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Classe LM-71 - Scienze e Tecnologie della Chimica Industriale

Synthesis of enantiopure cyclopentanones by desymmetrization of allylic cyclobutanols

Tesi di laurea sperimentale

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Abstract

The interest in five-membered ring molecules derives from their important application in many different fields, such as pharmaceutical and agrochemical areas. A common strategy for their formation is four-membered ring expansion, which also allows to add molecular complexity and functional handles within one single operation starting from readily available starting materials. Organocatalysis can be exploited to promote the reaction and to obtain a good enantio- and diastereoselection. This technique involves the exclusive use of organic molecules as catalysts, without resorting to metals. The aim of this work is to obtain enantiopure cyclopentanones starting from achiral allylic cyclobutanols. The reaction consists in a ring expansion promoted by the addition of a halogen to the double bond of the substrate, with formation of a haliranium ion as intermediate, followed by a semipinacol rearrangement to afford the cyclopentanone. The reaction is catalysed by a chiral phosphoric acid that, besides accelerating the rate of the reaction, transmits a specific chirality thanks to its chiral structure, following the asymmetric catalysis principles. Starting from symmetric *trans*-allylic cyclobutanols, the whole reaction is a desymmetrization and leads to the formation of two new stereogenic centres: a mixture of diastereoisomers is obtained, each as couple of enantiomers; the ratio between the possible configurations is determined by the relative position that the chiral catalyst and the reagent occupy during the reaction. Since the reaction is already optimized, the original aim was to study the scope: first, the synthesis of a set of allylic cyclobutanols and their relative precursors, in order to have a wider range of substrates; then, the identification of the type of substrate that undergoes the expansion, with the study of enantio- and diastereoselectivity obtained in each case. Due to the Covid-19 emergency, only a little experimental part has been carried out, and the whole topic has been developed as a bibliographic study.

Summary

CHAPTER 1

INTRODUCTION

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1. **Ring Expansion Reactions**
2. **Cyclopentanones from Cyclobutanols by Ring Expansion**
3. **Enantioselective Ring Expansion of Allylic Cyclobutanols via Haliranium Ions**

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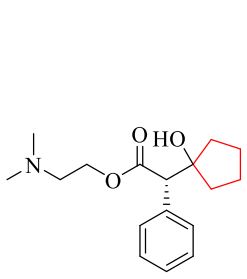
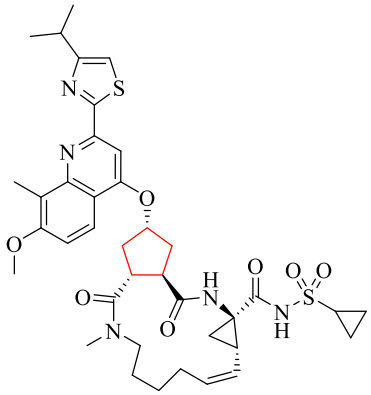
1. Ring expansion reactions

The interest in five-membered ring molecules comes from their important application in many different fields. Molecules containing cyclic scaffolds are indispensable to the pharmaceutical and agrochemical industry, with saturated four, five and six-membered rings being among the most frequently used ring systems in small molecule drugs.[1] Some examples are reported in *Figure 1*: on the left, cyclopentolate, commonly used as an eye drop during pediatric eye examinations to dilate and prevent the eye from focusing/accommodating. On the right, TMC435450, a potent inhibitor of hepatitis C virus NS3/4A protease and viral replication, identified by structure-activity relationship analysis performed with a set of cyclopentane-containing macrocycles.[2]



Cyclopentolate



TMC435350

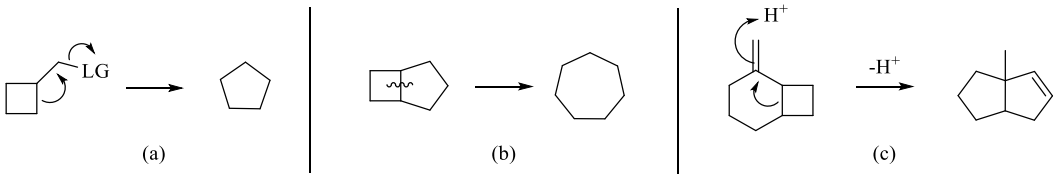
Figure 1 *Some cyclopentane containing drugs.*

Ring expansions can be valuable approaches to obtain structures that would be difficult to synthesize through standard cyclization methodologies. They also allow to add molecular complexity and functional handles within one single operation starting from readily available starting materials and, in particular, ring-enlargement reactions are very appropriate to access five-membered ring systems. A ring enlargement reaction consists in

[1] Tylor, R.D.; MacCoss, M.; Lawson, A.D.G. *J Med Chem*. **2014,** 57, 5845–5859.
[2] Raboisson, P.; De Kock, H.; Rosenquist, A.; Nilsson, M.; Salvador-Oden, L.; Lin, T.; Roue, N.; Ivanov, V.; Wähling, H.;Wickström, K.; Hamelink, E.; Edlund, M.; Vrang, L.; Vendeville, S.; Van de Vreken, W.; McGowan, D.; Tahri, A.; Hu, L.; Boutton, C.; Lenz, O.; Delouvroy, F.; Pille, G.; Surleraux, D.; Wigerinck, P.; Samuelsson, B.; Simmen, K.. *Bioorg. Med. Chem. Lett*. **2008,** 18, 4853-4858.

a rearrangement that interconverts small rings to larger ring sizes through relief of ring strain. For example, cyclobutanes can easily expand to cyclopentanes since a four-membered ring is more strained than a five-membered ring, which is more stable from a thermodynamic point of view. Expansion from cyclobutanes to cyclopentanes is associated with an energy release of 20 kcal/mol. This value is higher compared to enlargements from cyclopropanes to cyclobutanes or from cyclopentanes to cyclohexanes.[3] This reason makes this transformation very appealing.

Generally, enlargements can be triggered by: (a) insertion of an outside group already appended to the ring, as the carbon of the alkyl group in the first equation below, followed by expulsion of the leaving group; (b) opening of a bicycle to a single larger ring,[4] with release of strain of both rings to a single stable ring, or (c) coupling a ring expansion with a ring closing transformation, leading to, as in the last scheme, two five-membered rings from a six and a four-membered ones (*Scheme 1*).



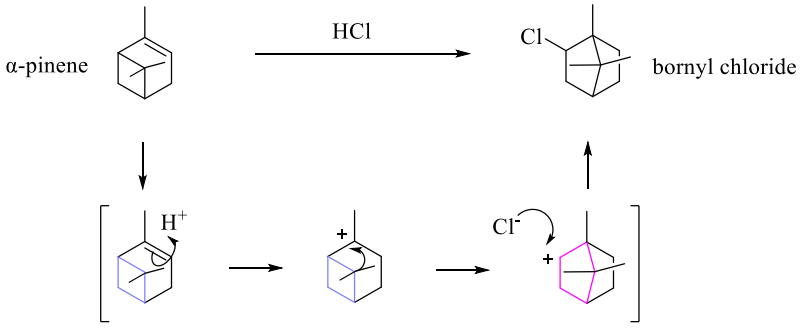
Scheme 1 *Common strategies for ring-enlargement reactions.*

The following pages will focus on ring-enlargements of four-membered molecules into five-membered ones, which is directly related to this work.

[3] The strain energies (kcal/mol) of cyclopropane (28,13), cyclobutane (26,90), cyclopentane (7,19) and cyclohexane (1,35), estimated based on single conformation increments. Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc*. **1970**, 92, 2377.
[4] Kantorowski, E. J.; Kurth, M. J. *Tetrahedron Lett*. **2000**, 56 (26), 4317-4353.

2. Cyclopentanones from cyclobutanols by ring expansion

There are several reactions that convert a four-membered carbocycle into a five-membered ring through a ring expansion. One of these is the one that takes place through the acid promoted Wagner-Meerwein rearrangement,[5] that consists in a 1,2 shift of a hydrogen, alkyl or aryl group from one carbon to a neighbouring carbon. This kind of reaction happens extensively in nature; a well-known example is represented by α-pinene, a bicyclic monoterpene that is an important constituent of pine resin. This compound undergoes an acid promoted Wagner-Meerwein shift of an alkyl group to a carbocationic centre, triggering the expansion from a four to a five-membered ring and affording a secondary carbocation; the following attack of chlorine leads to bornyl chloride (*Scheme 2*).

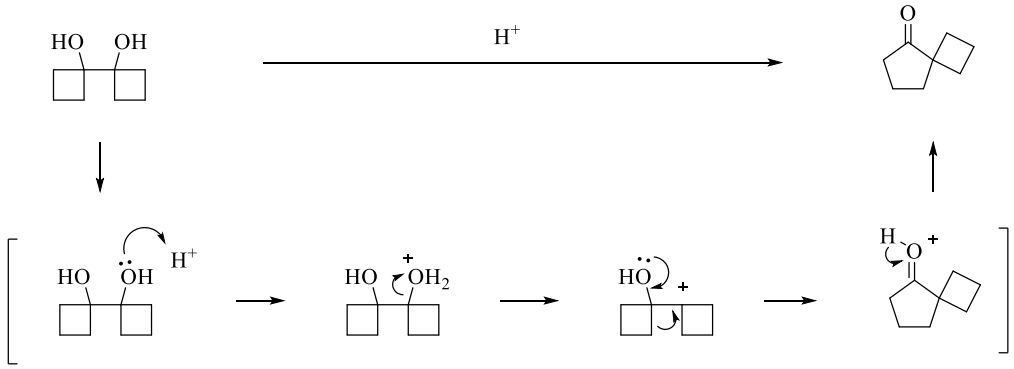


Scheme 2 *Example of Wagner-Meerwein rearrangement: pinene rearrangement.*

Another mechanistically related reaction is the pinacol rearrangement,[6] where a fully substituted 1,2-diol is converted to a carbonyl compound under acidic conditions. The reaction takes the name from "pinacol" (2,3-dimethyl-2,3-butanediol), that rearranges to pinacolone, and from which derives the corresponding class of compounds. Treating a substrate with a Brønsted acid allows the hydroxyl groups to leave as water, giving a tertiary carbocation intermediate, that is further stabilized by migration of the alkyl group and formation of an oxonium ion, whose stability is probably the driving force of the reaction, as every atom reaches the octet. This rearrangement occurs with both symmetrical

[5] Hanson, J. R. *Comprehensive Organic Synthesis.* **1991**, 3, 705-719.
[6] Rickborn, B. *Comprehensive Organic Synthesis.* **1991**, 3, 721-732.

diols, as the example in *Scheme 3*, in which 1,2-bis(cyclobuthyl)-1,2-diol is converted into aspirocyclic cyclopentanone, and unsymmetrical ones. In the second case regioselectivity is determined by the most stable cation formed in the first step after the leaving of the correspondent hydroxyl group.



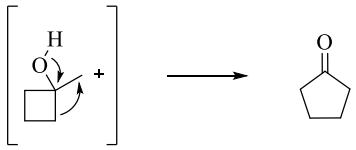
Scheme 3 *Example of pinacol rearrangement leading to a spirocyclic cyclopentanone.*[7]

The most studied and used reaction for ring expansions leading to cyclopentanones is the semipinacol rearrangement, which is also mechanistically related to the pinacol rearrangement and that will be covered with more detail in the following section, due to the close relationship with the chemistry described herein.

2.1 The general approach: Semipinacol rearrangement

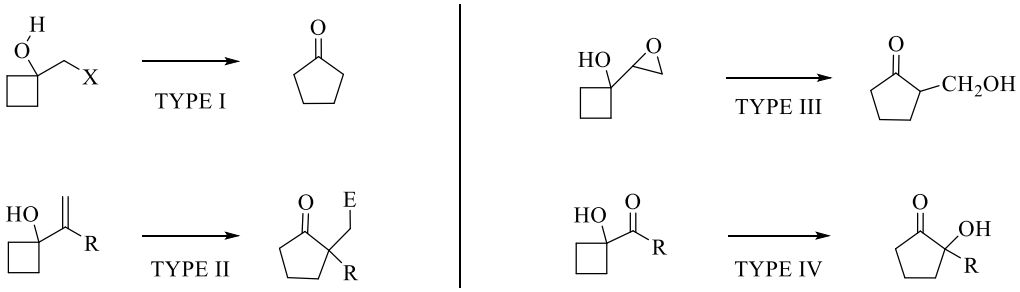
Semipinacol rearrangement reactions include all such rearrangements that are either related to, or reminiscent of, the pinacol rearrangement.[8] All such processes share a common reactive species where an electrophilic carbon centre, including but not limited to carbocations, is vicinal to an oxygen-containing carbon. The mechanism is shown in *Scheme 4*: the hydroxyl group provides the electrons to "push" the migrating group across, which is represented by one of the two alkyl chains, while the "pull" comes from the carbocation/electrophilic carbon; the migration is facilitated under either acidic or basic conditions. In the end a 1,2-alkyl shift occurs, driven by the formation of the carbonyl group and a less strained 5-membered carbocycle.

[7] Vogel, E. *Chem. Ber*. **1951**, 85, (1, 20), 25-29.
[8] Coveney, D. J. *Comprehensive Organic Synthesis.* **1991**, 777– 801.



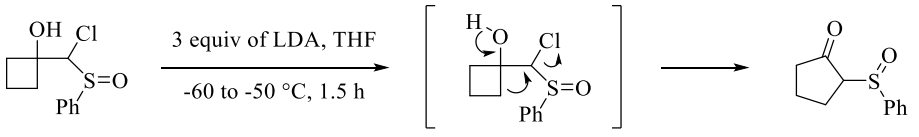
Scheme 4 *General mechanism of semipinacol rearrangement in a cyclobutanol to cyclopentanone expansion.*

Semipinacol rearrangements can be classified into four types of reactions, which are shown in *Scheme 5*. The distinction between these four depends on the nature of the electrophilic carbon centre of the substrate.[9]



Scheme 5 *Four types of the semipinacol rearrangement reaction.*

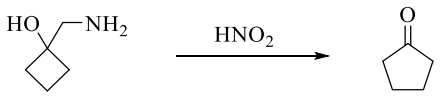
Type I refers to the rearrangement of 2-heterosubstituted alcohols and their derivatives. In this reaction the electrophile "X", usually represented by OMs, OTs, Cl, Br, I, N_2, SR, or SeR, makes the vicinal carbon electrophilic, and acts as the leaving group. In the example shown below, α-sulfinyl cyclopentanone was obtained from type I rearrangement of lithium 1-(chloro(phenylsulfinyl)methyl)cyclobutan-1-olate (*Scheme 6*).[10]



Scheme 6 *Cyclobutanol ring expansion through Type I semipinacol rearrangement.*

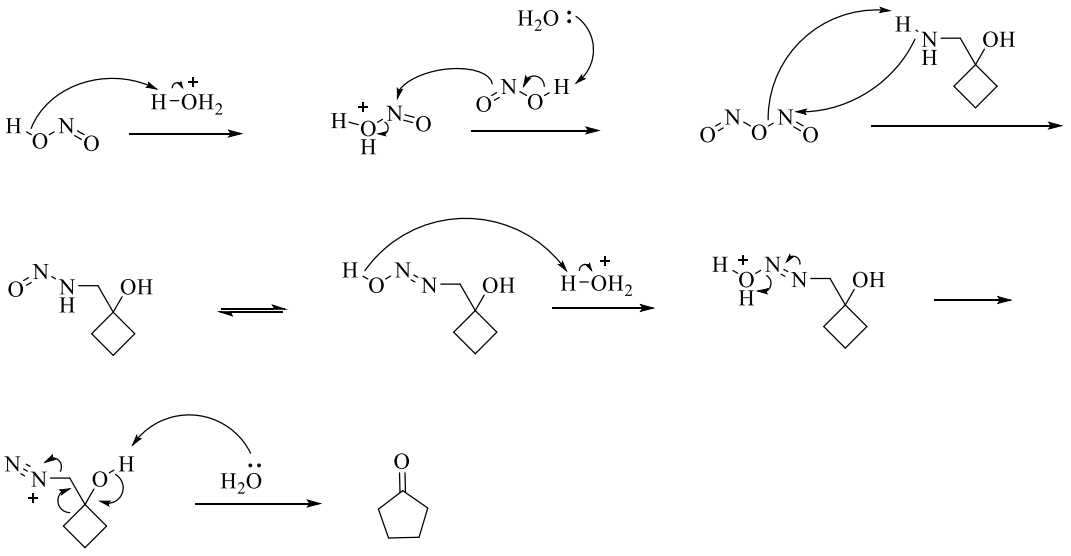
[9] Song, Z.; Fan, C.; Tu, Y. *Chem. Rev.* **2011**, 111 (11), 7523–7556.
[10] Satoh, T.; Itoh, N.; Gengyo, K.; Yamakawa, K. *Tetrahedron Lett.* **1992**, 33, 7543.

A variant of Type I semipinacol rearrangement with N_2 as leaving group is the Tiffeneau-Demjanov rearrangement (*Scheme 7*).[11] This reaction consists in the transformation of a 1-aminomethyl-cycloalkanol to an enlarged cycloketone using nitrous acid. This method provides an easy way to increase amino-substituted cycloalkanes and cycloalkanols in size by one carbon.



Scheme 7 *Synthesis of cyclopentanone through Tiffeneau-Demjanov rearrangement of 1-aminomethyl-cuclobutanol.*

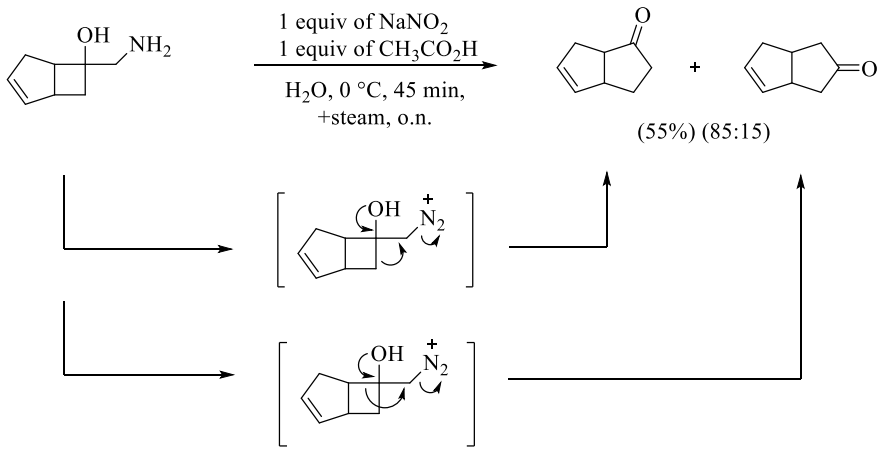
The Tiffeneau-Demjanov reaction mechanism, reported in *Scheme 8*, reckons on the conversion of the amino to a diazonium group through nitrous acid attack, with subsequent carbonyl formation and ring expansion of the intermediate.



Scheme 8 *Mechanism of the Tiffeneau-Demjanov rearrangement.*

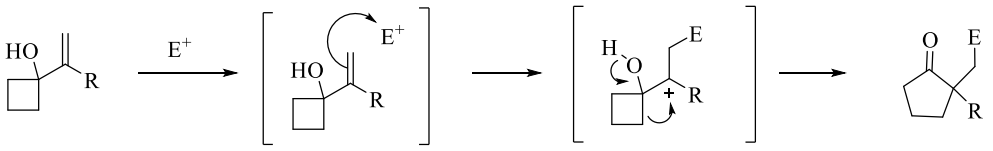
[11] Kohlbacher, S.M., Ionasz, V., Ielo, L. et al. *Monatsh Chem 150*. **2019**, 2011–2019.

An example of the Tiffeneau-Demjanov rearrangement is shown in *Scheme 9*, where the two isomers 3,3a,6,6a-tetrahydropentalen-1(2H)-one and 3,3a,6,6a-tetrahydropentalen-2(1H)-one are obtained from 6-(aminomethyl)bicylo[3.2.0]hept-2-en-6-ol.[12]



Scheme 9 *Cyclobutanol to cyclopentanone ring expansion through Tiffeneau-Demjanov rearrangement.*

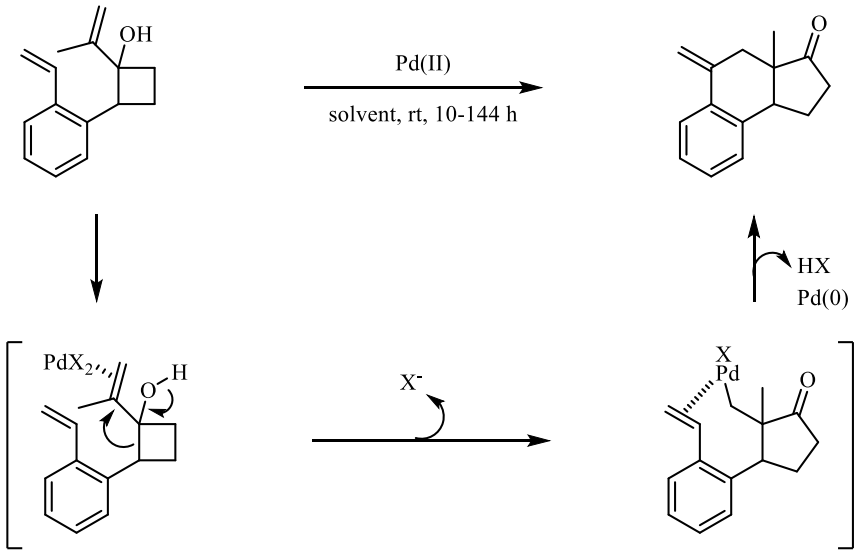
Type II semipinacol rearrangement refers to rearrangements of allylic alcohols and their derivatives. The electrophilic carbon centre is a carbocation that can be generated by the addition of an electrophile to a C═C bond (*Scheme 10*). Generally, electrophiles such as haloniums, selenium cations, and Brønsted and Lewis acids initiate intermolecularly the rearrangements. In contrast, oxocarbeniums, thiocarbeniums, and iminiums mainly undergo intramolecular processes.



Scheme 10 *General scheme of cyclobutanol to cyclopentanone expansion through Type II semipinacol rearrangement via carbocation.*

[12] (a) Roberts, J. D.; Gorham, W. F. *J. Am. Chem. Soc*. **1952**, 74, 2278. (b) Nee, M.; Roberts, J. D. *J. Org. Chem*. **1981**, 46, 67.

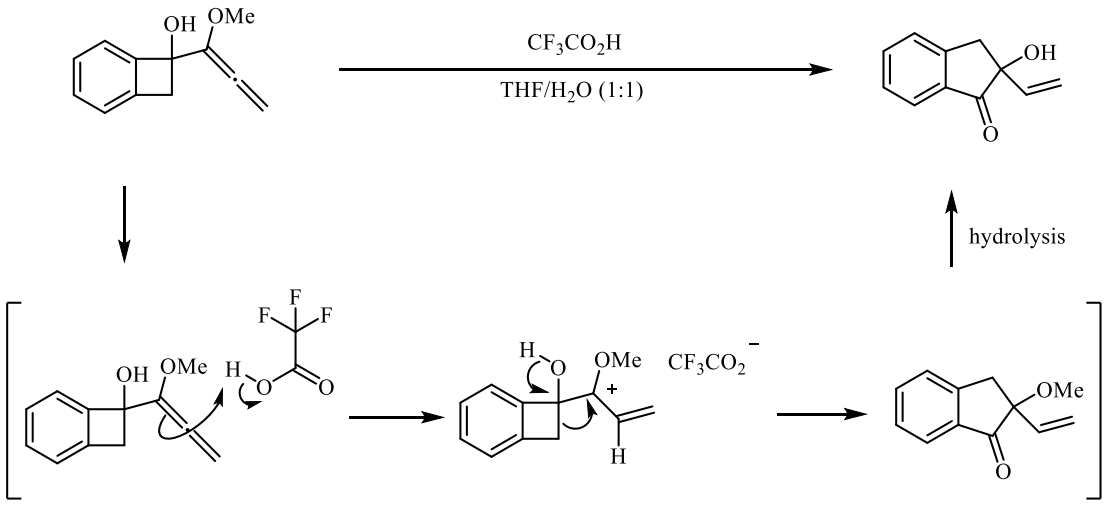
The presence of a double bond vicinal to the carbon containing oxygen offers many ways of activation to achieve electrophilicity, following type II semipinacol mechanism. One of the most studied of these ways is activation via transition metals. Transition metals are extensively used to catalyse organic reactions forming what are called organometallic compounds; their extensive use is due to their high efficiency, with high turnover number (number of moles of substrate that a mole of catalyst can convert before deactivation), high selectivity and broad scope of action; the mechanism consists in a catalytic cycle involving electron exchange processes such as redox reactions between the catalyst and the reagent, thus different oxidation states of the catalyst are needed; transition metals are the perfect choice for this because they can exist in different oxidation states, being easily oxidized and reduced from one to another state. In the example reported below, a palladium catalysis is used to achieve a four to five-membered ring expansion. The mechanism consists in complexation of palladium followed by ring expansion of the cyclobutanol ring to a cyclopentanone palladium complex, with resulting insertion of olefins and elimination of palladium to give the final product.[13] Pd(II) is the active species that catalyses the whole reaction, while at the end a reduced form of the metal, Pd(0), formed after a β-hydride elimination, has to be oxidized again to restart the cycle (*Scheme 11*).



Scheme 11 *Ring expansion by transition metal activation.*

[13] Yoshida, M.; Ismail, A.-H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1*. **2000**, 2629.

Transition metals catalysed electrophile-induced semipinacol rearrangements have been studied extensively with very good results, and many different transition metals have been used, such as copper,[14] cobalt,[15] or silver.[16] However, efforts have been made to move from transition-metal-catalysed ring expansion of cyclobutanols to transition-metal-free variants due to various problems linked to the cost, impact on environment, difficult reaction conditions and many others. An alternative allylic alcohol activation is activation via acid. Both Brønsted and Lewis acid can be exploited for this purpose. Brønsted acid catalysis consists in activation either by protonation or by hydrogen-bonding between the catalyst and the substrate, as these molecules contain a hydrogen source; Lewis acids activates by coordination between the two species: the electronic lack of the catalyst is exploited, and an electron-rich substrate like an olefin can easily coordinate to it. In the example reported in *Scheme 12*, a Brønsted acid catalysis has been used.[17]



Scheme 12 *Ring expansion via acid activation.*

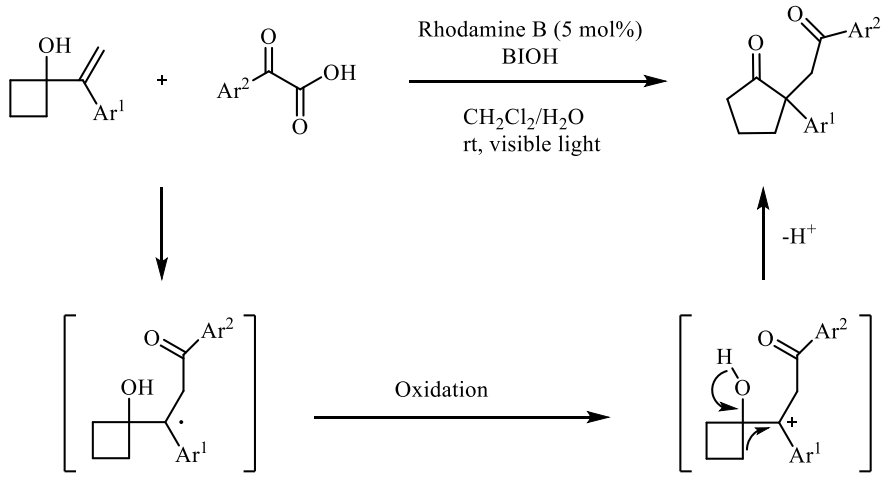
[14] a) Chen, Z.M.; Bai, W.; Wang, S.H.; Yang, B.M.; Tu, Y.Q.; Zhang, F.M. *Angew. Chem. Int. Ed*. **2013**, 52, 9781–9785. b) Shao, H.; Bao, W.; Jing, Z.R.; Wang, Y.P.; Zhang, F.M.; Wang, S.H.; Tu, Y.Q. *Org Lett*. **2017**, 19, 4648–4651.

[15] Shao, H.; Zhang, X.M.; Wang, S.H.; Zhang, F.M.; Tu, Y.Q.; Yang, C. *Chem. Commun*. **2014**, 50, 5691–5694.

[16] Tian, Q.; Chen, B.; Zhang, G. *Green Chem*. **2016,** 18, 6236–6240.

[17] (a) Stone, G. B.; Liebeskind, L. S. *J. Org. Chem*. **1990**, 55, 4614. (b) Paquette, L. A.; Hofferberth, J. E. *Org. React*. **2003**, 62, 477.

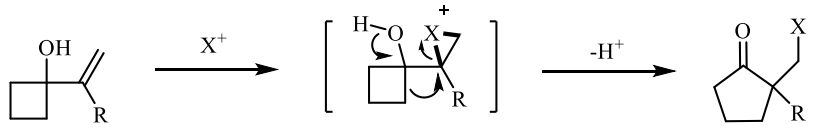
Another route of activation is via radical intermediates. This kind of mechanism occurs in many "green" alternatives to transition metals activation, such as electrochemical and photoredox semipinacol rearrangements.[4] Electrochemical rearrangements consist in transformations made in electrochemical cells with specific electrodes and solvents, where oxidation and reduction processes occur via electrons transfer through the two electrodes;[18] this approach represents a developing area that expects to gain more and more importance in the future. Photoredox rearrangements utilize light as an energy source to initiate chemical changes via single-electron transfer events; these reactions employ small quantities of a light-sensitive compound that, when excited by light, can mediate the transfer of electrons between chemical compounds, creating a series of radicals in a cascade reaction;[19] this method shows many advantages with respect to classical routes as can be inexpensive, environmentally sustainable, and infinitely available. The general mechanism is a neophyl-induced rearrangement (*Scheme 13*): first, the radical produced by the initiator adds to the allylic alcohol forming a stabilized tertiary radical; then the latter undergoes oxidation to a tertiary cation, inducing a 1,2-migration to form the cyclopentanone.



Scheme 13 *Ring expansion via radical activation.* [20]

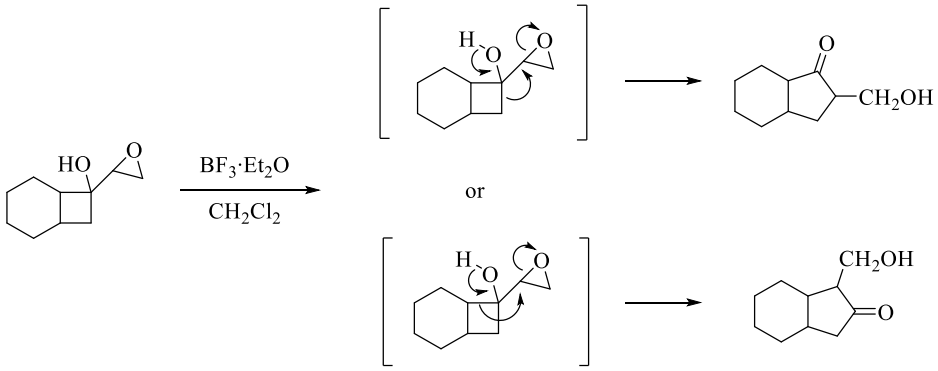
[18] Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev*. **2006**, 35 (7), 605–621.
[19] Romero, N. A; Nicewicz, D. A. *Chem. Rev.* **2016**, 116, 17, 10075–10166.
[20] Zhang, J-J.; Cheng, Y-B.; Duan, X-H. *Chinese J. Chem*. **2017**; 35, 311–315.

One last way of activation is via halofunctionalization (*Scheme 14*). This methodology is the one chosen for this work, and it will be better explained in the next section.



Scheme 14 *Cyclobutanol ring expansion via halofunctionalization.*

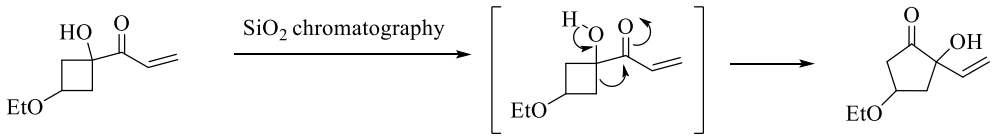
Type III semipinacol rearrangement refers to rearrangements of epoxides. Investigations in this field have focused largely on rearrangements of 2,3-epoxy alcohols and their derivatives. In this case, the electrophilic carbon centre corresponds to either carbon of the oxirane, and the migration is driven by acid-promoted epoxide ring-opening. Depending on the structural features of the substrate and on reaction conditions, different rearrangements can take place. The example reported in *Scheme 15* shows a four to five-membered ring expansion through epoxide opening.[21] Depending on which alkyl group migrates, different structural isomers are obtained.



Scheme 15 *Example of cyclobutanol to cyclopentanone expansion through Type III semipinacol rearrangement.*

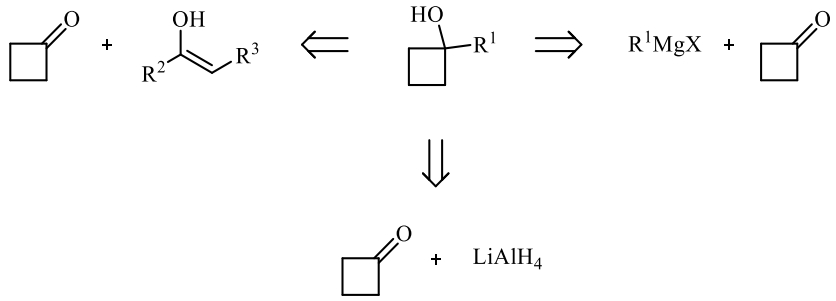
[21] (a) Hwang, C.-S.; Reusch, W. *Heterocycles.* **1987**, 25, 589. (b) Hwang, C.-S.; Ward, D. L.; Reusch, W. *J. Org. Chem*. **1989**, 54, 4318.

Finally, type IV refers to rearrangements of tertiary α-hydroxy ketones and imines. This reaction is also known as the "acyloin rearrangement" or "α-ketol rearrangement". Because an enolization/protonation is impossible for tertiary α-hydroxy ketones and imines, the 1,2-migration of the C–C bond toward the electrophilic carbon centre of the carbonyl or imine group is believed to account for this rearrangement. One example of this type of reaction is shown in *Scheme 16*, in which a 1-hydroxy-1-enoylcyclobutane substrate is converted into a 2-hydroxy-2-vinylcyclopentan-1-one. [22]



Scheme 16 *Example of cyclobutanol to cyclopentanone expansion Type IV semipinacol rearrangement.*

As shown in all the previous examples of semipinacol rearrangement, the required cyclobutanol substrate is a key compound for the formation of the target five-membered rings. It can be easily obtained from cyclobutanone by simple reactions such as aldol reactions with enolates, reduction, Grignard addition and many other reactions (see *Scheme 17*), while cyclobutanone is a readily available derivative and cheap reagent.[23]

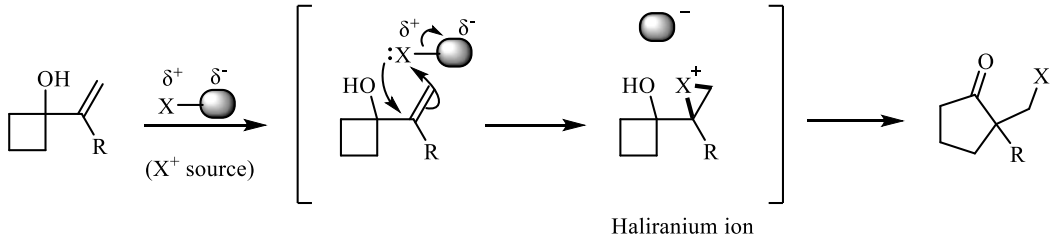


Scheme 17 *Straightforward accesses to cyclobutanols from cyclobutanone.*

[22] Stone, G. B.; Liebeskind, L. S. *J. Org. Chem*. **1990**, 55, 4614.
[23] Leemans, E.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2011**, 111, 5, 3268–3333.

2.2 Ring expansion of Allylic Cyclobutanols via Halofunctionalization

With the intention to exploit electrophile-induced semipinacol rearrangements to achieve five-membered ring molecules, we will consider the addition of a halogen to the double bond of an allylic cyclobutanol, without the use of any transition metal, to achieve electrophilicity. [24] As a classical addition of a halogen to an alkene, this process goes through addition of a halenium ion "X^+" to the double bond, and the intermediate that arises is a haliranium ion (or halonium ion). However, haliranium ion needs not necessarily to always be the intermediate and other possibilities include alkene-halogen π-complexes or the intermediacy of species featuring covalent bonds to metal or main group elements; we will focus only on the classical intermediate, without the use of metals or other elements. The general mechanism of cyclobutanol ring expansion via halogen activation is reported in *Scheme 18*. This kind of intermediate arises from the electrophilic attack of the halogen to the double bond and following stabilization of the resulting carbocation utilizing one of its lone pairs; this can also occur in a concerted way, as shown in *Scheme 18*. The final structure is a three-membered heterocycle, where the halogen bears a positive charge.

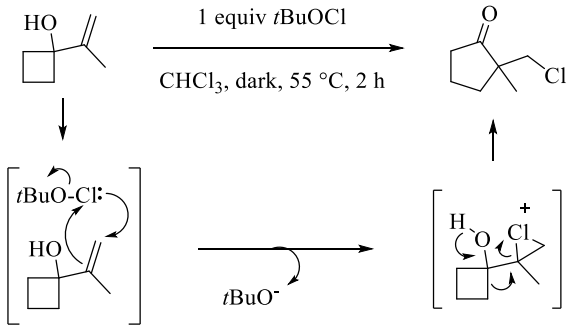


Scheme 18 *Haliranium ion formation.*

Although quite stable as every atom reaches the octet, these ions are usually only short-lived reaction intermediates: the high ring strain in the three-membered ring and the positive charge on the halogen make them great electrophiles. In almost all cases the haliranium ions are attacked even by weak nucleophiles within a very short time. Once that the intermediate has formed, ring expansion occurs by intramolecular nucleophilic trapping by one of the two alkylic chains of the four-membered ring. Many reagents can

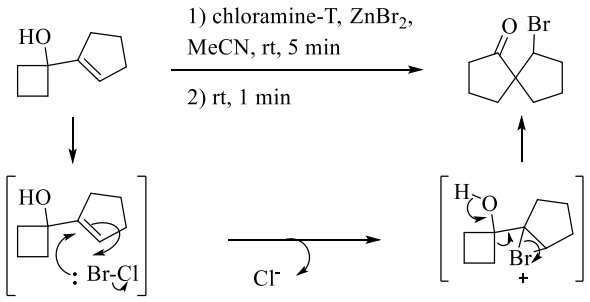
[24] Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E. *Angew. Chem. Int. Ed.* **2015**, 54, 15642.

be used as halenium ion source, and great attention has been focused to those which are easy to handle and offer a good reactivity, replacing classic hazardous reagents such as molecular dihalogens.[249] Some examples of ring expansion through haliranium ion are reported below. The first one is the reaction carried out by Johnson and Herr, where a chloronium ion is formed: 1-isopropenylcyclobutanol reacted with *tert*-butyl hypochlorite, resulting in 2- (chloromethyl)-2-methylcyclopentanone in 81% yield (*Scheme 19*).[25]



Scheme 19 *Allylic cyclobutanol ring expansion through chloronium ion.*

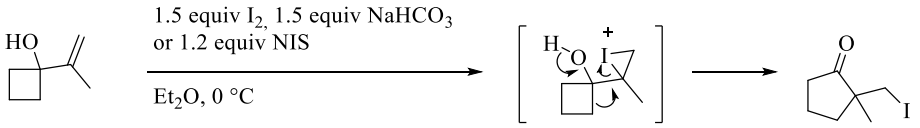
Bromonium ion formation was instead exploited by Chen et al. during the synthesis of 6-bromospiro-[4.4]nonan-1-one, starting from 1-cyclopent-1-enylcyclobutanol (*Scheme 20*).[26] The methodology used for this reaction consists in the combination of chloramine-T and ZnX_2, where it is presumed that the halogen anion in ZnX_2 was oxidized to a halogen cation by chloramine-T and existed in the form of XCl; an electrophilic addition of X^+, released from XCl, to the double bond occurred with concomitant 1,2-migration affording the spirononanone.



Scheme 20 *Allylic cyclobutanol ring expansion through bromonium ion.*

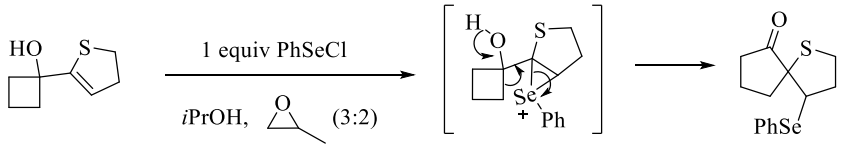
[25] Johnson, C. R.; Herr, W. *J. Org. Chem*. **1973**, 38, 3153-3159.
[26] Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Chen, W. M. *Synlett* **2003**, 1497.

Fukomoto et al. studied a iodonium ion-mediated ring expansion of olefinic cyclobutanols through addition of iodine in the presence of $NaHCO_3$, or by means of *N*-iodosuccinimide (*Scheme 21*).[27]



Scheme 21 *Allylic cyclobutanol ring expansion through iodonium ion.*

A last example of cation-promoted ring expansion of allylic cyclobutanols involved the rearrangement of selenonium ion, in analogy with the previous halonium ion rearrangements. In this example vinyl cyclobutanol was treated with phenylselenyl chloride in isopropylalcohol and propylene oxide, affording the spirocyclic ketone in 70% yield (*Scheme 22*).[28]

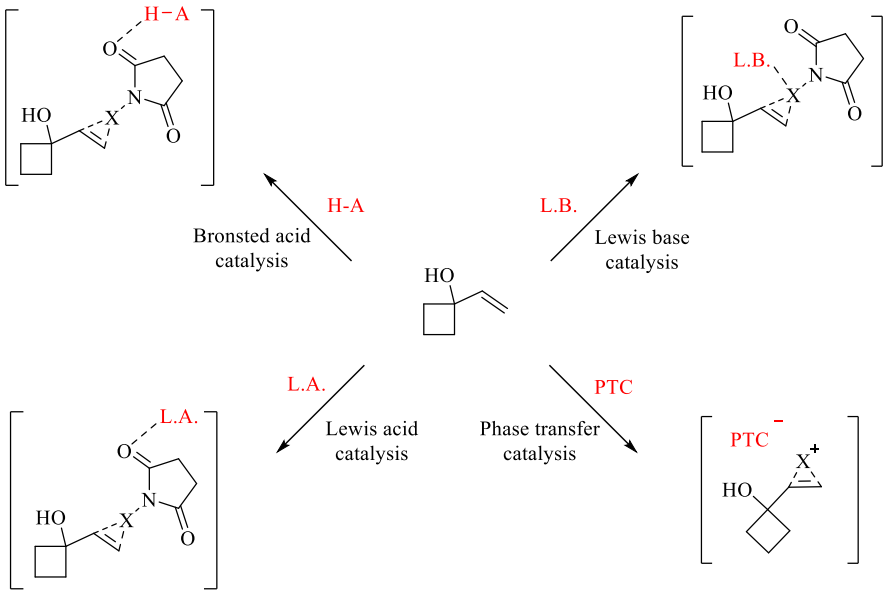


Scheme 22 *Allylic cyclobutanol ring expansion through selenonium ion.*

Anyway, whatever reagent we decide to use, the reaction must be catalysed to enhance the electrophilicity of an otherwise weakly reactive halenium ion source. There are few types of catalysts that can be exploited for this purpose: Brønsted acid, Lewis acid, Lewis base and phase-transfer catalysis (*Scheme 23*). Brønsted acid catalysis consists in activation either by protonation or by hydrogen-bonding between the catalyst and the halenium ion source; it may also lead to halenium ion transfer to the conjugate base of the Bronsted acid generating an alternative reactive electrophile; electrophilic attack of either the first or the second supposed active species on the alkene may generate a haliranium ion intermediate. Lewis acids activate the halenium ion source by coordination between the

[27] (a) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Tetrahedron Lett*. **1995**, 36, 8799. (b) Nemoto, H.; Shiraki, M.; Fukumoto, K. *J. Org. Chem*. **1996**, 61, 1347.
[28] Paquette, L. A.; Fabris, F.; Gallou, F.; Dong, S. *J. Org. Chem*. **2003**, 68, 8625.

two species, exploiting the electronic lack of the catalyst; the same type of coordination occurs with Lewis bases, but this time the catalyst uses its electronic excess to coordinate. Another type of catalysis is phase-transfer catalysis (PTC), in which the alkene substrate and reactive halogenating agent are physically separated in different phases until brought into contact by the catalyst.

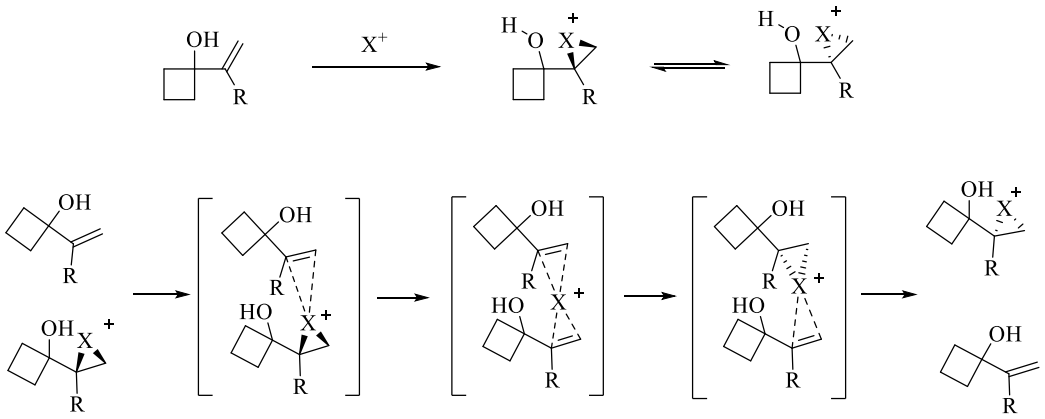


Scheme 23 *Brønsted acid, Lewis acid, Lewis base and phase-transfer catalysis.*

3. Enantioselective Ring Expansion of Allylic Cyclobutanols via Haliranium Ions

As the addition to a double bond generates two sp^3 carbons, two new stereogenic centres could be potentially formed; however, with respect to the chosen allylic cyclobutanols structure, as the one shown in *Scheme 18*, halofunctionalization creates only one new stereogenic centre, since the terminal carbon bears two hydrogen atoms. Enantioselective allylic cyclobutanol ring expansion can thus preferentially provide one specific enantiomer. The general course of halofunctionalization proceeds through two steps: haliranium ion formation and nucleophilic trapping. Both can occur to determine the geometry of the final product. Starting from the alkene, the halogen can attack both faces of the double bond, forming two possible enantiomers; the discrimination between the two

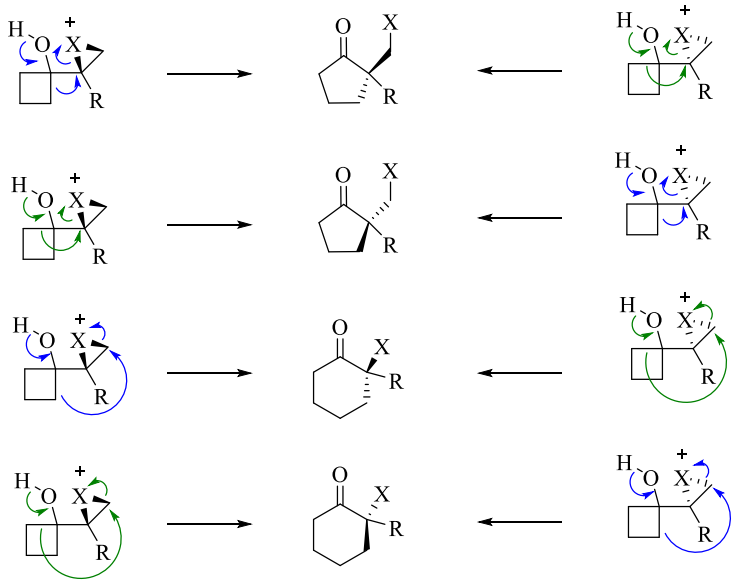
faces depends on the relative steric hindrance or electronic repulsion between the substrate, the halogenating reagent and the catalyst. A clear difficulty is that even if the haliranium ion can be formed with high enantioselectivity, intermolecular ion transfer from one alkene to another can lead to rapid racemization that occurs via a low barrier, associative displacement at the halogen (*Scheme 24*), unless the nucleophilic trapping event is kinetically more favourable.[29]



Scheme 24 *Haliranium ion racemization.*[24]

The nucleophilic trapping can occur at either one or the other electrophilic carbon of the haliranium ion, leading to different structural isomers; in any case, the attack occurs at the opposite face of the halogen: this step is stereospecific, with an anti-fashion. Moreover, both alkyl chains of the cyclobutanol ring can migrate, forming different enantiomers. All the different geometries of attack with the resulting products are reported in *Scheme 25*, wherein the formation of six-membered ring systems is considered too.

[29] Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1996**, 61, 962 –968.



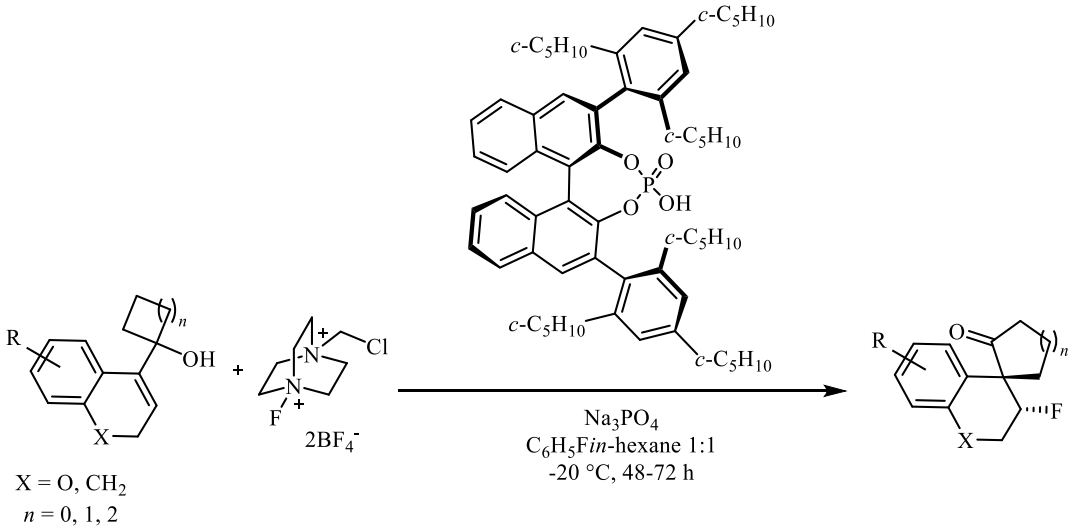
Scheme 25 *Geometries of nucleophilic trapping and relative products.*

With the purpose to achieve specific chemo- and enantioselectivity, it would be unproductive if both stages influenced the final configuration independently, because we would obtain a mixture of products. It is important thus to consider the aspects that make one of the two stages determining. When the nucleophilic trapping is enantiodetermining, either haliranium ion formation is fast and reversible, or the chiral haliranium ions can rapidly interconvert to each other: in this way the reaction is not selective toward the formation of a specific configuration of the intermediate. A chiral catalyst must then kinetically resolve the chiral haliranium ions, such that one enantiomer undergoes nucleophilic trapping faster than the other, and the catalyst must also control which of the two carbon atoms of the ion undergoes nucleophilic attack, unless a substrate-controlled bias for the site of attack is already present. When haliranium ion formation is enantiodetermining, the halenium ion transfer to the olefin from the "X^+" source must be irreversible, and the haliranium ion produced must be configurationally stable prior to its nucleophilic trapping; additionally, for haliranium ion formation alone to be enantiodetermining, the nucleophilic attack must be completely biased toward one of the two carbon centres of the haliranium ion intermediate, and this is most easily achieved by substrate control. In allylic cyclobutanol ring expansion there is substrate control: as it is an intramolecular reaction, the electrophilic carbon attacked is the one which is closest to the nucleophilic alkylic chain; moreover, the attack of the other carbon would generate a

six-membered ring from a four-membered one, that is not a favourable expansion. With respect to *Scheme 25*, the two five-membered enantiomers are believed to be easier to form. The only issue about selectivity is which of the two alkyl groups migrates, hence which enantiomer is formed.

3.1 Chiral Phosphoric Acid Catalysis

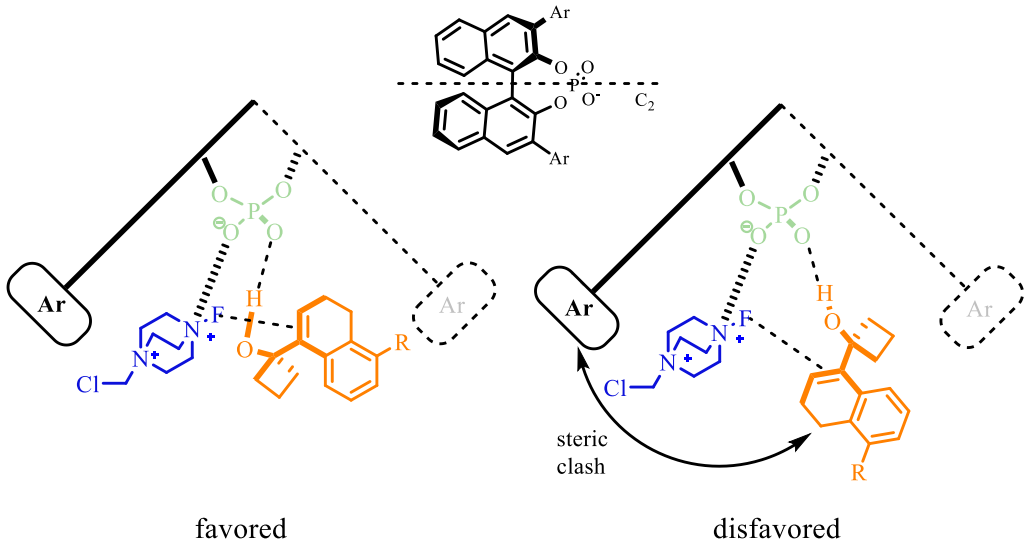
In order to control selectivity in the haliranium ion formation step, the idea is to use a chiral catalyst that, besides accelerating the rate of the reaction, transmits a specific chirality thanks to its chiral structure, following the asymmetric catalysis principles. This concept has been exploited by Alexakis and co-workers to achieve an enantioselective carbon-fluorine bond formation: in particular, it was the first highly enantioselective organocatalytic Wagner-Meerwein rearrangement of strained allylic alcohols initiated by an electrophilic fluorination event.[30] The reaction reported below in *Scheme 26* is a ring expansion from strained allylic alcohols with tetralone or chromanone scaffold. They decided to achieve this high selectivity by using a chiral Brønsted acid: a chiral phosphoric acid derived from BINOL, which in this case acts as a phase-transfer anionic agent.



Scheme 26 *Scheme of the reaction of Alexakis et al.*[30]

[30] Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Angew. Chem. Int. Ed*. **2013**, 52, 1-6.

Phosphoric acids are good catalysts as they are highly versatile and have been shown to catalyse a plethora of asymmetric transformations, typically using operationally simple and mild reaction conditions.[31] The site of action is the phosphate, where connections by hydrogen bonding or by ion-pairing between the negative charged oxygen and positively charged substrates are possible. Their chirality comes from a chirality axis present in the molecule, due to restricted rotation of the benzene rings, and this gives rigidity to the molecule. This chiral steric hindrance around the phosphate group creates a cavity where groups can attach at appropriate positions, depending on the structure of the catalyst itself. In this case reported by Alexakis et al., two new stereogenic centres formed in the final product, and it has been proved that the catalyst controls both enantio- and diasteroselectivity by influencing both formation of the fluorinated centre and migration to achieve the five-membered ring. These aspects in fact depend on the position that the fluorinating reagent and the substrate occupy inside the catalyst's cavity; the principle that determines the relative geometry between the three species is to reach the least steric bulk (*Scheme 27*).



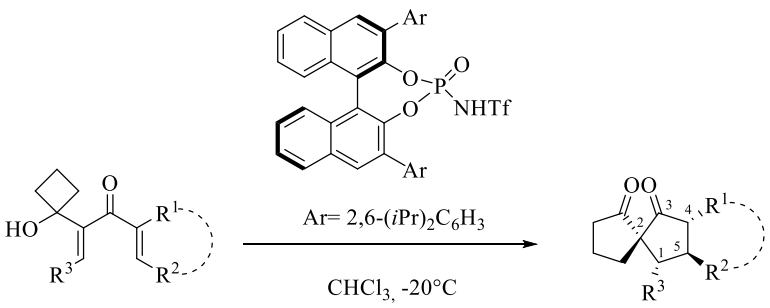
Scheme 27 *Expected arrangement of the substrates inside catalyst's chiral cavity.*[30]

Enantio- and diasteroselectivity is very high, and this makes this method very valuable. The substrate scope encompasses both allylic cyclobutanols and allylic cyclopropanols

[31] Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev*. **2014**, 114, 9047.

based on the tetralone as well as the chromanone scaffolds, with electron-releasing, electron-neutral and moderately electron-withdrawing substituents at C5 and C6 position.

Another example of a phosphoric acid catalysed cyclobutanol ring expansion via semipinacol rearrangement has been reported by Zhang et al.[32] They optimized an asymmetric tandem Nazarov cyclization[33]/semipinacol rearrangement reaction of "unactivated" substrates to yield a series of chiral spiro[4.4]nonane-1,6-diones using chiral Brønsted acid as the catalyst (*Scheme 28*). Within this tandem process, up to four consecutive stereocenters, one being the all-carbon quaternary stereogenic center, were successfully constructed in excellent enantioselectivities. Significantly, it is the first direct example to synthesize asymmetrically cyclopentanones with four stereocenters by using the Nazarov cyclization.



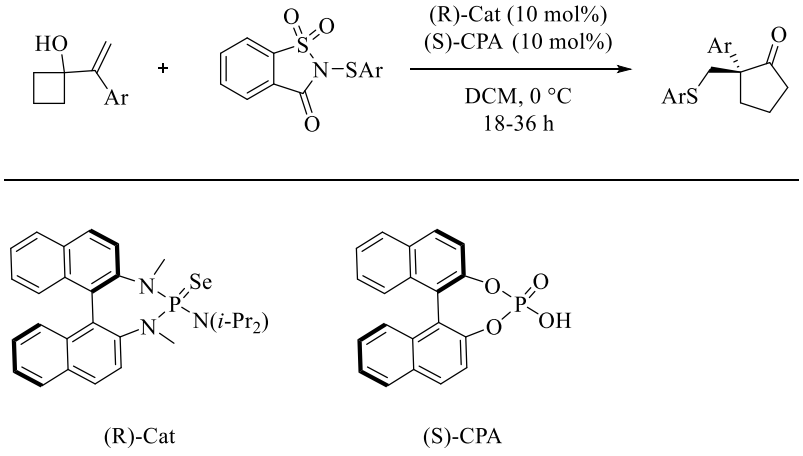
Scheme 28 *Scheme of the reaction of Zhang et al.*

The reaction mechanism and stereochemistry have also been studied by DFT calculations. It has been proved that the reaction undergoes Nazarov cyclization first, with the formation of the first stereogenic centre, and then cyclobutanol expansion via semipinacol rearrangement. Phosphoric acid as catalyst influences the stereochemistry of C_1; once the first chiral centre is determined, this chiral information can influence the stereochemistry at C_2 in the ring expansion step. Finally, the chiral catalyst environment influences the protonation from the forward face of the last intermediate and builds the chiral center at the C_4 atom.

[32] Yang, B-M.; Cai, P-J.; Tu, Y-O.; Yu, Z-X.; Chen, Z-M.; Wang, S-H.; Wang, S-H.; Zhang, F-M. *J. Am. Chem. Soc.* **2015**, 137, 26, 8344–8347.
[33] Frontier, A. J.; Collison, C. *Tetrahedron*. **2015**, 61 (32), 7577-7606.

3.2 Other types of chiral catalysts

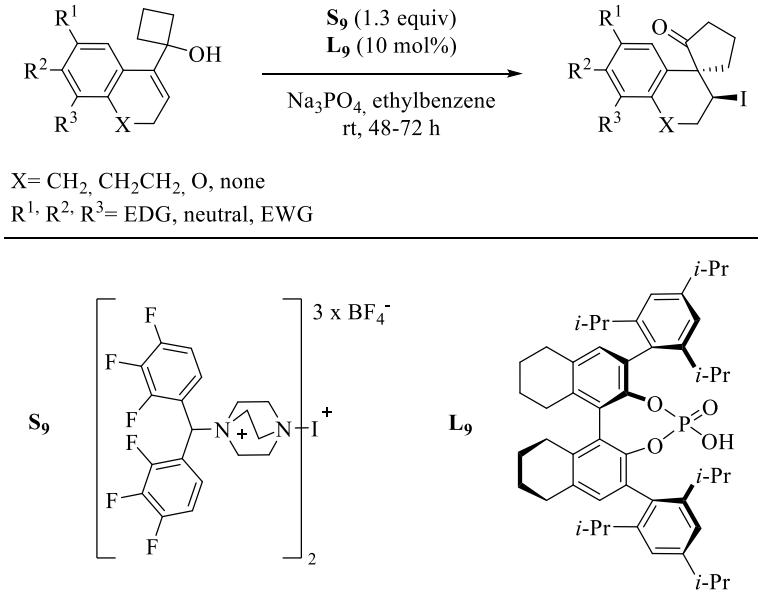
As previously mentioned, not only chiral Brønsted acids are exploited for this purpose. Some examples of enantioselective Lewis base, Lewis acid and phase-transfer catalysis are reported. First, enantioselective synthesis of β-arylthiocyclopentanones was carried out by Tian et al. using a combination of a chiral Lewis base and a chiral Lewis acid; the latter in particular was found to vastly enhance the outcome of the reaction in terms of yield and enantioselectivity. The methodology included the presence of a sulfenylating agent to trigger the expansion, and it was applied to several both 1,1-disubstituted and trisubstituted allylic alcohols, with differently substituted sulfenylating agents (*Scheme 29*).[34]



Scheme 29 *Lewis base and Lewis acid catalysis by Tian et al.*

The other type of catalysis was instead exploited by Alexakis et al.[35] The reaction is a high-yielding enantioselective semipinacol transposition initiated by an electrophilic iodination event. The title transformation makes use of the anionic phase-transfer catalysis paradigm for chirality induction. Thus, when combined appropriately, the insoluble cationic iodinating reagent **S9** and the lipophilic phosphoric acid **L9** act as an efficient source of chiral iodine that performs the semipinacol transposition of strained allylic alcohols $\mathbf{A_x}$ to β-spiroketones $\mathbf{B_x}$ in good yields and with high levels of diastereo- and enantio- induction (*Scheme 30*).

[34] Xie, Y-Y; Chen, Z-M; Luo, H-Y; Shao, H; Tu, Y-Q; Bao, X; Cao, R-F; Zhang, S-Y; Tian, J-M. *Angew. Chem. Int. Ed*. **2019**, 58, 12491– 12496.
[35] Romanov-Michailidis, F., Guénée, L., & Alexakis, A. *Organic Letters. **2013**,* 15(22), 5890–5893.



Scheme 30 *Phase transfer catalysis by Alexakis et al.*

CHAPTER 2

OBJECTIVES AND WORKPLAN

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1. **Background of the Research Group**
2. **Objectives and Workplan**

---

1. Background of the Research Group

The scientific interest of the research group directed by Prof. Jose Vicario is focused on the design and development of new practical and effective methods for the synthesis of enantiomerically pure chiral compounds. Extensive experience in stereocontrolled synthesis has been obtained, from its beginnings working with chiral auxiliaries to the development of methodologies relying on asymmetric organocatalysis, where the lines of this work are focused.

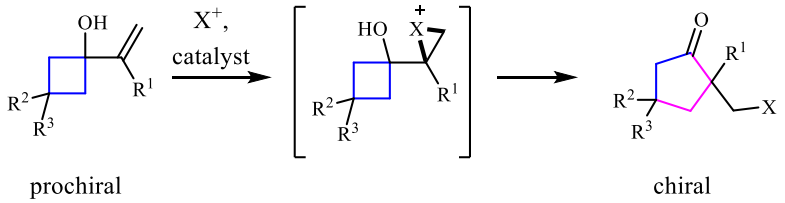
The aim of this project is to obtain enantiopure cyclopentanones from allylic cyclobutanols by ring expansion through semipinacol rearrangement, where the activation of the double bond is via halofunctionalization. This target reaction has been recently optimized by our group, with an extensive study in reaction conditions and materials. The chosen starting materials are symmetric allylic cyclobutanols, as the ones in *Figure 2*. These molecules are prochiral: there are two quaternary centres but two of the four substituents, the two alkyl chains of the ring, are identical, hence the symmetry of these molecules. However, there is a geometric isomerism that allows to distinguish between *cis* and *trans* configuration: the ring substituents can occupy different positions with respect to the ring itself.

cis *trans*

Figure 2 *Cis and trans configuration of a generic allylic cyclobutanol (assumption: R_2 has priority over R_3).*

When the ring expansion occurs, the symmetry plane of the molecule disappears, and the two alkyl chains are no longer identical (*Scheme 31*). The whole reaction is a desymmetrization,[36] and the two quaternary carbons are now stereogenic centres.

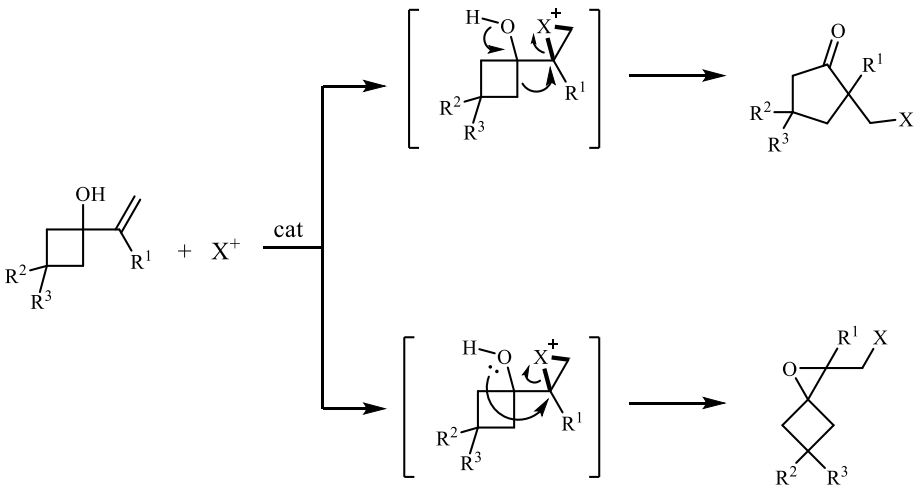
[36] Willis, M. C. *J. Chem. Soc., Perkin Trans. 1*. **1999**, 1765-1784.



Scheme 31 *Desymmetrization of allylic cyclobutanol.*

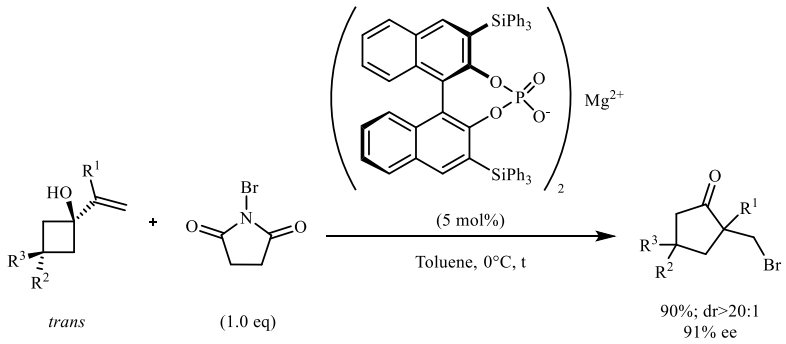
If carried out in a non-selective way, this transformation leads to a mixture of diasteroisomers, each one as a couple of enantiomers. Since the aim is to obtain an enantiopure compound, efforts are focused on investigating a method to make this reaction selective towards one specific geometry. As explained in the introduction, the hypothesis is that a chiral catalyst should promote the reaction in an enantioselective way, influencing the stereochemistry of the haliranium ion and thus giving a specific chiral information to the final product. Among the alternatives presented above, a chiral Brønsted acid has been chosen as catalyst for the reaction; in particular, a chiral phosphoric acid is used for this purpose.

Starting from both diasteroisomers *cis* and *trans*, the products generally obtained where the cyclopentanone diasteroisomers/enantiomers and an epoxidized side product resulting from the nucleophilic attack of oxygen on the electrophilic carbon of the haliranium ion (*Scheme 32*).



Scheme 32 *Main reaction products.*

The aim was to optimize this reaction towards a specific cyclopentanone enantiomer and reducing as much as possible the formation of the epoxide. First, both diasteroisomers *cis* and *trans* have been synthesized and used for the reaction, with poor results in yield and selectivity for diasteroisomer *cis*, hence the decision to carry out the reaction only with diasteroisomer *trans*. A screening of different catalysts has been carried out, starting with compounds like squaramide, thiourea and urea, but with a final yield in enantiopure cyclopentanone that didn't exceed 60%; chiral phosphoric acids with different substituents in the naphthyl ring have been used, with the best result in yield using $SiPh_3$. In particular, the performance of the catalyst improved when used as a salt, with magnesium giving complete conversion and highest selectivity, with only traces of the epoxidized product. As halenium ion, bromine has been chosen as it gave better results over chlorine, and it is easier to handle. Different bromine sources have been used, starting from molecular dibromine until aromatic compounds; the best reactant was *N*-bromosuccinimide, giving full conversion, good selectivity and yield. As solvent, toluene showed best results over xylene, mesytilene and 1,2,4-trimethylbenzene; the reaction was carried out at different temperatures, and 0 °C was chosen as running temperature (*Scheme 33*).

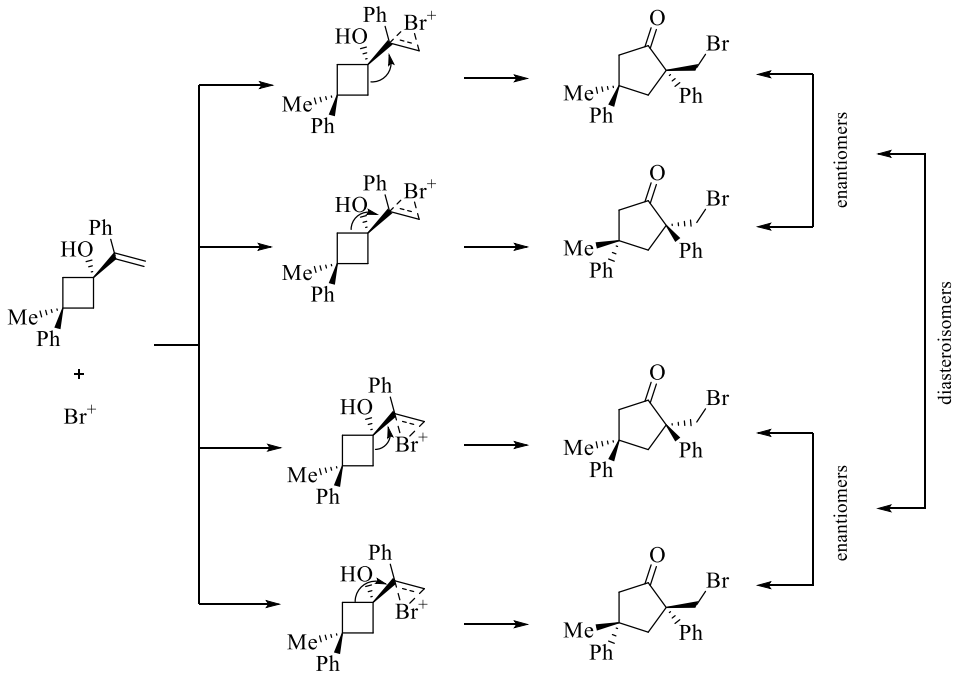


Scheme 33 *Scheme of the reaction.*

2. Objectives and Workplan

a. OBJECTIVES

With the aim to obtain an enantiopure compound from the optimised reaction, it is important to consider the routes that form all the possible isomers. Starting from a single diastereopure allylic cyclobutanol, four different isomers of cyclopentanone can be obtained. Determinant for this result are the ring expansion and the bromonium ion formation stages. During the first one, one of the two alkyl chains migrates, and the distinction between these two leads to different compounds: with the same bromonium ion geometry, both chiral centres change, and two enantiomers are obtained. The bromonium ion formation instead influences only one of the two centres, the one vicinal to the carbonyl, while the other keeps the original structure; with the same alkyl chain to undergo migration, this step leads to two diasteroisomers. All these possible routes are shown in the following *Scheme 34*.



Scheme 34 *Geometries of the possible products.*

In order to understand which is the major product of the reaction and why its formation is the most favoured, the plan is to carry out a set of reactions with different substrates and analyse the results.

b. WORKPLAN

First, the scope of the reaction will be examined: with the reaction conditions being already optimized, different reagents will be used to see which kind of substrates undergoes the reaction with good results. We will use first allylic alcohols bearing aromatic rings, with both electron donating and electron withdrawing as well electron neutral attitude. Afterwards, alkylic substituents can be considered. To all these purposes, it will be necessary to study first the synthetic strategies for the preparation of the substrates.

The product will be then analysed to understand the enantio- and diasteroselectivity of the reaction, hence which isomer is the most favourably formed among the others.

CHAPTER 3

RESULTS AND DISCUSSION

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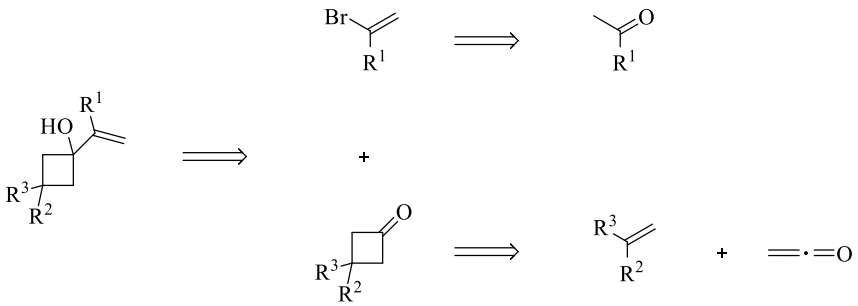
1. **Synthesis of precursors**
2. **Synthesis of allylic cyclobutanols**

---

1. Synthesis of precursors

First, the allylic cyclobutanol substrates have been synthesised. The selected synthetic strategy is a Grignard addition of a bromo-vinyl arene to a cyclobutanone scaffold. Bromo-vinyl arenes, in turn, are obtained from ketones, [37] while cyclobutanones are obtained from alkenes. [38] This retrosynthetic path is shown in *Scheme 35*, while the detailed reactions are explained below.

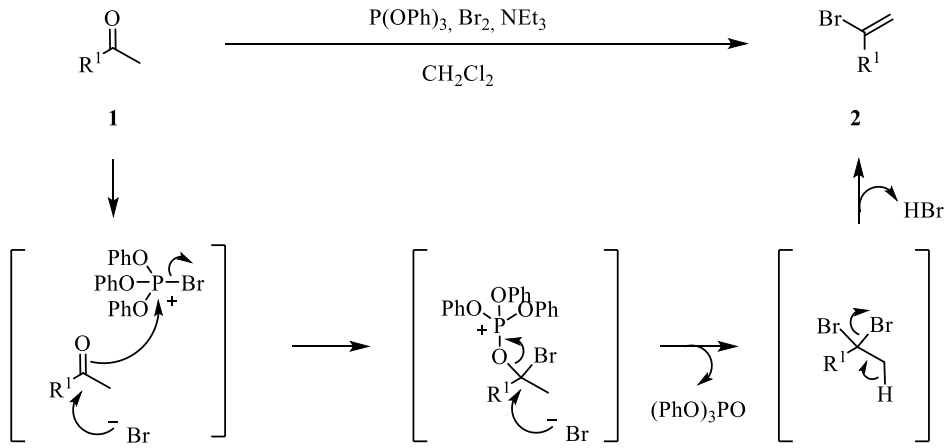


Scheme 35 *Retrosynthetic strategy of allylic cyclobutanol.*

1.1 Synthesis of bromo-vinyl arenes

As previously mentioned, vinyl halides were prepared in good to excellent yields from ketones upon treatment with triphenylphosphite and bromine. To afford vinyl halides, enolizable ketones are used, whereas aldehydes afforded the corresponding *gem*-dihalides. In particular, the ketone of interest must have a methyl as substituent, so that the alkene in the product is terminal. The mechanism, which is reported in *Scheme 36*, consists in a nucleophilic attach of a bromide ion on the carbonyl, with subsequent attach of oxygen on triphenylphosphite and leaving of another bromide ion; the latter undergoes another nucleophilic attach on the again electrophilic substrate, with leaving of triphenylphosphate. Loss of hydrobromic acid leads to the bromo-vinyl arene compound.

[37] Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. *J. Org. Chem*. **2007**, 72, 2216-2219.
[38] Chernykh, A. V.; Radchenko, D. S.; Chernykh, A. V.; Kondratov, I. S.; Tolmachova, N. A.; Datsenko, O. P.; Haufe, G. *J. Org. Chem*. **2015**, 6466- 6471.



Scheme 36 *Synthesis of bromo-vinyl arenes.*

A few ketones have been subjected to this reaction. The corresponding results are shown in *Table 1*, with compound **1a** giving no conversion and compounds **1b** ad **1c** giving 52 and 13% yield respectively.

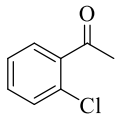
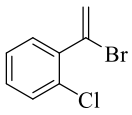
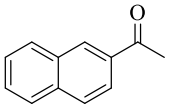
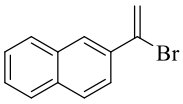
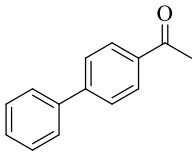
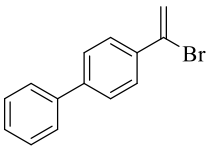
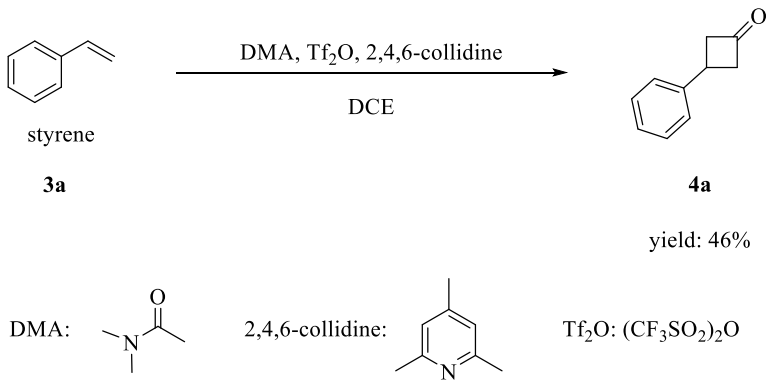
	reagent	product	yield
	1	**2**	
a			-
b			52%
c			13%

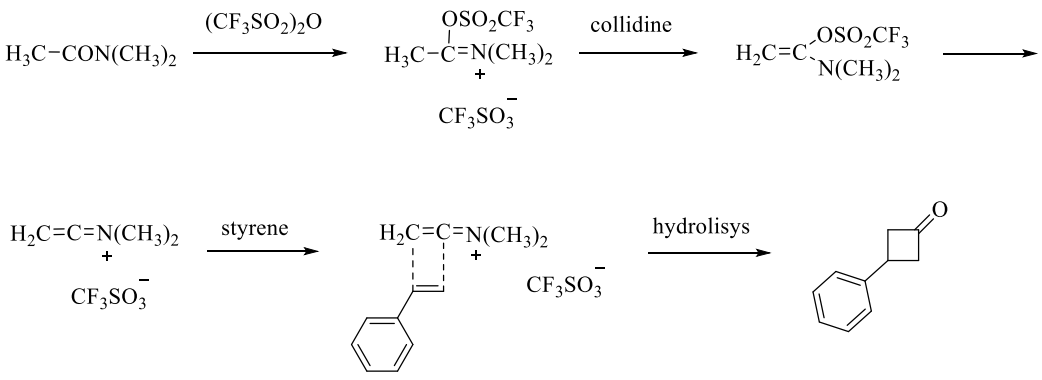
Table 1 *Results of the synthesized bromovinyl arenes.*

1.2 Synthesis of cyclobutanone

The synthesis of cyclobutanones has been attempted starting from alkenes, where dimethylacetamide, triflic anhydride, 2,4,6-collidine (2,4,6-trimethylaniline) in dichloroethane are used as reagents. Only compound **3a** was subjected to this reaction, with a final yield of 46% on compound **4a**. The scheme of the reaction with the relative mechanism is shown in *Scheme 37*: triflic anhydride activates DMA, forming a ketene iminium salt; then collidine converts the O-acylated intermediate into 1-dimethylaminoalkenyl trifluoromethylsulfonate, which directly ionizes to the corresponding ketene iminium salts and reacts with the alkene in a [2+2] cycloaddition, affording the cyclobutanone. [39]



Mechanism

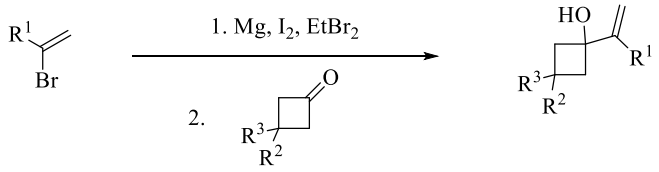


Scheme 37 *Synthesis of cyclobutanones.*

[39] Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem. Int. Ed*. **1981**, 20, 879–880.

2. Synthesis of allylic cyclobutanols

Once that both the bromo-vinyl arene and the cyclobutanone are synthesised, allylic cyclobutanols are obtained from the Grignard reaction[40] shown in (*Scheme 38*).



Scheme 38 *Synthesis of allylic cyclobutanol.*

The reactions carried out are reported in *Table 2*.

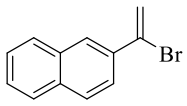
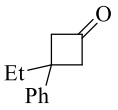
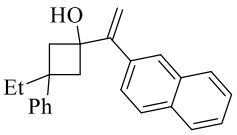
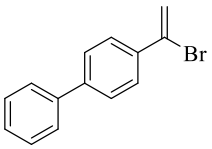
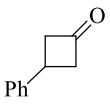
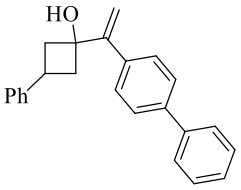
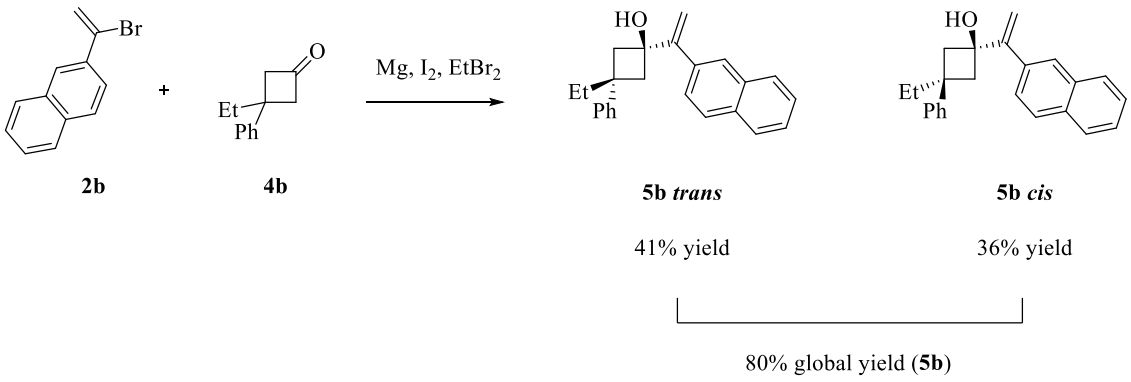
	reagents		product	
	2	**4**	**5**	yield
b				80%
c				70%

Table 2 *Results of the synthesized allylic cyclobutanols.*

Once that allylic cyclobutanols have been synthesised, only *trans* diastereoisomers will be used for the enantioselective ring expansion reaction. Only the separation of compound **5b** has been carried out and good results were obtained, while compound **5c** was not separable into the two diastereoisomers. Distinction between **5b *trans*** and **5b *cis***

[40] Alazet, S.; Preindl, J.; Simonet-Davin, R.; Nicolai, S.; Nanchen, A.; Meyer, T.; Waser, J. *J. Org. Chem.* **2018**, 83, 12334−12356.

diastereoisomers has been possible by NMR data analysis, comparing the NMR spectra obtained with the ones of literature (*Scheme 39*).



Scheme 39 5b *diastereoisomers with relative single yields.*

Another synthesis of an allylic cyclobutanol has been carried out between a Grignard reagent already formed and cyclobutanone **4c**. Compound **5d** was obtained in 78% yield (*Scheme 40*).

Scheme 40 *Synthesis of* ***5d****.*

CHAPTER 4

CONCLUSIONS AND FUTURE WORK

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1. **Conclusions**
2. **Future work**

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1. Conclusions

After the analysis of the experimental results obtained in the laboratory, it can be concluded that:

- The synthesis of a set of allylic cyclobutanols and the correspondent precursors has been carried out with good results.

- The separation between the diasteroisomers of compound **5b** has led to the *trans*-diasteroisomer in good amount.

2. Future work

After the analysis of the experimental results obtained, it is planned to continue with this line of research focusing on the following aspects:

- Continue to study the scope of the reaction, testing more substrates with the relative synthesis; in particular, investigate allylic alcohols bearing all such aromatic rings, electron donating, withdrawing and neutral, and alkylic substituents.

- Study the diastereo/enantioselectivity of the reaction, focusing on the relationship between the isomer obtained and the reaction conditions.

CHAPTER 5

EXPERIMENTAL

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1. **General methods**
2. **Synthesis of compounds**

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1. General methods

NMR: Monodimensional nuclear magnetic resonance proton and carbon spectra (^{1}H-NMR and ^{13}C-NMR) were acquired at 25ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and and 75.5 MHz for ^{13}C) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and and 125.7 MHz ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, and 77.0 ppm for ^{13}C NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distortionless Enhancement by Polarization Transfer) for assigning different types of carbon environment.

Miscellaneous: Analytical grade solvents and commercially available reagents were used without further purification.

Anhydrous solvents were purified and dried with activated molecular sieves prior to use. For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to utilizing in an oven at 140ºC and allowed to cool under a dehumidified atmosphere.[1]

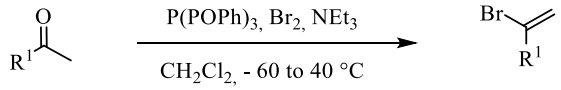
Reactions at reduced temperatures were carried out using a Termo Haake EK90 refrigerator.

Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kieselgel 60 F254). These were visualized by ultraviolet irradiation, permanganate potasium or *p*-anisaldehyde dips.[2] For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[3]

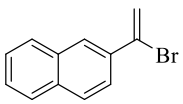
For the removal of solvents under reduced pressure Büchi R-210 rotary evaporators were used.

2. Synthesis of compounds

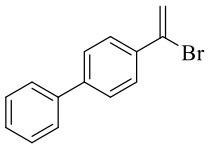
2.1 Synthesis of bromo-vinyl arenes



General procedure: to a cold solution of triphenylphosphite in anhydrous DCM (0,32 M) maintained at – 60 °C under Ar flow, bromine was dropped in. Anydrous triethylamine and the ketone were added to the faint orange solution. The reaction mixture was stirred 18 h, while warming at rt, and heated to reflux for a further 2 h. Purification by column chromatography was then carried out with a mixture of petroleum ether and DCM (95:5).

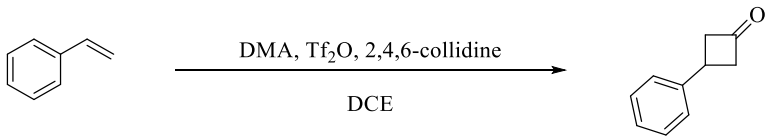


2-(1-bromovinyl)-naphthalene (2b). Following the general procedure **2b** (1.21 g, 5.22 mmol) was isolated by column chromatography purification in 52% yield starting from 1-(naphthalen-2-yl)ethan-1-one (**1b**, 1.7 g, 10 mmol), bromine (640 µL, 12.5 mmol), triethylamine (1.9 mL, 13.5 mmol) and triphenylphosphite (3 mL, 11 mmol) in DCM (33 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.05 (m, 1H, C_{arom}-H), 8.05 – 7.92 (m, 1H, C_{arom}-H), 7.92 – 7.78 (m, 4H, C_{arom}-H), 7.71 (dd, *J* = 8.7, 2.0 Hz, 1H, C_{arom}-H), 7.65 – 7.46 (m, 3H, C_{arom}-H), 6.29 (d, *J* = 2.1 Hz, 1H, CH_2), 5.90 (d, *J* = 2.1 Hz, 1H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.68 (C_{quat}), 133.55 (C_{quat}), 133.03 (C_{quat}), 131.27 (C_{arom}), 128.68 (C_{arom}), 128.06 (C_{arom}), 127.67 (C_{arom}), 127.00 (C_{arom}), 126.75 (C_{arom}), 124.27 (CH_2), 118.16 (CH_2).



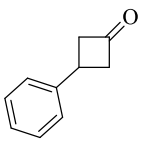
4-(1-bromovinyl)-1,1'-biphenyl (2c). Following the general procedure **2c** (0.327 g, 1.26 mmol) was isolated by column chromatography purification in 13% yield starting from 1-([1,1'-biphenyl]-4-yl)ethan-1-one (**1c**, 1.96 g, 10 mmol), bromine (640 µL, 12.5 mmol), triethylamine (1.9 mL, 13.5 mmol) and triphenylphosphite (3 mL, 11 mmol) in DCM (33 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 2H, C_{arom}-H), 7.80 – 7.73 (m, 2H, C_{arom}-H), 7.73 – 7.64 (m, 2H, C_{arom}-H), 7.64 – 7.54 (m, 2H, C_{arom}-H), 7.54 – 7.17 (m, 1H, C_{arom}-H), 6.20 (d, *J* = 2.1 Hz, 1H, CH_2), 5.83 (d, *J* = 2.0 Hz, 1H, CH_2).

2.2 Synthesis of cyclobutanone



General procedure: to a solution of DMA in 1,2-dichloroethane, triflic anhydride was added dropwise under stirring at 5 °C. The addition is accompanied by white solid precipitation. The mixture was stirred at 5 °C for 30 min and then a mixture of styrene and 2,4,6-trimethylpyridine in DCE was added dropwise. The reaction mixture was refluxed for 18 h, then DCE was removed in vacuum and the residue was treated with water and dichloromethane. The obtained mixture was refluxed under stirring for 18 h, then cooled and the water layer was extracted with CCl_4. Organic layers were combined, dried under Na_2SO_4, concentrated in vacuum, and purified over column chromatography with a mixture of petroleum ether and DCM (95:5).

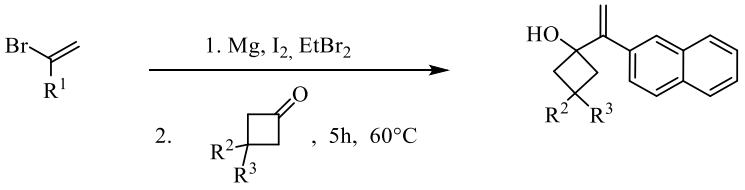
DMA was previously purified through fractionated distillation, while 2,4,6-collidine was purified through hot gun.



3-phenylcyclobutan-1-one (4a). Following the general procedure **4a** (1.72 g, 11.78 mmol) was isolated by column chromatography purification in 46% yield starting from styrene (**3a**, 2.6 g, 25.3 mmol), DMA (2.65 g, 30.4 mmol), triflic anydride (10 g, 35.4 mmol) and 2,4,6-collidine (4.3 g, 35.4 mmol) in DCE (36 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.23 (m, 5H, C_{arom}-H), 3.80 – 3.63 (m, 1H, CH_2), 3.62 – 3.49 (m, 1H, CH_2), 3.54 – 3.44 (m, 1H, CH_2), 3.37 – 3.27 (m, 1H, CH), 3.33 – 3.20 (m, 1H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.76 (CO), 143.62 (C_{quat}), 128.75 (2 x C_{arom}), 126.69 (C_{arom}), 126.55 (2 x C_{arom}), 54.74 (2 x CH_2), 28.47 (CH).

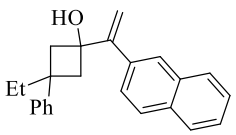
2.3 Synthesis of allylic cyclobutanols

First route



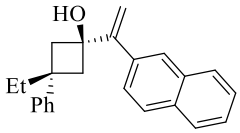
General procedure: one crystal of I_2 and 1,2-dibromoethane were added to a suspension of

Mg in THF (0,2 M) and heated to reflux for 10 min. Thereafter, a solution of (1-bromovinyl)-2-naphtene in THF was added dropwise (first, a very concentrated drop and then the diluted solution) while heating to maintain the addition temperature, and the reaction mixture was stirred for 1h at 60 °C. Then the corresponding cyclobutanone was added dropwise and stirring was continued at 60 °C for 5h. After being cooled at rt, the reaction was quenched with NH_4Cl and extracted with EtOAc. The orange extracts were washed with H_2O and brine, and then dried over Na_2SO_4. Purification over column chromatography was finally carried out with a mixture of petroleum ether and DCM (first 95:5 and then 90:10).

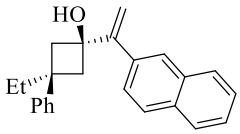


3-ethyl-1-(1-(naphthalen-2-yl)-vinyl)-3-phenylcyclobutan-1-ol (5b). Following the general procedure **5b** (0.447 g, 1.36 mmol) was isolated by column chromatography purification in 80% yield starting from 2-(1-bromovinyl)-naphthalene (**2b**, 513 mg, 2.2 mmol), 3-ethyl-3-phenylcyclobutan-1-one (300 mg, 1.7 mmol), magnesium (163 mg, 6.8 mmol), iodine (1 crystal), 1,2-dibromoethane (127.7 mg, 0.68 mmol) in THF (8.5 mL).

Separation between the two diasteroisomers was carried out through column chromatography with a mixture of petroleum ether and DCM (95:5). The dr was calculated through NMR analysis, resulting in dr = 57:43 (trans:cis).

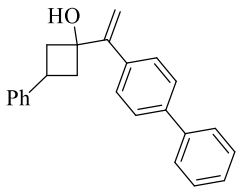


Diasteroisomer **5b*trans*** (D1, 0.229 g, 0.697 mmol) was isolated in 41% total yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H, OH), 7.82 (s, 2H, C_{Arom}-H), 7.88 – 7.75 (m, 2H, C_{Arom}-H), 7.58 (dd, *J* = 8.5, 1.8 Hz, 1H, C_{Arom}-H), 7.54 – 7.44 (m, 2H, C_{Arom}-H), 7.33 – 7.21 (m, 2H, C_{Arom}-H), 7.21 – 7.03 (m, 3H, C_{Arom}-H), 5.42 – 5.29 (m, 2H, CH_2), 2.89 (d, *J* = 13.5 Hz, 2H, C**H$_a$**H$_b$), 2.65 – 2.55 (m, 2H, CH$_a$**H$_b$**), 2.12 – 2.01 (m, 2H), 0.68 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.91 (C_{quat}), 149.03 (C_{quat}), 136.56 (C_{quat}), 133.50 (C_{quat}), 132.99 (C_{quat}), 128.55 (C_{Arom}), 128.00 (C_{Arom}), 127.95 (C_{Arom}), 127.79 (C_{Arom}), 127.75 (C_{Arom}), 126.61 (C_{Arom}), 126.57 (C_{Arom}), 126.33 (C_{Arom}), 126.16 (C_{Arom}), 126.08 (C_{Arom}), 126.05 (C_{Arom}), 125.47 (C_{Arom}), 113.88 (CH_2), 74.35 (C_{quat}), 46.04 (C_{quat}), 39.92 (CH_2), 39.89 (CH_2), 37.00 (CH_2), 9.07 (CH_3).



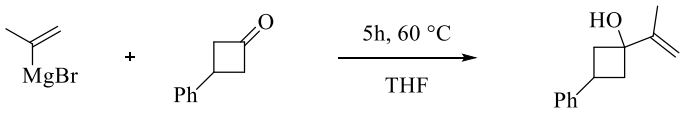
Diasteroisomer **5b*cis*** (D2, 0.203 g, 0.618 mmol) was isolated in 36% total yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 1.9, 0.7 Hz, 1H, OH), 7.87 (s, 2H, C_{Arom}-H), 7.94 – 7.80 (m, 2H, C_{Arom}-H), 7.71 (dd, *J* = 8.6, 1.8 Hz, 1H, C_{Arom}-H), 7.57 – 7.43 (m, 2H, C_{Arom}-H), 7.40 – 7.28 (m, 2H,

C_{Arom}-H), 7.26 – 7.14 (m, 3H, C_{Arom}-H), 5.62 (dd, *J* = 9.4, 0.8 Hz, 2H, CH_2), 2.89 – 2.70 (m, 4H, CH_2), 1.68 (q, *J* = 7.3 Hz, 2H, CH_2), 0.56 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.65 (C_{quat}), 149.26 (C_{quat}), 136.59 (C_{quat}), 133.45 (C_{quat}), 132.95 (C_{quat}), 128.46 (C_{Arom}), 128.09 (C_{Arom}), 127.82 (C_{Arom}), 127.71 (C_{Arom}), 126.58 (C_{Arom}), 126.45 (C_{Arom}), 126.24 (C_{Arom}), 126.09 (2xC_{Arom}), 126.07 (C_{Arom}), 125.51 (2xC_{Arom}), 114.79 (CH_2), 73.72 (C_{quat}), 46.68 (2xCH_2), 38.77 (C_{quat}), 36.25 (CH_2), 9.01 (CH_3).

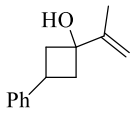


1-(1-([1,1'-biphenyl]-4-yl)-vinyl)-3-phenylcyclobutan-1-ol (5c). Following the general procedure **5c** (0.228 g, 0.7 mmol) was isolated by column chromatography purification in 70% yield starting from 4-(1-bromovinyl)-1,1'-biphenyl (2c, 283 mg, 1.3 mmol), 3-phenylcyclobutan-1-one (300 mg, 1 mmol), magnesium (96 mg, 4 mmol), iodine (1 crystal), 1,2-dibromoethane (75 mg, 0.4 mmol) in THF (5 mL).

Second route



General procedure: the cyclobutanone was added dropwise to a solution of isopropenylmagnesium bromide in THF (1M) and the solution was stirred for 5h at 60 °C. After being cooled at rt, the reaction was quenched with NH_4Cl and extracted with EtOAc. The organic extracts were washed with H_2O and brine, and then dried over Na_2SO_4. Purification over column chromatography was finally carried out with a mixture of petroleum ether and DCM (90:10).



3-phenyl-1-(prop-1-en-2-yl)-cyclobutan-1-ol (5d). Following the general procedure **5d** (0.295 g, 1.56 mmol) was isolated by column chromatography purification in 78% yield starting from isopropenylmagnesium bromide (**6**, 387 mg, 2.6 mmol), 3-phenylcyclobutan-1-one (**4c**, 300 mg, 2 mmol), in THF (2 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 1H, OH), 7.37 – 7.25 (m, 3H, C_{Arom}-H), 7.30 – 7.14 (m, 2H, C_{Arom}-H), 5.18 (t, *J* = 1.1 Hz, 1H, CH_2), 5.06 – 4.92 (m, 1H, CH_2), 3.12 – 2.95 (m, 1H, CH), 2.84 (ddt, *J* = 11.7, 8.2, 2.6 Hz, 2H, C**H$_a$**H$_b$), 2.28 (ddt, *J* = 11.9, 9.2, 2.6 Hz, 2H, CH$_a$**H$_b$**), 1.93 (dd, *J* = 1.4, 0.8 Hz, 3H, CH_3).

ANNEX

NMR Spectra

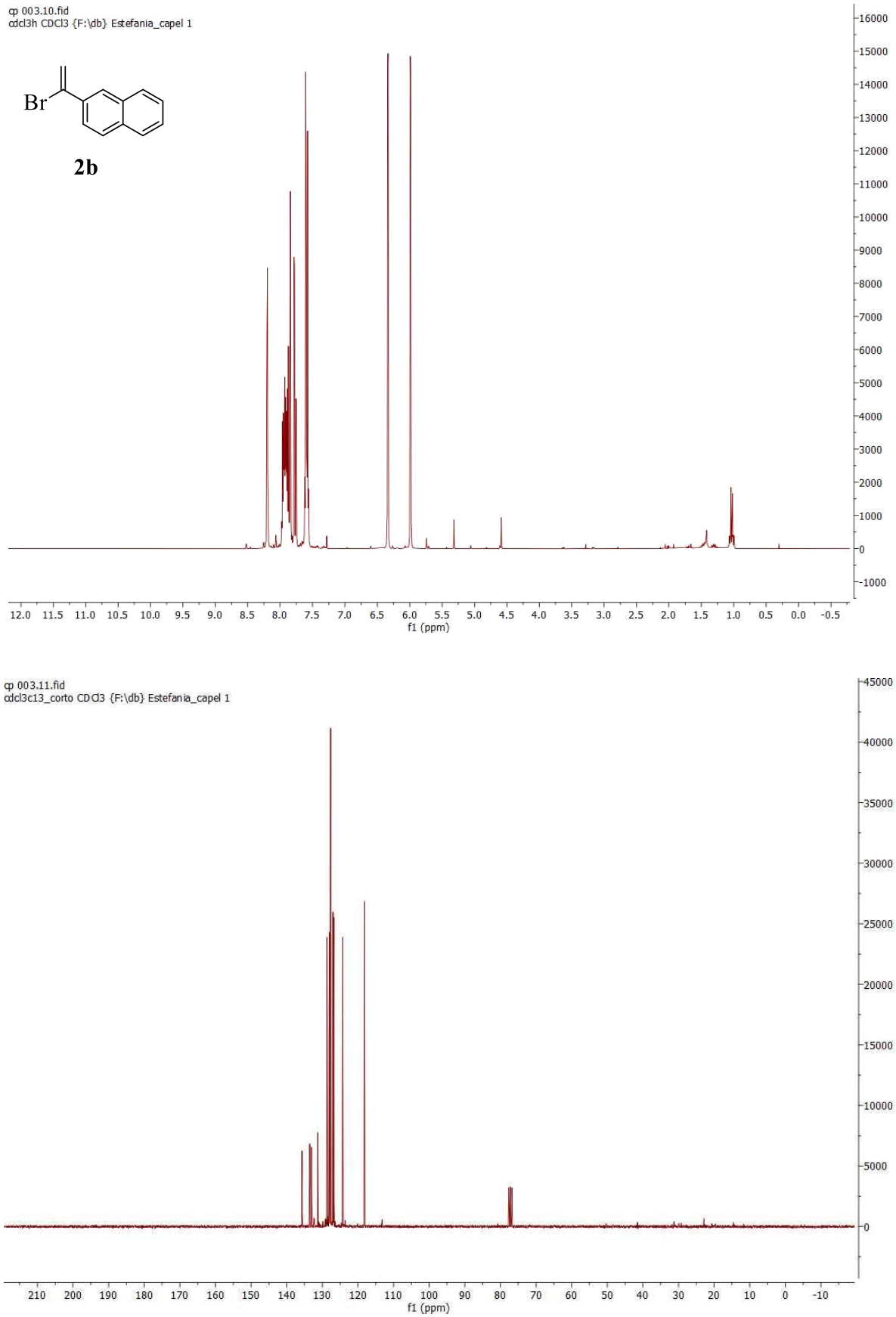


Figure 3 *^{1}H-NMR and ^{13}C-NMR spectra of compound 2b.*

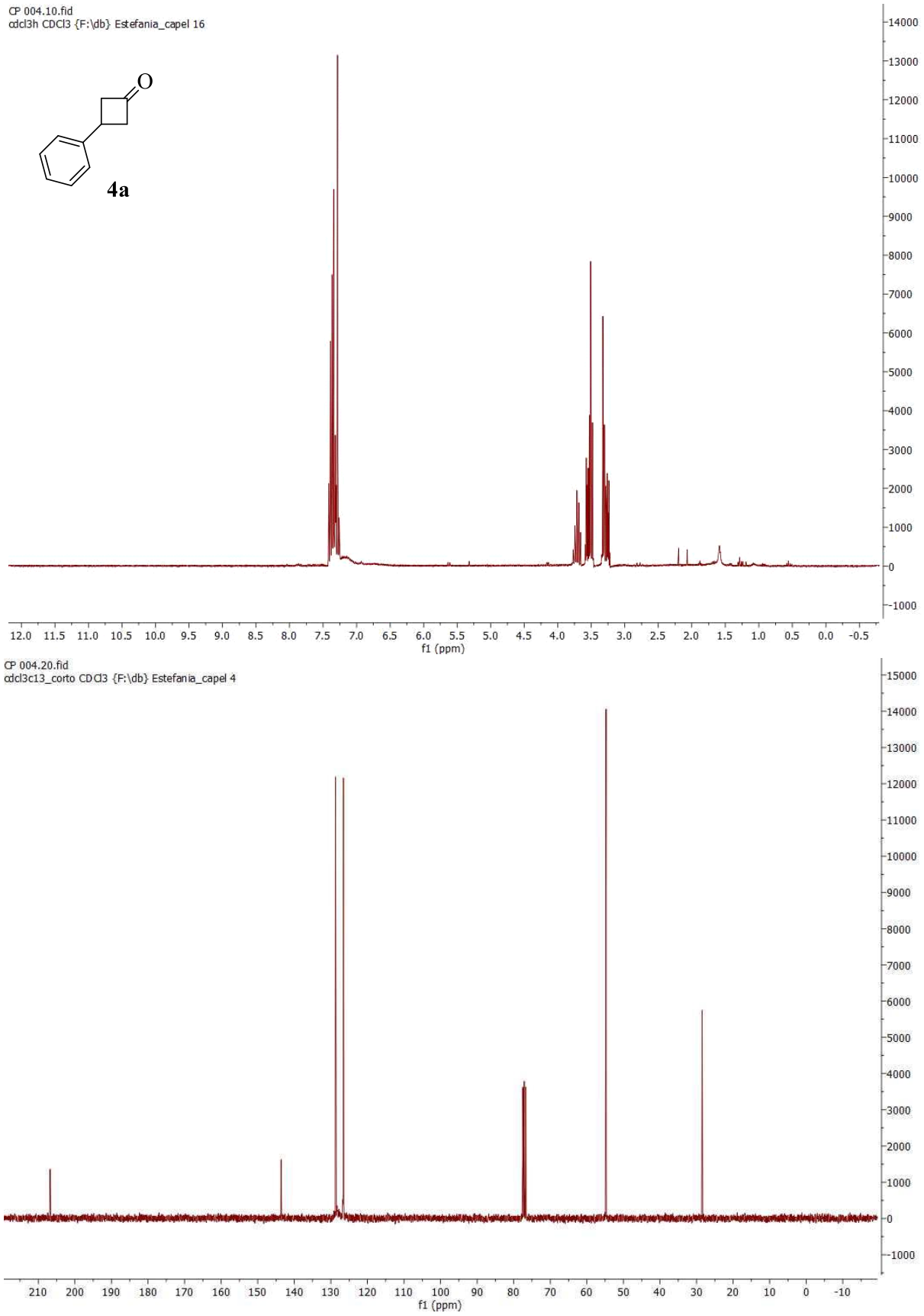


Figure 4 *^{1}H-NMR and ^{13}C-NMR spectra of compound 4a.*

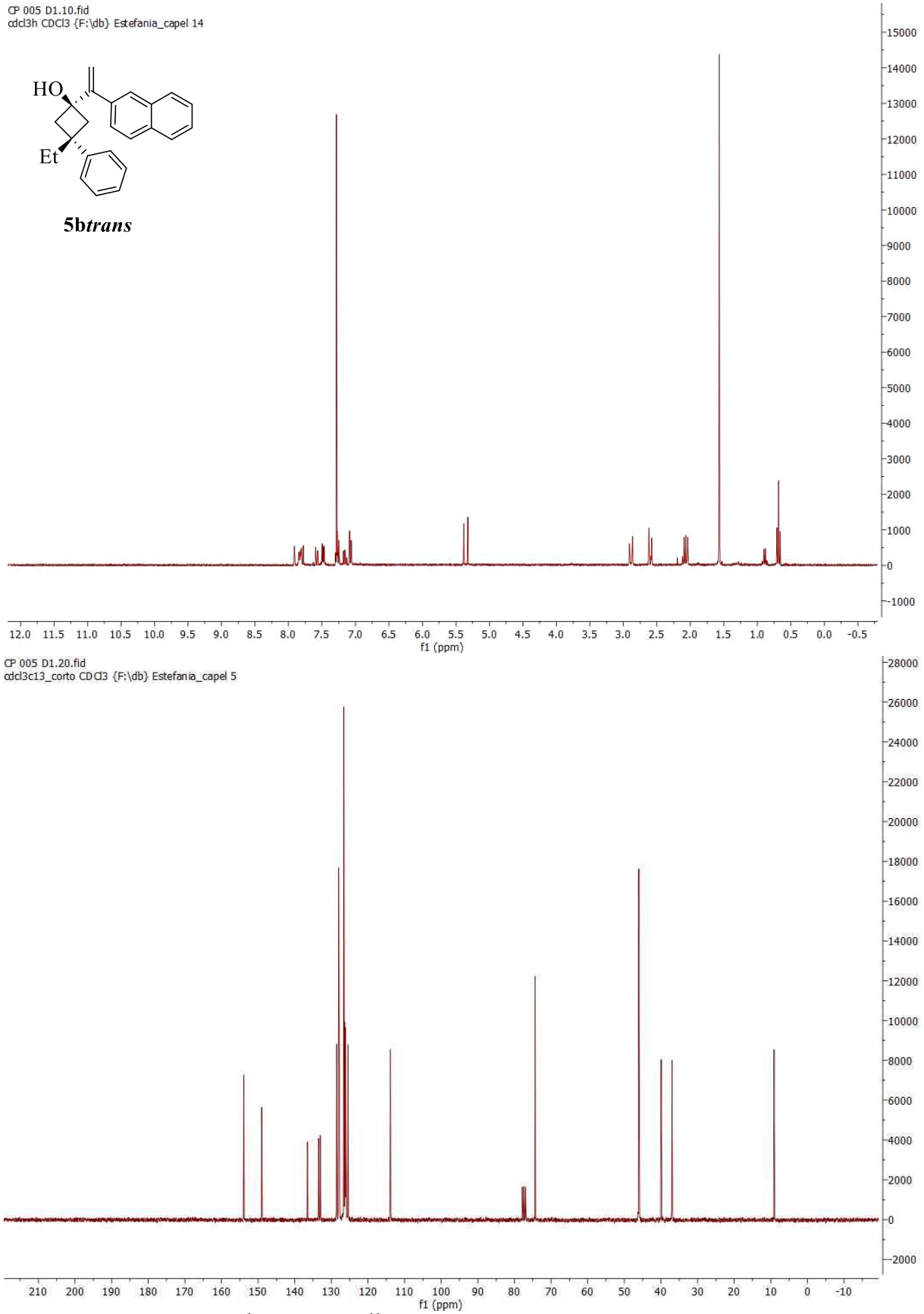
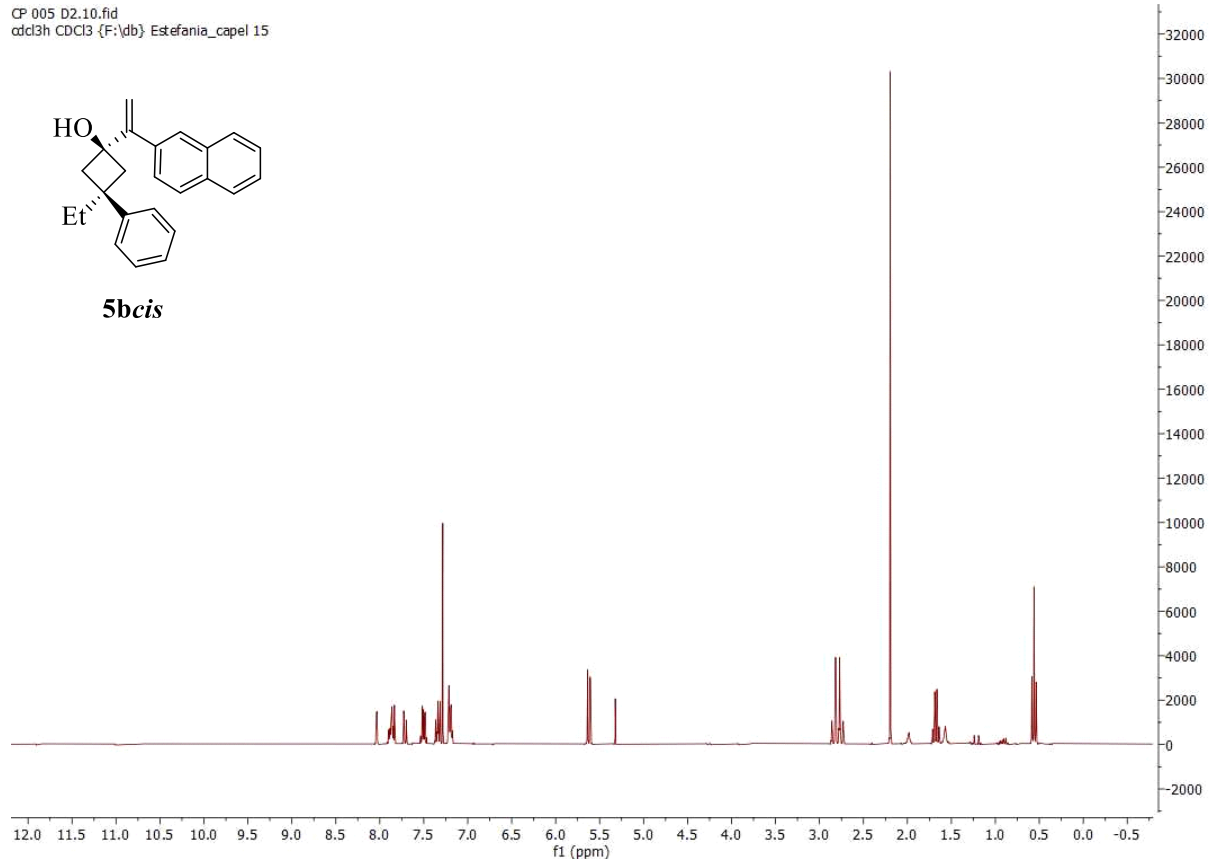


Figure 5 *^{1}H-NMR and ^{13}C-NMR spectra of compound 5btrans.*



5b*cis*

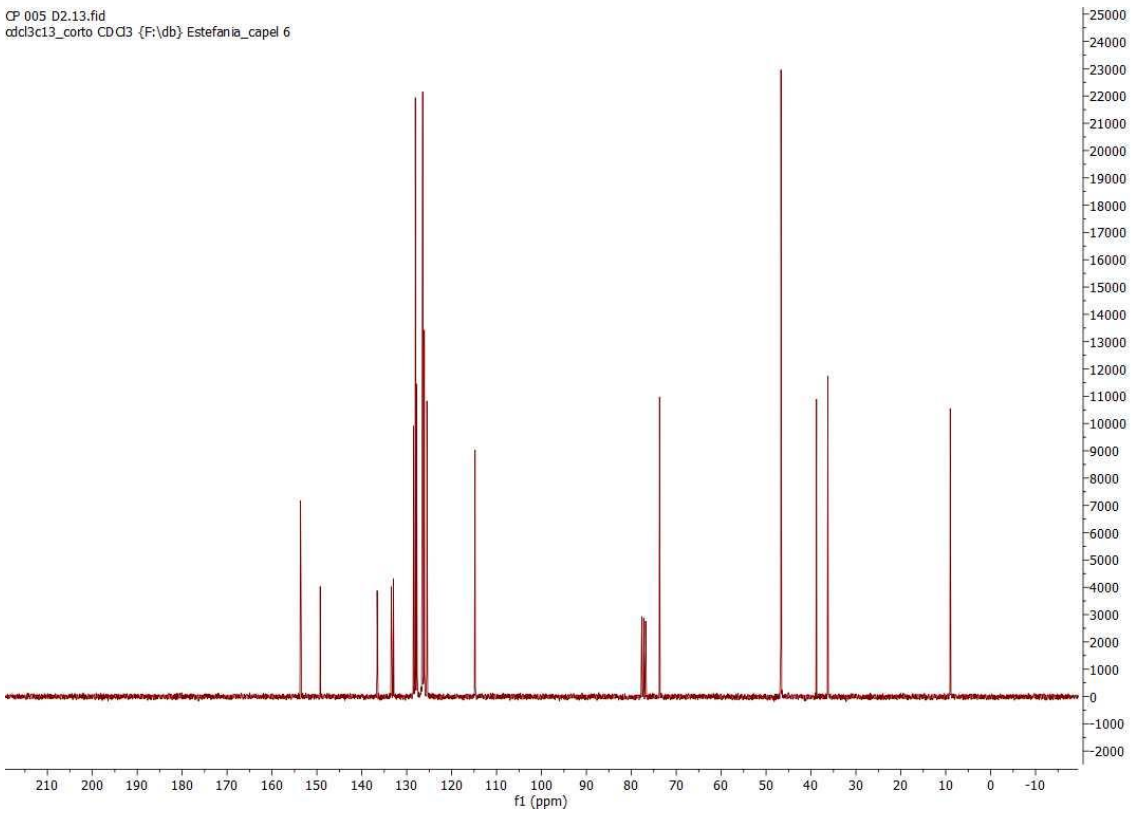


Figure 6 *^{1}H-NMR and ^{13}C-NMR spectra of compound 5bcis.*

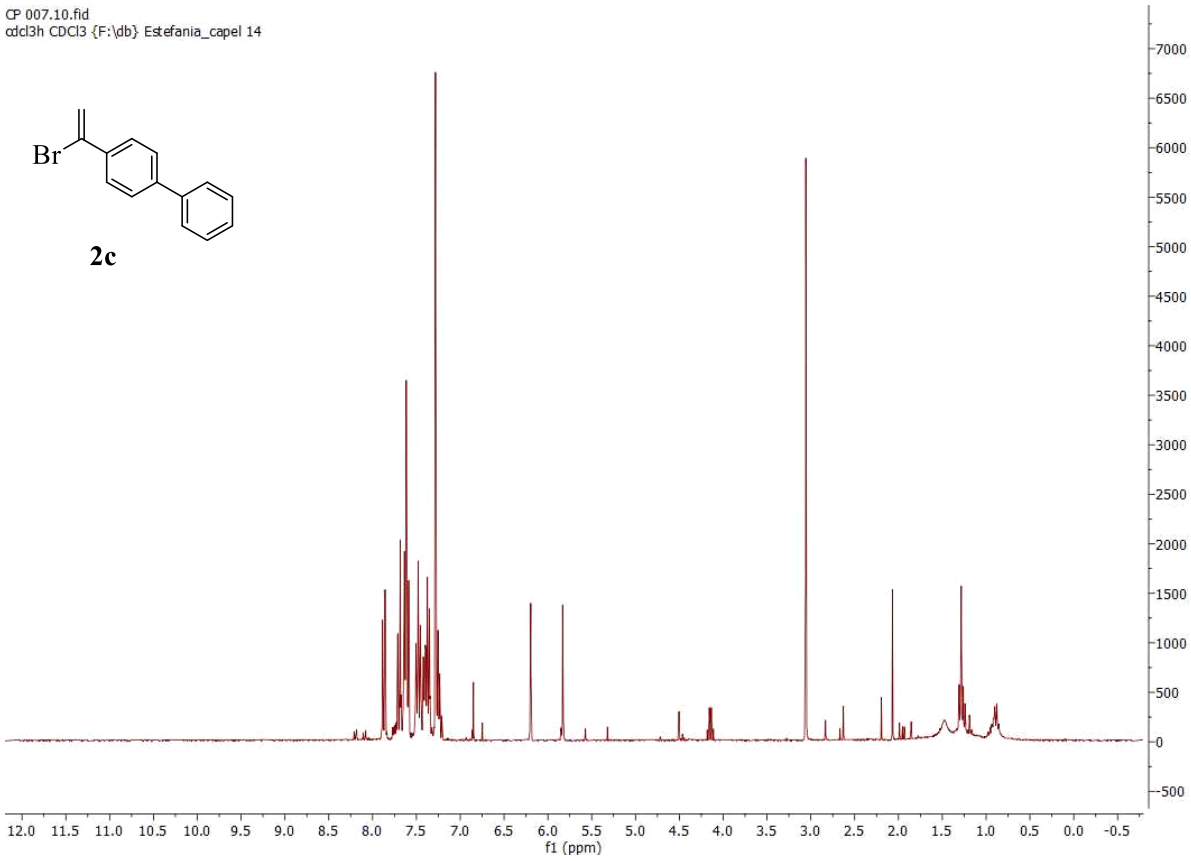


Figure 7 *^{1}H-NMR spectra of compound 2c.*

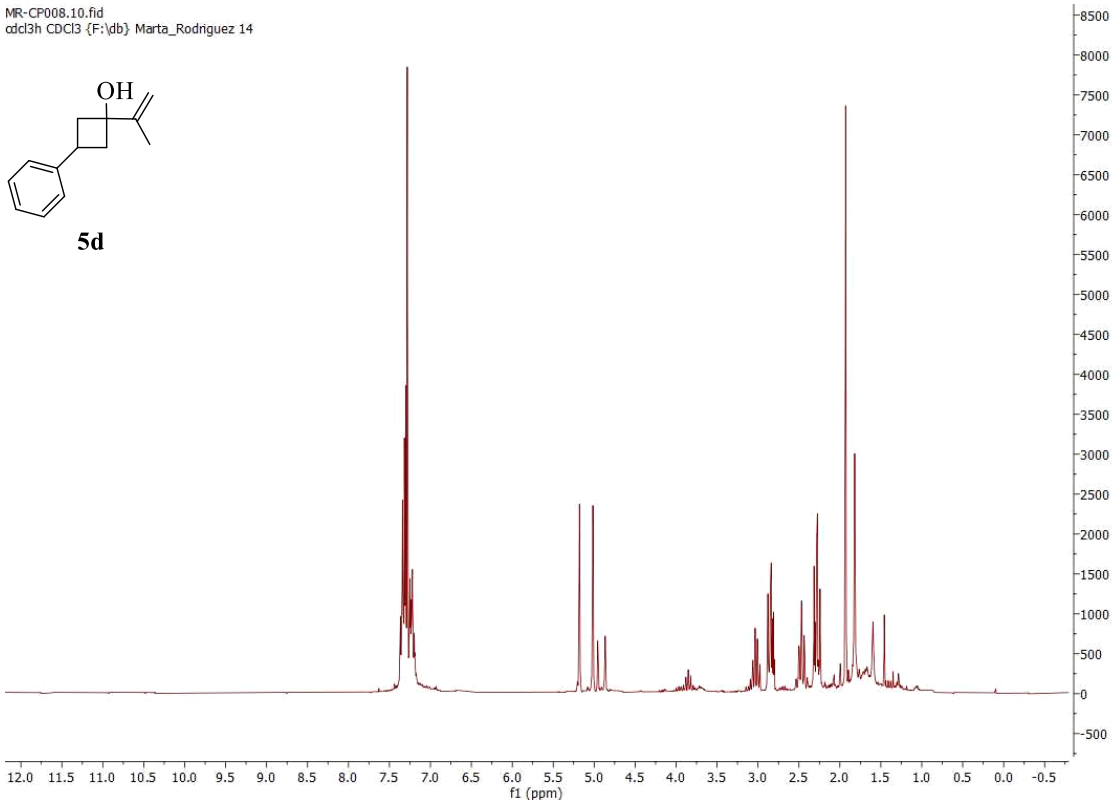


Figure 8 *^{1}H-NMR spectra of compound 5d.*