3, 18.0, 18.0

HRMS (pAPCI): Calculated for $C_{19}H_{27}S^+$: 287.18280, found: 287.18233

7.2.4 Synthesis of activated olefins

7.2.4.1 General procedure

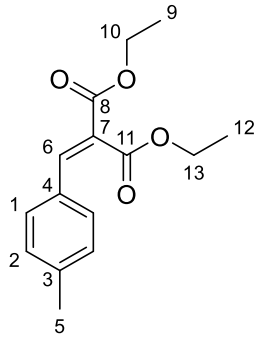


Scheme 125

Aldehyde (1 eq.), 1,3-diethyl propanedioate (1.1 eq.), piperidine (0.15 eq.), glacial acetic acid (0.15 eq) and absolute ethanol (10 mL/mmol of aldehyde) are introduced in a round-bottom flask with a condenser. The mixture is heated at reflux for 48 hours. Then, the solvent is evaporated under reduced pressure and the organic layer is whashed with brine. The brine solution is extracted three times with dichloromethane. The crude product is distilled under reduced pressure ($T°_{oil\ bath}$= 200°C) and the desired product is obtained as the distillation residue.

7.2.4.2 Product description

7.2.4.2.1 <u>1,3-Diethyl-2-[(4-methylphenyl)methylidene]propanedioate (**55b**)</u>



Chemical Formula: $C_{15}H_{18}O_4$
Molecular Weight: 262.31

CAS: 14111-33-2

Aspect: Colorless oil

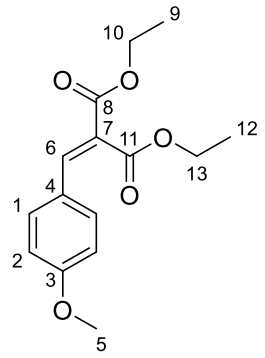
Yield: 77% (16.4 g)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (s, 1H, H^6), 7.35 (d, 2H, *J* = 8.2 Hz, H^1), 7.18 (d, 2H, *J* = 8.0 Hz, H^2), 4.32 (comp, 4H, $H^{10,13}$), 2.37 (s, 3H, H^5), 1.32 (m, 6H, $H^{9,12}$)

^{13}C NMR (300 MHz, $CDCl_3$): δ= 167.0, 164.3, 142.2, 141.2, 130.0, 129.6, 125.2, 61.7, 61.6, 21.5, 14.2, 13.9

HRMS (APCI): Calculated for $C_{15}H_{19}O_4$: 263.12779, found: 263.12770

7.2.4.2.2 1,3-Diethyl-2-[(4-methoxyphenyl)methylidene]propanedioate (**55c**)



Chemical Formula: $C_{15}H_{18}O_5$
Molecular Weight: 278.30

CAS: 6768-23-6

Aspect: white solid

Yield: 82% (30 g)

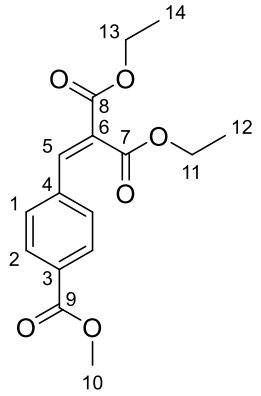
Melting point: 36°C

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.67 (s, 1H, H^6), 7.42 (m, 2H, H^1), 1.70 (m, 2H, H^2), 4.35 (q, 2H, *J* = 7.1 Hz,$H^{10 \text{ or } 13}$), 4.29 (q, 2H, *J* = 7.1 Hz, $H^{13 \text{ or } 10}$), 3.83 (s, 3H, H^5), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{9 \text{ or } 12}$), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{12 \text{ or } 9}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 167.3, 164.6, 161.7, 141.9, 131.7, 125.5, 123.7, 114.4, 61.8, 61.6, 55.5, 14.3, 14.1

HRMS (APCI): Calculated for $C_{15}H_{19}O_5$: 279.12270, found: 279.12284

7.2.4.2.3 <u>1,3-Diethyl-2-{[4-(methoxycarbonyl)phenyl]methylidene} propanedioate (**55d**)</u>



Chemical Formula: $C_{16}H_{18}O_6$
Molecular Weight: 306,31

Yield: 75% (32.5 g)

Aspect: white solid

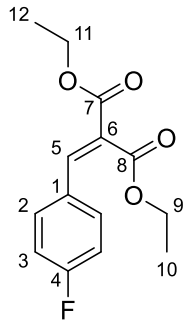
Melting point: 47°C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (m, 2H, H^2), 7.75 (s, 1H, H^5), 7.51 (m, 2H, H^1), 4.33 (q, 2H, *J* = 7.1 Hz, $H^{11 \text{ or } 13}$), 4.32 (q, 2H, *J* = 7.1 Hz, $H^{13 \text{ or } 11}$), 3.93 (s, 3H, H^{10}), 1.34 (t, 3H, *J* = 7.1 Hz, $H^{12 \text{ or } 14}$), 1.28 (t, 3H, *J* = 7.2 Hz, $H^{14 \text{ or } 12}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 166.3, 163.9, 140.9, 137.4, 131.6, 130.1, 129.3, 128.5, 62.1, 62.1, 52.5, 14.3, 14.0

HRMS (APCI): Calculated for $C_{16}H_{19}O_6$: 307.11761, found: 307.11745

7.2.4.2.4 1,3-Diethyl-2-[(4-fluorophenyl)methylidene]propanedioate (**55e**)



Chemical Formula: $C_{14}H_{15}FO_4$
Molecular Weight: 266.27

CAS: 790-53-4

Yield: 98%

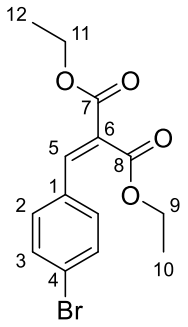
Aspect: Colorless oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (s, 1H, H^5), 7.46 (m, 2H, H^2), 7.08 (m, 2H, H^3), 4.31 (q, 2H, *J* = 7.1 Hz, $H^{9 \text{ or } 11}$), 4.34 (q, 2H, *J* = 7.1 Hz, $H^{11 \text{ or } 9}$), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{10 \text{ or } 12}$), 1.30 (t, 3H, *J* = 7.1 Hz, $H^{12 \text{ or } 10}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 166.9, 165.9, 164.4, 162.5, 141.2, 131.9 (*J* = 8.5 Hz), 126.4, 116.3 (*J* = 21.8 Hz), 62.1, 62.1, 14.5, 14.3

HRMS (APCI): Calculated for $C_{14}H_{16}O_4F$: 267.10268, found: 267.10271

7.2.4.2.5 1,3-Diethyl-2-[(4-bromophenyl)methylidene]propanedioate (**55f**)



Chemical Formula: $C_{14}H_{15}BrO_4$
Molecular Weight: 327.17

Aspect: orange oil

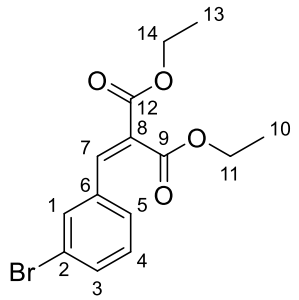
Yield: 86% (15.5 g)

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.65 (s, 1H, H^5), 7.52 (m, 2H, H^3), 7.32 (m, 2H, H^2), 4.32 (m, 4H, $H^{9,11}$), 1.33 (t, 3H, *J*=7.1 Hz, $H^{10 \text{ or } 12}$), 1.30 (t, 3H, *J*=7.1 Hz, $H^{12 \text{ or } 10}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 166.7, 165.3, 141.0, 132.4, 132.2, 131.2, 127.3, 125.4, 61.2, 62.1, 14.5, 14.3

HRMS (APCI): Calculated for $C_{14}H_{16}O_4{}^{79}Br$: 327.02265, found: 327.02250

7.2.4.2.6 1,3-diethyl-2-[(3-bromophenyl)methylidene]propanedioate (**55g**)



Chemical Formula: $C_{14}H_{15}BrO_4$
Molecular Weight: 327.17

Aspect: Yellow oil

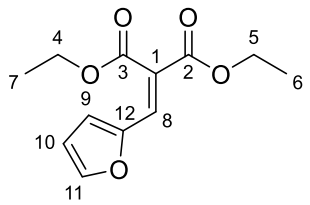
Yield: 95% (9.13 g)

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.65 (s, 1H, H^7), 7.59 (t, 1H, *J* = 1.8 Hz, H^{arom}), 7.52 (ddd, 1H, *J* = 8.0, 2.0, 1.1 Hz, H^{arom}), 7.37 (ddt, 1H, *J* = 7.7, 1.6, 0.8 Hz, H^{arom}), 7.26 (m, 1H, H^{arom}), 4.34 (q, 2H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 4.31 (q, 2H, *J* = 7.1 Hz, $H^{14 \text{ or } 11}$), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{10 \text{ or } 13}$), 1.30 (t, 3H, *J* = 7.1 Hz, $H^{13 \text{ or } 10}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 166.2, 163.8, 140.4, 135.0, 133.4, 132.1, 130.4, 128.0, 127.9, 122.9, 62.0, 62.0, 14.2, 14.1

HRMS (pAPCI): Calculated for $C_{14}H_{16}O_4Br$: 327.02265, found: 327.02271

7.2.4.2.7 1,3-Diethyl-2-[(furan-2-yl)methylidene]propanedioate (**55h**)



Chemical Formula: $C_{12}H_{14}O_5$
Molecular Weight: 238.24

CAS: 17448-96-3

Yield: 98%

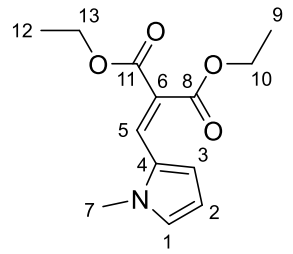
Aspect: black oil

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.51 (d, 1H, *J* = 1.8 Hz, H^{11}), 7.45 (s, 1H, H^8), 6.76 (d, 1H, *J* = 3.5 Hz, H^9), 6.50 (dd, 1H, *J* = 3.5, 1.8 Hz, H^{10}), 4.40 (q, 2H, *J* = 7.1 Hz, $H^{4 \text{ or } 5}$), 4.28 (q, 2H, *J* = 7.1 Hz, $H^{5 \text{ or } 4}$), 1.37 (t, 3H, *J* = 7.1 Hz, $H^{6 \text{ or } 7}$), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{7 \text{ or } 6}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 166.4, 164.3, 149.2, 146.2, 127.6, 122.2, 118.0, 112.7, 61.8, 61.7, 14.2, 14.1

HRMS (APCI): Calculated for $C_{12}H_{15}O_5$: 239.09140, found: 239.09151

7.2.4.2.8 <u>1,3-Diethyl-2-[(1-methyl-1*H*-pyrrol-2-yl)methylidene]propanedioate (**55i**)</u>



Chemical Formula: $C_{13}H_{17}NO_4$
Molecular Weight: 251.28

Yield: 77%

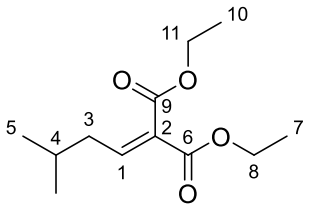
Aspect: Brown solid

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (s, 1H, H^5), 6.81 (dd, 1H, *J* = 2.5 1.6 Hz, H^1), 6.65 (dd, 1H, *J* = 4.2, 1.5, 0.6 Hz, H^3), 6.20 (m, 1H, H^2), 4.38 (q, 2H, *J* = 7.2 Hz, $H^{10 \text{ or } 13}$), 4.28 (q, 2H, *J* = 7.1 Hz, $H^{10 \text{ or } 13}$), 3.73 (s, 3H, H^7), 1.37 (t, 3H, *J* = 7.1 Hz, $H^{9 \text{ or } 12}$), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{9 \text{ or } 12}$)

^{13}C NMR (300 MHz, $CDCl_3$): δ= 167.51, 165.05, 128.94, 128.01, 126.69, 118.95, 115.01, 110.33, 61.70, 61.36, 36.36, 14.36, 14.15

HRMS (**pAPCI)**: Calculated for $C_{13}H_{18}NO_4$: 252.12303, found: 252.12284

7.2.4.2.9 Diethyl 2-(3-methylbutylidene)malonate (**55j**)



Chemical Formula: $C_{12}H_{20}O_4$
Molecular Weight: 228.29

CAS: 51615-30-6

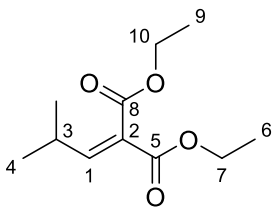
Yield: 82%

Aspect: Yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.01 (t, 1H, *J* = 8.0 Hz, H^1), 4.30 (q, 2H, *J* = 7.1 Hz, $H^{8 \text{ or } 11}$), 4.23 (q, 2H, *J* = 7.1 Hz, $H^{11 \text{ or } 8}$), 2.19 (dd, 2H, *J* = 7.9, 6.8 Hz, H^3), 1.82 (m, 1H, H^4), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{7 \text{ or } 10}$), 1.31 (t, 3H, *J* = 7.1 Hz, $H^{10 \text{ or } 7}$), 0.94 (d, 3H, *J* = 6.7 Hz, H^5)

Obtained data are in accordance with the literature: F. Lima, L. Grunenberg, B. A. Rahman, R. Labes, J. Sedelmeierb, S. V. Ley*; Chem. Commun.*, **2018**, *54*, 5606-5609

7.2.4.2.10 Diethyl 2-(2-methylpropylidene)malonate (**55k**)



Chemical Formula: $C_{11}H_{18}O_4$
Molecular Weight: 214.26

CAS: 5652-68-6

Aspect: Yellow oil

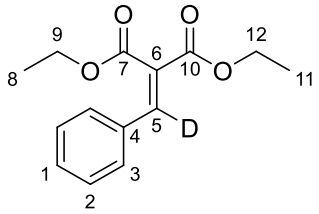
Yield: 92%

^{1}H NMR (300 MHz, $CDCl_3$): 6.77 (d, 1H, *J* = 10.6 Hz, H^1), 4.29 (q, 2H, *J* = 7.1 Hz, $H^{7 \text{ or } 10}$), 4.22 (q, 2H, *J* = 7.1 Hz, $H^{10 \text{ or } 7}$), 2.68 (m, 1H, H^3), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{6 \text{ or } 9}$), 1.28 (t, 3H, *J* = 7.1 Hz, $H^{9 \text{ or } 6}$), 1.06 (d, 6H, *J* = 6.6 Hz, H^4)

HRMS (pAPCI): Calculated for $C_{11}H_{19}O_4$: 215.12779, found: 215.12783

Data are in agreement with W. Fraser, C. J. Suckling, H. C. S. Wood, *J. Chem. Soc. Perkin Trans. 1,* **1990,** 3137-3144

7.2.4.2.11 <u>1,3-Diethyl 2-[phenyl(2H)methylidene]propanedioate (**55l**)</u>



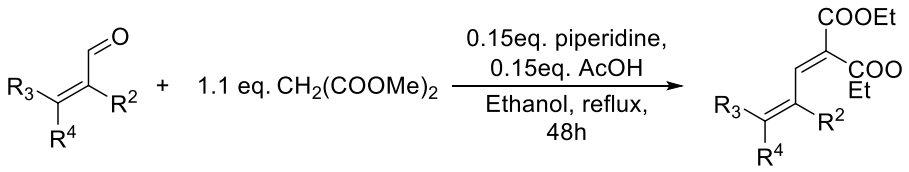
Chemical Formula: $C_{14}H_{15}DO_4$
Molecular Weight: 249.28

Yield: 93% (230 mg)

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.37 - 7.18 (m, 5H, H^{arom}), 4.20 (m, 4H, $H^{9,12}$), 1.18 (m, 6H, $H^{8,11}$)

7.2.5 Synthesis of 1,3-dienes

7.2.5.1 General procedure

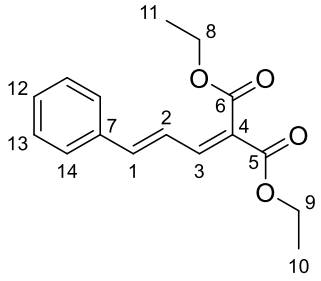


Scheme 126

Aldehyde (1eq.), 1,3-diethyl propanedioate (1.1 eq.), piperidine (0.15 eq.), glacial acetic acid (0.15 eq) and absolute ethanol (10 mL/mmol of aldehyde) are introduced in a round-bottom flask with a condenser. The mixture is heated at reflux for 48 hours. Then, the solvent is evaporated under reduced pressure and the organic layer is whashed with brine. The brine solution is extracted three times with dichloromethane. The crude product is distilled under reduced pressure ($T°_{oil\ bath}$= 200°C) and the desired product is obtained as the distillation residue.

7.2.5.2 Product descriptions

7.2.5.2.1 1,3-Diethyl-2-[(2*E*)-3-phenylprop-2-en-1-ylidene]propanedioate (**61m**)



Chemical Formula: $C_{16}H_{18}O_4$
Molecular Weight: 274.32

CAS: 25364-76-5, 66684-75-1

Yield: 71%

Aspect: Brown oil

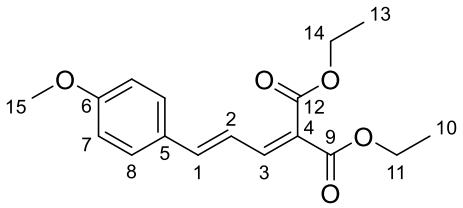
Melting point: 33-36°C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 to 7.21 (m, 7H, $H^{1 \text{ or } 3 \text{ and } 2,12,13,14}$), 7.04 (d, 1H, *J* = 15.4 Hz, $H^{3 \text{ or } 1}$), 4.38 (q, 2H, *J* = 7.1 Hz, $H^{8 \text{ or } 9}$), 4.28 (q, 2H, *J* = 7.1 Hz, $H^{9 \text{ or } 8}$), 1.38 (t, 3H, *J* = 7.1 Hz, $H^{10 \text{ or } 11}$), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 10}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 165.5, 164.8, 145.3, 144.6, 135.7, 129.9, 129.0, 127.9, 125.1, 123.4, 61.4, 61.4, 14.4, 14.3

HRMS (APCI): Calculated for $C_{16}H_{19}O_4$: 275.12779, found: 275.12767

7.2.5.2.2 Diethyl-(*E*)-2-(3-(4-methoxyphenyl)allylidene)malonate (**61n**)



Chemical Formula: $C_{17}H_{20}O_5$
Molecular Weight: 304.34

Yield: 89%

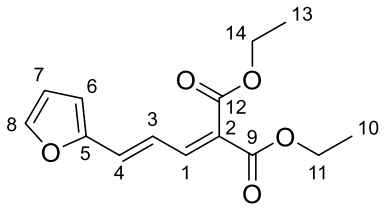
Aspect: Brown oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, 1H, *J* = 11.4 Hz, H^3), 7.49-7.42 (d, 2H, *J* = 8.8 Hz, H^8), 7.16 (dd, 1H, *J* = 15.4, 11.4 Hz, H^2), 7.0x (d, 1H, *J* = 15.4 Hz, H^1), 6.90 (d, 2H, *J* = 8.8 Hz, H^7), 4.37 (q, 2H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 4.27 (q, 2H, *J* = 7.1 Hz, $H^{14 \text{ or } 11}$), 3.84 (s, 1H, H^{15}), 1.38 (t, 3H, *J* = 7.1 Hz, $H^{10 \text{ or } 13}$), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{13 \text{ or } 10}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 165.1, 161.2, 146.2, 144.7, 131.7, 129.6, 128.6, 123.7, 121.4, 114.5, 61.4, 61.4, 55.5, 14.4, 14.3

HRMS (ESI): Calculated for $C_{17}H_{21}O_5$: 305.13890, found: 305.13826

7.2.5.2.3 Diethyl-(*E*)-2-(3-(furan-2-yl)allylidene)malonate (**61o**)



Chemical Formula: $C_{14}H_{16}O_5$
Molecular Weight: 264.28

Yield: 74%

Aspect: Black oil

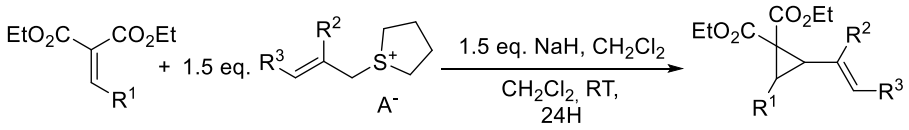
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49-7.43 (m, 2H, $H^{1,8}$), 7.11 (dd, 1H, *J* = 15.2, 12.0 Hz, H^3), 6.69 (d, 1H, *J* = 15.2 Hz, H^4), 6.54 (dd, 1H, *J* = 3.4, 0.9 Hz, H^6), 6.46 (dd, 1H, *J* = 3.4, 1.8 Hz, H^7), 4.36 (q, 2H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 4.27 (q, 2H, *J* = 7.1 Hz, $H^{14 \text{ or } 11}$), 1.37 (t, 3H, *J* = 7.1 Hz, $H^{10 \text{ or } 13}$), 1.31 (t, 3H, *J* = 7.1 Hz, $H^{13 \text{ or } 10}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 165.5, 164.9, 152.1, 144.7, 144.7, 130.5, 124.9, 121.7, 113.8, 112.5, 61.56, 61.4, 14.3, 14.3

HRMS (pAPCI): Calculated for $C_{14}H_{17}O_5$: 265.10760, found: 265.10750

7.2.6 Synthesis of vinylcyclopropanes

7.2.6.1 General procedure



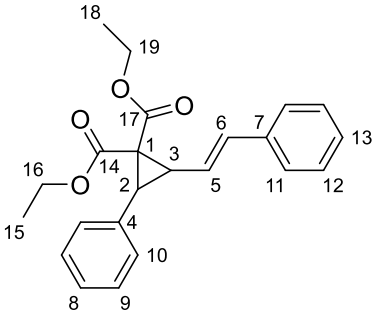
Scheme 127

NaH (1.5 eq.) is introduced into a dry round-bottom flask under argon atmosphere and is washed three times with dry n-hexane. Then, starting olefin (1 eq.) and dichloromethane (1 mL/20 mg of sulfonium salt) are added. The sulfonium salt (1.5 eq.) is added under stirring at room temperature. After 24h, water is added to stop the reaction. The two layers are separated and the organic one is washed with an aqueous solution of hydrochloric acid (1M) and brine. The organic layer is dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The vinylcyclopropane is then purified by flash column chromatography to yield a mixture of *trans* and *cis* isomers.

The eluent used for the chromatography column depends on the product and is given for each synthesized vinylcyclopropane in the next section.

7.2.6.2 Product descriptions

7.2.6.2.1 <u>1,1-Diethyl-2-phenyl-3-[(*E*)-2-phenylethenyl] cyclopropane-1,1-dicarboxylate (**56aa**)</u>



Chemical Formula: $C_{23}H_{24}O_4$
Molecular Weight: 364.44

This description for a mix of cis and trans vinylcyclopropane isomers (4/6)

Eluent for purification: *n*-hexane/AcOEt (82/18)

Yield: 90% (1.2 g)

d.r.: 4/6 (*cis/trans*)

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

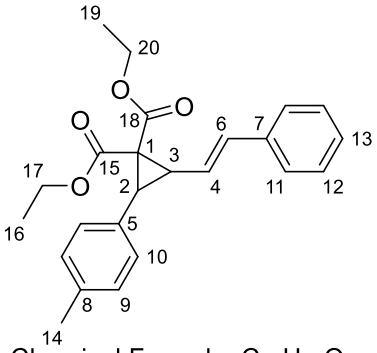
Aspect: white oil

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.37-7.16 (m, 20H, $H^{arom}{}_{cis,trans}$), 6.79 (d, 1H, *J* = 15.8 Hz, $H^6{}_{trans}$), 6.72 (d, 1H, *J* = 15.9 Hz, $H^6{}_{cis}$), 6.23 (dd, 1H, *J* = 15.9, 10.3 Hz, $H^5{}_{cis}$), 6.04 (dd, 1H, *J* = 15.8 Hz, 8.7 Hz, $H^5{}_{trans}$), 4.26 (m, 4H, $H^{16\ and/or\ 19}$), 4.10 (m, 2H, $H^{16\ and/or\ 19}{}_{cis}$), 3.90 (m, 2H, $H^{16\ and/or\ 19}{}_{trans}$), 3.48 (d, 1H, *J* = 7.9 Hz, $H^2{}_{trans}$), 3.38 (d, 1H, *J* = 9.7 Hz, $H^2{}_{cis}$), 3.32 (m, 1H, $H^3{}_{trans}$), 2.82 (dd, 1H, *J* = 10.0, 0.6 Hz, $H^3{}_{cis}$), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}{}_{cis}$), 1.25 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}{}_{trans}$), 1.15 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}{}_{cis}$), 0.93 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}{}_{trans}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 170.4, 167.8, 166.7, 166.6, 137.5, 137.1, 134.7, 134.2, 133.5, 133.2, 130.7, 129.0, 128.9, 128.9, 128.5, 128.4, 127.9, 127.7, 127.6, 126.5, 124.6, 124.5, 62.3, 62.1, 61.7, 61.5, 45.0, 40.5, 37.0, 35.9, 35.4, 33.9, 14.6, 14.4, 14.3, 14.1

HRMS (APCI): Calculated for $C_{23}H_{25}O_4$: 365.17445, found: 365.17474

7.2.6.2.2 1,1-Diethyl-2-(4-methylphenyl)-3-[(*E*)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (**56ab**)



Chemical Formula: $C_{24}H_{26}O_4$
Molecular Weight: 378,47

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

Eluent for purification: n-hexane/AcOEt (85/15)

Yield: 42% (180 mg)

d.r.: 4/6 (*cis/trans*)

Aspect: Yellow oil

Description of *trans* isomer

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.40 to 7.03 (m, 9H, H^{arom}), 6.78 (d, 1H, *J* = 15.8 Hz, H^6), 6.04 (dd, 1H, *J* = 15.8, 8.7 Hz, H^4), 4.24 (m, 2H, $H^{17\ or\ 20}$), 3.92 (m,

2H, $H^{20\ or\ 17}$), 3.45 (d, 1H, *J* = 7.9 Hz, H^{2}), 3.29 (dd, 1H, *J* = 8.7, 7.9 Hz, H^{3}), 2.31 (s, 3H, H^{14}), 1.25 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}$), 0.97 (t, 3H, *J* = 7.1 Hz, $H^{19\ or\ 16}$)

^{13}C NMR *Trans* product (300 MHz, $CDCl_3$): 168.0, 166.8, 137.3, 137.2, 134.1, 131.7, 129.2, 128.9, 128.8, 127.9, 126.5, 124.6, 62.1, 61.7, 45.0, 36.8, 34.0, 21.5, 14.6, 14.2

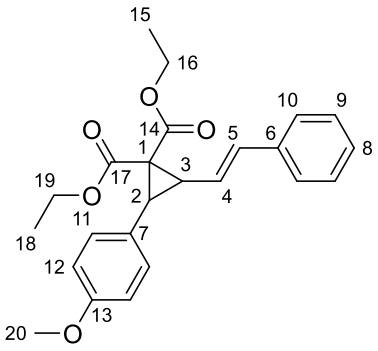
Description of *cis* isomer (from a mixture *cis* and *trans* isomers)

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.36-7.04 (m, 18H, H^{arom}), 6.78 (d, 1H, *J* = 15.8 Hz, H^{6}_{trans}), 6.71 (d, 1H, *J*=15.9 Hz, H^{6}_{cis}), 6.22 (dd, 1H, *J* = 15.9, 10.3 Hz,**^{13}C NMR (300 MHz, $CDCl_3$)**: δ= 133.1, 130.6, 129.2, 129.1, 128.9, 127.6, 126.6, 126.5, 124.8, 62.3, 62.1, 61.7, 61.5, 36.0, 35.2, 21.5, 14.6, 14.4, 14.3, 14.2, some carbons are missing

HRMS (APCI): Calculated for $C_{24}H_{27}O_4$: 379.19039, found: 379.19033

IR (cm^{-1}): 2982, 1723, 1287 (for cis/trans mixture 4/6)

7.2.6.2.3 1,1-Diethyl-2-(4-methoxyphenyl)-3-[(*E*)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (**56ac**)



Chemical Formula: $C_{24}H_{26}O_5$
Molecular Weight: 394.47

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

Eluent for purification: *n*-hexane/AcOEt (82/18)

Yield: 61% (5.36 g)

d.r.: 4/6 (*cis/trans*)

Aspect: Yellow oil

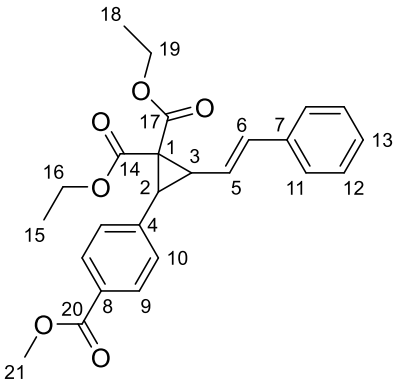
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 to 7.14 (m, 14H, $H^{arom}_{cis\ and\ trans}$), 6.82 (m, 2H, $H^{12}_{cis\ or\ trans}$), 6.80 (m, 2H, $H^{12}_{trans\ or\ cis}$), 6.80-6.75 (comp, 1H, H^{5}_{trans}), 6.71 (d, 1H, *J* = 15.9 Hz, H^{5}_{cis}), 6.21 (dd, 1H, *J* = 15.9, 10.3 Hz, $H^{4}_{cis\ or\ trans}$), 6.03 (dd, 1H, *J* = 15.8, 8.3 Hz, $H^{4}_{trans\ or\ cis}$), 4.26 (m, 4H, $H^{16\ and/or\ 19}_{cis\ or\ trans}$), 4.12 (m, 2H, $H^{16\ or\ 19}_{cis\ or\ trans}$), 3.93 (m, 2H, $H^{19\ or\ 16}_{trans\ or\ cis}$), 3.78 (s, 3H, $H^{20}_{cis\ or\ trans}$), 3.77 (s, 3H, $H^{20}_{trans\ or\ cis}$), 3.43 (d, 1H, *J* = 7.9 Hz, H^{2}_{trans}), 3.31 (d, 1H, *J* = 8.4 Hz, H^{2}_{cis}), 3.27 (t, 1H, *J* = 7.3 Hz, H^{3}_{trans}), 2.79 (t, 1H, *J* = 10.0 Hz, H^{3}_{cis}), 1.31 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}_{cis\ or\ trans}$), 1.24 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}_{cis\ or\ trans}$), 1.17 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}_{trans\ or\ cis}$), 0.98 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}_{trans\ or\ cis}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 170.3, 167.9, 159.2, 159.0, 137.6, 137.5, 134.1, 133.1, 131.9, 130.1, 128.9, 127.9, 127.7, 126.7, 126.5, 126.5, 125.4, 124.9, 124.6, 114.0, 113.8, 62.3, 62.0, 61.7, 61.5, 55.6, 55.5, 45.0, 40.5, 36.5, 36.0, 34.8, 34.0, 14.6, 14.4, 14.2

HRMS (APCI): Calculated for $C_{24}H_{27}O_5$: 395.18530, found: 395.18528

IR (cm^{-1}): 2986, 1720, 1516, 1175

7.2.6.2.4 1,1-Diethyl 2-[4-(methoxycarbonyl)phenyl]-3-[(E)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (**56ad**)



Chemical Formula: $C_{25}H_{26}O_6$
Molecular Weight: 422.48

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

Eluent for purification: *n*-hexane/AcOEt (8/2)

Yield: 53% (55 mg)

d.r.: 4/6 (*cis/trans*)

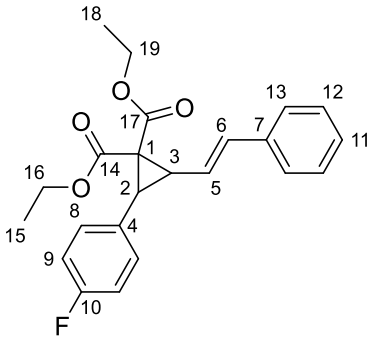
Aspect: Colorless oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, 2H, *J* = 8.3 Hz, H^9), 7.50-7.18 (m, 7H, H^{arom}), 6.80 (d, 1H, *J* = 15.9 Hz, $H^6{}_{Trans}$), 6.74 (d, 1H, *J* = 15.8 Hz, $H^6{}_{Cis}$), 6.14 (dd, 1H, *J* = 15.8, 10.3Hz, $H^5{}_{Cis}$), 6.02 (dd, 1H, *J* = 15.8, 8.6 Hz, $H^5{}_{Trans}$), 4.28 (m, 4H, $H^{16,19}$), 3.90 (s, 3H, H^{21}), 3.51 (d, 1H, *J* = 7.9 Hz, $H^2{}_{trans}$), 3.35 (m, 2H, $H^2{}_{Cis}$ and $H^3{}_{Trans}$), 2.87 (t, 1H, *J* = 10 Hz, $H^3{}_{Cis}$), 1.36-1.22 (m, 6H, $H^{15,18}$), 1.13 (m, 3H, $H^{15,18}$), 0.98 (m, 3H, $H^{15,18}$)

HRMS (APCI): Calculated for $C_{25}H_{27}O_6$: 423.17973, found: 423.18021

IR (cm^{-1}): 2982, 1719, 1274

7.2.6.2.5 1,1-Diethyl-2-(4-fluorophenyl)-3-[(*E*)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (**56ae**)



Chemical Formula: $C_{23}H_{23}FO_4$
Molecular Weight: 382.43

The characterization of this compound was made on a 1/1 mixture of cis and trans diastereomers

Eluent for purification: *n*-hexane/AcOEt (82/18)

Yield: 67% (0.96 g)

d.r.: 1/1 (*cis/trans*)

Aspect: Yellow oil

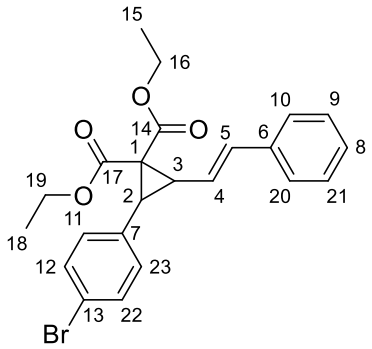
^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.39-7.19 (comp, 14H, H^{arom}), 6.99 (m, 5H, $H^{2,arom}$), 6.77 (m, 1H, $H^{2}_{cis\ or\ trans}$), 6.15 (dd, 1H, *J* = 15.9, 10.3 Hz, $H^{5}_{cis\ or\ trans}$), 6.02 (dd, 1H, *J* = 15.8, 8.7 Hz, $H^{5}_{trans\ or\ cis}$), 4.28 (m, 4H, $H^{16\ and/or\ 19}_{cis\ or/and\ trans}$), 4.12 (m, 2H, $H^{16\ or\ 19}_{cis\ or\ trans}$), 3.95 (m, 2H, $H^{19\ or\ 16}_{trans\ or\ cis}$), 3.45 (d, 1H, *J* = 7.9 Hz, $H^{2}_{cis\ or\ trans}$), 3.34-3.25 (m, 2H, $H^{2,3}_{cis\ and/or\ trans}$), 2.83 (m, 1H, $H^{2}_{cis\ or\ trans}$), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 19}_{cis\ or\ trans}$), 1.26 (t, 3H, *J* = 7.1 Hz, $H^{19\ or\ 15}_{cis\ or\ trans}$), 1.18 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 19}_{trans\ or\ cis}$), 0.98 (t, 3H, *J* = 7.1 Hz, $H^{19\ or\ 15}_{trans\ or\ cis}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 167.5, 166.4, 166.3, 137.2, 136.8, 134.2, 133.3, 132.26 (d, *J* = 7.9 Hz), 130.4 (d, *J* = 8.3 Hz), 128.9 (d, *J* = 2.87 Hz), 128.7, 127.8, 127.6, 126.3, 126.3, 124.0, 115.34 (d, *J* = 8.2 Hz) , 115.1 (d, *J* = 8.1 Hz), 110.1, 62.2, 62.0, 61.6, 61.4, 44.7, 40.2, 36.0, 35.6, 34.3, 33.8, 14.4, 14.2, 14.1, 14.0, some carbons are missing

HRMS (APCI): Calculated for $C_{23}H_{23}O_4F$: 383.16531, found: 383.16530

IR (cm^{-1}): 2982, 1721, 1512, 1221

7.2.6.2.6 1,1-Diethyl-2-(4-bromophenyl)-3-[(*E*)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (**56af**)



Chemical Formula: $C_{23}H_{23}BrO_4$
Molecular Weight: 443.34

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

Eluent for purification: cyclohexane/AcOEt (8/2)

Yield: 74% (450 mg)

d.r.: 4/6 (*cis/trans*)

Aspect: Brown oil

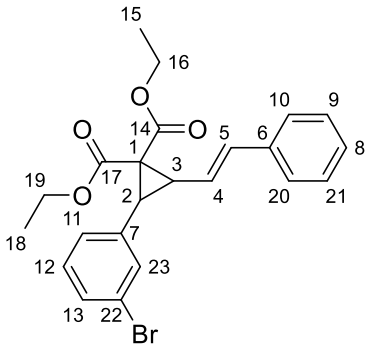
^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.70 to 7.20 (m, 9H, $H^{arom}_{Cis\ and\ Trans}$), 6.82-6.71 (comp, 2H, $H^{5}_{cis\ and\ trans}$), 6.11 (dd, 1H, *J* = 15.8, 10.3 Hz, H^4), 6.0 (dd, 1H, *J* = 15.8, 8.6 Hz, H^4), 4.26 (m, 4H, $H^{16,19}$), 4.12 (m, 2H, $H^{16\ or\ 19}$), 3.96 (m, 2H, $H^{16\ or\ 19}$), 3.68 (d, 1H, *J* = 10.2 Hz, H^2), 3.41 (d, 1H, *J* = 7.9 Hz, H^2), 3.34 (m, 1H, H^3), 2.83 (t, 1H, *J* = 10.0 Hz, H^3), 1.21 (m, 12H, $H^{15,18}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.17, 132.26, 132.21, 132.13, 131.49, 131.33, 131.22, 130.36, 129.45, 129.41, 128.60, 127.53, 126.20, 126.17, 123.65, 62.13, 61.90, 61.57, 61.48, 61.32, 57.66, 35.96, 35.93, 34.31, 33.55, 26.92, 14.23 (some carbons are missing)

HRMS (APCI): Calculated for $C_{23}H_{24}O_4$: 443.08525, found: 443.08521

IR (cm^{-1}): 2920, 1724

7.2.6.2.7 1,1-Diethyl-2-(3-bromophenyl)-3-[(E)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (**56ag**)



Chemical Formula: $C_{23}H_{23}BrO_4$
Molecular Weight: 443.34

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

Eluent for purification: cyclohexane/AcOEt (8/2)

NMR Yield: 53% (28 mg)

d.r.: 4/6 (*cis/trans*)

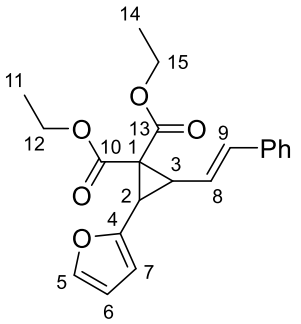
Aspect: yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.44 to 7.13 (m, 18H, $H^{arom}_{cis\ and\ trans}$), 6.79 (d, 1H, *J* = 15.8 Hz, $H^{5}_{cis\ or\ trans}$), 6.73 (d, 1H, *J* = 15.9 Hz, $H^{5}_{trans\ or\ cis}$), 6.13 (dd, 1H, *J* = 15.8, 10.3 Hz, $H^{4}_{cis\ or\ trans}$), 6.00 (dd, 1H, *J* = 15.8, 8.6 Hz, $H^{4}_{trans\ or\ cis}$), 4.27 (m, 4H, $H^{16,19}_{cis\ or\ trans}$), 4.14 (q, 2H, *J* = 7.3 Hz, $H^{16\ or\ 19}_{cis\ or\ trans}$), 3.97 (q, 2H, *J*=7.1 Hz, $H^{19\ or\ 16}_{trans\ or\ cis}$), 3.44 (d, 1H, *J* = 7.9 Hz, $H^{2}_{cis\ or\ trans}$), 3.32 (d, 1H, *J* = 9.7 Hz, $H^{2}_{trans\ or\ cis}$), 3.26 (m, 1H, $H^{3}_{trans\ or\ cis}$), 2.81 (t, 1H, *J* = 10.1 Hz, $H^{3}_{trans\ or\ cis}$), 1.33 (t, 3H, *J* = 7.2 Hz, $H^{15\ or\ 18}_{cis\ or\ trans}$), 1.25 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}_{trans\ or\ cis}$), 1.20 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}_{cis\ or\ trans}$), 1.00 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}_{trans\ or\ cis}$)

^{13}C NMR DEPT-Q (75 MHz, $CDCl_3$): δ = 129.9, 129.7, 126.4, 123.7, 62.3, 62.1, 61.8, 61.6, 14.4, 14.3, 14.2, 14.0, some carbons are missing

HRMS (APCI): Calculated for $C_{23}H_{24}O_4$: 443.08525, found: 443.08519

7.2.6.2.8 1,1-Diethyl-2-(furan-2-yl)-3-[(*E*)-2-phenylethenyl]cyclopropane-1,1-dicaboxylate (**56ah**)



Chemical Formula: $C_{21}H_{22}O_5$
Molecular Weight: 354.40

The characterization of this compound was made on a 4/6 (or 6/4) mixture of cis and trans diastereomers

No purification was required

Yield: 95% (165 mg)

d.r.: 4/6 (*cis/trans or trans/cis*)

Aspect: Yellow oil

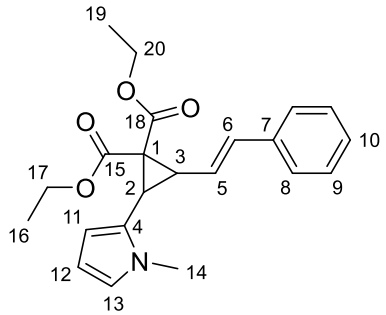
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 to 7.15 (m, 10H, H^{phenyl}), 6.78 (d, 1H, *J* = 15.8 Hz, H^9), 6.72 (d, 1H, *J* = 15.9 Hz, H^9), 6.36 (dd, 1H, *J* = 15.8, 10.2 Hz, H^8), , 6.32 (m, 1H, H^6), 6.30 (dd, 1H, *J* = 3.3, 1.9 Hz, H^6), 6.24 (m, 1H, $H^{5 \text{ or } 7}$), 6.18 (m, 1H, $H^{5 \text{ or/and } 7}$), 6.04 (dd, 1H, *J* = 15.8, 8.8 Hz, H^8), 4.27 (m, 4H, $H^{12,15}$), 4.20 (m, 2H, $H^{12 \text{ or } 15}$), 4.07 (qq, 2H, *J* = 7.2, 3.6 Hz, $H^{12 \text{ or } 15}$), 3.38 (d, 1H, *J* = 7.7 Hz, H^2), 3.25 (m, 1H, H^3), 3.22 (d, 1H, *J* = 7.9 Hz, H^2), 2.85 (m, 1H, H^3), 1.30 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 1.25 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 1.19 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 1.10 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.33, 166.94, 166.26, 165.52, 149.04, 148.31, 142.02, 137.07, 136.65, 134.43, 133.86, 128.58, 128.53, 127.66, 127.45, 126.26, 126.20, 123.43, 123.10, 110.51, 110.42, 109.36, 107.81, 62.23, 61.91,

61.65, 61.38, 43.94, 40.29, 35.17, 33.58, 31.95, 29.82, 29.72, 29.19, 22.71, 14.20, 14.15, 14.06, 13.97, 13.92, some carbons are missing

HRMS (APCI): Calculated for $C_{21}H_{22}O_5$: 355.15400 found: 355.15384

7.2.6.2.9 1,1-Diethyl-2(1-methyl-1H-pyrrol-2-yl)-3-[(*E*)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (**56ai**)



Chemical Formula: $C_{22}H_{25}NO_4$
Molecular Weight: 367.45

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

Note that in this case the reaction solvent, dichloromethane, was replaced by acetonitrile (1 mL/0.04 mmol of starting olefin) and the reaction as been performed at 0°C for 1h before to allow it to stir for 24h additional hours at room temperature

Eluent for purification: n-hexane/AcOEt (8/2)

Yield: 5% (10 mg)

d.r.: 4/6 (*cis/trans*)

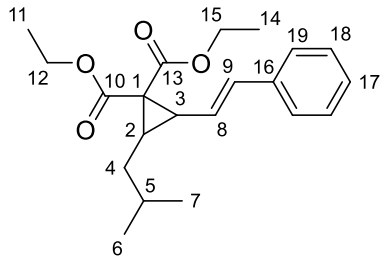
Aspect: white oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5H, H^{arom}), 6.78 (d, 1H, *J* = 15.8 Hz, H^6), 6.56 (dd, 1H, *J* = 2.7, 1.8 Hz, H^{13}), 6.05 (m, 1H, H^{11}), 5.99 (m, 1H, H^5), 5.94 (m, 1H, H^{12}), 4.24 (m, 2H, $H^{17 \text{ or } 20}$), 3.98 (q, 2H, *J* = 7.1 Hz, $H^{17 \text{ or } 20}$), 3.63 (s, 3H, H^{14}), 3.23 (m, 2H, $H^{2,3}$), 1.24 (t, 3H, *J* = 7.1 Hz, $H^{16 \text{ or } 19}$), 1.01 (t, 3H, *J* = 7.1 Hz, $H^{16 \text{ or } 19}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 163.3, 136.9, 134.3, 128.7, 127.7, 127.7, 126.3, 123.8, 122.9, 107.8, 106.9, 61.9, 61.6, 44.2, 33.9, 33.5, 29.3, 14.3, 14.0

HRMS (ESI): Calculated for $C_{22}H_{26}NO_4$: 368.18563 found: 368.18574

7.2.6.2.10 1,1-diethyl-2-(2-methylpropyl)-3-[(E)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (**56aj**)



Chemical Formula: $C_{21}H_{28}O_4$
Molecular Weight: 344.45

This description is for only one diastereoisomer of the vinylcyclopropane

Yield: 28 % (30 mg)

d.r. : 7/3 (*cis/trans or trans/cis*)

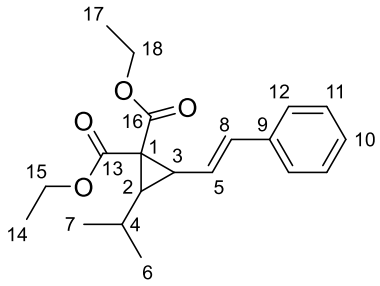
Aspect: clear oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (m, 5H, H^{arom}), 6.63 (d, 1H, *J* = 15.8 Hz, H^9), 5.87 (dd, 1H, *J* = 15.8, 9.0 Hz, H^8), 4.21 (m, 4H, $H^{12,15}$), 2.56 (m, 1H, H^3), 2.14 (td, 1H, *J* = 8.1, 6.0 Hz, H^2), 1.71 (m, 1H, H^5), 1.50 (m, 1H, H^4), 1.29 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 1.22 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 1.14 (m, 1H, H^4), 0.95 (d, 3H, *J* = 6.7 Hz, $H^{6 \text{ or } 7}$), 0.92 (d, 3H, *J* = 6.7 Hz, $H^{6 \text{ or } 7}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 168.2, 167.9, 136.9, 132.9, 128.5, 127.3, 126.0, 125.0, 61.5, 41.8, 36.3, 36.2, 31.8, 28.1, 22.7, 22.2, 14.23

HRMS (APCI): calculated for $C_{21}H_{29}O_4$: 345.20604, found: 345.20591

7.2.6.2.11 1,1-Diethyl-2-[(*E*)-2-phenylethenyl]-3-(propan-2-yl)cyclopropane-1,1-dicarboxylate (**56ak**)



Chemical Formula: $C_{20}H_{26}O_4$
Molecular Weight: 330.42

This description is for only one diastereoisomer of the vinylcyclopropane

Eluent for purification: *n*-hexane/AcOEt (9/1)

Yield: 31% (145 mg)

d.r.: 4/6 (*cis/trans*)

Aspect: Yellow oil

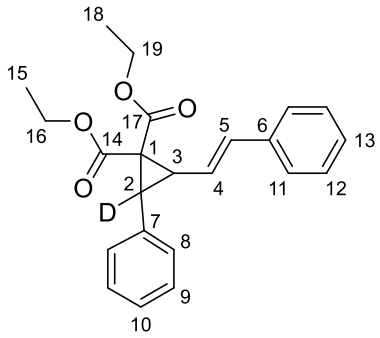
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.17 (m, 5H, H^{arom}), 6.62 (dd, 1H, *J* = 15.8, 0.7 Hz, H^8), 5.86 (dd, 1H, *J* = 15.8, 8.8 Hz, H^5), 4.32-4.07 (m, 4H, $H^{15,18}$), 2.61 (m, 1H, H^3), 1.94 (dd, 1H, *J* = 10.4, 7.7 Hz, H^2), 1.29 (t, 3H, *J* = 7.1 Hz, $H^{14\ or\ 17}$), 1.21 (t, 3H, *J* = 7.1 Hz, $H^{17\ or\ 14}$), 1.06 (d, 3H, *J* = 6.6 Hz, $H^{6\ or\ 7}$), 0.99 (d, 3H, *J* = 6.6 Hz, $H^{7\ or\ 6}$), *H^4 is hidden by $H^{14\ or\ 17}$ signal*

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 168.0, 136.9, 132.8, 128.5, 127.3, 126.1, 125.2, 61.5, 61.4, 42.6, 40.7, 35.4, 27.9, 22.2, 21.6, 14.2, 14.2

HRMS (APCI): Calculated for $C_{20}H_{27}O_4$: 331.19039, found: 331.19026

IR (cm^{-1}): 2960, 1719, 1284, 1199, 692

7.2.6.2.12 1,1-diethyl-2-phenyl-3-[(E)-2-phenylethenyl](2-2H)cyclopropane-1,1-dicarboxylate (**56al**)



Chemical Formula: $C_{23}H_{23}DO_4$
Molecular Weight: 365.45

This vinylcyclopropane was not purified because it was obtained in very small quantity and reactants are very expansive. Its characterization was made on a 4/6 mixture of cis and trans diastereomers

Eluent for purification: cyclohexane/AcOEt (9/1)

Yield: 70% (57 mg)

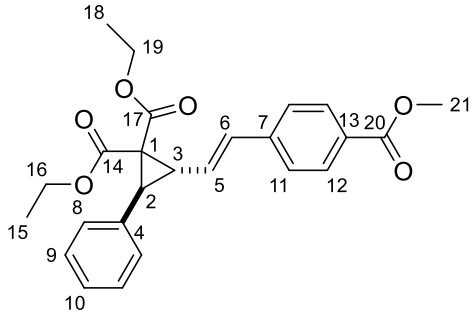
d.r.: 6/4 (*trans/cis*)

Aspect: White oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 to 7.17 (m, 10H, H^{arom}), 6.79 (d, 1H, *J* = 15.9 Hz, H^5_{trans}), 6.72 (d, 1H, *J* = 15.9 Hz, H^5_{cis}), 6.23 (dd, 1H, *J* = 15.8, 10.3 Hz, H^4_{cis}), 6.04 (dd, 1H, *J* = 15.9, 8.7 Hz,, H^4_{trans}), 4.16 (m, 4H, $H^{16\ and/or\ 19}$), 4.10 (m, 2H, $H^{16\ or\ 19}$), 3.91 (m, 2H, $H^{19\ or\ 16}$), 3.32 (d, 1H, *J* = 8.7 Hz, H^3_{trans}), 2.82 (d, 1H, *J* = 10.3 Hz, H^3_{cis}), 1.39-1.10 (m, 12H, $H^{15,18}$).

HRMS (APCI): Calculated for $C_{23}H_{24}DO_4$: 366.18082, found: 366.18256

7.2.6.2.13 1,1-diethyl-2-[(*E*)-2-[4-(methoxycarbonyl)phenyl]ethenyl]-3-phenylcyclopropane-1,1-dicarboxylate (**56ba**)



Chemical Formula: $C_{25}H_{26}O_6$
Molecular Weight: 422.48

This description for trans vinylcyclopropane isomer

Note that in this case the reaction solvent, dichloromethane, was replaced by dimethylformamide (1 mL/0.04 mmol of starting olefin)

Eluent for purification: *n*-hexane/AcOEt (8/2)

Yield: 55% (20 mg)

d.r.: 0/10 (*cis/trans*)

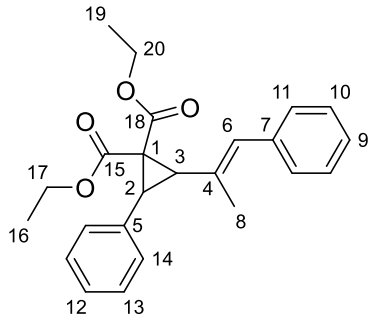
Aspect: Colorless oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (m, 2H, H^{12}), 7.40 (m, 2H, H^{11}), 7.31-7.21 (m, 5H, H^{arom}), 6.83 (d, 1H, *J* = 15.9 Hz, H^6), 6.17 (dd, 1H, *J* = 15.8, 8.8 Hz, H^5), 4.25 (m, 2H, $H^{16 \text{ or } 19}$), 3.91 (m, 2H, $H^{19 \text{ or } 16}$), 3.50 (d, 1H, *J* = 7.9 Hz, H^2), 3.33 (ddd, 1H, *J* = 8.6, 7.9, 0.7 Hz, H^3), 1.57 (s, 3H, H^{21}), 1.25 (t, 3H, *J* = 7.1 Hz, $H^{15 \text{ or } 18}$), 0.93 (t, 3H, *J* = 7.1 Hz, $H^{18 \text{ or } 15}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 167.8, 166.5, 141.5, 134.5, 133.3, 130.3, 128.9, 128.6, 127.8, 127.5, 126.4, 62.3, 61.8, 52.4, 45.2, 37.2, 33.8, some carbons are missing

HRMS (APCI): Calculated for $C_{25}H_{27}O_6$: 423.17973, found: 423.18022

7.2.6.2.14 1,1-Diethyl-2-phenyl-3-[(1*E*)-1-phenylprop-1-en-2-yl]cyclopropane-1,1-dicarboxylate (**56ca**)



Chemical Formula: $C_{24}H_{26}O_4$
Molecular Weight: 378.47

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

Eluent for purification: *n*-hexane/AcOEt (9/1)

Yield: 19 % (14 mg)

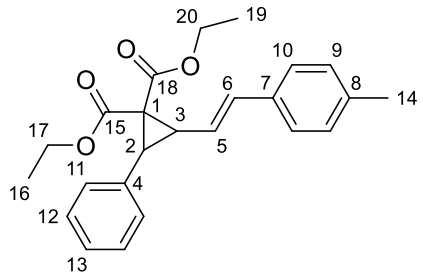
Aspect: colorless oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (m, 20H, $H^{arom}_{cis,\ trans}$), 6.41 (s, 2H, $H^{6}_{cis,\ trans}$), 4.29-3.77 (m, 8H, $H^{17,20}_{cis,\ trans}$), 3.63 (d, 1H, *J* = 8.6 Hz, H^{2}_{trans}), 3.26 (d, 1H, *J* = 8.5 Hz, H^{3}_{trans}), 3.06 (d, 1H, *J* = 10.3 Hz, H^{2}_{cis}), 2.76 (dd, 1H, *J* = 10.2, 0.9 Hz, H^{3}_{cis}), 1.91 (s, 3H, $H^{8}_{cis\ or\ trans}$), 1.89 (s, 3H, $H^{8}_{cis\ or\ trans}$), 1.24 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}_{cis}$), 1.16 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}_{trans}$), 0.96 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}_{cis}$), 0.87 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}_{trans}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 177.0, 167.4, 167.2, 166.5, 138.0, 137.7, 135.2, 134.6, 131.9, 131.5, 130.1, 130.0, 129.2, 129.1, 128.6, 128.5, 128.4, 128.4, 127.9, 127.7, 127.1, 126.9, 126.7, 62.4, 61.9, 61.7, 61.4, 44.9, 41.4, 39.8, 38.9, 35.8, 34.9, 19.7, 18.8, 14.6, 14.4, 14.2, 14.1

HRMS (ESI): Calculated for $C_{24}H_{27}O_4$: 379.19039, found: 379.19032

7.2.6.2.15 1,1-Diethyl-2-[(E)-2-(4-methylphenyl)ethenyl]-3-phenylcyclopropane-1,1-dicarboxylate (**56da**)



Chemical Formula: $C_{24}H_{26}O_4$
Molecular Weight: 378.47

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers

Eluent for purification: *n*-hexane/AcOEt (9/1)

Yield: 32% (55 mg)

d.r.: 4/6 (*cis/trans*)

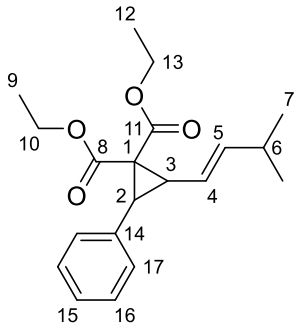
Aspect: Yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (m, 14H, $H^{arom}_{cis,\ trans}$), 7.02 (m, 4H, $H^{9}_{cis,\ trans}$), 6.68 (d, 1H, *J* = 15.8 Hz, H^{6}_{trans}), 6.62 (d, 1H, *J* = 15.9 Hz, H^{6}_{cis}), 6.09 (dd, 1H, *J* = 15.8, 10.3 Hz, H^{5}_{cis}), 5.91 (dd, 1H, *J* = 15.8, 8.6 Hz, H^{5}_{trans}), 4.17 (m, 3H, $H^{17,20}_{trans}$), 4.03 (m, 1H, $H^{17\ or\ 20}_{trans}$), 3.83 (m, 4H, $H^{17,20}_{cis}$), 3.40 (d, 1H, *J* = 7.9 Hz, H^{2}_{trans}), 3.29 (d, 1H, *J* = 9.9 Hz, H^{2}_{cis}), 3.24 (m, 1H, H^{3}_{trans}), 2.76 (t, 1H, *J* = 10.2 Hz, H^{3}_{cis}), 2.26 (s, 3H, H^{14}_{trans}), 2.24 (s, 3H, H^{14}_{cis}), 1.25 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}_{cis}$), 1.17 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}_{trans}$), 1.08 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}_{cis}$), 0.85 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}_{trans}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 167.9, 166.8, 166.7, 137.7, 137.5, 134.8, 134.8, 134.3, 134.1, 133.6, 133.2, 130.8, 129.6, 129.6, 129.0, 128.5, 128.4, 127.7, 127.5, 126.5, 126.4, 123.5, 123.3, 62.3, 62.1, 61.7, 61.5, 45.0, 40.4, 37.0, 36.0, 35.4, 33.9, 21.5, 14.6, 14.4, 14.3, 14.1,

HRMS (APCI): Calculated for $C_{24}H_{27}O_4$: 379.19039, found: 379.19031

7.2.6.2.16 1,1-Diethyl-2-[(1*E*)-3-methylbut-1-en-1-yl]-3-phenylcyclopropane-1.1-dicarboxylate (**56ea**)



Chemical Formula: $C_{20}H_{26}O_4$
Molecular Weight: 330.42

The characterization of this compound was made on a 3/7 mixture of cis and trans diastereomers

Eluent for purification: *n*-hexane/AcOEt (85/15)

Yield: 97% (125 mg)

d.r.: 3/7 (*cis/trans*)

Aspect: Transparent oil

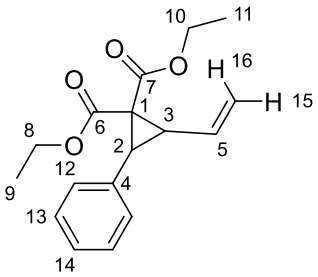
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 to 7.17 (m, 10H, H^{arom}), 5.84 (ddd, 2H, *J* = 15.5, 6.7, 0.8 Hz, H^5), 5.80 (dd, 1H, *J* = 15.1, 6.4 Hz, $H^5{}_{cis}$), 5.36 (ddd, 1H, *J* = 15.5, 10.1, 1.4 Hz, $H^4{}_{cis}$), 5.22 (ddd, 1H, *J* = 15.4, 8.1, 1.4 Hz, $H^4{}_{trans}$), 4.25 (m, 2H, $H^{10,13}$), 4.07 (m, 2H, $H^{10\ or\ 13}$), 3.88 (m, 2H, $H^{10\ or\ 13}$), 3.32 (d, 1H, *J* = 8.0 Hz, $H^2{}_{trans}$), 3.20 (d, 1H, *J* = 9.9 Hz, $H^2{}_{cis}$), 3.08 (dd, 1H, *J* = 8.1 Hz, $H^3{}_{trans}$), 2.64 (dd, 1H, *J* = 10.0 Hz, $H^3{}_{cis}$), 2.30 (m, 2H, H^6), 1.29 (m, 6H, $H^{9\ and/or\ 12}$), 1.13 (t, 3H, *J* = 7.1 Hz, $H^{9\ or\ 12}$), 0.98 (m, 6H, H^7), 0.90 (t, 3H, *J* = 7.1 Hz, $H^{9\ or\ 12}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 167.8, 167.0, 142.9, 142.1, 135.1, 133.9, 130.8, 129.0, 128.4, 128.1, 127.5, 127.3, 121.3, 121.2, 110.3, 62.2, 61.9, 61.6, 61.3, 44.7, 39.8, 36.5, 35.4, 34.9, 33.2, 31.5, 31.5, 22.7, 14.7, 14.4, 14.3, 14.1

HRMS (APCI): calculated for $C_{20}H_{27}O_4$: 331.19039 found: 331.19025

IR (cm^{-1}): 2960, 1723, 1093, 697

7.2.6.2.17 1,1-Diethyl-2-ethenyl-3-phenylcyclopropane-1,1-dicarboxylate (**56fa**)



Chemical Formula: $C_{17}H_{20}O_4$
Molecular Weight: 288.34

The characterization of this compound was made on a 1/1 mixture of cis and trans diastereomers

Eluent for purification: *n*-hexane/AcOEt (85/15)

Yield: 11% *(crude yield measured by NMR is 90%)* (13 mg)

d.r.: 1/1 (*cis/trans*)

Aspect: Transparent oil

^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.34 to 7.19 (m, 10H, $H^{arom}_{cis\ and\ trans}$), 5.82 (t, 1H, *J* = 10.3 Hz, $H^5_{cis\ or\ trans}$), 5.78 (t, 1H, *J* = 10.3 Hz, $H^5_{trans\ or\ cis}$), 5.47-4.39 (m, 2H, $H^{15,16}_{cis\ or\ trans}$), 5.25-5.20 (m, 2H, $H^{15,16}_{cis\ or\ trans}$), 4.32-4.18 (m, 4H, $H^{8\ and/or\ 10}_{cis\ and/or\ trans}$), 4.09 (m, 2H, $H^{8\ or\ 10}_{cis\ or\ trans}$), 3.89 (m, 2H, $H^{8\ or\ 10}_{cis\ or\ trans}$), 3.37 (d, 1H, *J* = 7.9 Hz, H^2_{trans}), 3.27 (d, 1H, *J* = 9.9 Hz, H^2_{cis}), 3.16 (t, 1H, *J* = 8.1 Hz, H^3_{trans}), 2.66 (t, 1H, *J* = 10.1 Hz, H^3_{cis}), 1.31 (t, 3H, *J* = 7.1 Hz, $H^{9\ or\ 11}_{cis\ or\ trans}$), 1.28 (t, 3H, *J* = 7.1 Hz, $H^{9\ or\ 11}_{cis\ or\ trans}$), 1.14 (t, 3H, *J* = 7.1 Hz, $H^{9\ or\ 11}_{cis\ or\ trans}$), 0.91 (t, 3H, *J* = 7.1 Hz, $H^{9\ or\ 11}_{cis\ or\ trans}$)

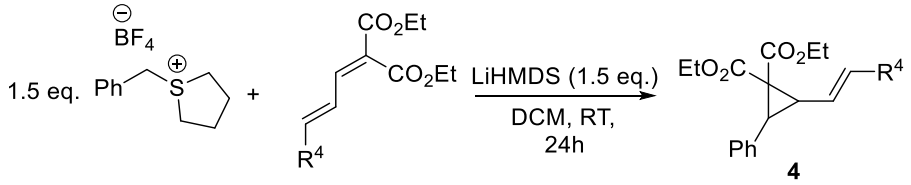
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 167.5, 166.5, 166.3, 134.5, 133.3, 132.6, 132.4, 130.5, 1128.7, 128.3, 128.0, 127.4, 118.9, 118.2, 62.1, 61.8, 61.4, 61.2, 44.5, 39.9, 36.1, 35.8, 34.8, 33.6, 14.4, 14.2, 14.0, 13.9

HRMS (pAPCI): calculated for $C_{17}H_{21}O_4$: 289.14344, found: 289.14318

IR (cm^{-1}): 2925, 1727, 1286

7.2.6.1 VCPs using benzylic ylide

7.2.6.1.1 General procedure



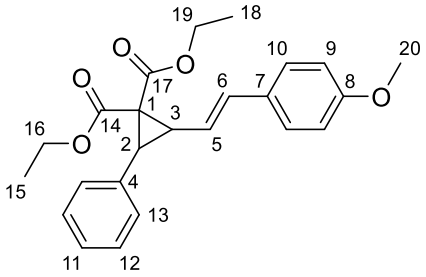
4

In a dry two necked flask, under argon atmosphere, 1-benzylthiolan-1-ium trifluoroborane fluoride (0.85 mmol, 1.5 eq.), dichloromethane (10 mL) and the corresponding 1,3-diene (0.57 mmol, 1.0 eq.) are introduced. The mixture is cooled down to -78°C with a acetone/dry-ice bath. Then, LiHMDS (0.43 mmol, 0.75 eq.) is added and the mixture is stirred for 15 min. Another portion of LiHMDS (0.43 mmol, 0.75 eq.) is added again and the media is stirred for 1h at -78°C before letting it warm to room temperature and stir for one additional hour. An aqueous solution of HCl (1M) is added to the mixture and the aqueous layer is extracted three times with dichloromethane. Organic fractions are combined and dryed over $MgSO_4$ before evaporating the solvent under reduced pressure. The obtained crude product is purified on a silica chromatography column.

The eluent used is described for each obtained compound

7.2.6.2 Product descriptions

7.2.6.2.1 Diethyl (*E*)-2-(4-methoxystyryl)-3-phenylcyclopropane-1,1-dicarboxylate (**56an**)



Chemical Formula: $C_{24}H_{26}O_5$
Molecular Weight: 394.47

The characterization of this compound was made on a 4/6 mixture of cis and trans diastereomers.

Eluent for purification: *n*-hexane/AcOEt (88/18)

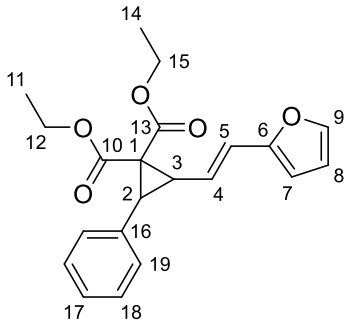
Yield: 62%

Aspect: colorless oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52-7.22 (m, 14H, H^{arom}), 6.73 (d, 1H, *J* = 15.8 Hz, H^6_{trans}), 6.66 (d, 1H, *J* = 15.8 Hz, H^6_{cis}), 6.07 (m, 1H, H^5_{cis}), 5.90 (dd, 1H, *J* = 15.8, 8.6 Hz, H^5_{trans}), 4.40-4.02 (comp, 6H, $H^{16,19}_{cis\ and\ trans}$), 3.90 (m, 2H, $H^{15\ or\ 19}_{cis\ or\ trans}$), 3.80 (s, 3H, H^{20}_{cis}), 3.79 (s, 3H, H^{20}_{trans}), 3.47 (d, 1H, *J* = 8.0 Hz, H^2_{trans}), 3.35 (d, 1H, *J* = 9.8 Hz, H^2_{cis}), 3.30 (dd, 1H, *J* = 8.7, 8.0 Hz, H^3_{trans}), 2.79 (m, 1H, H^3_{cis}), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}_{cis\ or\ trans}$), 1.24 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}_{trans\ or\ cis}$), 1.15 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}_{cis\ or\ trans}$), 0.92 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}_{trans\ or\ cis}$)

HRMS (APCI): Calculated for $C_{24}H_{27}O_5$: 395.18529, found: 395.18519

7.2.6.2.2 Diethyl-(*E*)-2-(2-(furan-2-yl)vinyl)-3-phenylcyclopropane-1,1-dicarboxylate (**56ao**)



Chemical Formula: $C_{21}H_{22}O_5$
Molecular Weight: 354.40

The characterization of this compound was made on a 7/3 mixture of cis and trans diastereomers.

Eluent for purification: *n*-hexane/AcOEt (83/17)

Yield: 13% (50 mg)

d.r.: 3/7 (*cis/trans*)

Aspect: colorless oil

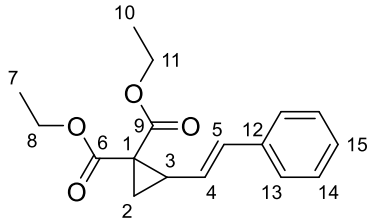
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.21 (m, 5H, $H^{arom,9}$), 6.58 (d, 1H, *J* = 15.9 Hz, H^5_{trans}), 6.52 (d, 1H, *J* = 16.0 Hz, H^5_{cis}), 6.34 (m, 2H, $H^{7\ or\ 8}_{cis\ and\ trans}$), 6.21 (m, 2H, $H^{8\ or\ 7}_{cis\ and\ trans}$), 6.18 (m, 1H, H^4_{cis}), 5.98 (dd, 1H, *J* = 15.8, 8.8 Hz, H^4_{trans}), 4.26 (m, 4H, $H^{12\ or\ 15}_{cis\ and\ trans}$), 4.09 (m, 2H, $H^{12\ or\ 15}_{cis}$), 3.90 (m, 2H, $H^{15\ or\ 12}_{trans}$), 3.46 (d, 1H, *J* = 7.9 Hz, H^2_{trans}), 3.35 (d, 1H, *J* = 9.6 Hz, H^2_{cis}), 3.25 (m, 1H, H^3_{trans}), 2.73 (m, 1H, H^3_{cis}), 1.31 (t, 3H, *J* = 7.1 Hz, $H^{11\ or\ 14}_{cis}$), 1.26 (t, 3H, *J* = 7.1 Hz, $H^{11\ or\ 14}_{trans}$), 1.14 (t, 3H, *J* = 7.1 Hz, $H^{14\ or\ 11}_{cis}$), 0.92 (t, 3H, *J* = 7.1 Hz, $H^{14\ or\ 11}_{trans}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 167.5, 166.5, 152.5, 151.7, 142.1, 134.5, 133.2, 130.5, 128.7, 128.3, 128.2, 127.5, 127.4, 123.0, 122.9, 122.2, 121.5, 111.4, 107.7, 107.3, 61.1, 61.9, 61.5, 61.3, 44.9, 36.8, 35.7, 35.3, 33.5, 14.3, 14.2, 14.0, 13.9

HRMS (APCI): Calculated for $C_{21}H_{23}O_5$: 355.15400 found: 355.15390

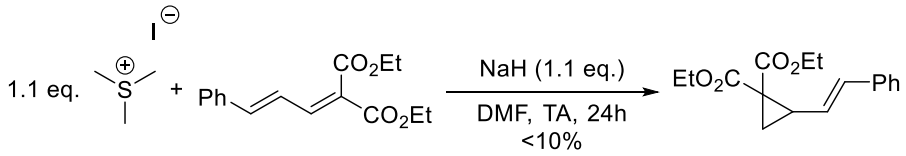
7.2.6.3 Synthesis of other vinylcyclopropanes

7.2.6.3.1 Diethyl (*E*)-2-styrylcyclopropane-1,1-dicarboxylate (**56ap**)



Chemical Formula: $C_{17}H_{20}O_4$
Molecular Weight: 288.34

Procedure:



NaH (5.3 mmol, 1.1 eq.) is introduced into a dry two necked flask under argon atmosphere and washed three times with dry *n*-hexane. Then, dry DMF (9 mL) and trimethylsulfonium iodide (5.3 mmol, 1.1 eq.) are added at room temperature and the mixture is allowed to stirr for 30 min. A solution of diethyl (*E*)-2-(3-phenylallylidene)malonate (4.75 mmol, 1 eq.) in solution in DMF (4 mL) is added to the mixture which is stirred for 24h additional hours.Brine is added to the mixture and the aqueous layer is extracted three times with dichloromethane. Organic fractions are combined and dried over $MgSO_4$ before evaporating the solvent under reduced pressure. The desired product is obtained after purification by chromatography over silica with *n*-hexane/AcOEt (85/15) as an eluent.

Yield: <10% (10 mg)

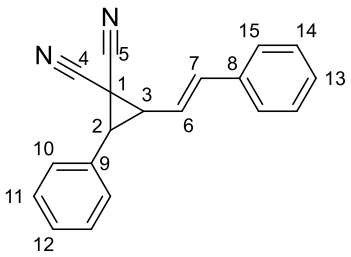
Aspect: colorless oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (m, 5H, H^{arom}), 6.64 (dd, 1H, *J* = 15.8, 0.8 Hz, H^{5}), 5.82 (dd, 1H, *J* = 15.8, 8.8 Hz, H^{4}), 4.22 (m, 4H, $H^{8,11}$), 2.73 (m, 1H, H^{3}), 1.82 (dd, 1H, *J* = 7.5, 4.9 Hz, H^{2}), 1.66 (dd, 1H, *J* = 9.0, 7.9 Hz, $H^{2'}$), 1.29 (t, 3H, *J* = 7.1 Hz, $H^{7 \text{ or } 10}$), 1.22 (t, 3H, *J* = 7.1 Hz, $H^{10 \text{ or } 7}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 169.8, 167.7, 136.9, 133.7, 128.7, 127, 126.3, 125.0, 61.8, 61.7, 36.5, 31.4, 21.2, 14.4, 14.2

HRMS (APCI): calculated for $C_{17}H_{21}O_4$: 289.14344, found: 289.14338

7.2.6.3.2 2-Phenyl-3-[(E)-2-phenylethenyl]cyclopropane-1,1-dicarbonirile



Chemical Formula: $C_{19}H_{14}N_2$
Molecular Weight: 270.34

The characterization of this compound was made on a 3/7 mixture of cis and trans diastereomers.

No prufication required

Yield : quant (340 mg)

d.r.: 3/7 (*cis/trans*)

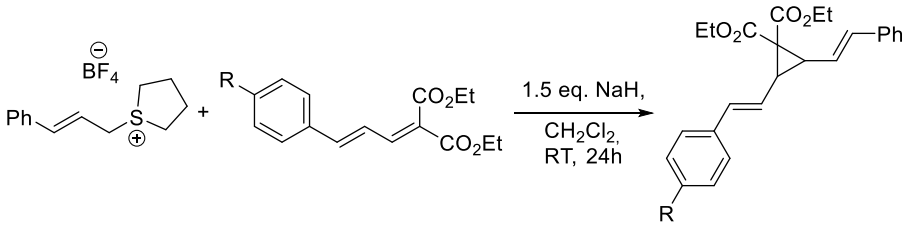
Aspect: Clear oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (m, 20H, $H^{arom}_{cis,\ trans}$), 7.00 (d, 1H, *J* = 5.7 Hz, H^7_{trans}), 6.95 (d, 1H, *J* = 5.7 Hz, H^7_{cis}), 6.08 (dd, 1H, *J* = 15.7, 8.0 Hz, H^6_{cis}), 5.67 (dd, 1H, *J* = 15.7, 10 Hz, H^6_{trans}), 3.52 (d, 1H, *J* = 9.7 Hz, H^2_{trans}), 3.36 (d, 1H, *J* = 8.4 Hz, H^2_{cis}), 3.26 (m, 2H, $H^3_{cis,\ trans}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.39, 138.17, 129.99, 129.55, 129.24, 129.16, 128.89, 128.82, 128.31, 126.74, 120.23, 118.39, 115.43, 113.60, 112.82, 111.96, 40.33, 38.71, 37.85, 37.70, 14.37, 11.71 some carbons are missing)

HRMS (APCI): calculated for $C_{19}H_{15}N_2$: 271.12298 found: 271.12292

7.2.6.4 Di-VCP synthesis



Scheme 128

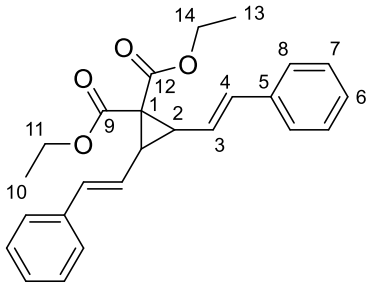
7.2.6.4.1 General procedure

NaH (1.5 eq.) is introduced into a dry round-bottom flask under argon atmosphere and washed three times with dry *n*-hexane. Then, starting 1,3-diene (1 eq.) and dichloromethane (1 mL/20 mg of sulfonium salt) are added. The sulfonium salt (1.5 eq.) is added under stirring at room temperature. After 24h, water is added to stop the reaction. The two layers are separated and the organic one is washed with an aqueous solution of hydrochloric acid (1M) and brine. The organic layer is dried over $MgSO_4$ and concentrated under reduced pressure The obtained di-VCP is then purified by flash column chromatography to yield a mixture of *trans* and *cis* isomers.

The eluent used for the chromatography column depends on the product and is given for each synthesized vinylcyclopropane in the next section.

7.2.6.4.2 Product descriptions

1,1-Diethyl 2,3-bis[(E)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (62aa)



Chemical Formula: $C_{25}H_{26}O_4$
Molecular Weight: 390.48

The characterization of this compound was made on a 3/7 mixture of cis and trans diastereomers.

Eluent for purification: *n*-hexane/AcOEt (8/2)

Yield: 32% (25 mg)

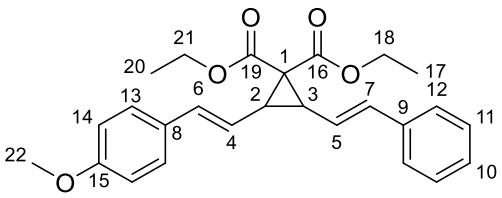
Aspect: Yellow oil

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.29 to 7.05 (m, 16H, H^{arom}), 6.74 (m, 4H, $H^{arom}{}_{cis}$), 6.64 (d, *J* = 15.8 Hz, 2H, $H^4{}_{trans}$), 6.09 (d, 2H, *J* = 11.7 Hz, $H^4{}_{cis}$), 5.95 (dd, 2H, *J* = 11.7, 6.1 Hz, $H^3{}_{cis}$) 5.83 (ddd, 2H, *J* = 15.8, 6.6, 2.0 Hz, $H^3{}_{trans}$), 4.30-4.05 (m, 8H, $H^{11,14}$), 4.06-3.98 (m, 2H, $H^2{}_{cis}$), 2.91 (m, 2H, $H^2{}_{trans}$), 1.28 (t, 3H, *J* = 7.1 Hz, $H^{10\ or\ 13}{}_{cis}$), 1.19 (m, 6H, $H^{10,13}{}_{trans}$), 0.85 (t, 3H, *J* = 7.4 Hz, $H^{13\ or\ 10}{}_{cis}$)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6, 137.0, 136.4, 134.2, 130.0, 128.9, 127.9, 127.9, 127.0, 126.5, 124.0, 62.6, 62.5, 62.1, 44.0, 14.6

HRMS (APCI): Calculated for $C_{25}H_{27}O_4$: 391.19039, found: 391.19019

1,1-diethyl-2-[(E)-2-(4-methoxyphenyl)ethenyl]-3-[(E)-2-phenylethenyl]cyclopropane-1,1-dicarboxylate (62am)



Chemical Formula: $C_{26}H_{28}O_5$
Molecular Weight: 420.51

The characterization of this compound was made on a 3/7 mixture of cis and trans diastereomers.

Yield: 26% (20 mg)

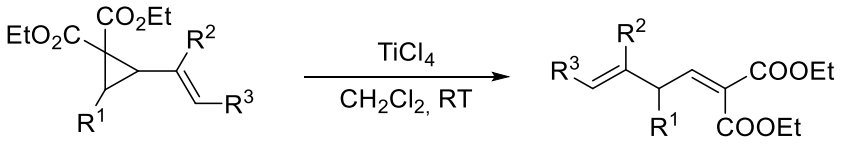
Aspect: transparent oil

^{1}H NMR (300 MHz, $CDCl_3$) : δ = 7.38-7.13 (m, H^{arom}), 6.83 (m, H^{arom}), 6.68 (m, H^{arom}), 6.27-5.71 (m, 4H, $H^{4,5,6,7}$), 4.38-4.08 (m, 8H, $H^{18,21}$), 3.78 (s, 6H, H^{22}), 2.96 (m, 2H, $H^{2,3}$), 2.80 (m, 2H, $H^{2.3}$), 1.27 (m, 12H, $H^{17,20}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.65, 167.45, 166.57, 159.30, 137.08, 136.91, 134.50, 134.12, 133.82, 133.38, 131.67, 129.92, 129.73, 128.65, 127.62, 127.51, 127.41, 126.32, 126.22, 123.99, 122.78, 121.47, 120.17, 114.08, 77.16, 62.08, 61.84, 61.49, 55.39, 43.78, 41.07, 36.19, 36.03, 36.00, 35.81, 14.35, 14.20, some carbons cannot be detected

7.2.7 Synthesis of 1,4-dienes

7.2.7.1 General procedures



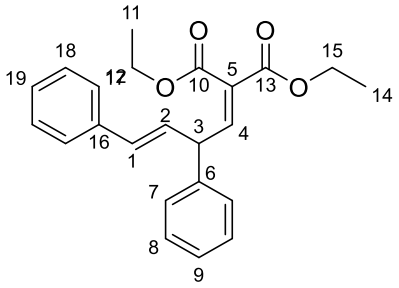
Scheme 129

Vinylcyclopropane (1 eq.) and dry dichloromethane (1 mL/10 mg of vinylcyclopropane) are introduced in a dry round-bottom flask under argon atmosphere. Titanium tetrachloride 1M in dichloromethane *(see product description for number of eq.)* is added and the mixture is stirred at room temperature for a defined time *(see description of the compound*). Then, an aqueous solution of hydrochloric acid (1M) is added to the mixture and the aqueous layer is extracted three times with dichloromethane. Organic fractions are combined and dried over $MgSO_4$ before evaporation of the solvent under reduced pressure. The crude product is purified by flash chromatography over silica gel.

Number of $TiCl_4$ equivalents, reaction time and eluent for purification depend on the nature of the compound and are reported in the description of each product.

7.2.7.2 Product descriptions

7.2.7.2.1 <u>1,3-Diethyl-2-[(3*E*)-2,4-diphenylbut-3-en-1-ylidene]propandioate (**63aa**)</u>



Chemical Formula: $C_{23}H_{24}O_4$
Molecular Weight: 364.44

Eq. of $TiCl_4$: 1 eq

Reaction time: 15 min

Eluent for purification: *n*-hexane/AcOEt (82/18)

Yield: 95% (100 mg)

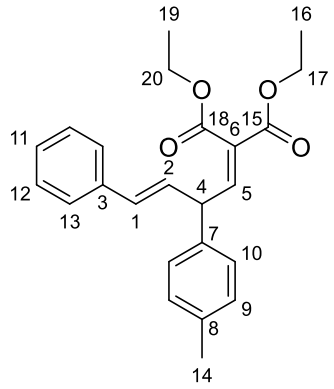
Aspect: Yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.19 (m, 10H, H^{arom}), 7.15 (d, 1H, *J* = 10.5 Hz, H^4), 6.50 (d, 1H, *J* = 16.5 Hz, H^1), 6.36 (dd, 1H, *J* = 16.5, 6.5 Hz, H^2), 4.69 (dd, 1H, *J* = 10.5, 6.5 Hz, H^3), 4.33 (q, 2H, *J* = 7.1 Hz, $H^{12 \text{ or } 15}$), 4.25 (q, 2H, *J* = 7.1 Hz, $H^{15 \text{ or } 12}$), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 1.29 (t, 3H, *J* = 7.1 Hz, $H^{14 \text{ or } 11}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 132.2, 128.9, 128.7, 128.5, 127.8, 127.6, 126.3, 61.5, 61.5, 48.0, 14.1, 14.0, some carbons are missing.

HRMS (APCI): Calculated for $C_{23}H_{25}O_4$: 365.17474, found: 365.17478

7.2.7.2.2 <u>1,3-Diethyl-2-[(3*E*)-2-(4-methylphenyl)-4-phenylbut-3-en-1-ylidene]propanedioate (**63ab**)</u>



Chemical Formula: $C_{24}H_{26}O_4$
Molecular Weight: 378.47

Eq. of $TiCl_4$: 1 eq.

Reaction time: 20 min

Eluent for purification: *n*-hexane/AcOEt (82/18)

Yield: 95% (50 mg)

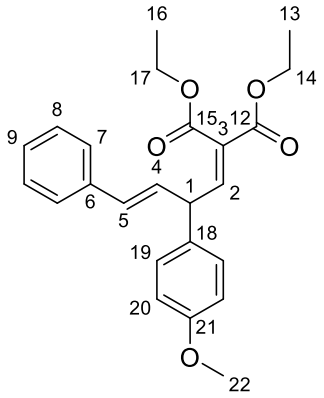
Aspect: Yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.14 (m, 9H, H^{arom}), 7.13 (d, 1H, *J* = 10.6 Hz, H^5), 6.49 (d, 1H, *J* = 16.1 Hz, H^1), 6.34 (dd, 1H, *J* = 16.0, 6.5 Hz, H^2), 4.65 (dd, 1H, *J* = 10.5, 6.5 Hz, H^4), 4.33 (q, 2H, *J* = 7.1 Hz, $H^{17 \text{ or } 20}$), 4.24 (q, 2H, *J* = 7.1 Hz, $H^{20 \text{ or } 17}$), 2.33 (s, 3H, H^{14}), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{16 \text{ or } 19}$), 1.29 (t, 3H, *J* = 7.1 Hz, $H^{19 \text{ or } 16}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 164.3, 148.3, 137.7, 137.3, 137.1, 132.4, 129.9, 129.3, 128.9, 128.1, 128.0, 126.7, 61.8, 47.9, 31.9, 23.0, 21.4, 14.5, 14.4

HRMS (APCI): Calculated for $C_{24}H_{27}O_4$: 379.19039, found: 379.19030

7.2.7.2.3 1,3-Diethyl-2-[(3*E*)-2-(4-methoxyphenyl)-4-phenylbut-3-en-1-ylidene]propanedioate (**63ac**)



Chemical Formula: $C_{24}H_{26}O_5$
Molecular Weight: 394.47

Eq. of $TiCl_4$: 0.4 eq.

Reaction time: 15 min

No purification required

Yield: 95% (55 mg)

Aspect: Yellow oil

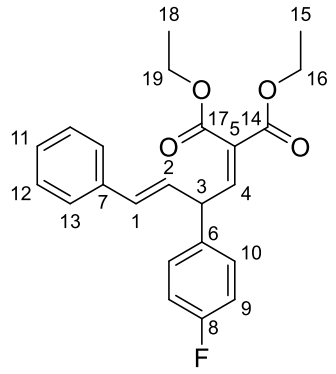
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.10 (m, 9H, H^{arom}), 6.88 (d, 1H, *J* = 8.7 Hz, H^2), 6.48 (d, 1H, *J* = 16.3 Hz, H^5), 6.33 (dd, 1H, *J* = 16.0, 6.4 Hz, H^4), 4.64 (m, 1H, *J* = 10.5, 6.4 Hz, H^1), 4.33 (q, 2H, *J* = 7.1 Hz, $H^{14 \text{ or } 17}$), 4.24 (q, 2H, *J* = 7.1 Hz, $H^{17 \text{ or } 14}$), 3.79 (s, 3H, H^{22}), 1.34 (t, 3H, *J* = 7.1 Hz, $H^{13 \text{ or } 16}$), 1.29 (t, 3H, *J* = 7.1 Hz, $H^{16 \text{ or } 13}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 165.7, 164.3, 158.9, 148.3, 137.1, 132.7, 132.4, 129.3, 129.3, 128.0, 127.9, 127.9, 126.7, 114.6, 61.8, 61.8, 55.6, 47.5, 14.5, 14.4

HRMS (APCI): Calculated for $C_{23}H_{27}O_5$: 395.18530, found: 395.18527

IR (cm^{-1}): 2978, 1720, 1059, 1237, 1030, 694

7.2.7.2.4 <u>1,3-Diethyl-2-[(3E)-2-(4-fluorophenyl)-4-phenylbut-3-en-1-ylidene]propanedioate (**63ae**)</u>



Chemical Formula: $C_{23}H_{23}FO_4$
Molecular Weight: 382.43

Eq. of $TiCl_4$: 1 eq.

Reaction time: 75 min

Eluent for purification: *n*-hexane/AcOEt (82/18)

Yield: 71% (430 mg)

Aspect: Colorless oil

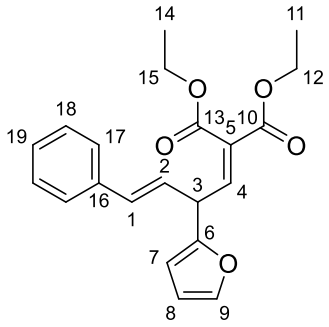
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.20 (7H, H^{arom}), 7.09 (d, 1H, *J* = 10.5 Hz, H^4), 7.03 (m, 2H, H^{arom}), 6.48 (d, 1H, *J* = 16.0 Hz, H^1), 6.32 (dd, 1H, *J* = 16.0, 6.6 Hz, H^2), 4.67 (dd, 1H, *J* = 10.5, 6.6 Hz, H^3), 4.31 (q, 2H, *J* = 7.1 Hz, $H^{16 \text{ or } 19}$), 4.26 (q, 2H, *J* = 7.1 Hz, $H^{19 \text{ or } 16}$), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{15 \text{ or } 18}$), 1.30 (t, 3H, *J* = 7.1 Hz, $H^{18 \text{ or } 15}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.4, 132.5, 129.5, 129.4, 128.6, 128.4, 127.9, 126.4, 115.9, 115.6, 61.6, 61.6, 47.2, 14.2, 14.1, some carbons are missing

HRMS (APCI): Calculated for $C_{23}H_{24}FO_4$: 383.16531, found: 383.16424

IR (cm^{-1}): 2986, 1723, 1508, 1223

7.2.7.2.5 1,3-Diethyl-2-[(E)-2-(furan-2-yl)-4-phenylbut-3-en-1-ylidene]propanedioate (**63ah**)



Chemical Formula: $C_{21}H_{22}O_5$
Molecular Weight: 354.40

Eq. of $TiCl_4$: 1 eq.

Reaction time: 15 min

No purification required

Yield: Quantative (55 mg)

Aspect: Black oil

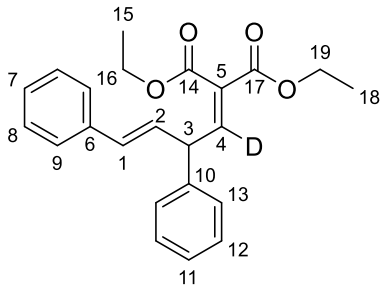
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (dd, 1H, *J* = 1.9, 0.8 Hz, H^9), 7.37 (m, 2H, H^{arom}), 7.31 (m, 2H, H^{arom}), 7.24 (m, 1H, H^{arom}), 7.11 (d, 1H, *J* = 10.1 Hz, H^4), 6.51 (d, 1H, *J* = 16.0 Hz, H^1), 6.34 (dd, 1H, *J* = 3.2, 1.9 Hz, H^8), 6.30 (dd, 1H, *J* = 15.9, 7.1 Hz, H^2), 6.18 (dd, 1H, *J* = 3.3, 0.9 Hz, H^7), 4.80 (dd, 1H, *J* = 10.1, 7.1 Hz, H^3), 4.32 (q, 2H, *J* = 7.1 Hz, $H^{12 \text{ or } 15}$), 4.26 (q, 2H, *J* = 7.1 Hz, $H^{12 \text{ or } 15}$), 1.33 (t, 3H, *J* = 6.8 Hz, $H^{11 \text{ or } 14}$), 1.30 (t, 3H, *J* = 6.8 Hz, $H^{11 \text{ or } 14}$)

^{13}C NMR (125 MHz, $CDCl_3$): δ= 152.9, 145.2, 142.4, 136.6, 128.7, 128.0, 126.6, 125.9, 110.5, 106.6, 99.7, 61.7, 42.3, 14.3, 14.2, some carbons are missing

HRMS : calculated for $C_{21}H_{23}O_5$: 355.15400 found: 355.15400

IR (cm^{-1}): 2988, 1722, 1229, 740, 693

7.2.7.2.6 1,3-diethyl-2-[(3*E*)-2,4-diphenyl(1-2H)but-3-en-1-ylidene]propanedioate (**63al**)



Chemical Formula: $C_{23}H_{23}DO_4$
Molecular Weight: 365.45

Eq. of $TiCl_4$: 1 eq

Reaction time: 15 min

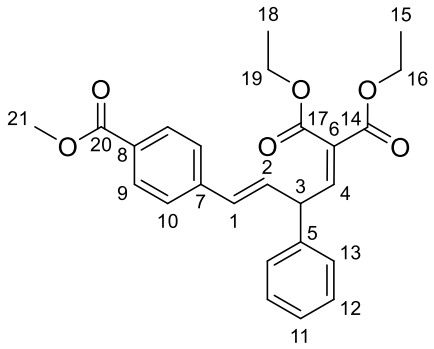
Yield: 70% (17 mg)

Aspect: Yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79 (d, 1H, *J* = 15.8 Hz, H^1), 6.36 (dd, 1H, *J* = 16.0, 6.5 Hz, H^2), 4.69 (d, 1H, *J* = 6.5 Hz, H^3), 4.33 (q, 2H, *J* = 7.1 Hz, $H^{16 \text{ or } 19}$), 4.25 (q, 2H, *J* = 7.1 Hz, $H^{19 \text{ or } 16}$), 1.38-1.18 (m, 6H, $H^{15,18}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 132.3, 128.9, 128.6, 127.9, 127.3, 126.4, 126.2, 61.8, 61.8, 30.1, 14.5, 14.5, some carbons are missing

7.2.7.2.7 1,3-Diethyl-2-[(3*E*)-4-[4-(methoxycarbonyl)phenyl]-2-phenylbut-3-en-1-ylidene]propanedioate (**63ba**)



Chemical Formula: $C_{25}H_{26}O_6$
Molecular Weight: 422.48

Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 30 min

No purification required

Yield: Quantitative (19 mg)

Aspect: Yellow oil

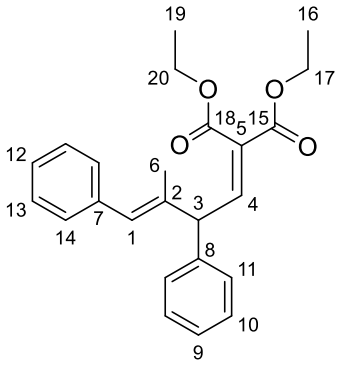
^{1}H NMR (300 MHz, $CDCl_3$) : δ = 7.98 (d, 2H, *J* = 8.4 Hz, H^9), 7.43-7.23 (m, 7H, H^{arom}), 7.14 (d, 1H, *J* = 10.5 Hz, H^4), 6.50 (m, 2H, $H^{1,2}$), 4.72 (dd, 1H, *J* = 10.4, 5.0 Hz, H^3), 4.41-4.27 (m, 4H, $H^{16,19}$), 3.91 (s, 3H, H^{21}), 1.39-1.24 (m, 6H, $H^{15,18}$)

^{13}C NMR (75 MHz, $CDCl_3$) : δ = 167.0, 165.3, 164.0, 147.4, 141.3, 140.1, 131.7, 131.5, 130.1, 129.3, 129.2, 128.5, 128.0, 127.6, 126.4, 61.8, 61.7, 52.2, 48.2, 14.3, 14.0

HRMS (APCI): Calculated for $C_{25}H_{27}O_6$: 423.18022, found : 423.17997

IR (cm^{-1}): 2982, 1717, 1276, 1238, 699

7.2.7.2.8 1,3-Diethyl-2-[(3*E*)-3-methyl-2,4-diphenylbut-3-en-1-ylidene]propanedioate (**63ca**)



Chemical Formula: $C_{24}H_{26}O_4$
Molecular Weight: 378.47

Eq. of $TiCl_4$: 0.4 eq.

Reaction time: 15 min

Eluent for purification: *n*-hexane/AcOEt (85/15)

Yield: 54% (8 mg)

Aspect: Colorless oil

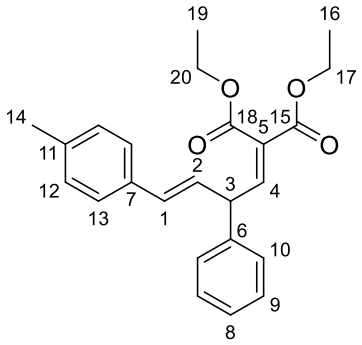
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.19 (m, 11H, $H^{4,arom}$), 6.43 (m, 1H, H^1), 4.58 (d, 1H, *J* = 10.7 Hz, H^3), 4.32 (q, 2H, *J* = 7.1 Hz, $H^{17\ or\ 20}$), 4.26 (q, 2H, *J* = 7.1 Hz, $H^{20\ or\ 17}$), 1.78 (d, 3H, *J* = 1.3 Hz, H^6), 1.32 (t, 3H, *J* = 7.1 Hz, $H^{16\ or\ 19}$), 1.30 (t, 3H, *J* = 7.1 Hz, $H^{19\ or\ 16}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.0, 129.0, 128.8, 128.2, 128.2, 128.1, 127.2, 126.5, 61.5, 61.4, 53.7, 17.1, 14.2, 14.1, some carbons are missing

HRMS (ESI): Calculated for $C_{24}H_{27}O_4$: 379.19039, found: 379.19038

IR (cm^{-1}): 2924, 2853, 1730, 1447, 1238, 740, 699

7.2.7.2.9 1,3-Diethyl-2-[(3E)-4-(4-methylphenylbut-3-en-1-ylidene]propanedioate (**63da**)



Chemical Formula: $C_{24}H_{26}O_4$
Molecular Weight: 378.47

Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 20 min

Eluent for purification: *n*-hexane/AcOEt (85/15)

Yield: 40% (14 mg)

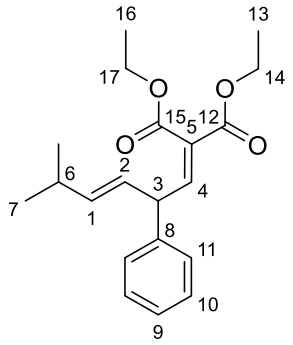
Aspect: Yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 7H, H^{arom}), 7.14 (d, 1H, *J* = 10.5 Hz, H^4), 7.11 (d, 2H, *J* = 8.0 Hz, H^{arom}), 6.46 (d, 1H, *J* = 15.8 Hz, H^1), 6.30 (dd, 1H, *J* = 16.0, 6.6 Hz, H^2), 4.67 (dd, 1H, *J* = 10.5, 6.7 Hz, H^3), 4.33 (q, 2H, *J* = 7.1 Hz, $H^{17 \text{ or } 20}$), 4.25 (q, 2H, *J* = 7.1 Hz, $H^{20 \text{ or } 17}$), 2.33 (s, 3H, H^{14}), 1.33 (t, 3H, *J* = 7.1 Hz, $H^{16 \text{ or } 19}$), 1.29 (m, 3H, $H^{19 \text{ or } 16}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.0, 132.2, 126.26, 129.2, 128.8, 127.9, 127.2, 126.3, 48.0, 61.5, 21.2, 14.2, 14.1, some carbons are missing

HRMS (APCI): Calculated for $C_{24}H_{27}O_4$: 379.19039, found: 379.19022

7.2.7.2.10 Diethyl (E)-2-(5-methyl-2-phenylhex-3-en-1-ylidene)malonate **(63ea)**



Chemical Formula: $C_{20}H_{26}O_4$
Molecular Weight: 330.42

Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 15 min

Eluent for purification: *n*-hexane/AcOEt (85/15)

Aspect: yellow oil

NMR Yield: 15% (7 mg)

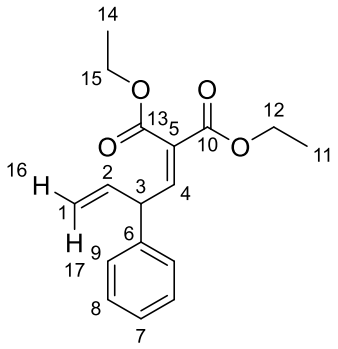
^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.21 to 7.37 (m, 5H, H^{arom}), 7.05 (d, 1H, *J*=10.7 Hz, H^4), 5.56 (d, 2H, *J*= 3.6, 1.6 Hz, $H^{2,3}$), 4.45 (dd, 1H, *J*=10.8, 3.5 Hz, H^3), 4.33 (q, 2H, *J*=7.1 Hz, $H^{10 \text{ or } 13}$), 4.24 (q, 2H, *J*=7.1 Hz, $H^{13 \text{ or } 10}$), 2.32 (m, 1H, H^6), 1.35 (t, 3H, *J*=7.1 Hz, $H^{9 \text{ or } 12}$), 1.29 (t, 3H, *J*=7.1 Hz, $H^{12 \text{ or } 9}$), 1.01 (dd, 6H, *J*=6.7, 0.9 Hz, H^7)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 166.6, 164.2, 148.9, 141.1, 140.8, 128.9, 127.9, 127.4, 127.1, 126.0, 61.5, 61.5, 47.9, 31.3, 22.5, 22.4, 14.3, 14.2

HRMS (APCI): calculated for $C_{20}H_{27}O_4$: 331.19039, found: 331.19012

IR (cm^{-1}): 2924, 1722, 1234, 1207

7.2.7.2.11 1,3-Diethyl-2-(2-phenylbut-3-en-1-ylidene)propanedioate (**63fa**)



Chemical Formula: $C_{17}H_{20}O_4$
Molecular Weight: 288,34

Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 2 h

Eluent for purification: *n*-hexane/AcOEt (85/15)

Aspect: Yellow oil

NMR Yield: 41% (11 mg)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39-7.23 (m, 5H, H^{arom}), 7.06 (d, 1H, *J* = 10.6 Hz, H^4), 6.01 (ddd, 1H, *J* = 17.3, 10.3, 6.3 Hz, H^2), 5.24 (dd, 1H, *J* = 10.3, 1.3 Hz, H^{16}), 5.17 (dd, 1H, *J* = 17.2, 1.3 Hz, H^{17}), 4.52 (dd, 1H, *J* = 10.7, 6.3 Hz, H^3), 4.33 (q, 2H, *J* = 7.1 Hz, $H^{12 \text{ or } 15}$), 4.23 (q, 2H, *J* = 7.1 Hz, $H^{15 \text{ or } 12}$), 1.34 (t, 3H, *J* = 7.1 Hz, $H^{11 \text{ or } 14}$), 1.28 (t, 3H, *J* = 7.1 Hz, $H^{14 \text{ or } 11}$)

^{13}C NMR (125 MHz, $CDCl_3$): δ= 128.9, 127.9, 127.3, 99.7, 61.6, 48.8, 29.8, 14.2, some carbons are missing.

HRMS (APCI): calculated for $C_{17}H_{21}O_4$: 289.14344, found: 289.14327

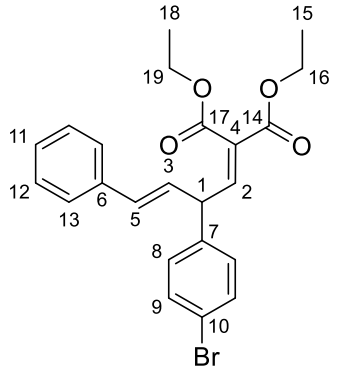
IR (cm^{-1}): 2925, 2853, 1730, 1239

7.2.7.3 General procedure for halogenated 1,4-dienes synthesis

The VCP is introduced into a dry two necked flask under argon atmosphere. Dichloromethane (8 mL/100 mg of VCP) is added and the flask is transferred in a dark room. TEMPO (0.1 eq.) and then a solution of $TiCl_4$ (1 eq.) (1M in dichloromethane) are added under stirring at room temperature. After 15 minutes, water is added to stop the reaction. The two layers are separated and the organic one is washed with an aqueous solution of hydrochloric acid (1M) and brine. The organic layer is dried over $MgSO_4$ and concentrated under reduced pressure. The 1,4-diene (**6**) is then purified by flash column chromatography.

7.2.7.4 Product descriptions

7.2.7.4.1 Diethyl-(*E*)-2-(2-(4-bromophenyl)-4-phenylbut-3-en-1-ylidene)malonate (**63af**)



Chemical Formula: $C_{23}H_{23}BrO_4$
Molecular Weight: 443.34

Eq. of $TiCl_4$: 1.5 eq.

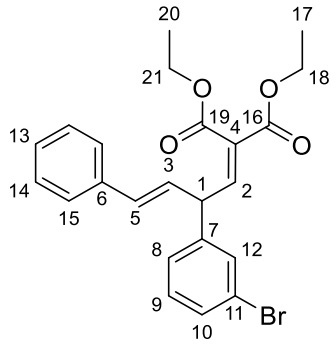
Reaction time: 15 min

NMR Yield: 20% (Dimethyl teterphtalate is used as internal standard), (136 mg of crude product were obtained)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60-7.13 (m, 9H, H^{arom}), 7.08 (d, 1H, *J* = 10.5 Hz, H^2), 6.42 (d, 1H, *J* = 16.0 Hz, H^5), 6.30 (dd, 1H, *J* = 16.0, 6.7 Hz, H^3), 4.66 (dd, 1H, *J* = 10.5, 6.7 Hz, H^1), 4.37-4.20 (m, 4H, $H^{16,19}$), 1.31 (m, 6H, $H^{15,18}$)

No additonnal analysis has been performed due to the separation difficulties encountered and the lack of time

7.2.7.4.2 Diethyl-(*E*)-2-(2-(3-bromophenyl)-4-phenylbut-3-en-1-ylidene)malonate (**53ag**)



Chemical Formula: $C_{23}H_{23}BrO_4$
Molecular Weight: 443.34

Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 15 min

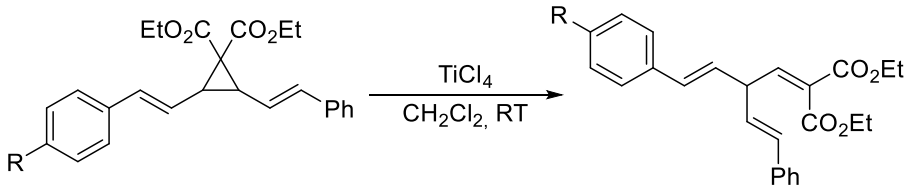
NMR Yield: 27% (Dimethyl teterphtalate is used as internal standard), (20 mg of crude product were obtained)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50-7.10 (m, 9H, H^{arom}), 7.08 (d, 1H, *J* = 10.5 Hz, H^2), 6.50 (d, 1H, *J* = 16.0 Hz, H^5), 6.30 (dd, 1H, *J* = 16.0 Hz, H^3), 4.67 (dd, 1H, *J* = 10.4, 6.7 Hz, H^1), 4.37-4.85 (comp, 4H, $H^{18, 21}$), 1.50-0.58 (comp, 6H, $H^{17,20}$)

No additonnal analysis has been performed due to the separation difficulties encountered and the lack of time

7.2.8 Trienes synthesis

7.2.8.1 General procedure



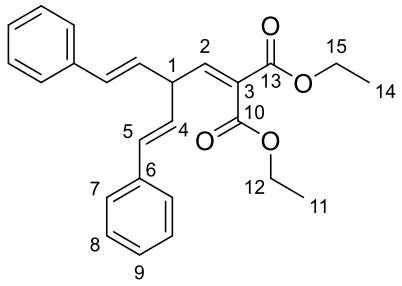
Scheme 130

Vinylcyclopropane (1 eq.) and dry dichloromethane (1 mL/10 mg of vinylcyclopropane) are introduced in a dry round-bottom flask under argon atmosphere. Titanium tetrachloride 1M in dichloromethane *(see product description for number of eq.)* is added and the mixture is stirred at room temperature for a defined time *(see description of the compound*). Then, the reaction is stopped by adding water. The two layers are separated and the organic one is washed with an aqueous solution of hydrochloric acid (1M) and brine. The organic layer is dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product is purified by flash chromatography over silica gel.

Number of $TiCl_4$ equivalents, reaction time and eluent for purification depend on the nature of the compound and are reported in the description of each product.

7.2.8.1 Product descriptions

7.2.8.1.1 <u>1,3-Diethyl-2-[(3*E*)-4-phenyl-2-[(*E*)-2-phenylethenyl]but-3-en-1-ylidene]propanedioate (**73am**)</u>



Chemical Formula: $C_{25}H_{26}O_4$
Molecular Weight: 390.48

Eq. of $TiCl_4$: 1 eq.

Reaction time: 15 min

Eluent for purification: *n*-hexane/AcOEt (82/18)

Yield: 80% (28 mg)

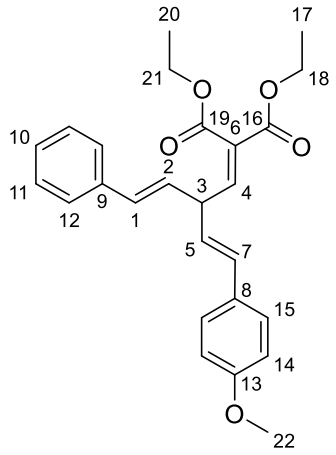
Aspect: Yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.13 (m, 10H, H^{arom}), 7.03 (d, 1H, *J* = 10.1 Hz, H^2), 6.94 (m, 1H, H^1), 6.53 (dd, 2H, *J* = 16.0, 1.3 Hz, H^5), 6.24 (dd, 2H, *J* = 16.0, 6.7 Hz, H^4), 4.31 (m, 4H, $H^{12,15}$), 1.34 (m, 6H, $H^{11,14}$),

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 164.3, 147.2, 136.9, 132.3, 128.7, 128.1, 127.9, 126.5, 61.7, 61.6, 45.7, 14.3, 14.3

HRMS (APCI): Calculated for $C_{25}H_{27}O_4$: 391.19039, found: 391.19035

7.2.8.1.2 Diethyl-2-((E)-4-(4-methoxyphenyl)-2-((E)-styryl)but-3-en-1-ylidene)malonate (**73an**)



Chemical Formula: $C_{26}H_{28}O_5$
Molecular Weight: 420.51

Eq. of $TiCl_4$: 0.5 eq.

Reaction time: 15 min

Eluent for purification: *n*-hexane/AcOEt (8/2)

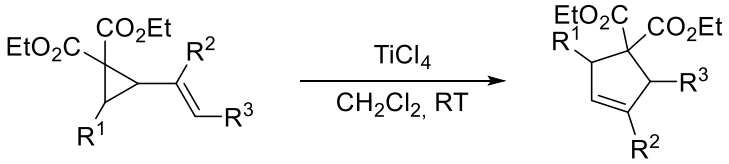
Yield: 10%

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.20 (m, 7H, H^{arom}), 7.11 (d, 1H, *J* = 10.5 Hz, H^4), 6.88 (m, 2H, $H^{14 \text{ or } 15}$), 6.48 (d, 1H, *J*=15.7 Hz, $H^{7 \text{ or } 1}$)

The amount of final product obtained and his purity were to low to allow the obtention of exploitable ^{13}C and ^{1}H NMR spectrum

7.2.9 Cyclopentene synthesis

7.2.9.1 General procedures



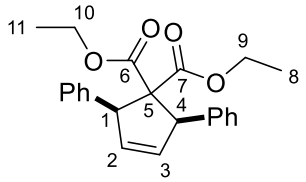
Scheme 131

Vinylcyclopropane (1 eq.) and dry dichloromethane (1 mL/10 mg of vinylcyclopropane) are introduced in a dry round-bottom flask under argon atmposphere. Titanium tetrachloride 1M in dichloromethane *(see product description for number of eq.)* was added and the mixture is stirred at room temperature for a defined time *(see description of the compound*). Then, the reaction is stopped by adding water. The two layers are separated and the organic one is washed with an aqueous solution of hydrochloric acid (1M) and brine. The organic layer is dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product is purified by flash chromatography over silica gel.

Number of $TiCl_4$ equivalents, reaction time and eluent for purification depend on the nature of the compound and are reported in the description of each product.

7.2.9.2 Product descriptions

7.2.9.2.1 1,1-Diethyl-2,5-diphenylcyclopent-3-ene-1,1-dicarboxylate (**57aa**)



Chemical Formula: $C_{23}H_{24}O_4$
Molecular Weight: 364.44

Eq. of $TiCl_4$: 5 eq.

Reaction time: 24h

Eluent for purification: n-hexane/AcOEt (85/15)

Yield: 41% (21 mg)

d.r.: 1/0 (*cis/trans*)

Aspect: Yellow oil

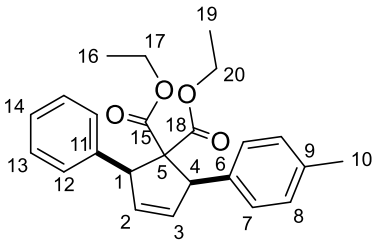
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.5-7.1 (m, 10H, H^{arom}), 5.96 (d, 2H, *J* = 0.7 Hz, $H^{2,3}$), 4.91 (s, 2H, $H^{1,4}$), 4.35 (q, 2H, *J* = 7.2 Hz, H^9), 2.99 (q, 2H, *J* = 7.2 Hz, H^{10}), 1.34 (t, 3H, *J* = 7.1 Hz, H^8), 0.46 (t, 3H, *J* = 7.2 Hz, H^{11})

^{13}C NMR, DEPT-Q (75 MHz, $CDCl_3$): δ = 132.3, 129.8, 129.4, 128.6, 128.2, 127.7, 127.0, 126.0, 132.4, 62.1, 60.4, 57.7, 14.3, 13.1, some carbons are missing.

HRMS (APCI): Calculated for $C_{23}H_{25}O_4$: 365.17474, found: 365.17478

FTIR (cm^{-1}): 2958, 1726

7.2.9.2.2 1,1-Diethyl-2-(4-methylphenyl)-5-phenylcyclopent-3-ene-1,1-dicarboxylate (**57ab**)



Chemical Formula: $C_{24}H_{26}O_4$
Molecular Weight: 378.47

Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 20 min

Eluent for purification: *n*-hexane/AcOEt (85/15)

Yield: 20 % (13 mg)

d.r.: 1/0 (*cis/trans*)

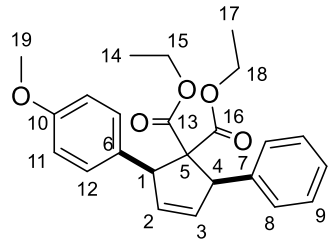
Aspect: white oil

^{1}H NMR (300 MHz, $CDCl_3$):δ = 7.45 (m, 2H, H^{arom}), 7.34 (m, 2H, H^8), 7.28-7.23 (m, H^{arom}), 6.01 (comp, 2H, $H^{2,3}$), 4.88 (comp, 2H, $H^{1,4}$), 4.41 (q, 2H, *J* = 7.1 Hz, $H^{17 \text{ or } 20}$), 3.10 (q, 2H, *J* = 7.1 Hz, $H^{17 \text{ or } 20}$), 2.29 (s, 3H, H^{10}), 1.40 (t, 3H, *J* = 7.2 Hz, $H^{16 \text{ or } 19}$), 0.56 (t, 3H, *J* = 7.2 Hz, $H^{19 \text{ or } 16}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 167.5, 139.9, 136.7, 136.5, 132.6, 132.1, 129.8, 129.8, 128.3, 128.0, 127.09, 72.1, 62.0, 60.3, 57.6, 57.5, 21.2, 14.2, 13.1

HRMS (APCI): calculated for $C_{24}H_{27}O_4$: 379.19039, found: 379.19016

7.2.9.2.3 Diethyl-2-(4-methoxyphenyl)-5-phenylcyclopent-3-ene-1,1-dicarboxylate (**57ac**)



Chemical Formula: $C_{24}H_{26}O_5$
Molecular Weight: 394.47

This product as been obtained as a secondary product and we did not reach to purify it. The product is described in a mixture containing a side product reported as the trans isomer of the CP.

Eq. of $TiCl_4$: 0.1 eq.

Reaction time: 15 min

Eluent for purification: not isolated

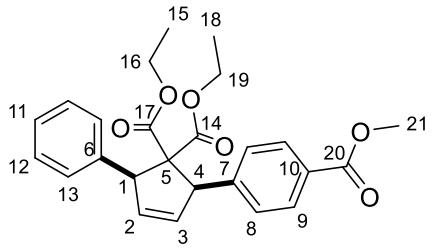
Crude yield: 70%

d.r.: 1/0 (*cis/trans*)

Aspect: clear oil

^{1}H NMR (300 MHz, $CDCl_3$):δ= 7.11 to 7.50 (comp, 9H, H^{arom}), 6.81 (m, 2H, H^{arom}), 6.0 (m, 2H, $H^{2,3}$), 4.87 (dd, 15.5, 2.9 Hz, $H^{1,4}$), 4.42 (q, 2H, *J*=7.1 Hz, $H^{15\ or\ 18}$), 3.78 (s, 3H, H^{19}), 3.13 (q, 2H, *J*=7.1 Hz, $H^{18\ or\ 15}$), 1.41 (t, 3H, *J*=7.1 Hz, $H^{14\ or\ 17}$), 0.58 (t, 3H, *J*=7.1 Hz, $H^{17\ or\ 14}$)

7.2.9.2.4 1,1-Diethyl-2-[4-(methoxycarbonyl)phenyl]-5-phenylcyclopent-3-ene-1,1-dicarboxylate (**57ad**)



Chemical Formula: $C_{25}H_{26}O_6$
Molecular Weight: 422.48

Eq. of $TiCl_4$: 1 eq.

Reaction time: 24 h

Eluent for purification: n-hexane/AcOEt (82/18)

Yield: 26% (41 mg)

d.r.: 1/0 (*cis/trans*)

Aspect: Colorless oil

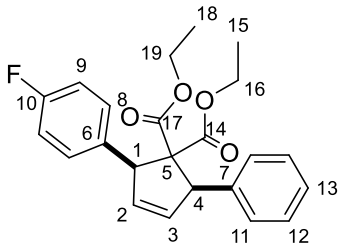
^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.94 (m, 2H, H^9), 7.55 (m, 2H, H^8), 7.44 (m, 2H, H^{arom}), 7.30-7.17 (m, 3H, H^{arom}), 6.05 (m, 2H, $H^{2,3}$), 4.93 (m, 2H, $H^{1,4}$), 4.43 (q, 2H, *J* = 7.2 Hz, $H^{16\ or\ 19}$), 3.89 (s, 3H, H^{21}), 3.06 (m, 2H, m, $H^{19\ or\ 16}$), 1.42 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}$), 0.52 (t, 3H, *J* = 7.2 Hz, $H^{18\ or\ 15}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 167.2, 145.5, 139.6, 133.0, 131.6, 129.8, 129.8, 128.9, 128.8, 127.7, 127.2, 72.1, 62.3, 60.6, 57.7, 57.5, 52.2, 14.3, 13.2,

HRMS (APCI): Calculated for $C_{25}H_{27}O_6$: 423.18022, found: 423.18011

IR (cm^{-1}): 2985, 1718, 1277, 1020, 700

7.2.9.2.5 1,1-Diethyl-2-(4-fluorophenyl)-5-phenylcyclopent-3-ene-1,1-dicarboxylate (**57ae**)



Chemical Formula: $C_{23}H_{23}FO_4$
Molecular Weight: 382.43

This product is described from a mixture containing a side product that has been identified to be the corresponding secondary cyclopentene.

Eq. of $TiCl_4$: 1.5

Reaction time: 24h

Eluent for purification: Cyclohexane/Dichloromethane (4/6)

Yield: 27% (26 mg)

d.r.: 1/0 (*cis/trans*)

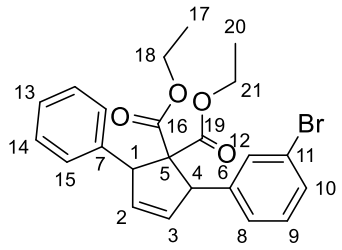
Aspect: clear oil

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (m, 4H, H^{arom}), 7.27 (m, 5H, H^{arom}), 6.95 (t, 1H, H^{arom}), 6.01 (comp, 2H, $H^{2,3}$), 4.89 (comp, 2H, *J* = 15.9, 2.5 Hz, $H^{1,4}$), 4.42 (q, 2H, *J* = 7.1 Hz, $H^{16 \text{ or } 19}$), 3.11 (q, 2H, *J* = 7.3 Hz, $H^{19 \text{ or } 16}$), 1.41 (t, 3H, *J* = 7.1 Hz, $H^{15 \text{ or } 18}$), 0.57 (t, 3H, *J* = 7.2 Hz, $H^{18 \text{ or } 15}$)

^{13}C NMR DEPT-Q (75 MHz, $CDCl_3$): δ = 172.6, 163.7, 160.4, 139.8, 135.6 (d, *J* = 3.5 Hz), 131.3 (d, *J*=7.9 Hz), 129.7, 129.3, 128.2, 127.7, 127.5, 121.1, 115.7, 115.4, 114.5, 114.3 (d, *J* = 21 Hz), 72.1, 62.1, 62.0, 61.4, 61.2, 60.5, 57.6, 57.2, 57.0, 41.1, 29.9, 14.3, 14.2, 13.6, 13.2, this description contain pics belonging to the corresponding CPsec.

HRMS (pAPCI): Calculated for $C_{23}H_{24}O_4F$: 383.16531, found: 383.16446

7.2.9.2.6 Diethyl-2-(3-bromophenyl)-5-phenylcyclopent-3-ene-1,1-dicarboxylate (**57ag**)



Chemical Formula: $C_{23}H_{23}BrO_4$
Molecular Weight: 443.34

This product has been obtained as a side product and only ^{1}H NMR has been performed due to the difficulties of separation encountered and the lack of time

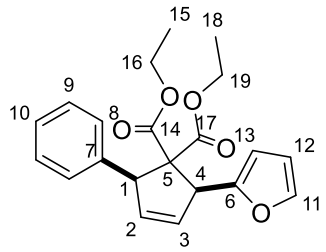
Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 15 min

NMR Yield: 58% (Dimethyl teterphtalate is used as internal standard)

^{1}H NMR (300 MHz, $CDCl_3$): 7.60-7.10 (m, 9H, H^{arom}), 6.02 (m, 2H, $H^{2,3}$), 4.94 (m, 1H, $H^{1 \text{ or } 4}$), 4.83 (m, 1H, $H^{4 \text{ or } 1}$), 4.42 (q, 2H, J = 7.1 Hz, $H^{18 \text{ or } 21}$), 3.12 (q, 2H, J = 7.2 Hz, $H^{21 \text{ or } 18}$), 1.43 (t, 3H, J = 7.1 Hz, $H^{17 \text{ or } 20}$), 0.61 (t, 3H, J = 7.2 Hz, $H^{20 \text{ or } 17}$).

7.2.9.2.7 1,1-Diethyl-2-(furan-2-yl)-5-phenylcyclopent-3-ene-1,1-dicarboxylate (**57ah**)



Chemical Formula: $C_{21}H_{22}O_5$
Molecular Weight: 354.40

A minor side product has been also obtained (<10%) and is identified to be either the trans isomer of the CP or the corresponding CPsec.

Eq. of $TiCl_4$: 1 eq.

Reaction time: 15 min

Eluent for purification: *n*-hexane/AcOEt (85/15)

Yield: 86 %

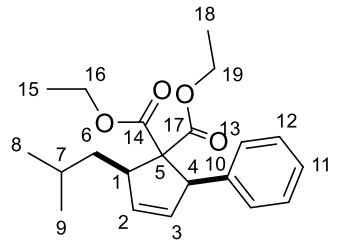
d.r.: 1/0 (*cis/trans*)

Aspect: clear oil

^{1}H NMR (300 MHz, $CDCl_3$):δ = 7.43 (m, 1H, $H^{11 \text{ or } 12}$), 7.40 (m, 1H, $H^{12 \text{ or } 11}$), 7.28-7.18 (m, 5H, H^{arom}), 6.31 (dd, 1H, *J* = 3.3, 1.8 Hz, $H^{2 \text{ or } 3}$), 6.27 (m, 1H, $H^{3 \text{ or } 2}$), 4.96 (m, 1H, $H^{1 \text{ or } 6}$), 4.75 (m, 1H, $H^{6 \text{ or } 1}$), 4.38 (q, 2H, *J* = 7.1 Hz, $H^{16 \text{ or } 19}$), 3.31 (m, 2H, $H^{19 \text{ or } 16}$), 1.38 (t, 3H, *J* = 7.1 Hz, $H^{15 \text{ or } 18}$), 0.67 (t, 3H, *J* = 7.1 Hz, $H^{18 \text{ or } 15}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 129.7, 127.8, 110.6, 110.1, 107.6, 62.0, 60.7, 57.2, 52.1, 14.2, 13.4, some carbons are missing.

7.2.9.2.8 1,1-diethyl-2-(2-methylpropyl)-5-phenylcyclopent-3-ene-1,1-dicarboxylate (**57aj**)



Chemical Formula: $C_{21}H_{28}O_4$
Molecular Weight: 344.45

Eq. of $TiCl_4$: 1 eq.

Reaction time: 20 min

Yield: 70 % (14 mg)

d.r.: 1/0 (*cis/trans*)

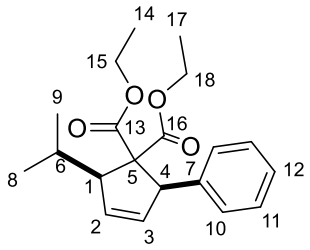
Aspect: withe oil

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 2H, H^{arom}), 7.22 (m, 3H, H^{arom}), 5.86 (ddd, 1H, *J* = 5.9, 2.9, 1.8 Hz, H^3), 5.78 (ddd, 1H, *J* = 5.9, 2.8, 1.9 Hz, H^2), 4.92 (m, 1H, H^4), 4.28 (q, 2H, *J* = 7.2 Hz, $H^{16 \text{ or } 19}$), 3.57 (m, 1H, $H^{16 \text{ or } 19}$), 3.37 (m, 1H, $H^{16 \text{ or } 19}$), 3.14 (m, 1H, H^1), 1.83 (ddd, 1H, *J* = 13.3, 10.8, 4.5 Hz, H^6), 1.69 (m, 1H, H^7), 1.51 (ddd, 1H, *J* = 13.3, 9.2, 2.8 Hz, H^6), 1.30 (t, 3H, *J* = 7.1 Hz, $H^{15 \text{ or } 18}$), 0.97 (d, 3H, *J* = 6.7 Hz, $H^{8 \text{ or } 9}$), 0.92 (d, 3H, *J* = 6.6 Hz, $H^{8 \text{ or } 9}$), 0.77 (t, 3H, *J* = 7.1 Hz, $H^{18 \text{ or } 15}$)

^{13}C NMR (125 MHz, $CDCl_3$): δ= 133.2, 130.2, 129.4, 127.7, 70.9, 61.4, 61.2, 60.3, 56.3, 51.5, 40.2, 27.5, 23.8, 22.2, 21.7, 14.1, 13.5 some carbons are missing.

HRMS (APCI): calculated for $C_{21}H_{29}O_4$: 345.20604 found: 345.20587

7.2.9.2.9 <u>1,1-Diethyl-2-phenyl-5-(propan-2-yl)cyclopent-3-ene-1,1-dicarboxylate (**57ak**)</u>



Chemical Formula: $C_{20}H_{26}O_4$
Molecular Weight: 330.42

Eq. of $TiCl_4$: 1 eq.

Reaction time: 20 min

Eluent for purification: *n*-hexane/AcOEt (9/1)

Yield: 82% (19 mg)

d.r.: 1/0 (*cis/trans*)

Aspect: Colorless oil

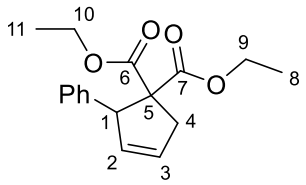
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37-7.18 (m, 5H, H^{arom}), 5.94 (ddd, 1H, *J* = 6.0, 2.7, 2.0 Hz, H^3), 5.76 (ddd, 1H, *J* = 6.0, 2.7, 2.0 Hz, H^2), 4.94 (m, 1H, H^4), 4.31 (m, 2H, $H^{15\ or\ 18}$), 3.49 (m, 2H, $H^{18\ or\ 15}$), 3.02 (m, 1H, H^1), 2.16 (m, 1H, H^6), 1.34 (t, 3H, *J* = 7.1 Hz, $H^{14\ or\ 17}$), 1.08 (d, 3H, *J* = 6.6 Hz, $H^{8\ or\ 9}$), 0.96 (d, 3H, *J* = 6.7 Hz, $H^{9\ or\ 8}$), 0.85 (t, 3H, *J* = 7.2 Hz, $H^{17\ or\ 14}$)

^{13}C NMR (125 MHz, $CDCl_3$): δ= 172.9, 168.4, 140.1, 132.6, 130.1, 129.8, 127.7, 127.1, 69.8, 61.7, 60.9, 60.5, 58.0, 30.0, 23.4, 22.6, 14.2, 13.6

HRMS (APCI): Calculated for $C_{20}H_{27}O_4$: 331.19039, found: 331.19034

IR (cm^{-1}): 2970, 1724, 1249, 1041, 753, 700

7.2.9.2.10 <u>1,1-Diethyl-2-phenylcyclopent-3-ene-1,1-dicarboxylate (**57ap**)</u>



Chemical Formula: $C_{17}H_{20}O_4$
Molecular Weight: 288.34

Eq. of $TiCl_4$: 3 eq.

Reaction time: 1h

Eluent for purification: *n*-hexane/AcOEt (8/2)

Yield: <10% (<10 mg)

Aspect: Yellow oil

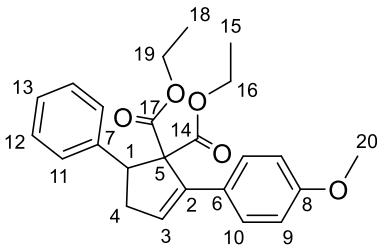
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (m, 5H, H^{arom}), 5.86 (dq, 1H, *J* = 5.9, 2.2 Hz, H^3), 5.89-5.68 (m, 1H, H^2), 4.88 (m, 1H, H^1), 4.25 (comp, 4H, $H^{9,10}$), 2.79 (m, 1H, H^4), 1.25 (t, 3H, *J* = 7.1 Hz, $H^{8 \text{ or } 11}$), 0.81 (t, 3H, *J* = 7.2 Hz, $H^{8 \text{ or } 11}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.19, 169.59, 139.16, 132.31, 129.14, 128.57, 127.94, 127.19, 64.92, 61.61, 61.05, 56.84, 40.63, 14.05, 13.48

HRMS (APCI) : Calculated for $C_{17}H_{21}O_4$: 289.14344,found: 289.14339

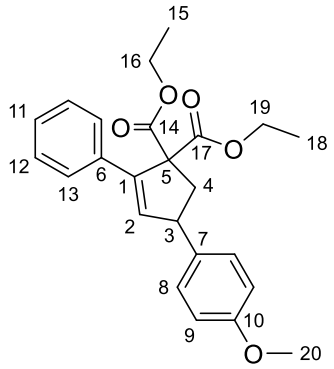
7.2.10 Obtained side products

7.2.10.1 Mixture of diethyl 2-(4-methoxyphenyl)-5-phenylcyclopent-2-ene-1,1-dicarboxylate and diethyl 4-(4-methoxyphenyl)-2-phenylcyclopent-2-ene-1,1-dicarboxylate (ratio 1:1)



Chemical Formula: $C_{24}H_{26}O_5$
Molecular Weight: 394.47

A



Chemical Formula: $C_{24}H_{26}O_5$
Molecular Weight: 394.47

B

We did not succeed in separating these two products. Furthermore, because of the complexity of their spectra, we can only propose these two structure that fit with the analysis. However, it would be necessary to separate these compounds via HPLC in order to allow an accurate and exact analysis of the NMR spectra.

Conditions: see general reaction conditions for cyclopentene preparation

Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 24h

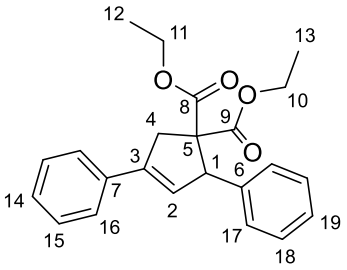
Eluents for purifications: first purification with cyclohexane/CH_2Cl_2 (8/2), second purification with cyclohexane/AcOEt (92/8)

Aspect: clear oil

^{1}H NMR (300 MHz, $CDCl_3$):δ= 7.49 (m, 2H, H^{arom}), 7.44 (m, 2H, H^{arom}), 7.31 to 7.15 (m, 10H, H^{arom}), 6.91 (m, 2H, H^{arom}), 6.88 (m, 2H, H^{arom}), 6.16 (dd, 1H, *J* = 2.3, 1.4 Hz, H^{3}_{A}), 5.99 (m, 1H, H^{2}_{B}), 5.01 (m, 1H, H^{3}_{B}), 4.45 (dd, 1H, *J* = 8.2 Hz, 3.5 Hz, H^{1}_{A}), 4.23 (m, 5H, $H^{16\ or\ 19}_{A\ or\ B}$), 3.90 (dt, 1H, *J* = 16.9, 2.3 Hz, H^{4}_{B}), 3.83 (s, 3H, $H^{20}_{A\ or\ B}$), 3.82 (s, 3H, $H^{20}_{B\ or\ A}$), 3.79-3.35 (m, 5H, $H^{16\ and/or\ 19,\ 4}_{A\ and/or\ B}$), 3.13 (m, 1H, $H^{4'}_{B}$), 3.01 (ddd, 1H, *J* = 16.2, 3.6, 1.4 Hz, $H^{4'}_{A}$), 1.26 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}_{A\ or\ B}$), 1.26 (t, 3H, *J* = 7.1 Hz, $H^{15\ or\ 18}_{B\ or\ A}$), 0.85 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}_{A\ or\ B}$), 0.84 (t, 3H, *J* = 7.1 Hz, $H^{18\ or\ 15}_{B\ or\ A}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 129.3, 128.4, 128.1, 128.0, 127.6, 127.3, 127.1, 124.5, 120.7, 113.9, 61.8, 61.7, 61.2, 61.0, 57.1, 55.4, 48.7, 41.2, 40.9,14.1, 14.1, 13.6, 13.6

7.2.10.2 1,1-Diethyl-2,4-diphenylcyclopent-3ene-1,1-dicarboxylate (66aa)



Chemical Formula: $C_{23}H_{24}O_4$
Molecular Weight: 364.44

This product was analyzed in a mixture containing 40% of cyclopentene described at the point 7.2.9.2.1

Conditions: see general reaction conditions for cyclopentene preparation

Eq. of $TiCl_4$: 1.5 eq.

Reaction time: 24h

Aspect: colorless oil

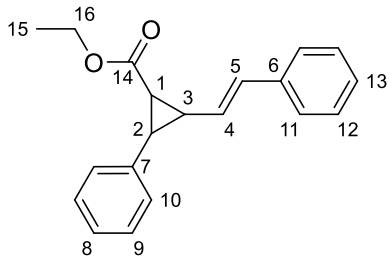
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45-7.11 (m, 10H, H^{arom}), 6.06 (m, 1H, H^2), 4.96 (m, 1H, H^1), 4.17 (m, 2H, $H^{10 \text{ or } 11}$), 3.87 (dm, 1H, *J* = 16.9 Hz, H^4), 3.66 (dq, 1H, *J* = 10.7, 7.1 Hz, $H^{11 \text{ or } 10}$), 3.39 (m, 1H, $H^{10 \text{ or } 11}$), 3.09 (dm, 1H, *J* = 16.9 Hz, H^4), 1.19 (t, 3H, *J* = 7.1 Hz, $H^{12 \text{ or } 13}$), 0.78 (t, 3H, *J* = 7.1 Hz, $H^{13 \text{ or } 12}$)

^{13}C NMR (75MHz, $CDCl_3$): δ= 172.7, 172.1, 169.6, 167.5, 140.1, 139.9, 139.4, 135.2, 132.3, 129.8, 129.4, 128.6, 128.2, 127.9, 127.7, 127.5, 127.0, 126.7, 126.0, 77.4, 72.1, 65.0, 62.1, 61.9, 61.3, 60.4, 57.7, 57.2, 40.9, 14.3, 14.2, 13.7, 13.1, some described pics belong to the corresponding cyclopentene.

HRMS (APCI): Calculated for $C_{23}H_{25}O_4$: 365.17474, found: 365.17456

FTIR (cm^{-1}): 2958, 1726

7.2.10.3 Ethyl-(E)-2-phenyl-3-styrylcyclopropane-1-carboxylate (72aa)



Chemical Formula: $C_{20}H_{20}O_2$
Molecular Weight: 292.38

Time: 24h

Lewis acid: $Sc(OTf)_3$, 0.4 eq.

For the rest of the reaction conditions see general reaction conditions for cyclopentene preparation

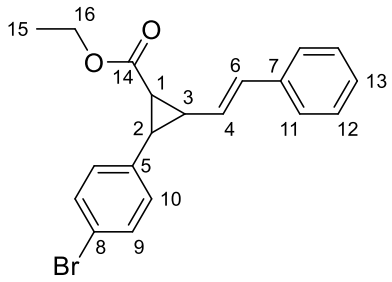
Yield: 85%

Eluent for purification: *n*-hexane/AcOEt (85/15)

^{1}H NMR (300 MHz, $CDCl_3$):δ = 7.41-7.20 (m, 10H, H^{arom}), 6.58 (d, 1H, *J* = 15.9 Hz, H^5), 6.23 (dd, 1H, *J* = 15.9, 7.2 Hz, H^4), 5.04 (m, 1H, H^1), 4.24 (m, 2H, H^{16}), 3.87-4.02 (comp, 2H, $H^{2,3}$), 1.28 (t, 3H, *J* = 7.1 Hz, H^{15})

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 135.4, 129.7, 129.4, 128.8, 128.7, 128.5, 127.7, 127.0, 123.7, 85.2, 62.5, 52.6, 52.2, 52.1, 14.2

7.2.10.1 Ethyl-(E)-2-(4-bromophenyl)-3-styrylcyclopropane-1-carboxylate (72af)



Chemical Formula: $C_{20}H_{19}BrO_2$
Molecular Weight: 371.27

Time: 15 min

Eq. of $TiCl_4$: 1.5

For the rest of the reaction conditions see general reaction conditions for cyclopentene preparation

Yield: 73%

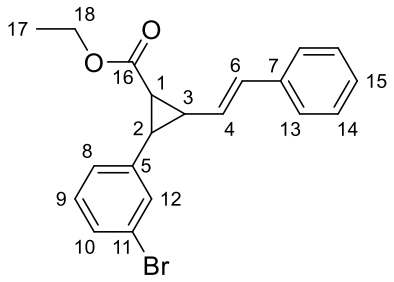
Eluent for purification: n-hexane/AcOEt (82/18)

^{1}H NMR (300 MHz, $CDCl_3$):δ = 7.50 (m, 2H, $H^{9 \text{ or } 10}$), 7.33 (m, 5H, $H^{11,12,13}$), 7.17 (m, 2H, $H^{10 \text{ or } 9}$), 6.57 (dd, 1H , *J* = 15.9, 0.9 Hz, H^6), 6.19 (dd, 1H, *J* = 15.9, 7.3 Hz, H^4), 4.97 (m, 1H, H^1), 4.24 (m, 2H, H^{16}), 3.89 (m, 2H, $H^{2,3}$), 1.28 (t, 3H, *J* = 7.1 Hz, H^{15})

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 135.8, 135.3, 134.5, 132.6, 129.4, 128.9, 128.9, 127.0, 123.3, 122.5, 85.0, 62.7, 54.4, 51.6, 14.2

HRMS (APCI): Calculated for $C_{20}H_{20}O_2{}^{79}Br$: 371.06412, found: 371.06382

7.2.10.2 Ethyl-(E)-2-(3-bromophenyl)-3-styrylcyclopropane-1-carboxylate (72ag)



Chemical Formula: $C_{20}H_{19}BrO_2$
Molecular Weight: 371.27

Time: 15 min

Eq. of $TiCl_4$: 1.5

For the rest of the reaction conditions see general reaction conditions for cyclopentene preparation

Crude yield: 85%

No purification is required

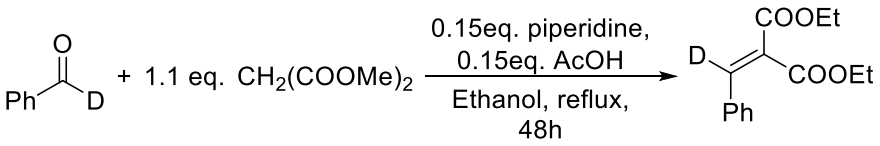
^{1}H NMR (300 MHz, $CDCl_3$):δ = 7.49-7.19 (m, 9H, H^{arom}), 6.60 (d, 1H, *J* = 15.9 Hz, H^6), 6.20 (dd, 1H, *J* = 15.9 Hz, 7.3 Hz, H^4), 5.01 (m, 1H, H^1), 4.26 (m, 2H, H^{18}), 3.89 (m, 2H, $H^{2,3}$), 1.29 (t, 3H, *J* = 7.1 Hz, H^{17})

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 166.7, 137.9, 135.8, 135.3, 131.7, 130.9, 130.7, 128.9, 128.8, 127.0, 126.6, 123.4, 123.3, 84.8, 62.6, 54.5, 51.7, 14.2

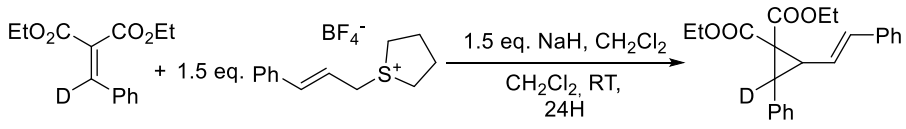
HRMS (APCI): Calculated for $C_{20}H_{20}O_2{}^{79}Br$: 371.06412, found: 371.06379

7.3 Isotopic experiments

Deuterated olefin was synthesized from benzaldehyde-d1 deuterated at 95% (Scheme 132). All reactions using deuterated species have followed the classical described procedures in this document (Scheme 133). Products were not isolated because only a small amount was available.



Scheme 132

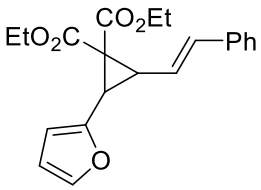


Scheme 133

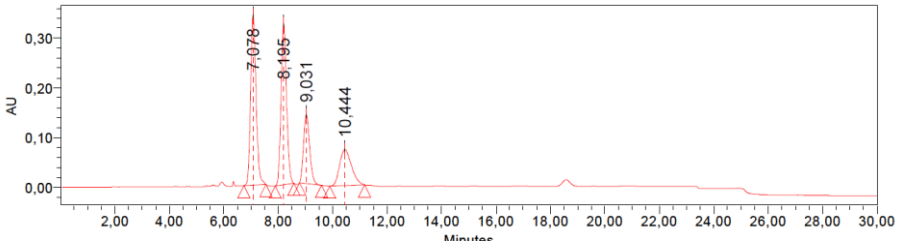
7.4 HPLC analysis

An HPLC method has been developed for the separation of the compounds bearing a furanyl group. Indeed, it was found that compounds containing this structural motif were easier to separate via HPLC.

7.4.1 Separation of the enantiomers and diastereoisomers of diethyl (E)-2-(furan-2-yl)-3-styrylcyclopropane-1,1-dicarboxylate (56ah)



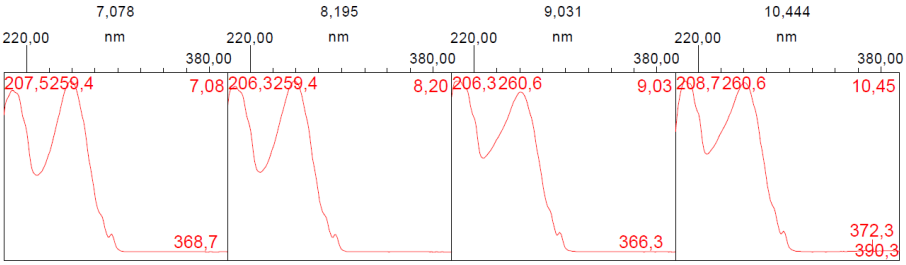
- **Column**: Chiralpack IC
- **Flow rate**: 1 mL/min
- **Eluent:** Isohexane **:** isopropanol (95:5)
- **Mode:** Isocratic
- **Injection volume:** 10 µL
- **Observed chromatogram:**



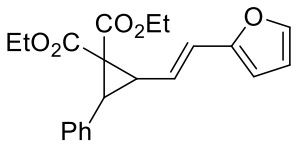
Scheme 134

Retention time (min)	Relative area (%)
7.078	34.64
8.195	33.58
9.031	15.93
10.444	15.85

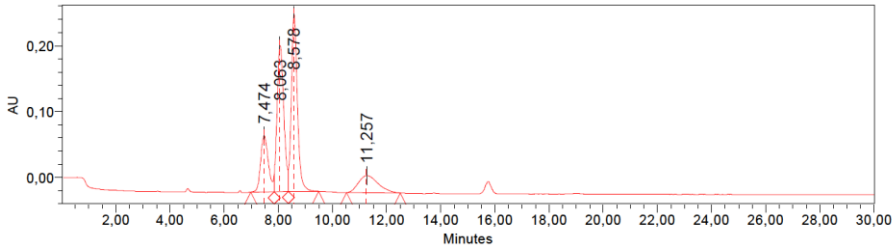
- In agreement with NMR analysis, the two first peaks are attributed to the enantiomers of the *trans* VCP isomer whereas the two last peaks correspond to the enantiomers of the *cis* VCP isomer.
- **Observed UV-spectra:**



7.4.2 Separation of the enantiomers and diastereoisomers of diethyl (E)-2-(2-(furan-2-yl)vinyl)-3-phenylcyclopropane-1,1-dicarboxylate (56ao)



- **Column**: Chiralpack IC
- **Flow rate**: 1 mL/min
- **Eluent:** Isohexane **:** isopropanol (97:3)
- **Mode:** Isocratic
- **Injection volume:** 10 µL
- **Observed chromatogram:**



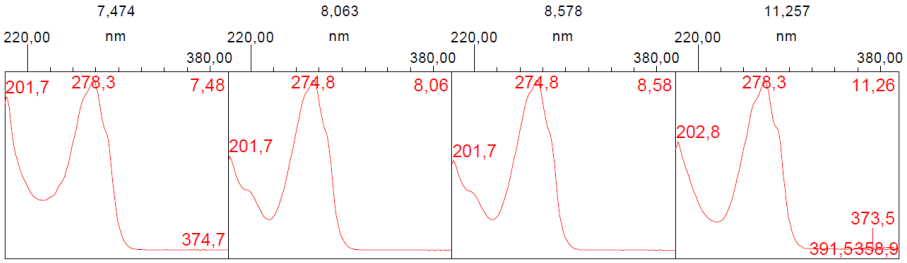
Scheme 135

Retention time (min)	Relative area (%)
7.474	15.40
8.063	34.67
8.578	37.94
11.257	11.99

In agreement with NMR analysis, the peak at 7.474 min is attributed to one enantiomer of the *cis* isomer. The peaks at 8.063 and 8.578 correspond

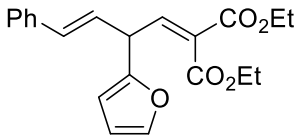
to the two enantiomers of the *trans* VCP and, finally, the peak a 11.257 coincides with the last enantiomer of the *cis* isomer.

- **Observed UV-spectra:**

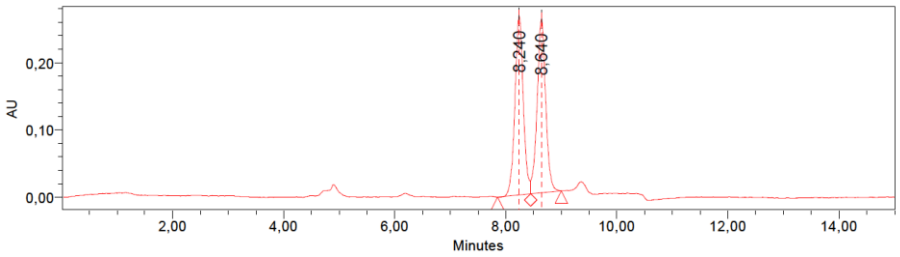


Scheme 136

7.4.3 Separation of the enantiomers of diethyl (E)-2-(2-(furan-2-yl)-4-phenylbut-3-en-1-ylidene)malonate (63ah)



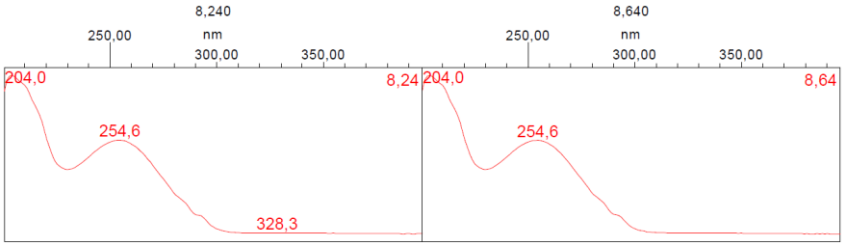
- **Column**: Chiralpack IB
- **Flow rate**: 0.7 mL/min
- **Eluent:** Isohexane **:** isopropanol (98:2)
- **Mode:** Isocratic
- **Injection volume:** 5 µL
- **Observed chromatogram:**



Scheme 137

Retention time (min)	Relative area (%)
8.240	49.98
8.640	50.02

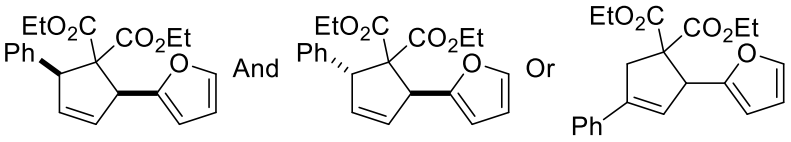
- **Observed UV-spectra:**



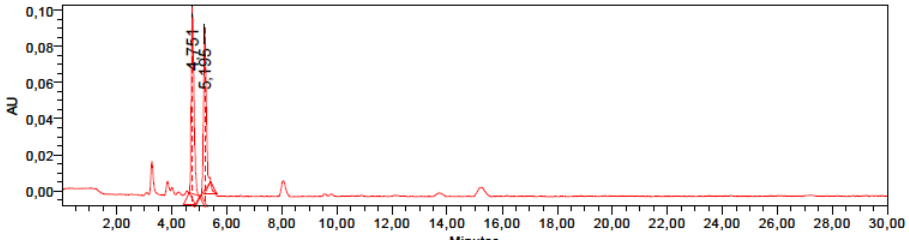
Scheme 138

7.4.4 Separation of diethyl 2-(furan-2-yl)-5-phenylcyclopent-3-ene-1,1-dicarboxylate (57ao)

7.4.4.1 Separation of isomer CP cis and CP trans or CPsec



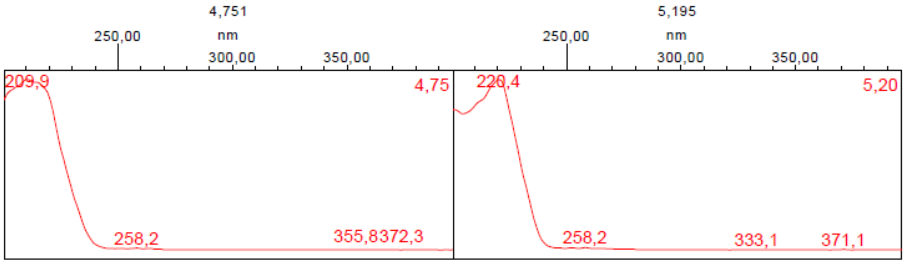
- **Column**: Chiralpack IA
- **Flow rate**:1 mL/min
- **Eluent:** Isohexane **:** isopropanol (95:5)
- **Mode:** Isocratic
- **Injection volume:** 5 µL
- **Observed chromatogram:**



Scheme 139

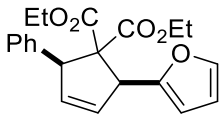
Retention time (min)	Relative area (%)
4.751	53.57
5.195	46.43

- **Observed UV-spetra:**

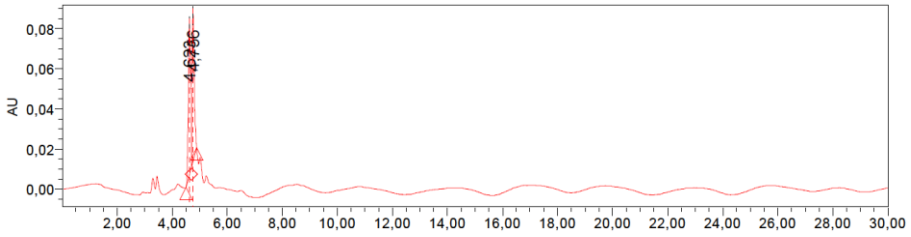


Scheme 140

7.4.4.2 Separation of CP cis enantiomers



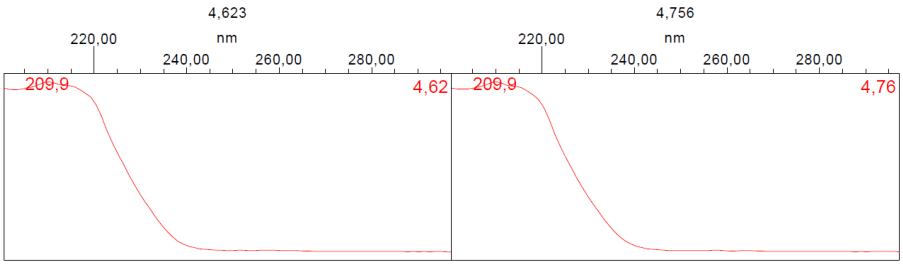
- **Column**: Chiralpack IA
- **Flow rate**: 1 mL/min
- **Eluent:** Isohexane : ethanol (95:5)
- **Mode:** Isocratic
- **Injection volume:** 5 µL
- **Observed chromatogram:**



Scheme 141

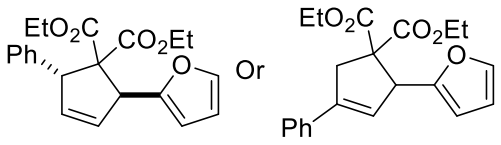
Retention time (min)	Relative area (%)
4.623	49.10
4.756	50.90

- **Observed UV-spectra:**

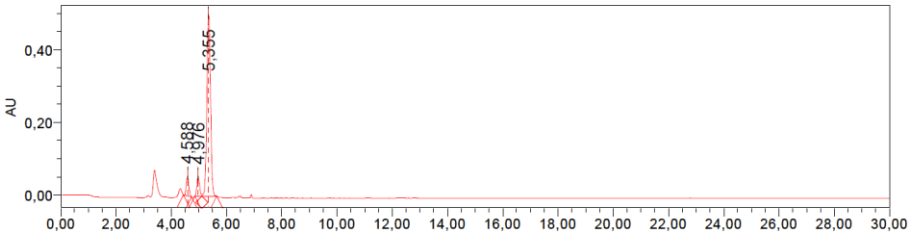


Scheme 142

7.4.4.3 Separation of the enantiomers of pic attributed to CP trans or CPsec as minor product



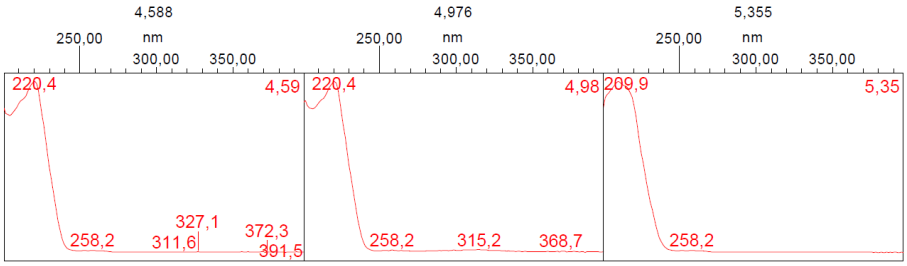
- **Column**: Chiralpack IB
- **Flow rate**: 1 mL/min
- **Eluent:** Isohexane : ethanol (97:3)
- **Mode:** Isocratic
- **Injection volume:** 20 µL
- **Observed chromatogram:**



Scheme 143

Retention time (min)	Relative area (%)
4.588	6.43
4.976	6.69
5.355	86.88

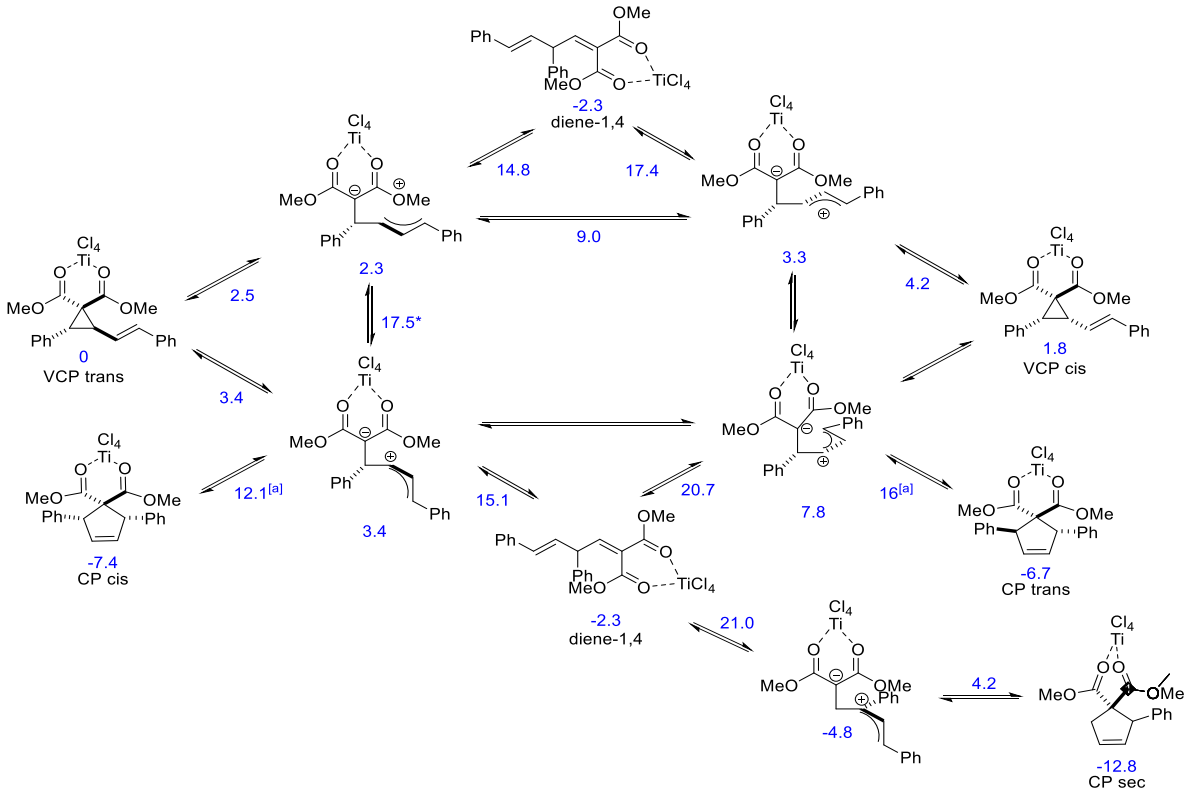
- **Observed UV-spectra:**



Scheme 144

Chapter 8 Appendices

General proposed mechanism for CP and 1,4-diene formation



Proposed general mechanism with relative free energy (kcal/mol) values obtained at the B3LYP-D3/6-311+G**(CH2Cl2)//B3LYP-D3/6-31+G*(CH2Cl2) level of theory. [a]: Benchmark calculations showed that these values are highly underestimated by the method used (by at least 8 kcal/mol). However, the difference between these two values can be interpreted since the errors are expected to cancel out.

Chapter 9 Bibliography

[1] a) E. I. Eger Ii, L. J. Saidman and R. N. Westhorpe, *The Wondrous Story of Anesthesia*, **2014**, p; b) A. Freund, *Journal für Praktische Chemie* **1882**, *26*, 367-377; c) J. Boyd, *Anesthesiology: The Journal of the American Society of Anesthesiologists* **1947**, *8*, 433-434.

[2] G. Gustavson, *J. Prakt. Chem* **1896**, *54*, 97.

[3] J. E. Baldwin, *Chem Rev* **2003**, *103*, 1197-1212.

[4] S. Chandrasekaran and V. Ganesh, *Synthesis* **2016**, *48*, 4347-4380.

[5] J. Sweeney, *European Journal of Organic Chemistry* **2009**, *2009*, 4911-4919.

[6] a) C. A. André, Beauchemin in *Simmons-Smith Cyclopropanation Reaction*; b) H. E. Simmons and R. D. Smith, *Journal of the American Chemical Society* **1958**, *80*, 5323-5324.

[7] P. Helquist, *Methylene and Nonfunctionalized Alkylidene Transfer to Form Cyclopropanes*, **1991**, p.

[8] a) R. D. Rieke, P. T.-J. Li, T. P. Burns and S. T. Uhm, *The Journal of Organic Chemistry* **1981**, *46*, 4323-4324; b) N. Kawabata, I. Kamemura and M. Naka, *Journal of the American Chemical Society* **1979**, *101*, 2139-2145.

[9] P. Helquist in *4.6 - Methylene and Nonfunctionalized Alkylidene Transfer to Form Cyclopropanes*, Eds.: B. M. Trost and I. Fleming), Pergamon, Oxford, **1991**, pp. 951-997.

[10] https://www.sciencedirect.com/topics/chemistry/simmons-smith-cyclopropanation in *Vol. 2019*.

[11] A. B. Charette, C. Molinaro and C. Brochu, *Journal of the American Chemical Society* **2001**, *123*, 12168-12175.

[12] W. D. Wulff, D. C. Yang and C. K. Murray, *Journal of the American Chemical Society* **1988**, *110*, 2653-2655.

[13] W. D. Wulff, W. E. Bauta, R. W. Kaesler, P. J. Lankford, R. A. Miller, C. K. Murray and D. C. Yang, *Journal of the American Chemical Society* **1990**, *112*, 3642-3659.

[14] a) A. de Meijere and L. Wessjohann, *Synlett* **1990**, *1990*, 20-32; b) E. Schaumann, A. Kirschning and F. Narjes, *The Journal of Organic Chemistry* **1991**, *56*, 717-723.

[15] a) H. M. L. Davies, H. D. Smith and O. Korkor, *Tetrahedron Letters* **1987**, *28*, 1853-1856; b) H. M. L. Davies, D. M. Clark and T. K. Smith, *Tetrahedron Letters* **1985**, *26*, 5659-5662.

[16] J. L. Thompson and H. M. L. Davies, *Journal of the American Chemical Society* **2007**, *129*, 6090-6091.

[17] Y. Yang, J. Li, B. Du, C. Yuan, B. Liu and S. Qin, *Chemical Communications* **2015**, *51*, 6179-6182.

[18] A. G. Steinig and A. de Meijere, *European Journal of Organic Chemistry* **1999**, *1999*, 1333-1344.

[19] K. Jiang and Y.-C. Chen, *Tetrahedron Letters* **2014**, *55*, 2049-2055.

[20] V. H. Gessner, *Modern Ylide Chemistry*, Springer International Publishing, **2018**, p.

[21] P. A. Byrne and D. G. Gilheany, *Chemical Society Reviews* **2013**, *42*, 6670-6696.

[22] a) R. Greenwald, M. Chaykovsky and E. J. Corey, *The Journal of Organic Chemistry* **1963**, *28*, 1128-1129; b) J. J. Gajewski and M. P. Squicciarini, *Journal of the American Chemical Society* **1989**, *111*, 6717-6728.

[23] Y. Tang, Y.-Z. Huang, L.-X. Dai, Z.-F. Chi and L.-P. Shi, *The Journal of Organic Chemistry* **1996**, *61*, 5762-5769.

[24] M. Winter, C. Gaunersdorfer, L. Roiser, K. Zielke, U. Monkowius and M. Waser, *European J Org Chem* **2018**, *2018*, 418-421.

[25] O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns and R. Robiette, *Chemistry – A European Journal* **2015**, *21*, 12899-12902.

[26] A. W. Johnson and H. Schubert, *The Journal of Organic Chemistry* **1970**, *35*, 2678-2680.

[27] https://www.sciencedirect.com/topics/chemistry/ylide in *Ylide*, *Vol. 2019*.

[28] W.-W. Liao, K. Li and Y. Tang, *Journal of the American Chemical Society* **2003**, *125*, 13030-13031.

[29] N. A. Varinder K. Aggarwal , Enda Bergin , Alexander Buitrago Santanilla , Erick M. Carreira, *Science of Synthesis*, Thieme, **2014**, p.

[30] a) T. Naito, S. Nagase and H. Yamataka, *Journal of the American Chemical Society* **1994**, *116*, 10080-10088; b) J.-P. Cheng, B. Liu, Y. Zhao, Y. Sun, X.-M. Zhang and Y. Lu, *The Journal of Organic Chemistry* **1999**, *64*, 604-610; c) V. K. A. N. d. K. S. J. C. M. D. W. Eberbach, *Science of Synthesis*, Thieme, **2004**, p.

[31] S. S. Bhattacharjee, H. Ila and H. Junjappa, *Synthesis* **1982**, *1982*, 301-303.

[32] A. Jończyk and A. Konarska, *Synlett* **1999**, *1999*, 1085-1087.

[33] C. D. Papageorgiou, S. V. Ley and M. J. Gaunt, *Angewandte Chemie International Edition* **2003**, *42*, 828-831.

[34] E. J. Corey and M. Chaykovsky, *Journal of the American Chemical Society* **1965**, *87*, 1353-1364.

[35] H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chemical Reviews* **2003**, *103*, 977-1050.

[36] R. Robiette and J. Marchand-Brynaert, *Synlett* **2008**, *2008*, 517-520.

[37] V. K. Aggarwal and E. Grange, *Chemistry – A European Journal* **2006**, *12*, 568-575.

[38] O. Illa, M. Namutebi, C. Saha, M. Ostovar, C. C. Chen, M. F. Haddow, S. Nocquet-Thibault, M. Lusi, E. M. McGarrigle and V. K. Aggarwal, *Journal of the American Chemical Society* **2013**, *135*, 11951-11966.

[39] Q.-Z. Li, X. Zhang, R. Zeng, Q.-S. Dai, Y. Liu, X.-D. Shen, H.-J. Leng, K.-C. Yang and J.-L. Li, *Organic Letters* **2018**, *20*, 3700-3704.

[40] B. P. S. Khambay, *Pesticide Outlook* **2002**, *13*, 49-54.

[41] N. A. M. Manoj C. Desai, *Successful Strategies for the Discovery of Antiviral Drugs*, **2013**, p.

[42] a) K. Hayakawa, S.-i. Matsuoka and M. Suzuki, *Polymer Chemistry* **2017**, *8*, 3841-3847; b) D. Du and Z. Wang, *Tetrahedron Letters* **2008**, *49*, 956-959.

[43] Z. Goldschmidt and B. Crammer, *Chemical Society Reviews* **1988**, *17*, 229-267.

[44] a) T. K. Macklin and G. C. Micalizio, *Nature Chemistry* **2010**, *2*, 638; b) K. L. Malloy, T. L. Suyama, N. Engene, H. Debonsi, Z. Cao, T. Matainaho, C. Spadafora, T. F. Murray and W. H. Gerwick, *Journal of Natural Products* **2012**, *75*, 60-66; c) B. C. Ranu, M. Kavka, L. A. Higgs and T. Hudlickyl, *Tetrahedron Letters* **1984**, *25*, 2447-2450; d) B. M. Trost, Y. Nishimura and K. Yamamoto, *Journal of the American Chemical Society* **1979**, *101*, 1328-1330; e) T. Hudlicky and M.

Natchus, *The Journal of Organic Chemistry* **1992**, *57*, 4740-4746; f) J. A. V. Coates, H. J. Inggall, B. A. Pearson, C. R. Penn, R. Storer, C. Williamson and J. M. Cameron, *Antiviral Research* **1991**, *15*, 161-168; g) H. Miyaoka, D. Honda, H. Mitome and Y. Yamada, *Tetrahedron Letters* **2002**, *43*, 7773-7775; h) H. Xu, F. Wang, W. Xue, Y. Zheng, Q. Wang, F. G. Qiu and Y. Jin, *Organic Process Research & Development* **2018**, *22*, 377-384; i) T. E. Smith, W.-H. Kuo, V. D. Bock, J. L. Roizen, E. P. Balskus and A. B. Theberge, *Organic Letters* **2007**, *9*, 1153-1155; j) J. Lee and J. Hong, *The Journal of Organic Chemistry* **2004**, *69*, 6433-6440.

[45] T. Hudlicky and J. W. Reed, *Angewandte Chemie International Edition* **2010**, *49*, 4864-4876.

[46] N. Neureiter, *The Journal of Organic Chemistry* **1959**, *24*, 2044-2046.

[47] J. M. Simpson and H. G. Richey, *Tetrahedron Letters* **1973**, *14*, 2545-2548.

[48] B. M. Trost and M. J. Bogdanowicz, *Journal of the American Chemical Society* **1973**, *95*, 5311-5321.

[49] a) E. R. J. and F. H. M., *Proceedings of the Chemical Society* **1964**, 221; b) H. M. Frey and D. C. Marshall, *Journal of the Chemical Society (Resumed)* **1962**, 3981-3983.

[50] a) S. C. Wang and D. J. Tantillo, *Journal of Organometallic Chemistry* **2006**, *691*, 4386-4392; b) K. N. Houk, M. Nendel, O. Wiest and J. W. Storer, *Journal of the American Chemical Society* **1997**, *119*, 10545-10546; c) D. Sperling, H.-U. Reißig and J. Fabian, *European Journal of Organic Chemistry* **1999**, *1999*, 1107-1114; d) J. E. Baldwin, *Journal of Computational Chemistry* **1998**, *19*, 222-231.

[51] W. V. E. Doering, *Preprints* **1972**, *17*.

[52] Y.-L. Lin and E. Turos, *The Journal of Organic Chemistry* **2001**, *66*, 8751-8759.

[53] R. L. Danheiser, C. Martinez-Davila and J. M. Morin, *The Journal of Organic Chemistry* **1980**, *45*, 1340-1341.

[54] T. Hudlicky, N. E. Heard and A. Fleming, *The Journal of Organic Chemistry* **1990**, *55*, 2570-2572.

[55] C. H. Heathcock and S. R. Poulter, *Journal of the American Chemical Society* **1968**, *90*, 3766-3769.

[56] a) W. E. Farneth, M. W. Thomsen and M. A. Berg, *Journal of the American Chemical Society* **1979**, *101*, 6468-6470; b) W. E. Farneth, M. W. Thomsen, N. L. Schultz and M. A. Davies, *Journal of the American Chemical Society* **1981**, *103*, 4001-4006.

[57] L. Encarnacion and R. D. Doepker, *The Journal of Physical Chemistry* **1979**, *83*, 573-578.

[58] T. Okazaki, F. Sanda and T. Endo, *Journal of Polymer Science Part A: Polymer Chemistry* **1997**, *35*, 2487-2492.

[59] L. A. Paquette, G. V. Meehan, R. P. Henzel and R. F. Eizember, *The Journal of Organic Chemistry* **1973**, *38*, 3250-3256.

[60] a) R. I. Khusnutdinov and U. M. Dzhemilev, *Journal of Organometallic Chemistry* **1994**, *471*, 1-18; b) M. M. Schulze and U. Gockel, *Journal of Organometallic Chemistry* **1996**, *525*, 155-158.

[61] C.-H. Liu, Z. Zhuang, S. Bose and Z.-X. Yu, *Tetrahedron* **2016**, *72*, 2752-2755.

[62] C. Aïssa, *Synthesis* **2011**, *2011*, 3389-3407.

[63] a) T. Hudlicky, F. F. Koszyk, T. M. Kutchan and J. P. Sheth, *The Journal of Organic Chemistry* **1980**, *45*, 5020-5027; b) V. Aris, J. M. Brown, J. A. Conneely, B. T. Golding and D. H. Williamson, *Journal of the Chemical Society, Perkin Transactions 2* **1975**, 4-10.

[64] M. Rubin, M. Rubina and V. Gevorgyan, *Chemical Reviews* **2007**, *107*, 3117-3179.

[65] B. M. Trost and E. Keinan, *Journal of the American Chemical Society* **1978**, *100*, 7779-7781.

[66] Y. Morizawa, K. Oshima and H. Nozaki, *Tetrahedron Letters* **1982**, *23*, 2871-2874.

[67] K. Hiroi and Y. Arinaga, *Tetrahedron Letters* **1994**, *35*, 153-156.

[68] K. A. P. Lingam and P. Shanmugam, *Tetrahedron Letters* **2013**, *54*, 4202-4206.

[69] R. Grigg, R. Hayes and A. Sweeney, *Journal of the Chemical Society D: Chemical Communications* **1971**, 1248-1249.

[70] a) N. W. Alcock, J. M. Brown, J. A. Conneely and D. H. Williamson, *Journal of the Chemical Society, Perkin Transactions 2* **1979**, 962-971; b) N. W. Alocock, J. M. Brown, J. A. Conneely and D. H. Williamson, *Journal of the Chemical Society, Chemical Communications* **1975**, 792-793.

[71] L. Jiao, M. Lin and Z.-X. Yu, *Chemical Communications* **2010**, *46*, 1059-1061.

[72] a) M. Masashi and N. Shinya, *Chemistry Letters* **1979**, *8*, 927-930; b) I. Ryu, K. Ikura, Y. Tamura, J. Maenaka, A. Ogawa and N. Sonoda, *Synlett* **1994**, *1994*, 941-942; c) G. Zuo and J. Louie, *Angewandte Chemie International Edition* **2004**, *43*, 2277-2279.

[73] a) D. F. Harvey and M. F. Brown, *Tetrahedron Letters* **1991**, *32*, 2871-2874; b) O. A. Ivanova, A. O. Chagarovskiy, A. N. Shumsky, V. D. Krasnobrov, I. I. Levina and I. V. Trushkov, *The Journal of Organic Chemistry* **2018**, *83*, 543-560.

[74] H. M. L. Davies, N. Kong and M. R. Churchill, *The Journal of Organic Chemistry* **1998**, *63*, 6586-6589.

[75] P. A. Pinke, R. D. Stauffer and R. G. Miller, *Journal of the American Chemical Society* **1974**, *96*, 4229-4234.

[76] a) D. C. Braddock, D. M. Badine and T. Gottschalk, *Synlett* **2001**, *2001*, 1909-1912; b) D. C. Braddock, D. M. Badine, T. Gottschalk, A. Matsuno and M. Rodriguez-Lens, *Synlett* **2003**, *2003*, 0345-0348; c) D. C. Braddock and A. Matsuno, *Synlett* **2004**, *2004*, 2521-2524.

[77] Z.-Y. Zhang, Z.-Y. Liu, R.-T. Guo, Y.-Q. Zhao, X. Li and X.-C. Wang, *Angewandte Chemie International Edition* **2017**, *56*, 4028-4032.

[78] M. Thangamani and K. Srinivasan, *The Journal of Organic Chemistry* **2018**, *83*, 571-577.

[79] a) R. P. Murelli and M. L. Snapper, *Organic Letters* **2007**, *9*, 1749-1752; b) D. A. Mundal, K. E. Lutz and R. J. Thomson, *Organic Letters* **2009**, *11*, 465-468; c) Y. Wang and F. G. West, *Synthesis* **2002**, *2002*, 0099-0103.

[80] a) H. Irschik, R. Jansen, G. Hofle, K. Gerth and H. Reichenbach, *J Antibiot (Tokyo)* **1985**, *38*, 145-152; b) M. S. F. L. K. Jie, M. K. Pasha and M. S. K. Syed-Rahmatullah, *Natural Product Reports* **1997**, *14*, 163-189; c) M. C. Wilson, S.-J. Nam, T. A. M. Gulder, C. A. Kauffman, P. R. Jensen, W. Fenical and B. S. Moore, *Journal of the American Chemical Society* **2011**, *133*, 1971-1977.

[81] a) http://www.hmdb.ca/metabolites/HMDB0032712 in *Vol. 2019*; b) G. A. Burdock, *Fenaroli's Handbook of Flavor Ingredients*, CRC Press, **2016**, p.

[82] a) L. Cornelissen, S. Vercruysse, A. Sanhadji and O. Riant, *European Journal of Organic Chemistry* **2014**, *2014*, 35-38; b) K. Akiyama, F. Gao and A. H. Hoveyda, *Angew Chem Int Ed Engl* **2010**, *49*, 419-423.

[83] J. Y. Hamilton, D. Sarlah and E. M. Carreira, *J Am Chem Soc* **2013**, *135*, 994-997.

[84] C. Feng, D. Feng and T. P. Loh, *Chem Commun (Camb)* **2015**, *51*, 342-345.

[85] a) Y. Huang, M. Fananas-Mastral, A. J. Minnaard and B. L. Feringa, *Chem Commun (Camb)* **2013**, *49*, 3309-3311; b) H. Li and A. Alexakis, *Angew Chem Int Ed Engl* **2012**, *51*, 1055-1058; c) Y. Lee, K. Akiyama, D. G. Gillingham, M. K. Brown and A. H. Hoveyda, *J Am Chem Soc* **2008**, *130*, 446-447.

[86] Y. N. Timsina, R. K. Sharma and T. V. RajanBabu, *Chem Sci* **2015**, *6*, 3994-4008.

[87] I. Masao and Y. Sadao, *Bulletin of the Chemical Society of Japan* **1966**, *39*, 2001-2004.

[88] A. Zhang and T. V. RajanBabu, *Journal of the American Chemical Society* **2006**, *128*, 54-55.

[89] B. Moreau, J. Y. Wu and T. Ritter, *Organic Letters* **2009**, *11*, 337-339.

[90] R. Cramer, *Journal of the American Chemical Society* **1967**, *89*, 1633-1639.

[91] G. Hilt, F.-X. du Mesnil and S. Lüers, *Angewandte Chemie International Edition* **2001**, *40*, 387-389.

[92] T. Alderson, E. L. Jenner and R. V. Lindsey, *Journal of the American Chemical Society* **1965**, *87*, 5638-5645.

[93] X. Lian, W. Chen, L. Dang, Y. Li and C.-Y. Ho, *Angewandte Chemie International Edition* **2017**, *56*, 9048-9052.

[94] a) M. Arndt, M. Dindaroğlu, H.-G. Schmalz and G. Hilt, *Organic Letters* **2011**, *13*, 6236-6239; b) V. A. Schmidt, C. R. Kennedy, M. J. Bezdek and P. J. Chirik, *Journal of the American Chemical Society* **2018**, *140*, 3443-3453.

[95] a) P. S. Diez and G. C. Micalizio, *J Am Chem Soc* **2010**, *132*, 9576-9578; b) T. Kazuhiko, Y. Masashi, O. Hidetoshi, U. Kiitiro, F. Takeshi and F. Isao, *Chemistry Letters* **1995**, *24*, 315-316; c) M. Mailig, A. Hazra, M. K. Armstrong and G. Lalic, *Journal of the American Chemical Society* **2017**, *139*, 6969-6977.

[96] a) B. M. Trost, A. B. Pinkerton, F. D. Toste and M. Sperrle, *Journal of the American Chemical Society* **2001**, *123*, 12504-12509; b) B. M. Trost, G. D. Probst and A. Schoop, *Journal of the American Chemical Society* **1998**, *120*, 9228-9236.

[97] B. M. Trost and H. Gholami, *Journal of the American Chemical Society* **2018**, *140*, 11623-11626.

[98] J. Pospíšil and I. E. Markó, *Journal of the American Chemical Society* **2007**, *129*, 3516-3517.

[99] V. Jeso and G. C. Micalizio, *Journal of the American Chemical Society* **2010**, *132*, 11422-11424.

[100] O. Rousseau in *Development of the (4 + 1) Annulation Reaction between 1,3-Dienes and Sulfonium Ylides, Vol. PhD* Université catholique de Louvain, Louvain-la-Neuve, **2016**.

[101] a) S. Clergue, O. Rousseau, T. Delaunay, G. Dequirez, T.-V. Tran, S. El Aakchioui, G. Barozzino-Consiglio and R. Robiette, *Chemistry – A European Journal* **2018**, *24*, 11417-11425; b) O. Rousseau, T. Delaunay and R. Robiette, *Synlett* **2014**, *25*, 519-522.

[102] V. K. Aggarwal, I. Bae, H.-Y. Lee, J. Richardson and D. T. Williams, *Angewandte Chemie* **2003**, *115*, 3396-3400.

[103] O. Illa, M. Arshad, A. Ros, E. M. McGarrigle and V. K. Aggarwal, *Journal of the American Chemical Society* **2010**, *132*, 1828-1830.

[104] V. K. Aggarwal and J. Bi, *Beilstein Journal of Organic Chemistry* **2005**, *1*, 4.

[105] Y. Nagao, K. Inoue, M. Yamaki, S. Takagi and E. Fujita, *Chem. Pharm. Bull.* **1988**, *36*, 495-508.

[106] D. R. Nicponski, *Tetrahedron Letters* **2014**, *55*, 2075-2077.

[107] D. Basavaiah, K. Padmaja and T. Satyanarayana, *Synthesis* **2000**, *2000*, 1662-1664.

[108] S. Clergue in *The (4+1) asymmetric annulation reaction between 1,3-dienes and sulfonium ylides: mechanism and scope*, *Vol. Ph.D.* Université catholique de Louvain, **2019**.

[109] U. o. W. Hans J. Reich in *Vol.* **2018**.

[110] A. Delbrassinne in *Synthèse de diènes-1,4 à partir d'ylure de sulfonium et diènes-1,3*, *Vol. Master* UCLouvain, Louvain-la-Neuve, **2018**.

[111] a) R. K. Chaudhuri and K. Bojanowski, *International Journal of Cosmetic Science* **2014**, *36*, 221-230; b) L. Fernández-Cabezón, B. Galán and J. L. García, *Frontiers in Microbiology* **2018**, *9*.

[112] a) M. S. McCammant, L. Liao and M. S. Sigman, *Journal of the American Chemical Society* **2013**, *135*, 4167-4170; b) J. Y. Hamilton, D. Sarlah and E. M. Carreira, *Journal of the American Chemical Society* **2014**, *136*, 3006-3009; c) T. E. Smith, W.-H. Kuo, E. P. Balskus, V. D. Bock, J. L. Roizen, A. B. Theberge, K. A. Carroll, T. Kurihara and J. D. Wessler, *The Journal of Organic Chemistry* **2008**, *73*, 142-150.

[113] a) D. Lebœuf, V. Gandon, J. Ciesielski and A. J. Frontier, *Journal of the American Chemical Society* **2012**, *134*, 6296-6308; b) Z. Pachuau and R. H. D. Lyngdoh, *Journal of Chemical Sciences* **2004**, *116*, 83-91.

[114] a) S. Fukuzumi, J. Yuasa, N. Satoh and T. Suenobu, *Journal of the American Chemical Society* **2004**, *126*, 7585-7594; b) P. Hanson, J. R. Lindsay Smith and V. A. Osborne, *Journal of the Chemical Society, Perkin Transactions 2* **1998**, 2653-2658.

[115] L. Candish, M. Freitag, T. Gensch and F. Glorius, *Chemical Science* **2017**, *8*, 3618-3622.

[116] a) O. K. Onajole, Y. Coovadia, T. Govender, H. G. Kruger, G. E. M. Maguire, D. Naidu, N. Singh and P. Govender, *Chemical Biology & Drug Design* **2011**, *77*, 295-299; b) R. P. Tripathi, S. S. Bisht, A. Ajay, A. Sharma, M. Misra and M. P. Gupt, *Current Medicinal Chemistry* **2012**, *19*, 488-517.

[117] A. F. Thomas and B. Willhalm, *Tetrahedron Letters* **1964**, *5*, 3775-3778.

[118] a) F. Habib, Bajpai, M., *Chemistry & Chemical Technology* **2011**, *5*, 317-326; b) J. Dale, O. I. Eriksen, P. Groth, U. Norinder, G. Wittman, L. Gera, M. Bartók, I. Pelczer and G. Dombi, *Acta Chemica Scandinavica* **1988**, *42b*, 573-582.

[119] X.-L. Du, H.-L. Chen, H.-J. Feng and Y.-C. Li, *Helvetica Chimica Acta* **2008**, *91*, 371-378.

[120] T. V. Nguyen, J. M. Hartmann and D. Enders, *Synthesis* **2013**, *45*, 845-873.

[121] K. M. Chigboh, D.; Nadin, A.; Stockman, R., *Tetrahedron Lett.* **2008**, *49*, 4768-4770.