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# NEW METHODOLOGIES IN ORGANOCATALYSIS: FROM DISCOVERY TO APPLICATION AND MECHANISTIC

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**Abstract**

This PhD thesis deals with three different topics: i) sulfoxonium ylides, ii) donor-acceptor cyclopropanes, and iii) desymmetrization reactions. Catalysis, and in more detail organocatalysis, is the *fil rouge* linking the three subjects of study.

The main focus treated during this doctorate period is the reactivity of sulfoxonium ylides, and in particular stabilized sulfoxonium ylides. Special attention has been dedicated to the behavior of these particular substrates under asymmetric and non-asymmetric reaction conditions. Moreover, also similarities and differences with the related, less stable, sulfonium ylides were fully analyzed, both experimentally and from a theoretical point of view. Two different reactions were developed in full. One conducted under acidic reaction conditions and the second one exploiting the asymmetric aminocatalysis.

Subsequently, the reactivity of donor-acceptor cyclopropanes was studied. After different attempts in the development of a new catalytic methodology based on these substrates, a non-conventional reactivity conducted under phase transfer catalysis was discovered and optimized. In particular, a chemodivergent reaction depending on the reaction conditions was developed.

Finally, during the period spent abroad, a preliminary study of a desymmetrization reaction was carried out. The studied reaction is based on an asymmetric elimination reaction conducted under asymmetric phosphoric acid catalysis.

In summary, this PhD thesis shows the versatility of different organocatalytic methodologies when applied to different reactions and substrates.

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# 1 Introduction

## 1.1 Definition of Chirality

A molecule is defined as *chiral* if its mirror-image is not superimposable with itself[1], moreover, a molecule is defined as *chiral* if it does not possess an improper axis of rotation as element of symmetry. An improper axis of rotation can be simplified into two interchangeable steps, a proper rotation, and a reflection with respect to the perpendicular plane of the rotation axis. After these two steps, if the final molecule presents an equivalent configuration, it possesses an improper axis, while if the obtained molecule is characterized by a different configuration, the molecule taken into consideration can be defined as *chiral*. Taking into consideration the ethane represented in *Figure 1.1 left* (all the hydrogen atoms are represented by numbers) performing first a 60° rotation and then a reflection operation with respect to a virtual plane perpendicular to the axis, or on the contrary first the reflection operation and then the 60° rotation, the obtained conformation is perfectly superimposable with the starting one, so the ethane has an improper axis, and it is not a chiral compound. Now, considering *Figure 1.1 right* where one of the $CH_3$ of the ethane was replaced by three different substituents (represented by the different colors), performing the same set of symmetry operations, the resulting molecule presents a different conformation, so the starter and the final molecule are not superimposable. This molecule does not possess an improper axis, so is a *chiral* compound.

1 IUPAC, Compendium of Chemical Terminology, 2nd ed., 1997

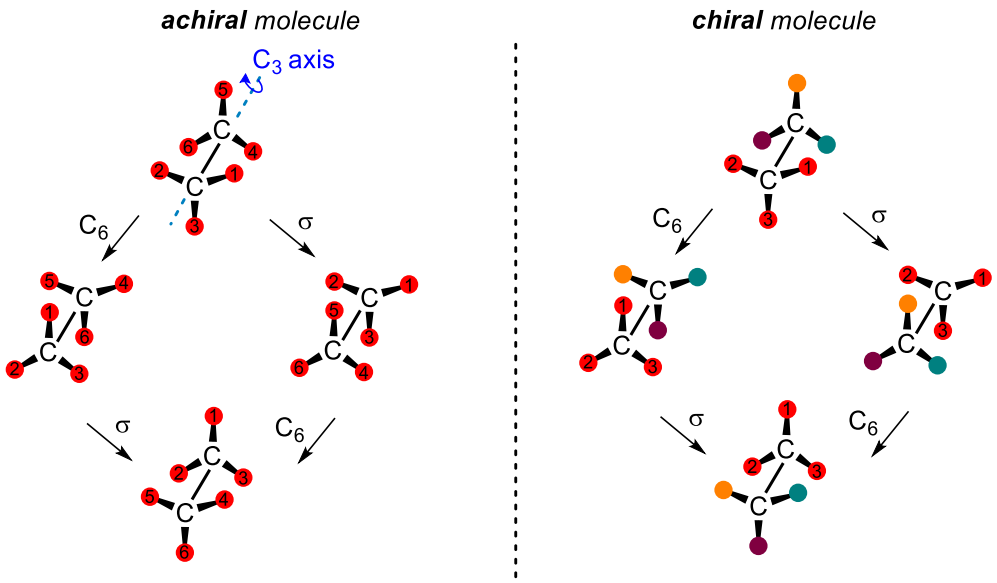



*Figure 1.1. Example of improper axis*

A chiral compound may exist in two distinct enantiomeric forms, which, when present in an equimolar ratio give rise to a *racemic* mixture. The single enantiomer of the same structure has equal chemical and physical proprieties if subjected to an achiral environment, while, if the surrounding environment is chiral and enantiopure, the enantiomers present different proprieties due to the diastereoisomeric interaction they are subjected to.

## 1.2 Catalysis, organocatalysis, and asymmetric organocatalysis

A catalyst is a substance able to increase the rate of a reaction or able to provide a different reaction pathway, without alteration of its structure at the end of the transformation. In particular, as represented in *Figure 1.2*, the reaction between starting materials **A** and **B** generates product **C** and the energy barrier of this transformation is for example 20 kcal/mol. Performing the same reaction in the presence of a catalyst, two different behavior can be observed. First of all the presence of the catalyst generates a lowering of the energy barrier of the reaction, for example from 20 kcal/mol to 15 kcal/mol. This lowering may be translated into an increment of the reaction rate, lowering considerably the time for the obtainment of product **C**. Otherwise, a catalyst can generate an alternative pathway for the reaction, obtaining in this way a completely different product, product **D**.

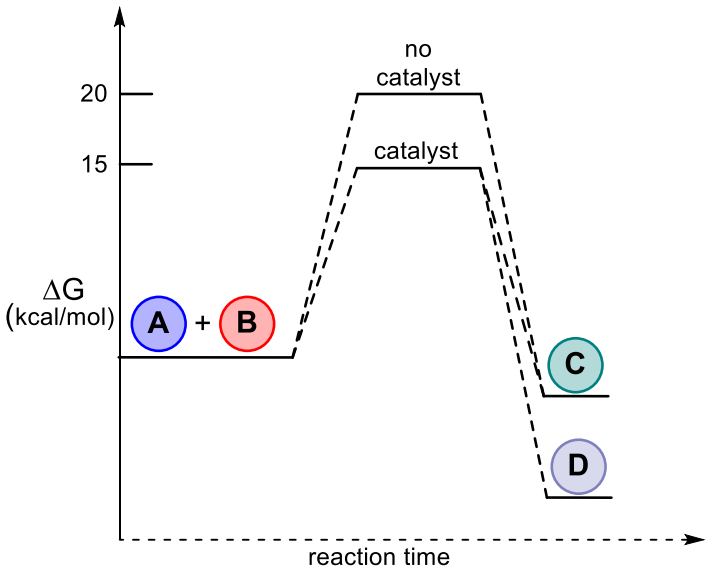



*Figure 1.2. Reaction pathway with and without catalyst*

A catalyst could also induce enantioselection to a reaction if it is a chiral and enantiopure compound, due to the diastereomeric interaction with the prochiral substrate, or, more specifically, by giving diastereomeric transition states. Taking into consideration the example shown in *Figure 1.3*, the chiral and enantiopure catalyst interacts with the substrate, the enolizable aldehyde, forming a chiral and enantiopure enamine intermediate. At this point, the nucleophilic enamine can attack the electrophile from the two sides of the enamine double bond plane thus forming two diastereoisomeric transition states. The two transition states are characterized by different energy barriers due to the steric interaction between the electrophile and the bulky group of the enamine catalyst. In the example shown below $\Delta G^{\ddagger}_{R} < \Delta G^{\ddagger}_{S}$ (the electrophile is attacked from an opposite direction to the bulky substituents) so the reaction pathway which provides (*R*)-product is favored. The enantiomeric excess of the product depends on the value of $\Delta\Delta G^{\ddagger}$. An enantiomeric excess of 99% means a $\Delta\Delta G^{\ddagger}$ of 3 kcal/mol at 25 °C.

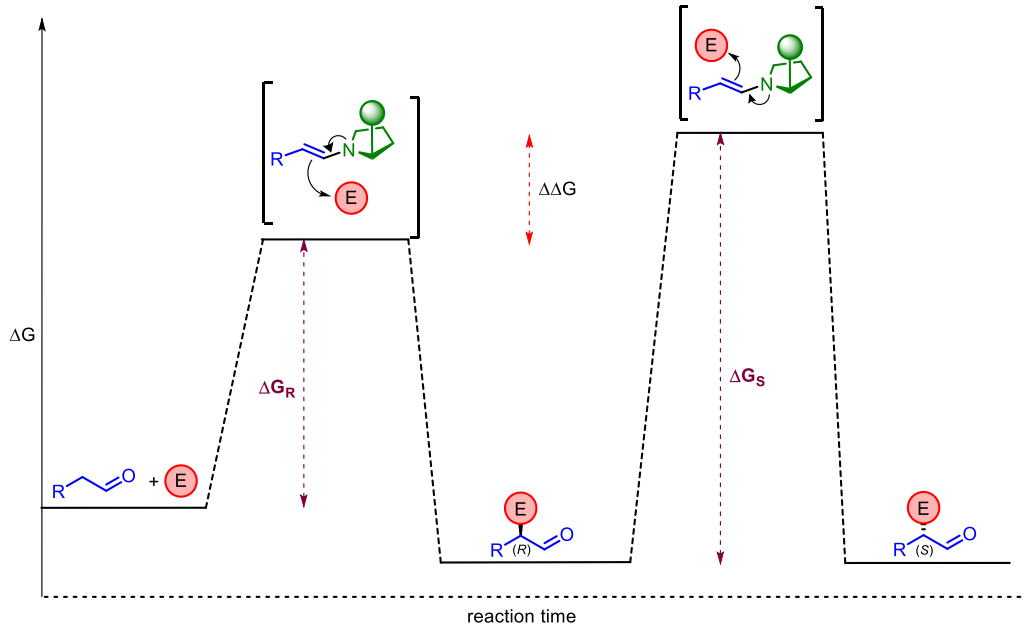



*Figure 1.3. Interaction catalyst-substate and energy barriers*

A chiral and enantiopure catalyst can have different natures, opening the doors to several fields. Asymmetric organometallic catalysis can induce high enantioselection to a rection in function of the nature of the ligand coordinated to the central metallic atom. This branch of asymmetric catalysis permits to modulate the activity and the selectivity of the catalyst by modifying the nature of the metal atom, increasing or decreasing the Lewis acidity, or adjusting the structure of the ligand to increase/decrease the coordination with the starting material. Another area of asymmetric catalysis is the biocatalysis. Generally, in this field the catalysts are enzymes. The enzymes display high enantioinduction but often require specific substates and mild reaction conditions. Moreover, the enzymes exist as single enantiomers, so they can provide only one enantiomer of the product. Another field of asymmetric catalysis is represented by asymmetric organocatalysis. In this area, the catalysts for the chemical transformations are small chiral and enantiopure organic molecules.[2] The idea is inspired by biomimetic concepts, to reproduce the catalytic activity and selectivity of enzymes.[3] Different classes of organic catalysts exist, with different activation modes. The main ones are reported in the following sections.

2 Selected reviews on asymmetric organocatalysis: a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) B. List, *Asymmetric Organocatalysis.* Wiley VHC, Weinheim, **2005**; c) B. List, *Chem. Rev.* **2007**, *107*, 5413; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 926; e) M. F. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8. f) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; g) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638.
3 L. Bernardi, M. Fochi, M. Comes Franchini, A. Ricci, *Org. Biomol. Chem.* **2012**, *10*, 2911

## 1.3 Hydrogen-bond donor catalysis

The hydrogen bond interaction plays a dominant role in asymmetric organocatalytic reactions. The main principle of operation is the coordination of the electrophilic species to a H-bond donor, activating it and subsequently assisting the attack of a nucleophile. The activation mode exploits the formation of H-bonds causing a decrease in the electronic density of the acceptor molecule. The functional groups generally exploited as H-bond donors are ureas, thioureas and squaramides. The hydrogen atoms related to the nitrogen atoms of these groups are able to coordinate the lone pairs of the electrophilic species activating it. Moreover, embedding the H-bond donor in a chiral and enantiopure structure, it is possible in principle to control the stereochemistry of the nucleophilic attack. The more privileged chiral substituents used in asymmetric organocatalysis are *Chinchona* alkaloids derivatives. The use of *Cinchona* alkaloids derivatives is privileged for different reasons. The *Cinchona* alkaloids in addition to being natural products, cheap and easily available, possess on their structure a basic nitrogen able to coordinate a H-Nu species, thus increasing at the same time both the activity and the selectivity of the catalyst (bifunctional catalysis). The structure of *Cinchona* alkaloids consists of two pairs of pseudoenantiomers,[4] namely Quinine (**QN**) – Quinidine (**QD**) and Cinchonidine (**CD**) – Cinchonine (**CN**) (*Figure 1.4*).

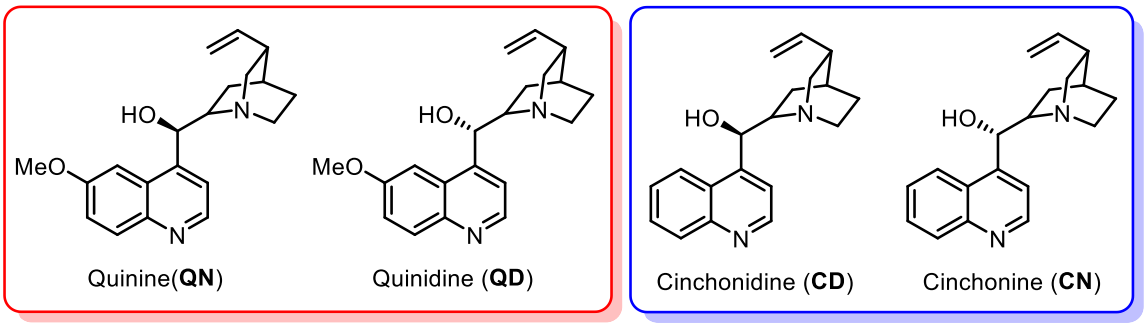



Figure 1.4. *Cinchona* alkaloids

Some of the first examples of the employment of these kinds of catalysts were reported by Jacobsen[5] and Corey.[6] The authors reported an asymmetric Strecker reaction promoted by hydrogen-bonding catalysts (*Figure 1.5*). In particular, the N-H bonds of the thiourea

4 a) J. Kacprzak, J. Gawroński, *Synthesis* **2001**, 961; b) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229
5 M. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901
6 E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157

group coordinate the nucleophile, $CN^-$, while, the amide oxygen coordinates the imine activating it and promoting the nucleophilic attack in an enantioselective fashion.[7]

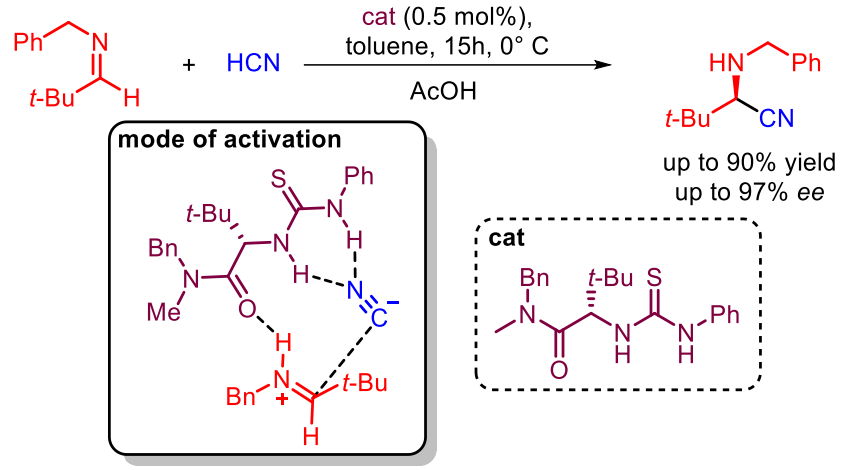



*Figure 1.5. Asymmetric Strecker reaction*

## 1.4 Aminocatalysis: enamine and iminium ion activation

Asymmetric aminocatalysis is based on the use of chiral and enantiopure amines as catalysts for the asymmetric functionalization of carbonyl compounds.[8] The activation modes in aminocatalysis are based on covalent interaction generated upon the condensation of a chiral amine with a carbonyl group leading new activated compounds able to react faster with the reaction partners. Exploiting this type of catalysis is possible to obtain either nucleophilic or electrophilic new activated compounds.

The condensation of an enantiopure amine and an aldehyde generates an enantiopure nucleophilic enamine. This activated compound results to be more nucleophilic having higher energy of the highest occupied molecular orbital (HOMO), compared to the parent enolate. This HOMO-raising activation allowed the α-functionalization of carbonyl compounds with different electrophilic species (*Figure 1.6*). Propagation of the HOMO-raising activation mode has led to the development of dienamine- and trienamine- based reactions, enabling γ- and ε-functionalizations.[9]

7 a) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature*, **2009**, *461*, 968. b) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.*, **2009**, *131*, 15358

8 Review on aminocatalysis: a) S. Bertelsen, K. A. Jørgensen, *Acc. Chem. Res.* **2009**, *38*, 2178; b) M. Nielsen, D. Worgull, B. Zwifel, S. Bertelsen, K. A. Jørgensen *Chem. Commun.* **2011**, *47*, 632; c) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrect, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248. d) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860.

9 Earliest reports: a) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973; b) Z.-J. Jia, B. Gschwend, Q.-Z. Li, X. Yin. J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *135*, 5053

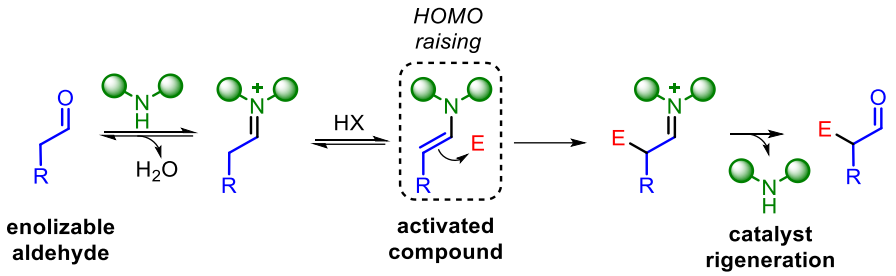



*Figure 1.6. Enamine activation*

The condensation of an enantiopure amine and more in general an α,β-unsatured aldehyde leads also to the formation of an electrophilic iminium ion, due to the lowering of the LUMO orbitals, able to interact with different nucleophilic species. (*Figure 1.7*)

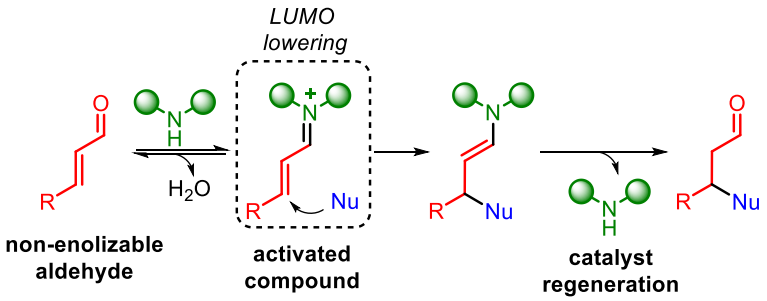



*Figure 1.7. Iminium ion activation*

The potential generation of both nucleophilic and electrophilic species, along with the possibility to extend the reactivity through conjugated systems, enlightens the broad applicability of aminocatalysis as a powerful tool to achieve a wide range of functionalizations of carbonyl compounds.

The most common and efficient catalysts for this chemistry are proline-derived compounds and in particular diarylprolinol silyl ethers, independently developed by Jørgensen[10] and Hayashi[11] in 2005. The bulky diaryl silyl ether group is the key to the high enantioselectivities generally displayed by these catalysts. This sterically demanding moiety forces the enamine in the conformation shown (*s-trans* and *π-trans*), and shields one of its two faces very efficiently, thus determining the approach of the electrophile from the opposite face (*Figure 1.8*). This mode for the enantioinduction is the same for the iminium ion. Here, the bulky fragment is extended enough to shield effectively the more distant β-position, allowing the nucleophilic attack only from the less hindered face (*Figure 1.8*).

10. M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2005**, *44*, 794
11 Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212

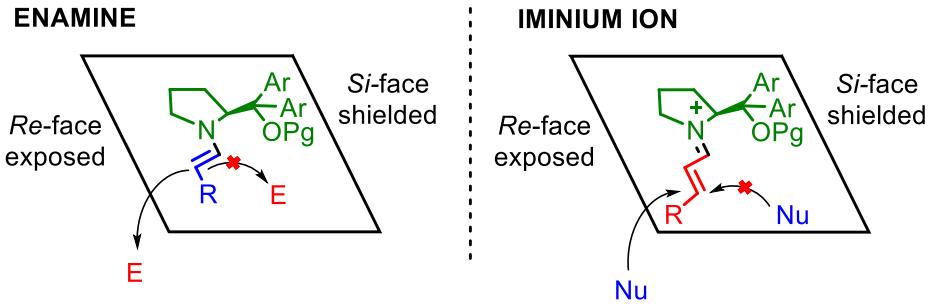



*Figure 1.8. Examples of Jørgensen-Hayashi catalysts and models accounting for the enantioinduction through enamine activation and iminium ion activation*

## 1.5 Phosphoric acid catalysis

Another important class of organic catalysts is represented by phosphoric acid catalysis.[12] The bifunctional phosphoric acids contain both a Brønsted acid site (OH) and a Lewis basic site (P=O) prone to coordinate, in a chiral pocket, the two partners of the reaction. Generally, these types of catalysts are based on a BINOL or SPINOL core which induces chirality to the whole structure. (*Figure 1.9*)

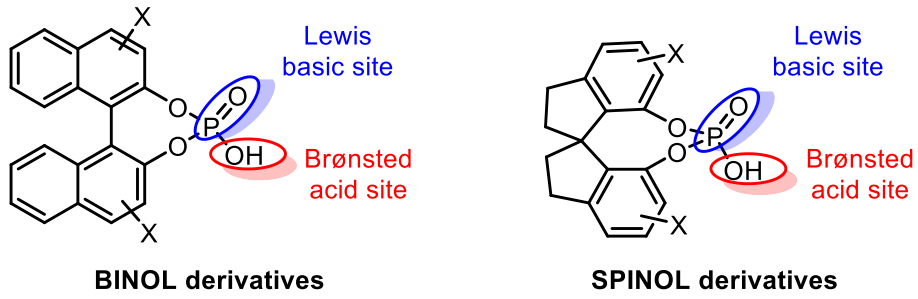



*Figure 1.9. Phosphoric acids backbone*

The structure of these catalysts, and in particular the nature of the substituents in *ortho* position to the oxygen atoms on the aromatic rings are crucial for the enantioselection of the reactions. Generally, these substituents can be aromatic fragments such as 2,4,6-*i*Pr-$C_6H_2$, 3,5-$CF_3$-$C_6H_3$, $^p$-$NO_2$ but also silicon based such as $SiPh_3$, $SiMePh_2$. Moreover, these substituents contribute to the formation of a chiral pocket that accommodates the reaction partners activating them, through the formation of hydrogen bonds, and inducing at the same time enantioselectivity to the reaction. (*Figure 1.10*)

12 D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047.

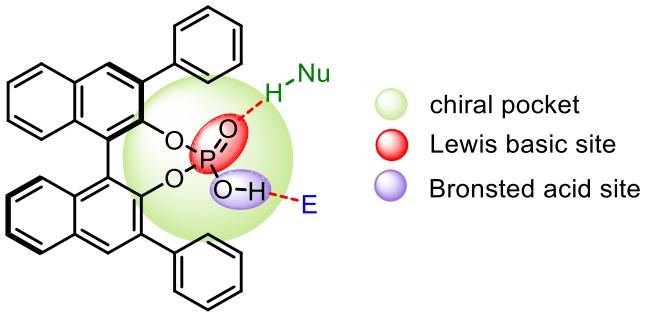



*Figure 1.10. Activation mode of phosphoric acids*

One of the first examples of the use of these types of catalysts is reported by Akiyama.[13] (*Figure 1.11*). The authors take into consideration a Mannich-type reaction between ketone silyl acetals and *o*-OH-aldimines. In this example, the catalyst coordinates the *o*-OH-aldimines through the Lewis base functionality, while the ketene silyl acetal is coordinated to the Brønsted acid site. The coordination of the substrate to the catalyst leads to the formation of a rigid activated complex and this permits, in this case, both a high enantio- and diastereoselection because only one specific couple of the two faces of the two substrates can interact together.

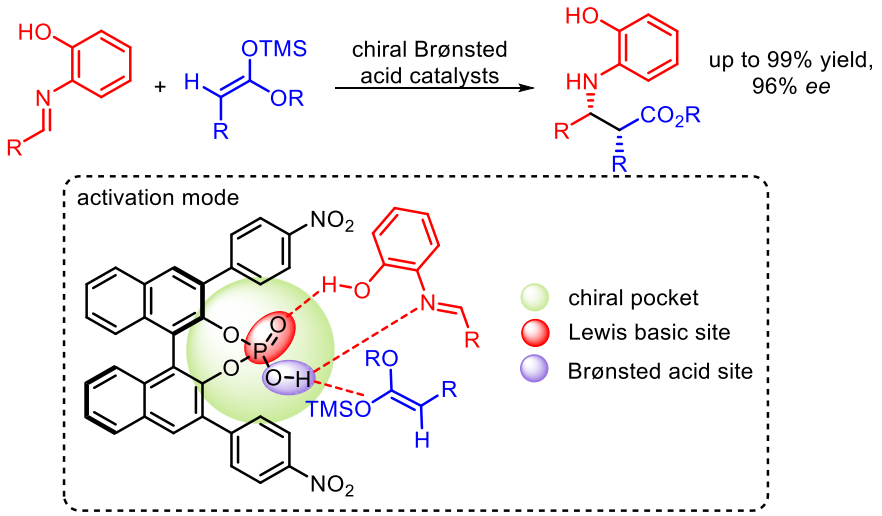



*Figure 1.11. Mannich-type reaction between a ketone silyl acetals and an aldimine*

## 1.6 Phase-transfer catalysis

The phase-transfer catalysis is a methodology that exploits, in general, organic salts able to catalyze a reaction between two or more reagents in two or more phases. It means that the organic salt is aimed to transport the reagents between the two phases. The organic salt

13 T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1566.

employed is usually made up of a lipophilic organic cation (typically a quaternary ammonium salt such as tetra-*n*-butyl ammonium) and a halogen as the anion, so the nature of the catalyst allows solubility in the considered phases.

Taking into consideration the example reported below (*Figure 1.12*), the considered system is formed by two unmiscible phases, an organic and an aqueous one, separated by an interface. The examined reaction is a substitution reaction between the reagents HY and RX to form RY in the presence of catalyst $Q^+Z^-$. The first step of this process is the deprotonation of reagent HY by the inorganic base (BOH) to form the ionic couple $B^+Y^-$. At this point an ion exchange near the interface occurs. Since the catalyst $Q^+Z^-$is an organic salt, it is soluble in both phases, so the ion exchange sees involved the cation $Q^+$ of the catalyst and the cation $B^+$ of the base, and the newly formed specie is $Q^+Y^-$. Then, once formed the specie $Q^+Y^-$, this one can cross the interface going into the organic phase due to the organic nature of cation $Q^+$. Once the anion $Y^-$is in the organic phase, the substitution reaction can occur forming product RY. If the cation $Q^+$ of the catalyst is a chiral and enantiopure specie, the interaction between $Q^+$ and the substrate in the organic phase can induce enantioselection to the reaction allowing the final product in an enantioenriched form. The example reported below takes into consideration an organic and an aqueous phase, but the same concept can be applied also to systems formed by two or more immiscible phases.

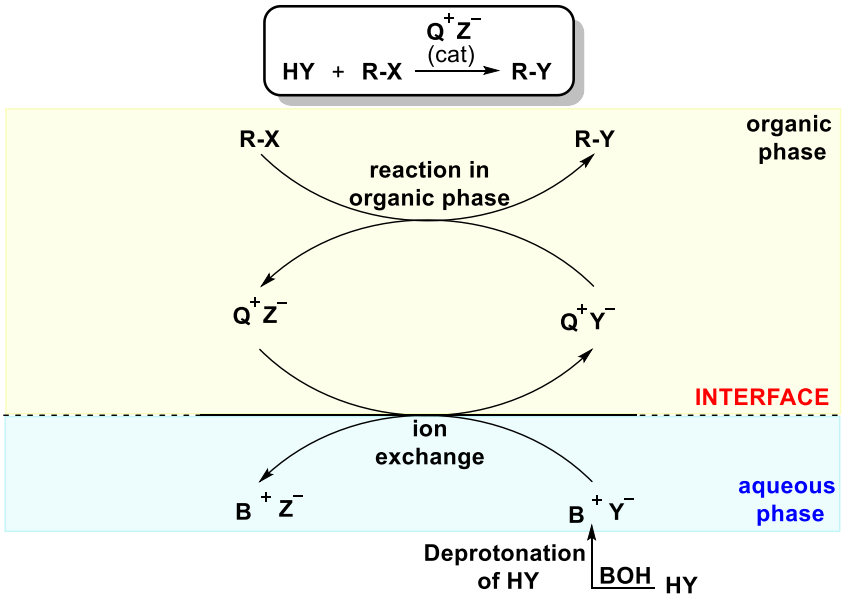



*Figure 1.12. Simplified mechanism for phase transfer catalysis*

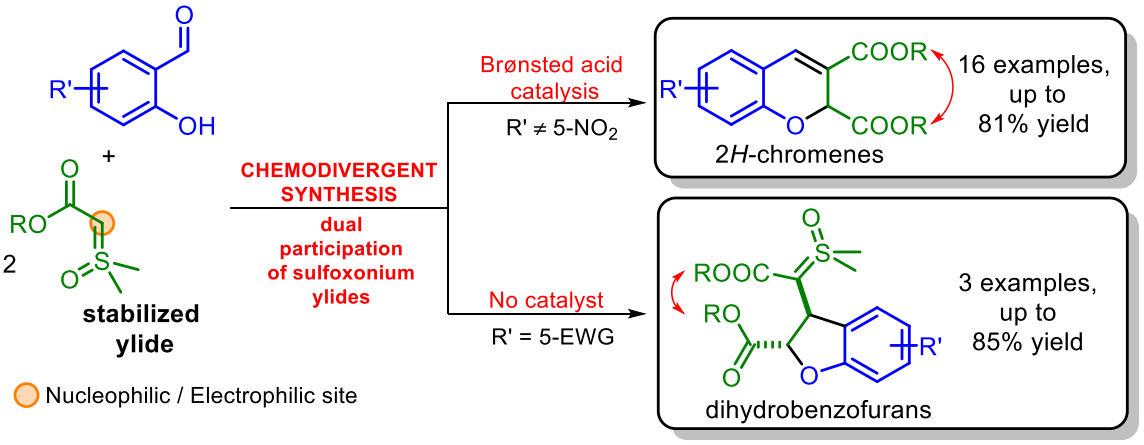
# 2 Summary of the Research work

In the next chapters, the versatility of organocatalysis applied to different substrates will be discussed. In particular, this thesis is based on three main topics, the reactivity of sulfoxonium ylides, the reactivity of donor-acceptor cyclopropanes, and asymmetric desymmetrization reactions.

The first chapters (chapters 3-5) will describe the chemistry of sulfoxonium ylides.[14] Sulfur ylides are formal internal salts characterized by a carbanion flanked by a positively charged sulfur atom. These ylides can react via typical (2 + 1) pathways (Corey-Chaykovsky epoxidation and related reactions) or can display less conventional reactivity such as insertion reactions[15] into X-H, C-H, C-X, and X-Y bonds.

More in detail, chapter 4 will examine a tandem chemodivergent cyclization reaction between sulfoxonium ylides and salicylaldehydes. The literature reports the reaction of an unstabilized sulfoxonium ylide with these aldehydes, giving benzofurans as products.[16] In our case,[17] reacting stabilized sulfoxonium ylides with salicylaldehydes, two different compounds are obtained, 2*H*-chromene and dihydrobenzofuran scaffolds, depending on the substituents around the aromatic ring and the presence of the catalyst (*Scheme 2.1*). In particular, using electron-poor salicylaldehydes, in the absence of a catalyst, three different dihydrobenzofuran derivatives were achieved in excellent yields, while, using electron-neutral or electron-rich salicylaldehydes in the presence of 5 mol% of diphenyl phosphate as catalyst, 16 examples of differently substituted 2*H*-chromenes were obtained in good yields. Mechanistic insight and comparison with the reactivity of sulfonium ylides are also investigated.

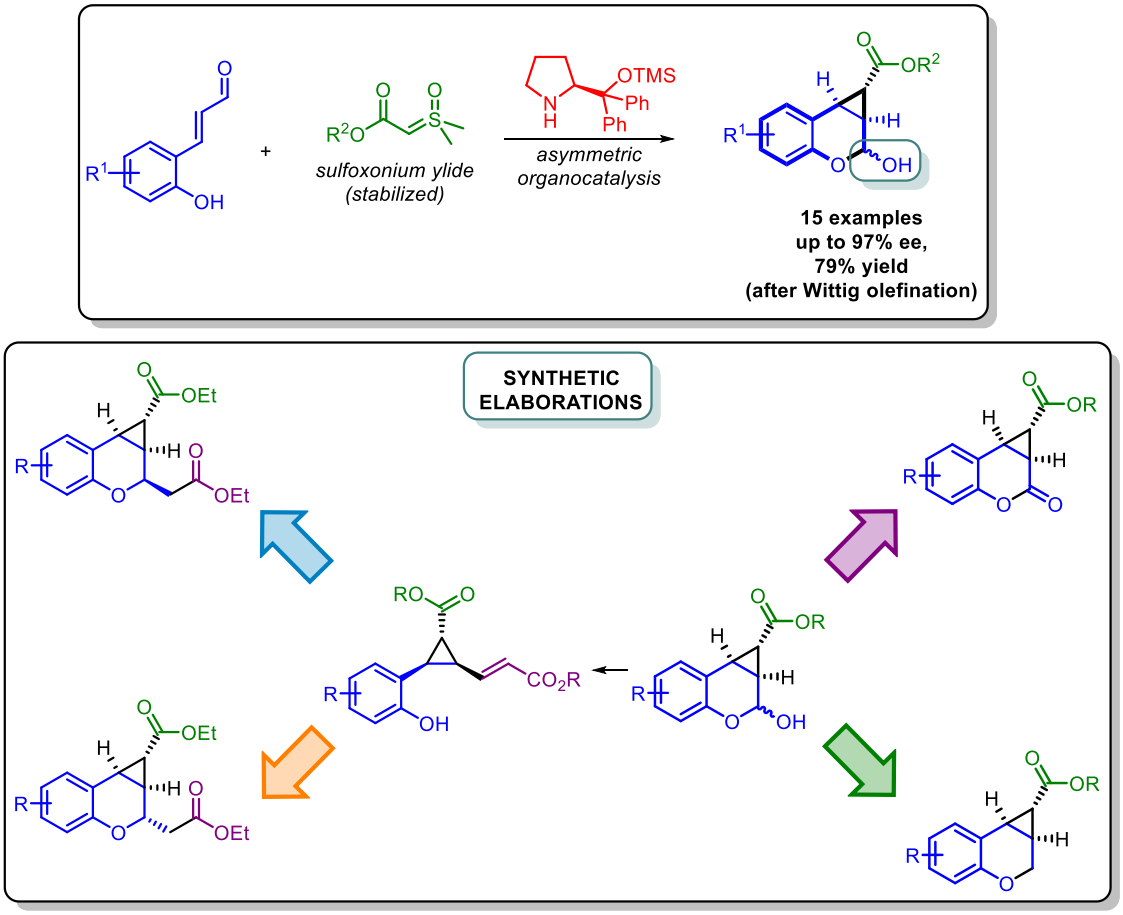
14 G. D. Bisag, S. Ruggieri, M. Fochi, L. Bernardi, *Org. Biomol. Chem.*, **2020**, *18*, 8793
15 a) D. Wang, M. D. Schwinden, L. Radesca, B. Patel, D. Kronenthal, M.-H. Huang and W. A. Nugent, *J. Org. Chem*. **2004**, *69*, 1629. b) P. B. Momo, A. N. Leveille, E. H. E. Farrar, M. N. Grayson, A. E. Mattson and A. C. B. Burtoloso, *Angew. Chem. Int. Ed*. **2020**, *59*, 15554.
16 B. Holt and P. A. Love, *Tetrahedron Lett*. **1966**, 683.
17 G. D. Bisag, S. Ruggieri, M. Fochi, L. Bernardi, *Adv. Synth.Catal.*, **2021**,*363*, 3053




*Scheme 2.1. Tandem chemodivergent cyclization between sulfoxonium ylides and salicylaldehydes*

Subsequently, we moved to investigate the reactivity of sulfoxonium ylides with α,β-unsaturated carbonyl compounds, and all the experimental detail will be reported in chapter 5. Due to the interesting reactivity shown with salicylaldehyde, we tried to understand the behavior of sulfoxonium ylides with its homologous 2'-hydroxy-cinnamaldehyde under asymmetric catalysis (*Scheme 2.2*). The reaction provides a convenient route for the synthesis of enantioenriched cyclopropane-fused chromanol structures.[18] Besides the synthetic versatility offered by the hemiacetal moiety, the cyclopropane-fused chromane scaffold is recurrent in pharmacologically active compounds. Unfortunately, the product of the reaction, characterized by a hemiacetal structure is not stable in HPLC so its derivatization into the Wittig adduct was carried out for a correct determination of the enantiomeric excess. Performing the reaction in the presence of a Jørgensen-Hayashi catalyst, fifteen different products were obtained in moderate yields and very good diastereo- and enantioselectivities. Moreover, the synthetic versatility of these compounds was demonstrated by performing different synthetic manipulations. The 1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene product turned out to be a versatile substrate for both oxidation and reduction reactions. Moreover, also the Wittig adduct shows great adaptability. After extensive screenings, a diastereodivergent Michael addition was developed with good yield, enantio-, and diastereoselectivity.

18 G. D. Bisag, P. Pecchini, M. mancinelli, M. Fochi, L. Bernardi, *Org. Lett.*, **2022**, *24*, 5468




*Scheme 2.2. Enantioselective cyclopropanation reaction between sulfoxonium ylides and 2'-hydroxycinnamaldehyde under asymmetric catalysis*

Then, we moved our attention to the interesting reactivity of donor-acceptor cyclopropanes. The typical reactivity and the experimental investigation carried out in our laboratory are reported in chapters 6 and 7.

Donor-acceptor cyclopropanes are constricted rings characterized by the presence of electron-donating and electron-withdrawing groups and specific architecture. In particular, the two groups with such electronic characteristics are the substituents of two of the three carbons of the cycle (*Figure 2.1*). This specific design allows an easier ring-opening reaction with ensuing reactivity.[19]

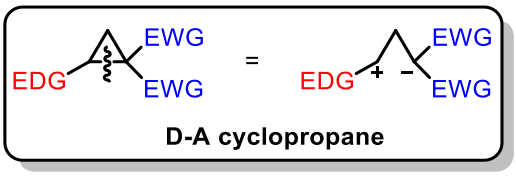
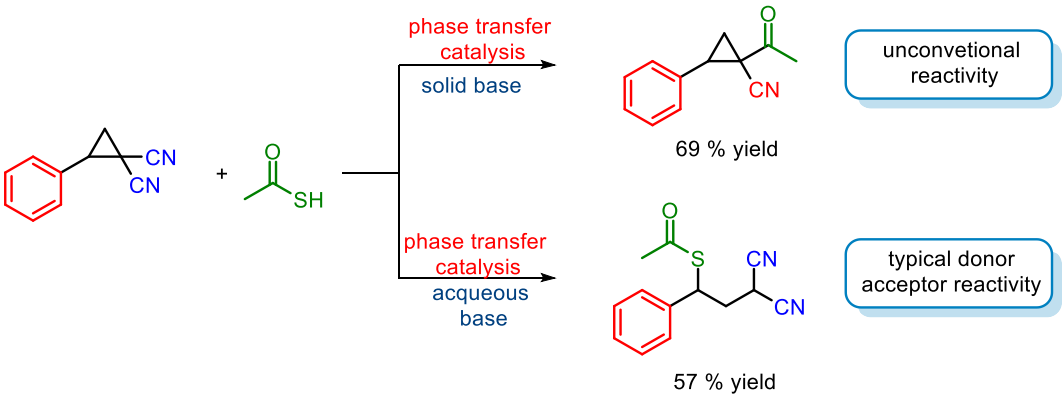



*Figure 2.1. Structure of standard donor-acceptor cyclopropanes*

19 T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5505

We found that performing the reaction with thioacetic acid under phase transfer catalysis two different products can be obtained depending on the reaction conditions (*Scheme 2.3*). In one case the classical reactivity of the donor-acceptor cyclopropanes was observed, in particular a ring-opening reaction. In the second case, a non-reductive decyanation reaction occurs. Once identified the reaction conditions that permit us to obtain the two products in moderate to good yields we began to evaluate preliminarily the generality of the reaction. In the future, it will be necessary to rationalize the mechanisms that permit the obtainment of the two different products.

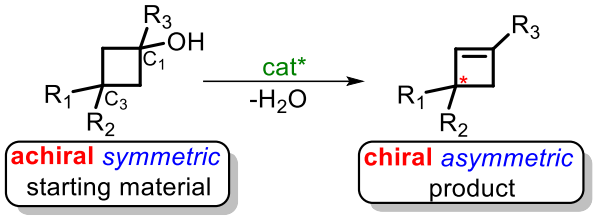



*Scheme 2.3. Reaction between a donor-acceptor cyclopropane and thioacetic acid*

Finally, during my period abroad an enantioselective desymmetrization reaction was investigated. The desymmetrization principles and the experimental details are reported in chapters 8 and 9. Asymmetric desymmetrization reactions are chemical manipulation of the substrates able to remove one or more symmetry elements, to obtain chiral and enantioenriched compounds.[20]

The aim of the period spent abroad was to develop an asymmetric desymmetrization approach of cyclobutanols exploiting a dehydration reaction under asymmetric acidic conditions (*Scheme 2.4*). To realize this approach different starting materials were synthesized changing both the substituents installed in positions $C_1$ and $C_3$ of the cyclobutanol. Moreover, screenings of acids, solvents, and additives were carried out to improve both yield and enantioselectivity leading to moderate results.

20 X.-P. Zeng, Z. -Y. Cao, Y. -H. Wang, F. Zhou, J. Zhou, Chem. Rev., **2016**, *116*, 7330




*Scheme 2.4. Aim of the work*

# 3 Sulfoxonium ylides: literature background and preliminary investigations

## 3.1 Ylides: definition and types

An *ylide* is a formally neutral compound containing a negatively charged atom, generally a carbanion, directly bonded to a positively charged atom, generally a heteroatom. Different types of ylides exist, with their own reactivity in function of the nature of the heteroatom. Moreover, each type of ylide can be divided into stabilized or unstabilized. An ylide is stabilized if an electron-withdrawing group is attached to the atom carrying the negative charge, thus "stabilizing" it.

The most famous ylides are phosphorus ylides, with a positive charge on a phosphorus atom. These compounds are the main players of the Wittig olefination, which allows the synthesis of olefins starting from the corresponding aldehydes/ketones. Other ylides are represented by nitrogen ylides such as pyridinium ylides and diazocompounds. Pyridinium ylides are synthetically useful due to their ability to react with E-Nu reagents, allowing the formation of fused cycles with simultaneous dearomatization of the pyridine ring, but also for cyclopropanation reactions. Diazocompounds are exceedingly useful too, especially as precursors of metal carbenes. However, their use is generally discouraged on large scale, due to the danger in handling them. Indeed, diazocompounds can explode when decompose, limiting significantly their use. Sulfur ylides are often considered safe surrogates of diazocompouds. Sulfur ylids can be divided into sulfonium or sulfoxonium ylides. Sulfoxonium ylides are the main argument of the next chapters. The section below reports the main theoretical aspects of the reactivity of these types of compounds. (*Figure 3.1*)

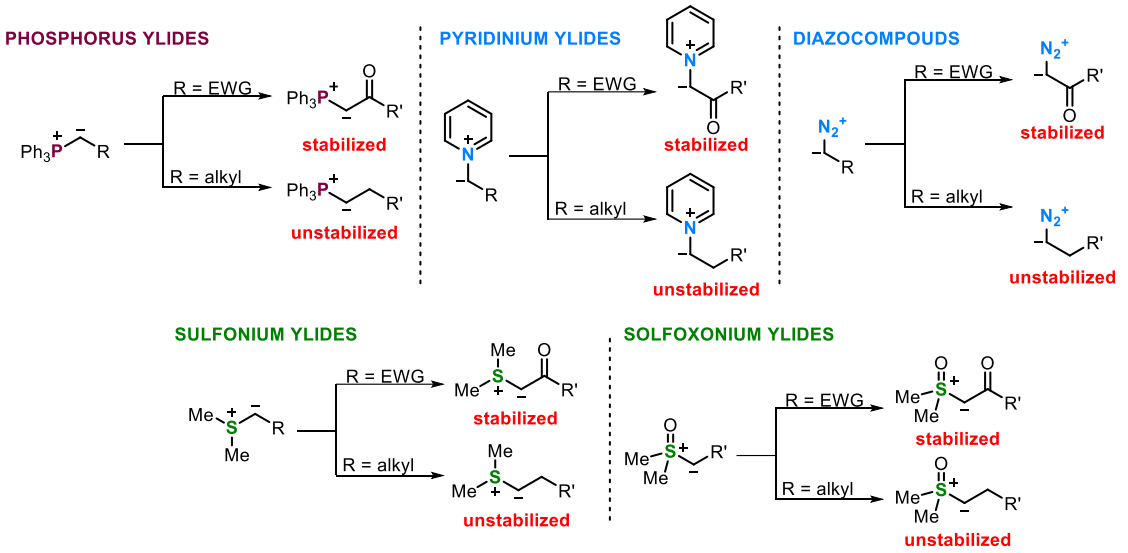



*Figure 3.1. Examples of ylides*

## 3.2 Sulfoxonium ylides

Sulfur ylides are formal internal salts characterized by a carbanion flanked by a positively charged sulfur atom. These ylides can be divided into two main classes, sulfonium, and sulfoxonium ylides, depending on the sulfur oxidation state. The first example of sulfur ylides was reported in 1930 by Ingold and Jessop.[21] However, the synthetic prowess of these compounds was revealed in the 1960s, when the works by Johnson and LaCount,[22] Franzen,[23] Corey, and Chaykovsky[24] showed their utility in small ring syntheses. The amazing growth that the chemistry of sulfur ylides has experienced in the last few years is largely due to the similarities of their structure and reactivity to the corresponding – arguably problematic – diazo compounds. Indeed, the three structures reported below (*Figure 3.2*) are characterized by a negative charge near to a good leaving group.

21 C. K. Ingold, J. A. Jessop, *J. Chem. Soc.*, **1930**, 713.
22 A. W. Johnson, R. B. LaCount, *J. Am. Chem. Soc*., **1961**, *83*, 417.
23 a) V. Franzen, H. J. Schmidt, C. Mertz, *Chem. Ber.*, **1961**, *94*, 2942. b) V. Franzen, H.-E. Driesen, *Chem. Ber.*, **1963**, *96*, 1881
24 a) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.*, **1962**, *84*, 3782. b) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.*, **1964**, *86*, 1960. c) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.*, **1965**, *87*, 1345.

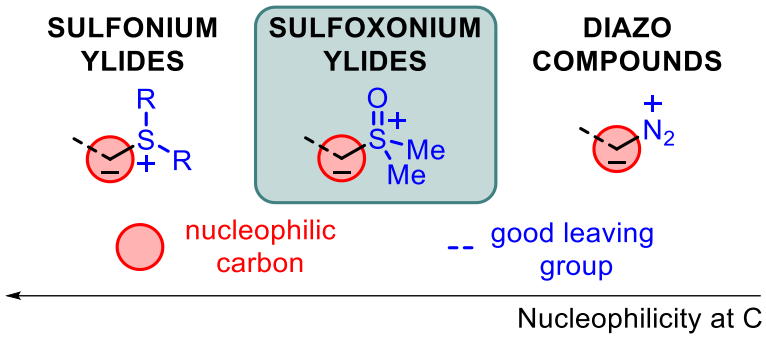
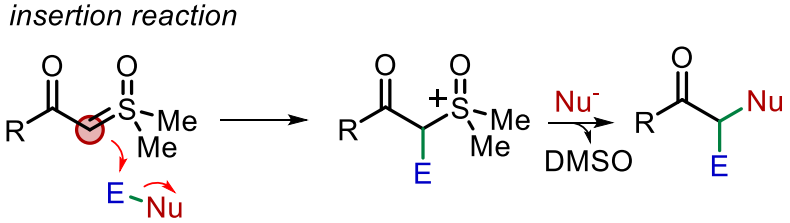



*Figure 3.2. . Sulfonium and sulfoxonium ylides, diazo compounds, and their order of nucleophilicity at carbon*

Understandably, the sulfur oxidation state influences the properties of the ylides too. The presence of the electron-withdrawing oxygen at sulfur atom gives two important consequences on the reactivity of sulfoxonium ylides. First, these compounds are considerably more stable and less C-nucleophilic, compared to their sulfonium counterparts, thanks to a better delocalization of the negative charge. Nevertheless, sulfoxonium ylides are more C-nucleophilic than the corresponding diazo compounds. Second, the oxygen atom can function as a Lewis base, coordinating a catalytic species and interfering with its action.

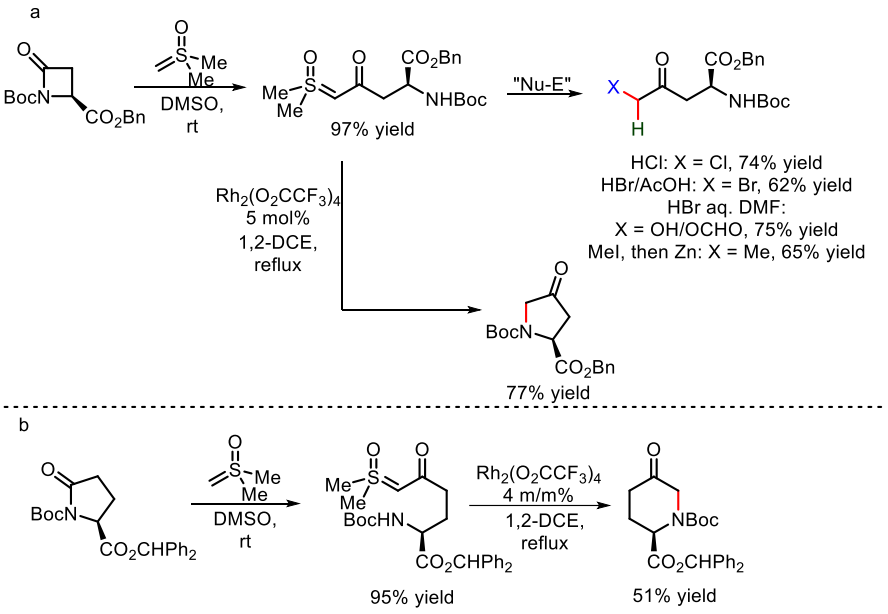
## 3.3 Sulfoxonium ylides reactivity

Sulfoxonium ylides can undergo numerous types of reactions, the main ones are insertions and cyclizations. Regarding the insertion reactions, sulfoxonium ylides can react with a polarised Nu–E bond by first attacking the electrophile portion with the nucleophilic carbon. Then, DMSO displacement by the nucleophilic species follows, resulting in the formal insertion of the ylide into the Nu–E bond (*Scheme 3.1*). The two steps can be subjected to catalytic promotion by acidic species or transition metals. In the latter case, an electrophilic carbene is formed, which reacts first with the nucleophile and then with the electrophile, analogously to the reactions of diazo compounds.




*Scheme 3.1. Typical reactivity of sulfoxonium ylides*

To better understand this concept is necessary to mention some works by Baldwin and coworkers dealing with the ring-opening of *N*-Boc lactams by dimethylsulfoxonium methylide, and subsequent functionalization of the resulting β-keto sulfoxonium ylide (*Scheme 3.2*).[25] While the highly basic sulfonium ylide causes degradation of the starting β-lactam, its milder sulfoxonium counterpart furnishes the ring-opened β-ketosulfoxonium ylide in nearly quantitative yield (*Scheme 3.2a*). Treatment of this ylide with different H–X reagents, gives a series of functionalized products with variable results. Conversely, to effect an intramolecular insertion into the N–H bond, the authors had to resort to a transition metal catalyst ($Rh_2(O_2CCF_3)_4$), to channel the reaction through the formation of an electrophilic metal carbenoid intermediate. This was the first disclosure of a metal catalysed insertion reaction in combination with sulfoxonium ylides. The overall sequence brings about a one carbon ring expansion of a lactam. It was also applied with reasonably good results to the conversion of a pyroglutamic acid derivative into a piperidin-3-one (*Scheme 3.2*b).

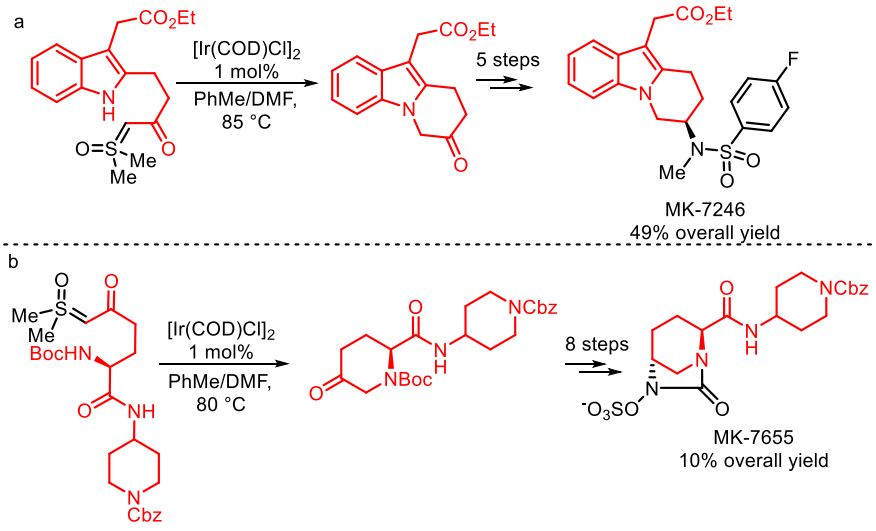



*Scheme 3.2. Ring-opening of N-Boc lactams by dimethylsulfoxonium methylide, and ensuing functionalizations.*

Similar ring expansion strategies (γ-lactam → piperidin-3-one) were later exploited at Merck, using an iridium-based catalyst, for the synthesis of MK-7246 (*Scheme 3.3a*),[26] a

25 a) J. E. Baldwin, R. M. Adlington, C. R. A. Godfrey, D. W. Gollins, J. G. Vaughan, *J. Chem. Soc. Chem. Commun.*, **1993**, 1434. b) J. E. Baldwin, R. M. Adlington, C. R. A. Godfrey, D. W. Gollins, M. L. Smith, A. T. Russel, *Synlett*, **1993**, 51.
26 I. K. Mangion, R. T. Ruck, N. Rivera, M. A. Huffman, M. Shevlin, *Org. Lett.*, **2011**, *13*, 5480.

CRTH2 antagonist for respiratory disorders, and of MK-7655 (*Scheme 3.3b*),[27] a β-lactamase inhibitor. Several features of these works are worth to be highlighted: i) the metal catalyzed N-H insertion reaction allowed to overcome the unfeasibility of more conventional intramolecular nucleophilic substitutions via halide displacement by the amine, although recent disclosures towards MK-7655 point to an H-Cl insertion followed by $S_N2$ as a viable pathway if an oxime, instead of a ketone, is used;[28] ii) a medicinal chemistry approach to a related piperidin-3-one involved an identical ring-expansion strategy, but was based on a diazo compound. However, diazo compounds are generally characterized by poor thermal stability and can be explosive.[29] Process development thus resorted to sulfoxonium ylides due to their inherent higher appeal for scale-up (increased safety, stability, crystalline nature). iii) Industrialisation of the reaction leading to MK-7246 was carried out to produce this clinical candidate on a multi-Kg scale.




*Scheme 3.3. Applications of the metal-catalyzed insertion reaction to medicinal agents*

Along these lines, stabilized sulfoxonium ylides have been employed in a range of formal insertion reactions into X-H, C-H, C-X, and X-Y bonds (*Figure 3.3*). Such transformations are powerful tools for the preparation of numerous classes of compounds, building blocks of drugs, and natural products.

27 C. Molinaro, P. G. Bulger, E. E. Lee, B. Kosjek, S. Lau, D. Gauvreau, M. E. Howard, D. J. Wallace and P. D. O'Shea, *J. Org. Chem*., **2012**, *77*, 2299.
28 J. Y. L. Chung, D. Meng, M. Shevlin, V. Gudipati, Q. Chen, Y. Liu, Y.-H. Lam, A. Dumas, J. Scott, Q. Tu, F. Xu, J. *Org. Chem.*, **2020**, *85*, 994.
29 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller, J. A. Bull, *Org. Process Res. Dev.*, **2020**, *24*, 67.

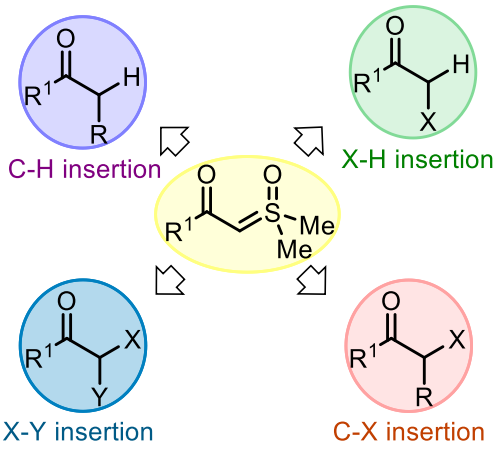
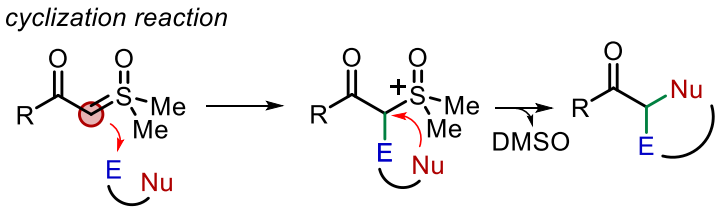


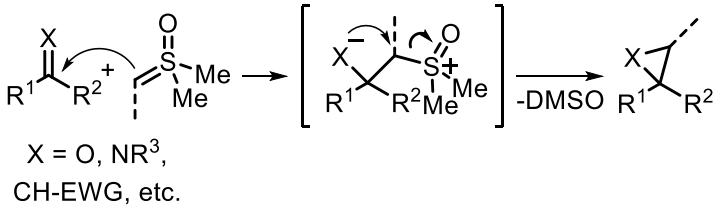

*Figure 3.3. Formal insertion reactions of sulfoxonium ylides*

Regarding cyclization reactions, the reaction partners of the sulfoxonium ylide must contain on their skeleton an electrophilic site, able to be attacked by the nucleophilic carbon of the ylides, and a nucleophilic site able to displace DMSO (*Scheme 3.4*). Also in this case, the steps of the reaction can be subjected to catalytic promotion by different species.




*Scheme 3.4. Typical reactivity of sulfoxonium ylides during a cyclization reaction*

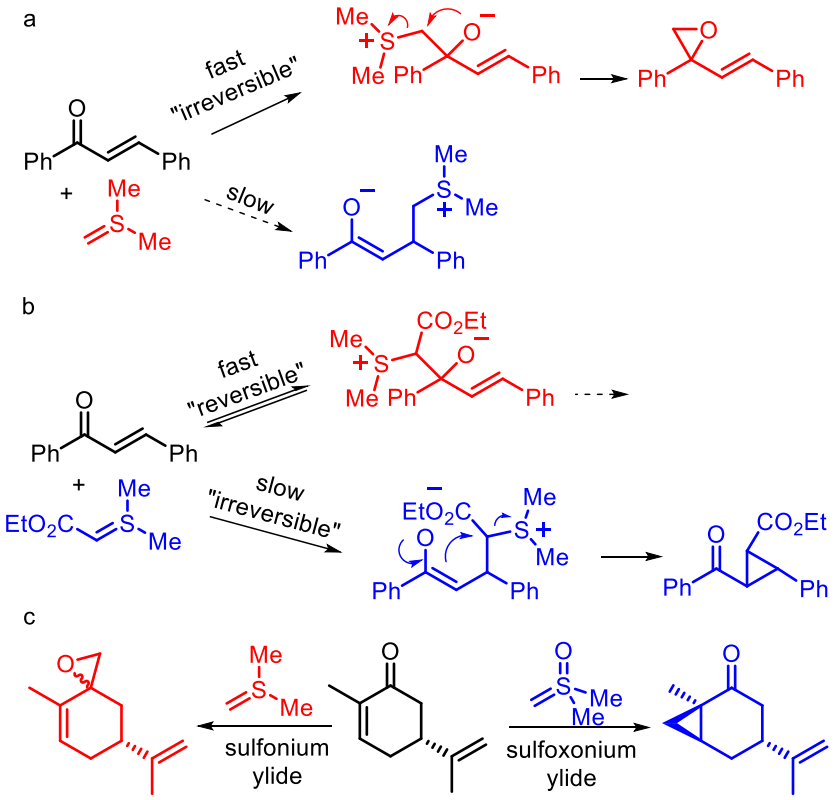
The formation of epoxides, aziridines, and cyclopropane rings follow a two-step pathway, involving the nucleophilic addition of the ylide to a π-acceptor C = X followed by DMSO displacement by the resulting negatively charged X atom (*Scheme 3.5*). From another perspective, the reaction can be considered as the formal insertion of the ylide into the π-bond, along the lines of a (2 + 1) cycloaddition reaction.




*Scheme 3.5. Two-step pathway for the formation of constrained rings from sulfoxonium ylides.*

Oxirane motifs can be obtained by exploiting the reactivity of sulfoxonium ylides, first disclosed by Johnson and LaCount[30] and then broadly investigated by Corey and Chaykovsky.[31] However, when sulfur ylides, both sulfonium and sulfoxonium ones, react with α,β-unsaturated carbonyl compounds, two different products can be obtained, oxiranes or cyclopropanes, due to the two electrophilic sites present in the substrates. The kinetically favored 1,2-addition of the ylide to the carbonyl leads to the oxirane, while the slower 1,4-addition gives the thermodynamically favored cyclopropane. The regiodivergency of the reactions of stabilized *vs* unstabilized sulfonium ylides is rationalized considering the higher degree of reversibility in additions of stabilized ylides to carbonyls.[32] Thus, with *unstabilized sulfonium ylides*, the 1,2-addition is a fast and irreversible process, favoring the formation of the oxirane[33] (*Scheme 3.6a*). With *stabilized sulfonium ylides*, the 1,2-addition, which is still kinetically favored, tends to be reversible, ultimately resulting in the thermodynamic cyclopropane product[34] via the slower but irreversible 1,4-addition pathway (*Scheme 3.6b*). Similar arguments can be put forward to justify the preference of *sulfoxonium ylides* for cyclopropanes *vs* the oxiranes[35] obtained with *sulfonium ylides* (*Scheme 3.6c*). The additional oxygen of sulfoxonium ylides stabilizes the anion to a sufficient extent to render the 1,2-addition reversible, even without additional electron-withdrawing groups on the ylide.

30 A. W. Johnson, R. B. LaCount, *J. Am. Chem. Soc.*, **1961**, *83*, 417.
31 a) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc*., **1962**, *84*, 3782. b) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc*., **1964**, *86*, 1960. c) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.*, **1965**, *87*, 1345.
32 J. Clayden, N. Greeves, S. Warren, P. Wothers, Organic Chemistry 1st Ed., Oxford University Press, Oxford, UK, 2012, Ch. 46, pp. 1249–1277.
33 a) P. Mosset, R. Grée, *Synth. Commun.*, **1985**, *15*, 749. b) S. Li, P. Li, J. Xu, *Helv. Chim. Acta*, **2019**, 102, art. no. E1900164.
34 G. A. Tolstikov, F. Z. Galin, V. N. Iskandarova, *Russ. Chem. Bull.*, **1983**, *32*, 1098.
35 a) L. de C. Alves, A. L. Desiderá, K. T. de Oliveira, S. Newton, S. V. Ley, T. J. Brocksom, *Org. Biomol. Chem.*, **2015**, *13*, 7633. (b) G. A. Molander and C. Alonso-Alija, Tetrahedron, 1997, 53, 8067-8084.




*Scheme 3.6. Regioselectivity in the reaction of sulfur ylides with α,β-unsaturated carbonyl compounds: a) unstabilised sulfonium ylide; b) stabilised sulfonium ylide; c) sulfonium vs sulfoxonium ylide.*

Cyclization reactions can be divided in (2 + 1) and (n + 1) cyclization reactions. Regarding (2 + 1) cyclization reactions, sulfoxonium ylides in combination with the π-system of carbonyl compounds (imines, saturated and unsaturated aldehydes, or ketones) can generate a wide range of constricted rings such as cyclopropanes, aziridines and oxiranes (*Figure 3.4 left*), scaffolds often recurring in biologically active natural and unnatural compounds, as well as powerful synthetic intermediates.[36] Also (n + 1) cyclization reactions see sulfoxonium ylides as main characters. The most common processes developed in the last few years are interrupted Corey-Chaykovsky reactions, ring expansions, and olefinations reactions. These transformations lead to original syntheses of

36 a) T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T.-Y. Wu, Y. He, *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 2105. b) F. M. D. Ismail, D. O. Levitsky, V. M. Dembitsky, *Eur. J. Med. Chem.*, **2009**, *44*, 3373.

important heterocycles, for example γ-lactones,[37] γ-lactams,[38] tetrahydrofurans, pyrrolidines,[39] oxetanes[40] and dihydropyrazoles.[41]

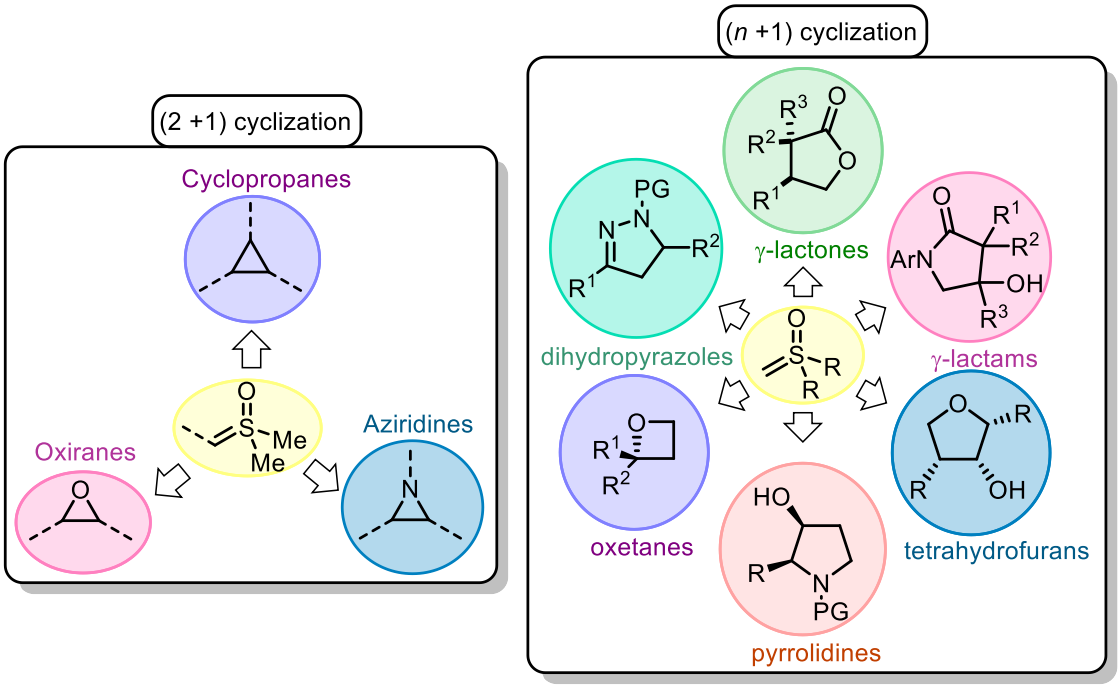



*Figure 3.4. Cyclization reaction of sulfoxonium ylides*

## 3.4 Experimental evolution

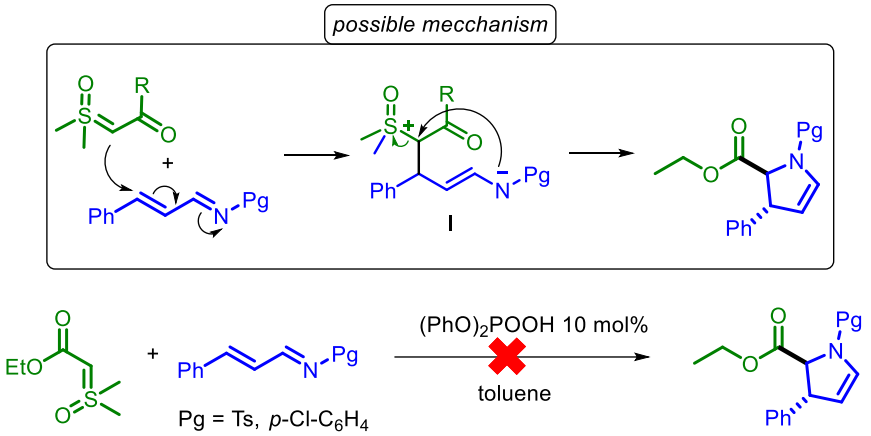
The previous section briefly showed that sulfoxonium ylides present different reactivity. In our recent review,[42] we have defined these compounds as synthetic chameleons. Moreover, utilisation of stabilized sulfoxonium ylides appears particularly attractive, due to their ease of synthesis and thermal stability (as opposed to their diazo analogues). However, examples of the utilization of these ylides in the presence of (chiral) catalysts are not abundant, with only a handful of examples being reported until 2019 – when these PhD studies began. We surmised that the reactivity of these convenient compounds had been not fully explored, leaving space for uncovering conceptually innovative and

37 M. Mondal, H.-J. Ho, N. J. Peraino, M. A. Gary, K. A. Wheeler, N. J. Kerrigan, *J. Org. Chem.*, **2013**, *78*, 4587.
38 D. Zhang, Q. Zhang, N. Zhang, R. Zhang, Y. Liang, D. Dong, *Chem. Commun.*, **2013**, *49*, 7358.
39 J. M. Schomaker, V. R. Pulgam, B. Borhan, *J. Am. Chem. Soc.*, **2004**, *126*, 13600.
40 a) U. K. Nadir and V. K. Koul, *J. Chem. Soc.*, **1981**, 417-418. (b) K. Okuma, Y. Tanaka, S. Kaji and H. Ohta, *J. Org. Chem.*, **1983**, *48*, 5133-5134. (c) E. D. Butova, A. V. Barabash, A. A. Petrova, C. M. Kleiner, P. R. Schreiner and A. A. Fokin, *J. Org. Chem.*, **2010**, 75, 6229-6235.
41 S. Hu, S. Du, Z. Yang, L. Ni, Z. Chen, *Adv. Synth. Catal.*, **2019**, *361*, 3124.
42 G. D. Bisag, S. Ruggieri, M. Fochi, L. Bernardi, *Org. Biomol. Chem.*, **2020**, *18*, 8793.

interesting transformations. Taking into consideration the experience of the laboratory in organocatalysis, at the beginning of my PhD studies it was decided to set up a wide-range exploration of the reactivity of these convenient compounds towards a series of reaction partners, under the action of different organocatalysts.

In the next paragraphs, some of the reactions tested employing sulfoxonium ylides as substrates will be briefly analyzed and discussed.

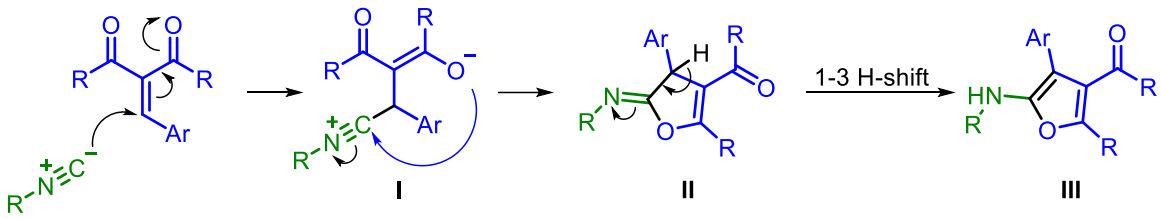
One of the first tested reactions was a (4 + 1) cycloaddition reaction between two α,β-unsaturated imine differently protected and stabilized sulfoxonium ylides (*Scheme 3.7*). The aim of this reaction was the synthesis of differently substituted dihydropyrrolidines. As is possible to observe in the proposed mechanism, the first nucleophilic attack of the sulfoxonium ylides occurs at the γ-position of the imine, forming the zwitterionic intermediate **I**. Then, an intramolecular ring closure reaction should give the formation of dihydropyrrolidines. Unfortunately, performing the reaction under acidic conditions, only decomposition of the imine was detected in the reaction mixture.




*Scheme 3.7. Imine tested*

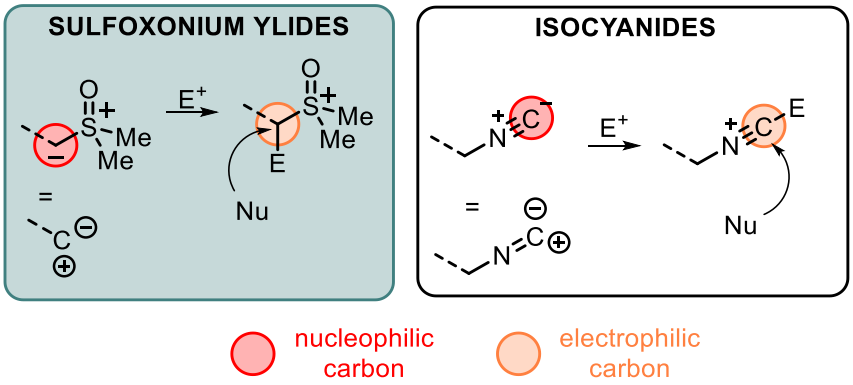
Subsequently, we moved to analyze another 4 + 1 cyclization using an α,β-unsaturated dicarbonyl compound. Generally, these types of substrates are employed in (4 + 1) cyclization reactions with isocyanide-based compounds.[43] The possible mechanism of this reaction is reported in *Scheme 3.8*. The nucleophilic carbon of the isocyanade compound attacks the γ-position of the α,β-unsaturated dicarbonyl derivatives forming the zwitterionic intermediate **I**. At this point, an intramolecular ring closure reaction occur generating intermediate **II**, which evolves into the furan product after a 1,3-H shift.

43 T. Kaur, P. Wadhwa, S. Bagchi, A. Sharma, *Chem. Commun.*, **2016**, *52*, 6958.



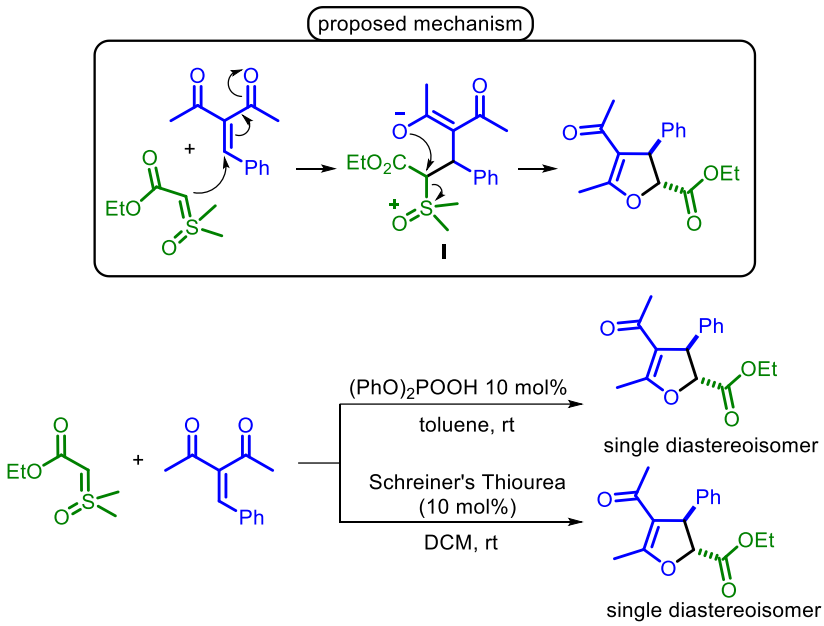

*Scheme 3.8. Possible mechanism of the reaction between isocyanide-based compounds and α,β-unsaturated dicarbonyls*

Isocyanide-based compounds have structure and reactivity similar to the solfoxonium ylides. Indeed, both compounds are characterized by a carbon atom that acts first as a nucleophile and then as an electrophile (*Scheme 3.9*).




*Scheme 3.9. Similarities between sulfoxonium ylides and isocyanides*

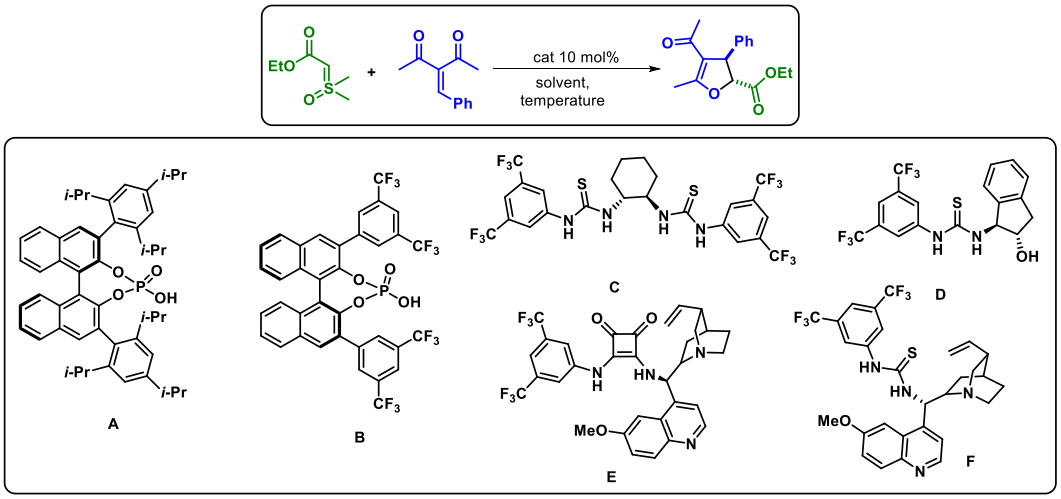
The examined reaction and its possible mechanism are reported in *Scheme 3.10*. First of all the stabilized sulfoxonium ylide makes a nucleophilic attack to the γ-position of the α,β-unsaturated dicarbonyl derivative forming the zwitterionic intermediate **I**. Then, the enolate oxygen undergoes a ring closure reaction displacing DMSO and forming directly the dihydrofuran product. Performing the reaction under different acidic conditions, in particular using diphenylphosphate as catalyst or under H-bond donor catalysis, the (4 + 1) cyclization reaction occurs, giving the dihydrofuran reported as a single diastereoisomer.




*Scheme 3.10. Reaction between an α,β-unsaturated dicarbonyl compound and sulfoxonium ylides*

Given the promising reactivity, a short catalyst screening was carried out to understand if the reaction could be developed under asymmetric acidic conditions and the results are reported in *Table 3.1*. Performing the reaction with catalyst **A** good results in terms of conversion were obtained but the enantiomeric excess was very low (entry 1). Subsequently, other catalysts were tested (cat **B**-**F**), but in all cases, the product was obtained in a racemic form (entries 2-4 and entries 6,7). Taking into consideration the obtained results, the behavior of the reaction in the absence of the catalyst was also examined (entries 5 and 8). Performing the reaction without a catalyst at room temperature an even higher conversion was obtained (entry 5). This result suggests that, paradoxically, the presence of the catalyst inhibits the reaction. Probably, the coordination of the ylide is strong enough to decrease its nucleophilicity. To slow down the background reaction, an experiment performed at low temperature was carried out (entry 8), but also in this case a good conversion was obtained. For this reason, we decided to abandon the development of this reaction.

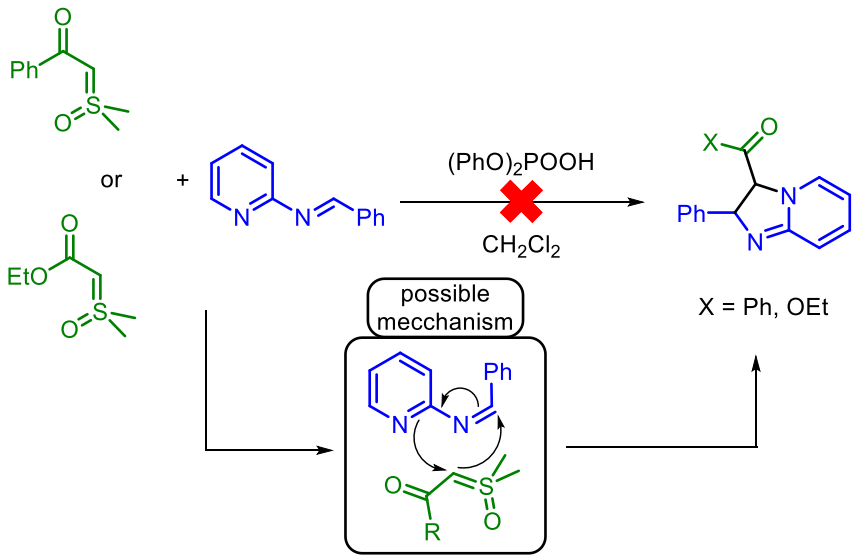
*Table 3.1. Catalysts screening*




| entryEntry[a] | cat | solvent | temperature | time | conversion[b] | ee |
|---|---|---|---|---|---|---|
| **1** | **A** | toluene | rt | 44 h | 66 % | 5 % |
| 2 | **B** | toluene | rt | 44 h | 60 % | rac |
| **3** | **C** | DCM | rt | 44 h | 87% | rac |
| 4 | **D** | DCM | rt | 44 h | 30 % | rac |
| **5** | / | toluene | rt | 64 h | 80 % | / |
| 6 | **E** | DCM | -20-rt | 48 | 40% | rac |
| **7** | **F** | DCM | rt | 48 | 50% | rac |
| 8 | / | DCM | -20 | 48 | 50% | rac |

[a] Reaction conditions:0.15 mmol of sulfoxonium ylides, 0.1 mmol of α,β-unsatured diketone, 10 mol% catalyst were dissolved in 250μL of the opportune solvent. [b] Calculated on the crude mixture. [c] Enantiomeric excess determined by CSP-HPLC.

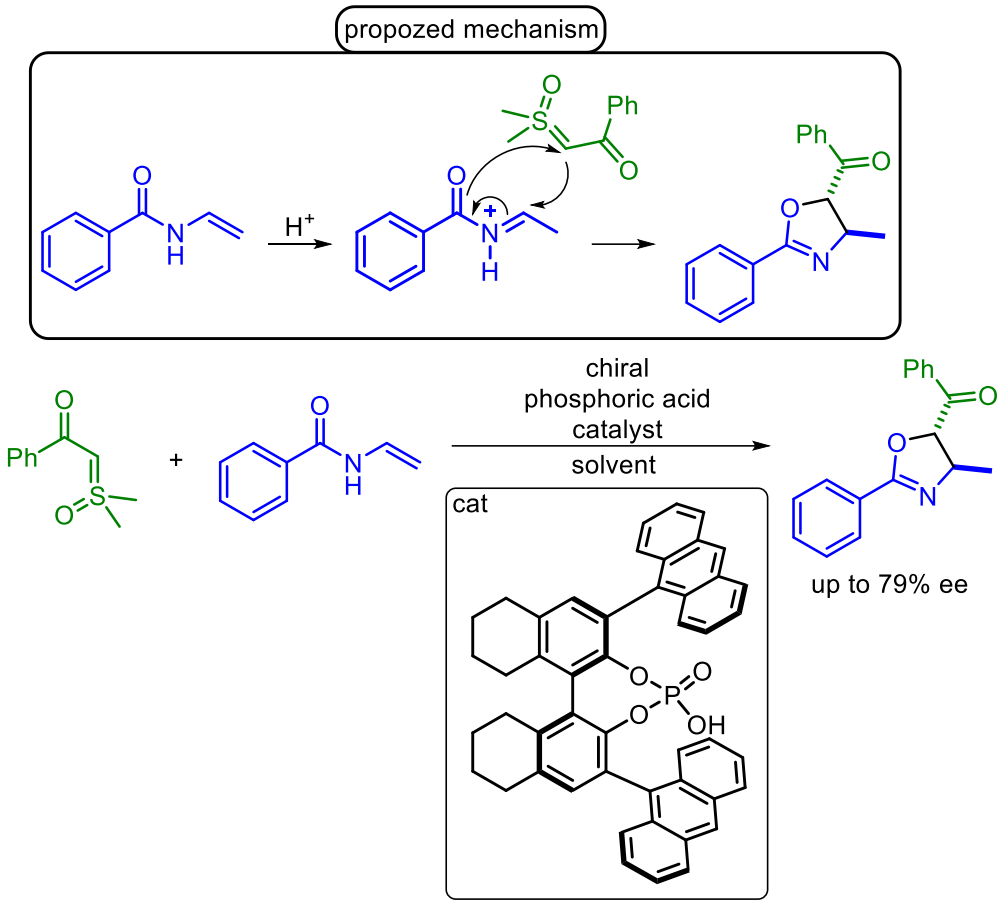
Subsequently, we moved our attention to the study of a Groebke–Blackburn–Bienaymé type reaction, another typical isocyanide reaction. The hypothesized reaction mechanism is reported in *Scheme 3.11*. The sulfoxonium ylide makes a nucleophilic attack on the iminium carbon, then the dearomatization of the pyridine ring occurs displacing DMSO and forming the final product. Unfortunately, performing the reaction with the 2-aminopyridine derivative reported below, and two different stabilized ylides under acidic conditions, no reactivity was observed, only partial hydrolysis of the imine.




*Scheme 3.11. Groebke–Blackburn–Bienaymé type reaction*

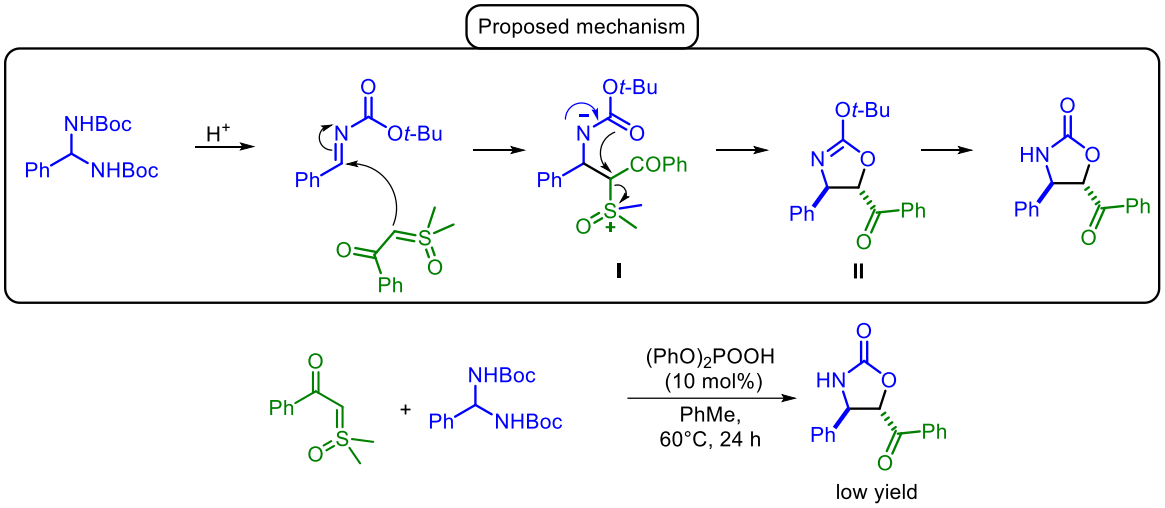
Thus, we moved our focus away from isocyanide reactions, testing instead a (4 + 1) cyclization reaction already developed in a racemic form and which mechanism is reported in *Scheme 3.12*.[44] This reaction was analyzed for a possible enantioselective development, hypothesizing that a chiral phosphoric acid could not only isomerize the enamide to the imine but also activate the imine for the formal cycloaddition. In line with the literature, a sulfoxonium ylides with a ketone as stabilizing group was considered. After different solvents and catalysts screening, promising results in terms of enantiomeric excess (up to 79%) were obtained using the H8-Binol derivative reported below. However, a very low conversion was observed in all the reactions, less than 15%. Possibly, the leaving DMSO or the dihydrooxazoline product inhibits the activity of the catalyst. For this reason, also this investigation was stopped.

44 N. Luo, Z. Zhan, Z. Ban, G. Lu, J. He, F. Hu, G.. Huang, *Adv. Synth.Catal.*, **2020**, *362*, 3126.




*Scheme 3.12. (4 + 1) cyclization reaction*

Another (4 + 1) cyclization reaction tested is reported in *Scheme 3.13*. In this case, a stabilized sulfoxonium ylides and an *N*-Boc aminal react together under acidic conditions to form a cyclic carbamate as product. The possible reaction mechanism is reported below. First of all, the aminal reagent, under acidic conditions, can generate the *N*-Boc protected imine reported, which could undergo a nucleophilic attack by the sulfoxonium ylides generating intermediate **I**. Then, a ring closure reaction can occur generating intermediate **II**, which under acidic conditions lose the *t*-butylic moiety generating a more stable carbamate group. Unfortunately, this reaction did not give promising results, affording the cycloadducts in less than 10% yield under a range of acidic reaction conditions.



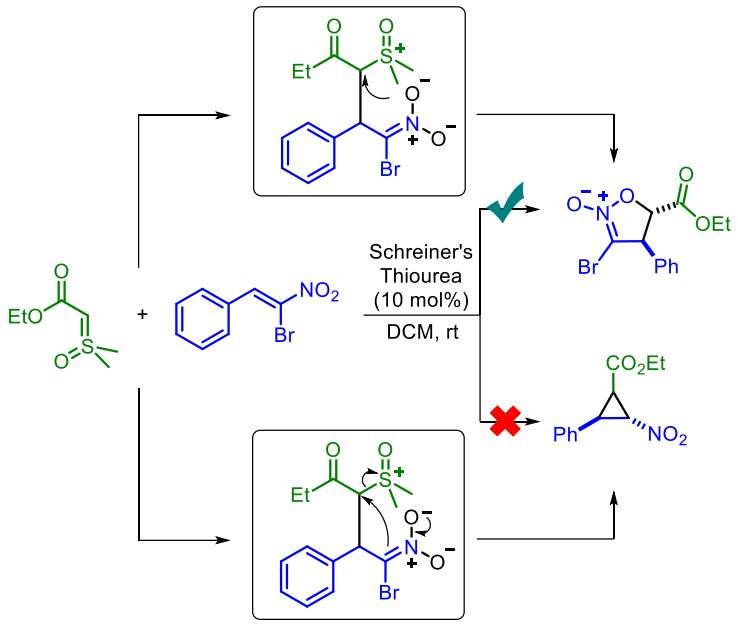




*Scheme 3.13. (4 + 1) cyclization reaction*

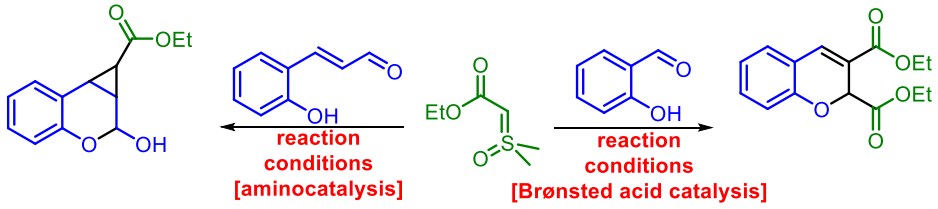
Other formal cycloadditions were tested by exploring the reactivity of nitroalkenes with stabilized sulfoxonium ylides (*Scheme 3.5*). The combination of nitroalkenes with sulfonium ylides under asymmetric reaction conditions is already reported using chiral thiourea catalysts and leads to oxazolidinone derivatives via an intriguing reaction pathway.[45] Taking into consideration these examples, we decided to investigate the reaction between a brominated nitroalkene derivative and sulfoxonium ylides *Scheme 3.14*. In particular, we wanted to see if the reaction follows a 4+1 pathway generating an isooxazoline N-oxide, or a (2 + 1) cyclization generating a cyclopropane. Due to the same reactivity of sulfonium and sulfoxonium ylides, we decided to move our attention to more interesting reactions.

45 a) L.-Q. Lu, Y.-J. Cao, X.-P. Liu, J. An, C. -J. Yao, Z.-H. Ming, W. -J. Xiao, *J. Am. Chem. Soc.*, **2008**, *130*, 6946. b) L. -Q. Lu, F. Li, J. An, Y. Cheng, J.-R. Chen, W.-J. Xiao, *Chem. Eur. J.*, **2012**, *18*, 4073.




*Scheme 3.14. Reactivity of sulfoxonium ylides and nitrolefines*

Finally, we decided to evaluate the reactivity of salicylaldehyde and salicylaldehyde derivatives (*Scheme 3.15*). In this case, we rapidly understood that both reactions reported below are characterized by promising and interesting results. For these reasons, these reactions were fully developed, and analyzed in detail in the following chapters. The most peculiar behavior is represented in the reaction with simple salicylaldehyde, wherein the first experiments performed with a phosphoric acid promoter provided an unexpected 2*H*-chromene product, with the double participation of the ylide in the reaction.



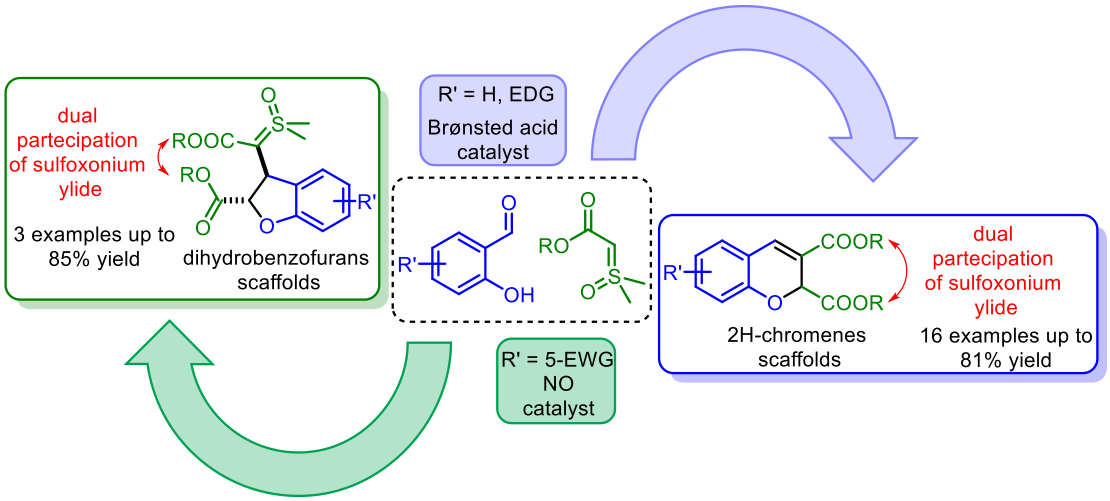

*Scheme 3.15. Reactivity of salicylaldehyde, salicylaldehyde derivatives, and sulfoxonium ylides*

# 4 Catalyst- and substate- dependent chemodivergent reactivity of stabilized sulfur ylides with salicylaldehydes.

All the procedures and results here described are part of- and can be found in:

- G. D. Bisag, S. Ruggieri, M. Fochi, L. Bernardi, "Catalyst- and substate- dependent chemodivergent reactivity of stabilized sulfur ylides with salicylaldehydes". *Adv. Synth. Catal.* **2021**, *363*, 3053–3059.

ABSTRACT

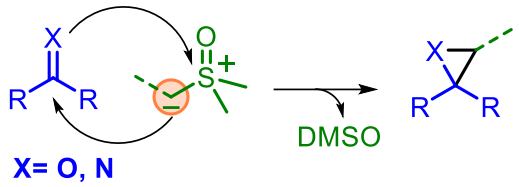



The reactivity of stabilized sulfoxonium ylides under acidic conditions is a topic still poorly investigated. Herein we report a new catalyst and substrate dependent chemodivergent reaction between stabilized sulfur ylides and salicylaldehydes, leading to unexpected 2*H*-chromene or dihydrobenzofuran products. Particular attention was set on the unusual mechanism involved, and after numerous mechanistic experiments two unique reaction routes including two ylide units are proposed. Moreover, in some cases it was observed a selectivity switch by modulating the nucleophilicity of the sulfur ylide and the electrophilicity of the employed salicylaldehyde.

## 4.1 Background

The traditional prominence of sulfoxonium ylides, and especially of their unstabilized methylidene congener (the Corey-Chaykovsky reagent, dimethylsulfoxonium methylidene

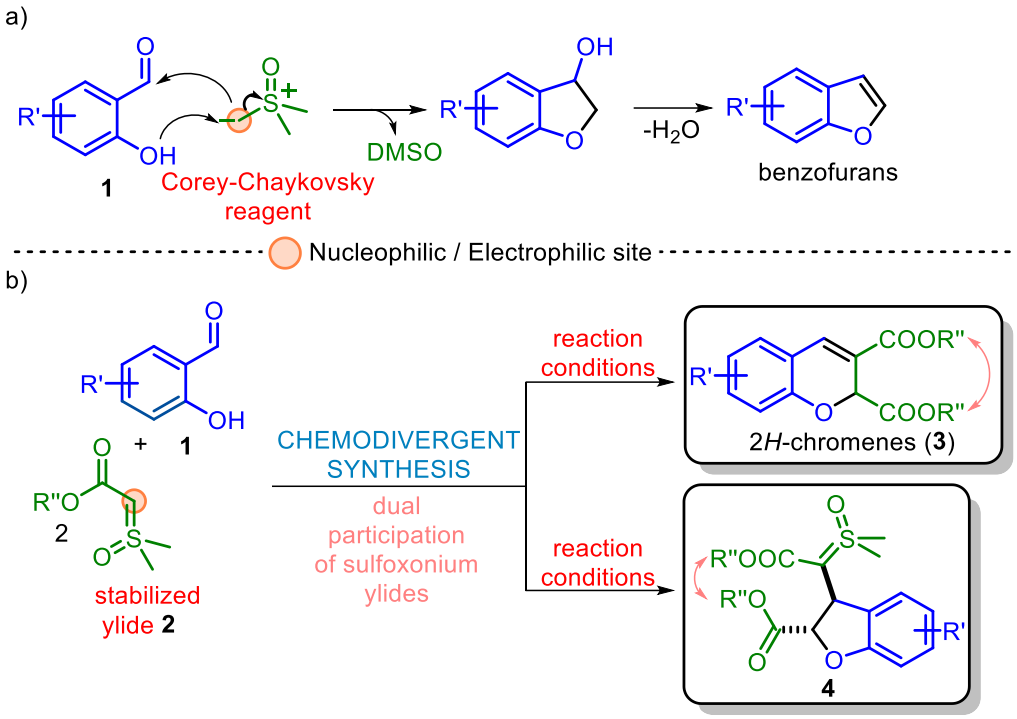
ylide), is due to their proficiency in formal (2 + 1) cycloadditions with carbonyl compounds, delivering epoxides, aziridines,[46] and cyclopropanes.[47] (*Scheme 4.1*)




*Scheme 4.1. Reaction between a dimethylsulfoxonium ylide and a generic carbonyl compound*

However, sulfoxonium ylides can also undergo different types of reactions when combined with bifunctional substrates. For example, the reaction between the Corey-Chaykovsky reagent and salicylaldehydes generates benzofurans as products,[48] wherein DMSO is displaced by the nucleophilic phenolic, instead of carbonylic, oxygen (*Scheme 4.2a*). In this chapter, the reactivity of *stabilized* sulfoxonium ylides **2** with salicylaldehydes **1** is explored.[49] It was quickly realized that stabilized sulfoxonium ylides **2** lead to distinct outcomes, compared to their unstabilized methylidene counterpart. Indeed, we discovered that 2*H*-chromenes **3** or dihydrobenzofurans **4** are obtained as products. The type of product depends on the reaction conditions and the substituents around the aromatic ring of the aldehyde. Moreover, for both products, 2*H*-chromenes **3** and dihydrobenzofurans **4**, a dual participation of the sulfoxonium ylides was observed. (*Scheme 4.2b*).

46 D. Morton, D. Pearson, R. A. Field, R. A. Stockman, *Synlett*. **2003**, *13*, 1985. M. A. Marsini,J. T. Reeves, J.-N. Desrosiers, M. A. Herbage, J. Savoie, Z. Li, K. R. Fandrick, C. A. Sader, B. McKibben, D. A.Gao, J. Cui, N. C. Gonnella, H. Lee, X. Wei, F. Roschangar, B. Z. Lu, C. H. Senanayake, *Org. Lett.* **2015**, *17*, 5614.
47 R. J. Paxton, R. J. K. Taylor, *Synlett*. **2007**, *4*, 633. H. Kakei, T. Sone, Y. Sohtome, S. Matsunaga, M. Shibasaki, *J. Am. Chem.Soc*. **2007**, *129*, 13410. P. K. Kundu, R. Singh, S. K. Ghosh, *J. Organomet. Chem.* **2009**, *694*, 382. L. Wang, W. Cao, H. Mei, L. Hu, X. Feng, *Adv. Synth. Catal.* **2018**, *360*, 4089.
48 B. Holt, P. A. Lowe, *Tetrahedron Lett*. **1966**, *7*, 683
49 G.-D. Xu, K. L. Huang, Z.-Z. Huang, *Adv. Synth. Catal.* **2019**, *361*, 3318. K. Cheng, L. Chen, L. Jin, J. Zhou, X. Jiang, C. Yu, *J. Chem. Res.* **2019**, *43*, 392.



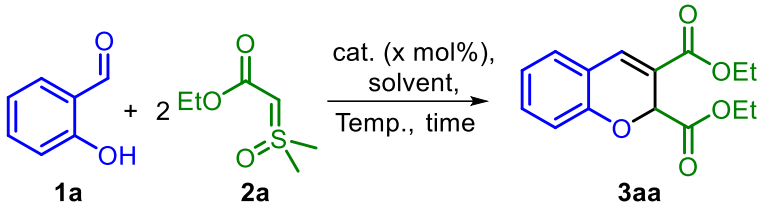

*Scheme 4.2. a) Reaction between dimethylsulfoxonium methylide and salicylaldehydes **1**. b) Chemodivergent reactions between stabilized sulfoxonium ylides **2** and salicylaldehydes **1***

## 4.2 Results and Discussion

### 4.2.1 Optimization of the reaction conditions

We began our investigation by reacting salicylaldehyde **1a** and sulfoxonium ylide **2a** in the absence of any catalyst. However, only starting materials were recovered from the reaction mixture (*Table 4.1*, entry 1). On the contrary, product **3aa** embedding two ester groups and featuring a 2*H*-chromene skeleton was observed in the presence of Lewis or Brønsted acid catalysts. Performing the reaction with $Sc(OTf)_3$ (entry 2) a lower yield was obtained than with diphenyl phosphoric acid (entry 3).

*Table 4.1. Preliminary results*

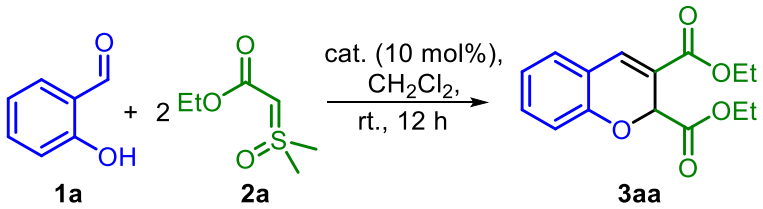



| Entry[a] | Cat. (x mol%) | Solvent | Temp. (time) | Yield[b] (%) |
|---|---|---|---|---|
| **1** | / | $CH_2Cl_2$ | rt (18 h) | <5 |
| **2** | $Sc(OTf)_3$ (10) | THF | rt (18 h) | 32 |
| **3** | $(PhO)_2POOH$ (10) | THF | rt (18 h) | 49 |

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.63 mmol), cat. (X mol%), solvent (0.5 mL), temp., time. [b] Determined after column chromatography on silica gel.

Subsequently, the evaluation of the catalyst nature was carried out and the results are reported in *Table 4.2*. Performing the reaction with Lewis acids, such as $Sc(OTf)_3$, $Zn(OTf)_2$, $Yb(OTf)_3$, and $Hf(OTf)_4$ (entry 2-5) lower values of $^1H$ NMR yields were observed, compared to the Brønsted acid $(PhO)_2P(O)OH$ (entry 1). The strong acidity of the Lewis acids could compromise the stability of the sulfoxonium ylide **2a** producing a decrease in the yield. Indeed using 10 mol% of $Yb(OTf)_3$ as catalyst, a significative decomposition was observed in the reaction mixture with sulfoxonium ylide **2a** present only in traces. For this reason, we decided to proceed with our investigations by using diphenyl phosphoric acid as catalyst.

*Table 4.2. Catalyst screening*

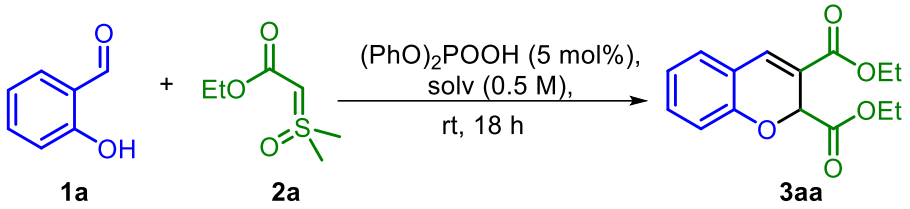



| Entry[a] | Cat. (10 mol%) | $^1H$ NMR Yield[b] (%) |
|---|---|---|
| **1** | $(PhO)_2POOH$ | 52 |
| **2** | $Sc(OTf)_3$ | 46 |
| **3** | $Zn(OTf)_2$ | 30 |
| **4** | $Yb(OTf)_3$ | / |
| **5** | $Hf(OTf)_4$ | 45 |

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.63 mmol), cat. (10 mol%), solvent (0.5 mL), temp., time. [b] Determined with $^1H$ NMR using bibenzyl as internal standard.

Later, different solvents have been tested using diphenylphosphoric acid (5 mol%) as catalyst and the results are shown in *Table 4.3*. Various results were obtained during this screening. For example, solvents such as $Et_2O$, $CH_3CN$, MTBE (entries 3, 5, and 7, respectively) gave product **3aa** with unsatisfactory yields, while solvents such as toluene (entry 1), and chlorinated ones such as DCE (entry 6) significantly improved the yield of the reaction. However, the best results have been obtained using $CH_2Cl_2$ (entry 2) or THF (entry 4) as solvents, which were therefore chosen for further screenings.

*Table 4.3. Solvent Screening*



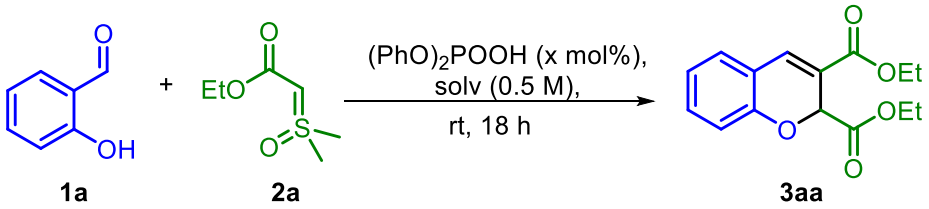

**1a** **2a** **3aa**

| Entry[a] | Solvent [Conc. (M)] | Yield[b] (%) |
|---|---|---|
| 1 | PhMe [0.5] | 30 |
| 2 | $CH_2Cl_2$ [0.5] | 50 |
| 3 | $Et_2O$ [0.5] | 15 |
| 4 | THF [0.5] | 48 |
| 5 | $CH_3CN$ [0.5] | 16 |
| 6 | DCE [0.5] | 45 |
| 7 | MTBE [0.5] | 22 |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.25 mmol, 2.5 equiv.), $(PhO)_2POOH$ (5 mol%), solvent (0.2 mL), rt., 18 h. [b] Determined after column chromatography on silica gel.

We moved then to evaluate the catalyst loading (*Table 4.4*) and, since very similar results were obtained with 5 and 10 mol% (compare entries 1 and 2), we decided to continue the optimisation studies using the lower loading (entry 2).

*Table 4.4. Catalyst loading*



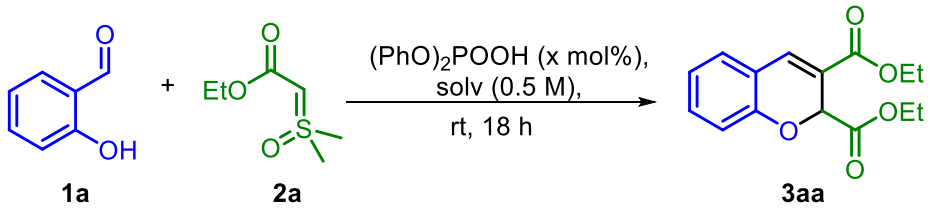

**1a** **2a** **3aa**

| Entry[a] | Cat. (x mol%) | Solvent | Temp. (time) | Yield[b] (%) |
|---|---|---|---|---|
| **1** | $(PhO)_2POOH$ (10) | $CH_2Cl_2$ | rt (18 h) | 52 |
| **2** | $(PhO)_2POOH$ (5) | $CH_2Cl_2$ | rt (18 h) | 50 |
| **3** | $(PhO)_2POOH$ (2.5) | $CH_2Cl_2$ | rt (18 h) | 20 |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.25 mmol, 2.5 equiv.), $(PhO)_2POOH$ (x mol%), solvent (0.2 mL), rt., 18 h. [b] Determined after column chromatography on silica gel.

We subsequently studied the influence of the temperature and the use of additives (*Table 4.5*). By running the reaction in THF as solvent, either at room temperature or at 40 °C (entries 1 and 2), similar results were obtained. Inasmuch as temperature had no relevant influence, we moved back to use $CH_2Cl_2$ as solvent, and considered the possible influence of adventitious water, which was not found to be detrimental to the reaction. Using $MgSO_4$ as additive (entry 3), a decrease of the yield was in fact observed.

*Table 4.5. Temperature and additives*



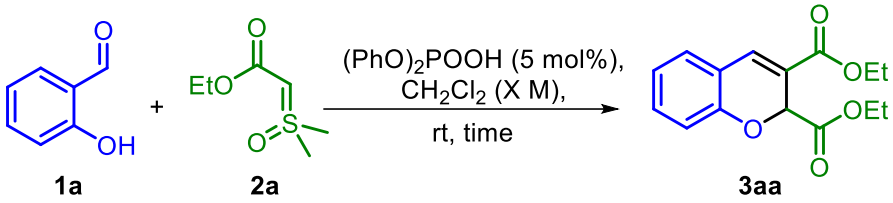

**1a** **2a** **3aa**

| Entry[a] | Cat. (x mol%) | Solvent | Temp. (time) | Yield[b] (%) |
|---|---|---|---|---|
| **1** | $(PhO)_2POOH$ (5) | THF | rt (18 h) | 48 |
| **2** | $(PhO)_2POOH$ (5) | THF | 40 °C (18 h) | 50 |
| **3**[c] | $(PhO)_2POOH$ (5) | $CH_2Cl_2$ | rt (18 h) | 35 |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.25 mmol, 2.5 equiv.), $(PhO)_2POOH$ (x mol%), solvent (0.2 mL), rt., 18 h. [b] Determined after column chromatography on silica gel. [c] Reaction performed with 45 mg of $MgSO_4$

In order to understand which parameters influence the yield of the product **3aa**, the reaction time, the dilution, as well as the equivalents of the ylide **2a**, and its addition in portions, were evaluated (*Table 4.6*). First of all, the reaction conducted for 72 h (entry 2) did not significantly improve the yield of **3aa**, if compared to the same reaction performed for only 48 hours (entry 1). Another parameter taken into consideration was the dilution of the reaction medium. Both a higher and a lower concentration (entries 3 and 4, respectively) compared to the standard (entry 1), considerably decreased the yield. Later on, a different amount of ylide was considered. A stoichiometric amount or a large excess of **2a** gave the desired product in lower yields (compared entries 5 and 6 with entry 1).

*Table 4.6. Other parameters*

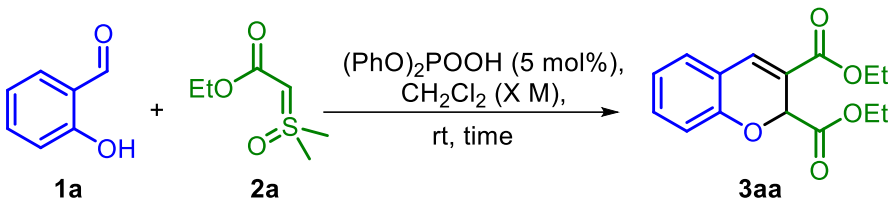



| Entry[a] | Equiv. 2a | Solvent [Conc. (M)] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 2.5 | [0.5] | 48 | 52 |
| 2 | 2.5 | [0.5] | 72 | 55 |
| 3 | 2.5 | [1.0] | 48 | 33 |
| 4 | 2.5 | [0.1] | 48 | 12 |
| 5 | 2 | [0.5] | 48 | 36 |
| 6 | 4 | [0.5] | 48 | 30 |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (X equiv.), $(PhO)_2POOH$ (5 mol%), $CH_2Cl_2$ (0.2 mL), rt., time. [b] Determined after column chromatography on silica gel.

Considering a possible partial degradation of the relatively unstable ylide **2a** under the acidic reaction conditions, as well as an observed slow catalyst deactivation during the reaction, we tested the addition of the sulfoxonium ylide **2a** and/or the catalyst in portions. (*Table 4.7*). Portionwise addition of ylide **2a** improved the yield only slightly (entry 1), while the addition in portions of the catalyst led to a more pronounced improvement (entry 2). Portionwise addition of both catalyst and ylide **2a** was instead unproductive (entry 3). So we have chosen a portionwise addition of the catalyst (entry 2) as the best reaction conditions for this reaction.

*Table 4.7. Addition Mode*

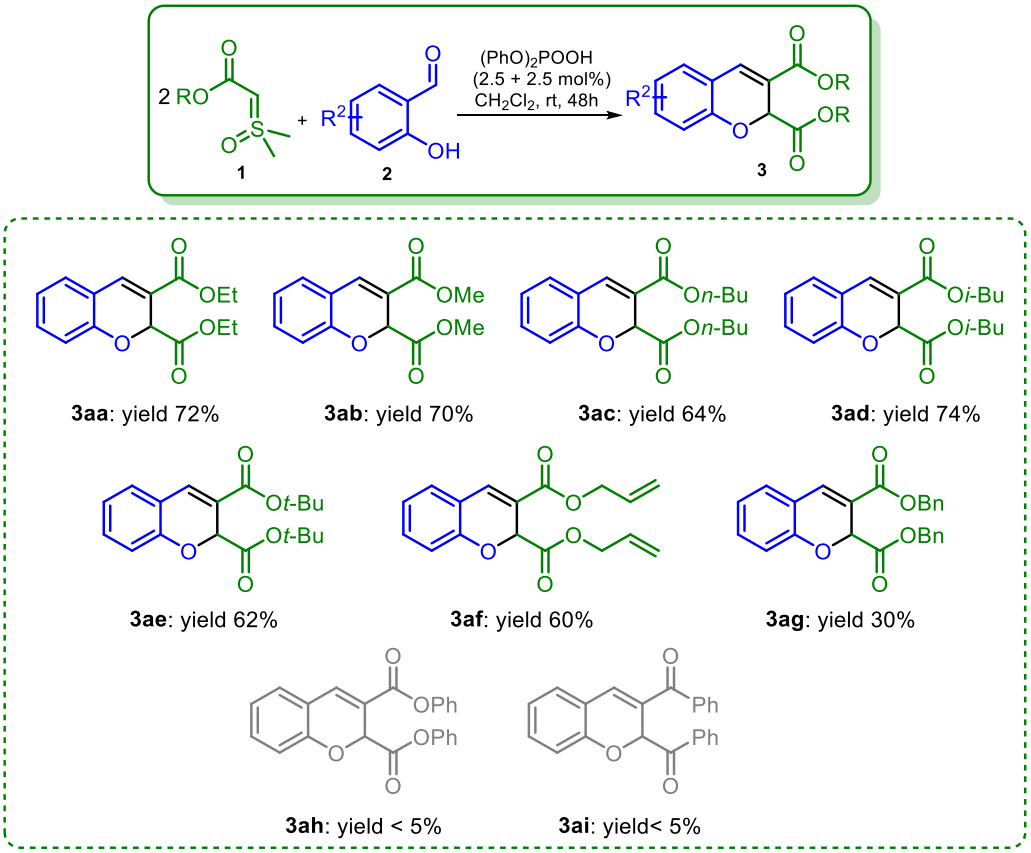



| Entry[a] | Solvent | Temp. (time) | Yield[b] (%) |
|---|---|---|---|
| 1[c] | $CH_2Cl_2$ | rt (48 h) | 65 |
| **2** [d] | **$CH_2Cl_2$** | **rt (48 h)** | **72** |
| 3[e] | $CH_2Cl_2$ | rt (48 h) | 63 |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.25 mmol, 2.5 equiv.), $(PhO)_2POOH$ (2.5 + 2.5 mol%), solvent (0.2 mL), rt., 18 h. [b] Determined after column chromatography on silica gel. [c] 1.5 equiv. of **2a** were added at the reaction start, the other 1.5 equiv. after 8 h of stirring. [d] 2.5 mol% of catalyst was added at the reaction start, the other 2.5 mol% after 8 h of stirring. [e] ] 1.5 equiv. of **2a** and 2.5 mol% of catalyst were added at the reaction start, the other 1.5 equiv. of ylide **2a** and 2.5 mol% of catalyst after 8 h of stirring.

### 4.2.2 Scope of the reaction

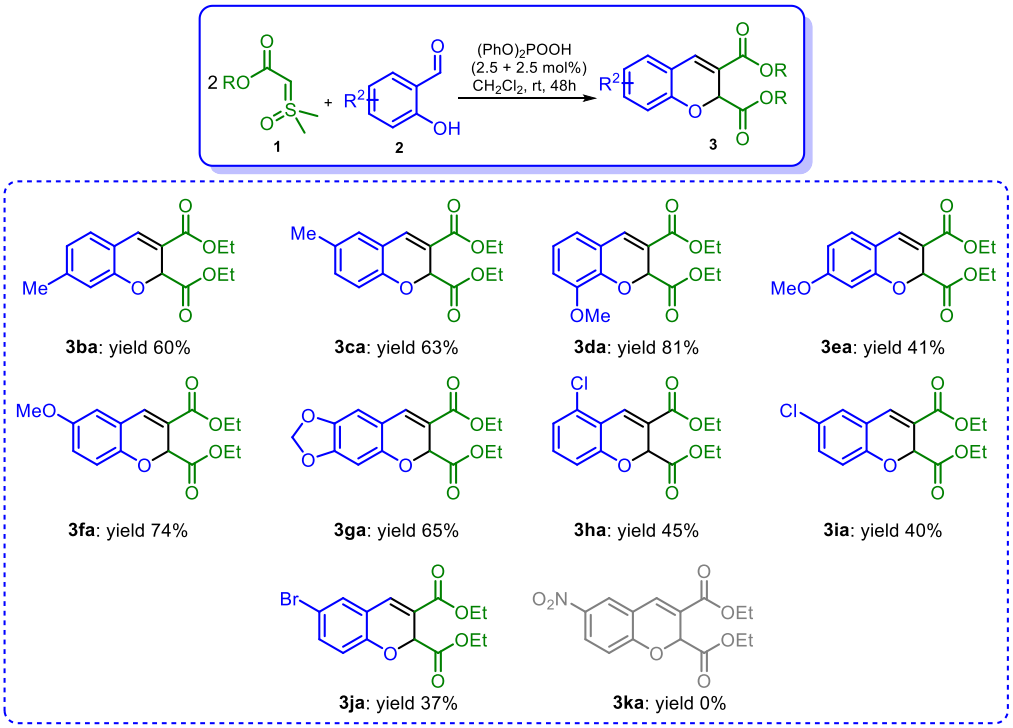
Once identified the best reaction conditions for this reaction we moved to evaluate the generality of the reaction. Regarding sulfoxonium ylides **2** (*Scheme 4.3*), variation of the ester moiety could be smoothly achieved with short-chain substituents like a methyl group (product **3ab**), as well as with longer-chain ones (product **3ac**). Moreover, good results were obtained employing bulkier substituents such as the *iso*-butyl and the *tert*-butyl groups (products **3ad** and **3ae** respectively). The use of an allylic ester did not significantly affect the yield of product **3af**, while benzylic sulfoxonium ylide **2g** gave the corresponding 2*H*-chromene **3ag** in a low 30% yield. Less nucleophilic ylides bearing a phenol ester (**2h**) or a ketone (**2i**) as electron withdrawing groups, were found to be unreactive under these conditions.




*Scheme 4.3. Reaction Scope of sulfoxonium ylides **1***

We then explored the reactivity of sulfoxonium ylide **2a** with differently substituted salicylaldehydes **1b-j** (*Scheme 4.4*). Methyl-substituted salicylaldehydes **1b** and **1c** delivered products **3ba** and **3ca** in comparable, yet somewhat lower, yields compared to parent 2*H*-chromene **3aa**. An electron donating group at the *ortho* (3-MeO) or *para* (5-MeO) position to the hydroxylic group led to slightly increased

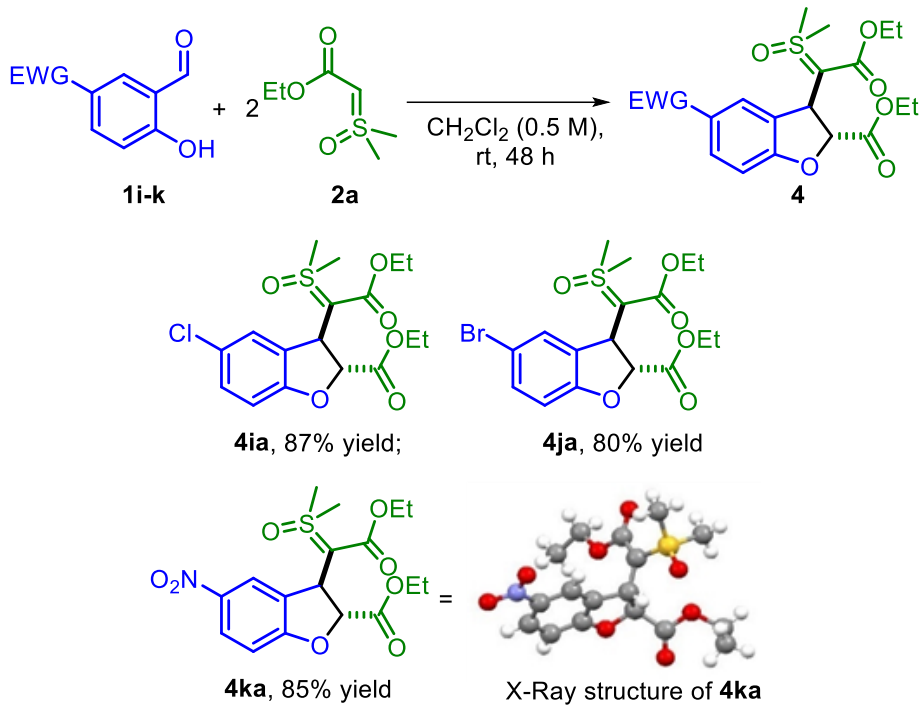
yields for products **3da** and **3fa**. On the contrary, the same methoxy substituent, at position 4, caused a drop in the yield for product **3ea**. When sesamol-derived aldehyde **1g** was employed, product **3ga** was obtained with good results. Conversely, lower yields were generally achieved employing salicylaldehydes having electron-withdrawing substituents on the aromatic ring. A chloro substituent, at the *ortho* (6-Cl) or *meta* (5-Cl) position to the formyl group, led to products **3ha** and **3ia** in moderate yields. When 5-bromosalicylaldehyde **1j** was subjected to the optimized reaction conditions, the yield for chromene **3ja** dropped even further. Finally, 5-nitrosalicylaldehyde **1k** did not afford the desired product **3ka**.




*Scheme 4.4. Reaction Scope of salicylaldehydes 2*

In fact, performing the reaction with 5-nitrosalicylaldehyde **2k** the only product present in the crude mixture of the reaction between **1k** and **2a** was not the expected chromene **3ka**, but a different compound **4ka** still embedding two ester units but featuring a 2,3-dihydrobenzofuran core and a peculiar exocyclic disubstituted sulfoxonium ylide. (*Scheme 4.5*) The structure and stereochemistry of **4ka** were established by single-crystal X-ray analysis. Additional investigation indicated that formation of this product does not require the presence of the catalyst. Furthermore, salicylaldehydes **1i** and **1j** could also undergo the same type of uncatalyzed reaction, leading to products **4ia** and **4ja** in 80-87% yields. The presence of **4ia** and **4ja** in the

crude mixtures of the catalyzed reactions towards **3ia** and **3ja** (*Scheme 4.4*) justifies, at least in part, the low yields obtained for these chromenes.

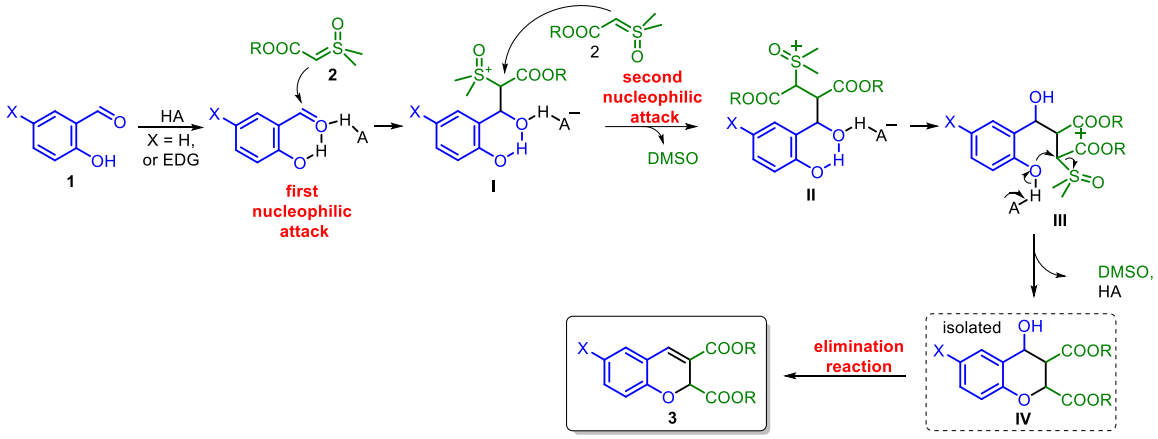



*Scheme 4.5. Uncatalyzed reaction between ylide **2a** and electron-poor salicylaldehydes **1i-k**, and X-ray structure of product **4ka**.*

### 4.2.3 Mechanism investigation for product 3

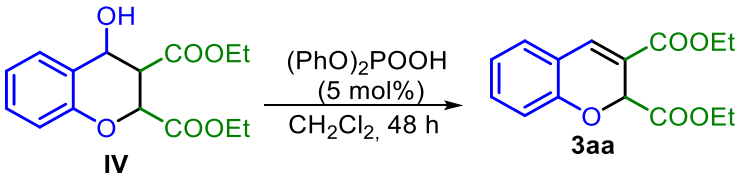
First of all, we tried to devise a mechanism justifying the formation of products **3**. On the basis of the control experiments reported in the following paragraphs, a plausible reaction pathway is represented in *Scheme 4.6*. First of all, the catalyst coordinates the salicylaldehyde **1** promoting the first nucleophilic attack by the ylide **2**, generating intermediate **I**. At this point, a second nucleophilic attack with subsequent release of DMSO can occur,[50] forming intermediate **II** and then intermediate **III**. A ring-closing reaction produces then intermediate **IV**, which has been observed and isolated, with concomitant regeneration of the catalyst and displacement of DMSO.

50 a) M. L. Jamieson, N. Z. Brant, M. A. Brimble, D. P. Furkert, *Synthesis* **2017**, *49*, 3952. b) M. Liu, C.-F. Liu, J. Zhang, Y.-J. Xu, L. Dong, *Org. Chem. Front*. **2019**, *6*, 664. c) I. K. Mangion, I. K. Nwamba, M. Shevlin, M. A. Huffman, *Org. Lett.* **2009**, *11*, 3566-3569. d) J. Vaitla, A. Bayer, K. H. Hopmann, *Angew. Chem. Int. Ed.* **2017**, *56*, 4277-4281. e) Vaitla, A. Bayer, K. H. Hopmann, *Angew. Chem. Int. Ed.* **2017**, *56*, 4277. f) A. I. O. Suarez, M. P. del Río, K. Remerie, J. N. H. Reek, B. de Bruin, *ACS Catal.* **2012**, *2*, 2046. g) Y. Tian, Z. Zhang, T. Wang, *Eur. J. Org. Chem.* **2021**, 1592.




*Scheme 4.6. Proposed reaction pathway for products 3*

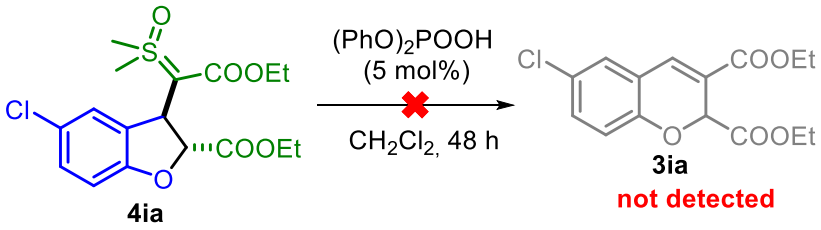
The last step of the mechanism is an elimination reaction with subsequent formation of the 2*H*-chromene **3**. The elimination step of the reaction was verified thanks to the control experiment reported below (*Scheme 4.7*). Indeed, subjecting the isolated diethyl 4-hydroxychromane-2,3-dicarboxylate **IV** under the standard reaction conditions, only product **3aa** was detected in the reaction mixture after 48 h.




*Scheme 4.7. Control experiment demonstrating possible water elimination from **IV** to **3aa** under the reaction conditions.*

### 4.2.3.1 Excluded reaction pathways

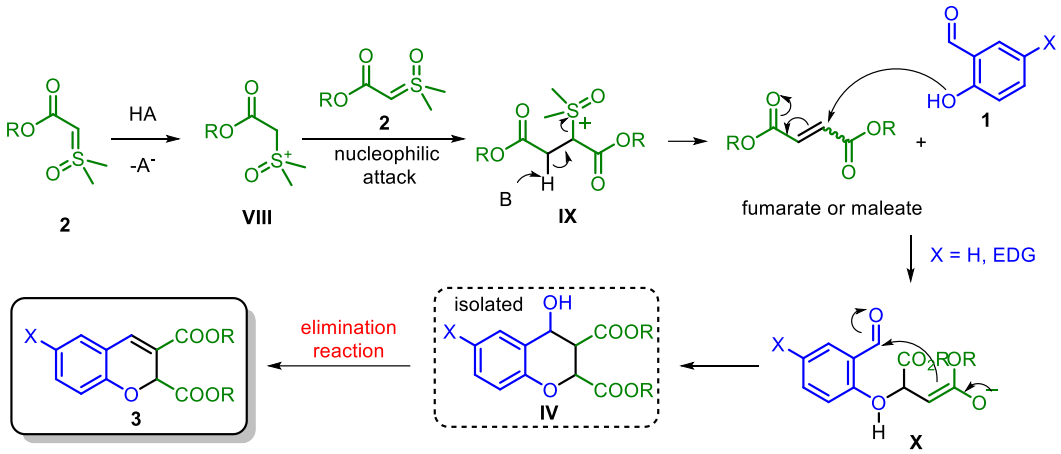
In order to understand if ylides **4** were intermediates in the reaction pathway towards the formation of **3**, we treated isolated product **4ia** under the standard reaction conditions (*Scheme 4.8*). This experiment shows that **4ia** does not convert into product **3ia**. Therefore, ylides **4** are not intermediates in the reaction pathway which generate **3**, but products deriving from a different route.




*Scheme 4.8. Control experiment excluding ylides **4** in the reaction pathway leading to **3**.*

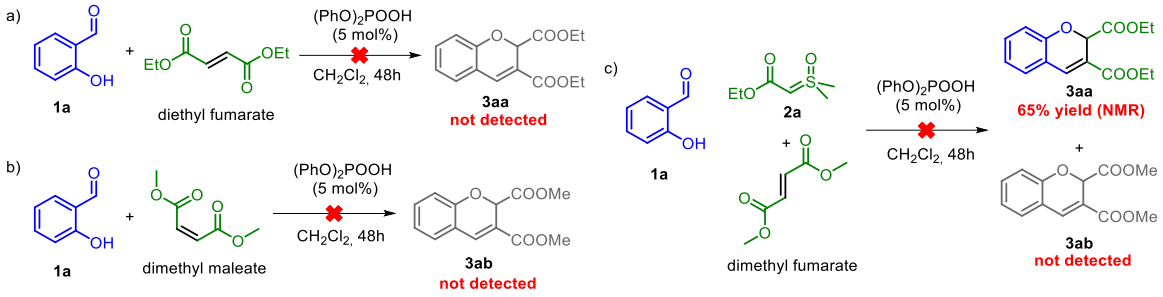
On the basis of numerous conducted control experiments, other possible reaction pathways could be excluded.

1. Dimerization of sulfoxonium ylide **2**: first of all, a dimerization of sulfoxonium ylide **2** can occur (*Scheme 4.9*). The acidic condition of the reaction can promote the protonation of sulfoxonium ylide **2** generating the electrophilic intermediate salt **VIII**, which can suffer a nucleophilic attack by a second equivalent of sulfoxonium ylide **2** generating intermediate **IX**. At this point, the conjugated base of the catalyst, or the sulfoxonium ylide itself, can encourage an elimination reaction generating the diethyl fumarate or maleate, depending on the configuration of the double bond. Now, a Michael addition can occur, generating intermediate **X**, which evolves into **IV** and then into **3**.



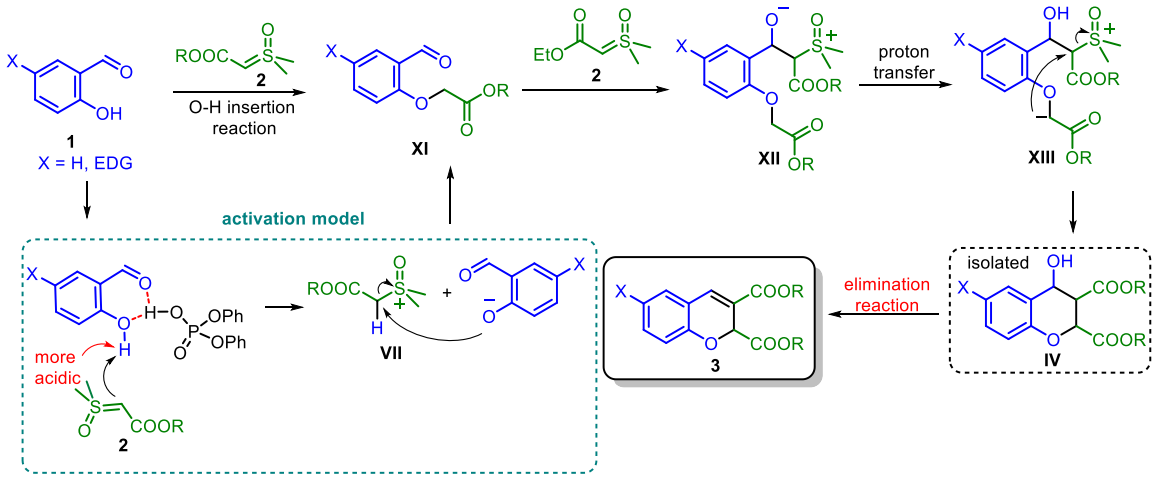

*Scheme 4.9. Possible pathway involving dimerization of sulfoxonium ylide **2***

This reaction pathway was excluded due to the following reasons. $^{1}$H NMR analysis allows us to verify that no protonation of sulfoxonium ylide **2** occurs. Indeed, performing $^{1}$H NMR experiments of sulfoxonium ylide **2a** with both 5 mol% and an equimolar amount of catalyst in $CDCl_3$, no variation of the ylide signals in terms of the chemical shift was observed. More importantly, no formation of fumarate or maleate was observed by leaving these NMR mixtures at room temperature for prolonged times. Moreover, performing the reaction under standard conditions but using diethyl fumarate and dimethyl maleate instead of sulfoxonium ylide **2a** (*Scheme 4.10*, equation a and b), only the starting materials were detected in the crude mixture. Finally, we also performed a cross experiment using both sulfoxonium ylide **2a** and dimethyl fumarate (equation c); the only product detected in the crude mixture was **3aa** with not even traces of product **3ab**.




*Scheme 4.10. Control experiments excluding fumarates or maleates from the reaction pathway*

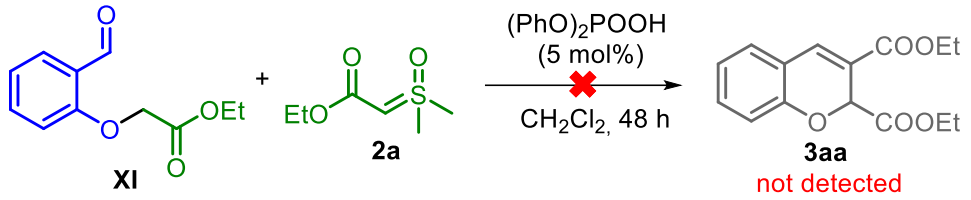
2. O-H insertion reaction: another possible pathway concerns the alkylation of the hydroxylic moiety of salicylaldehyde **1** (*Scheme 4.11*). In analogy with the "Brønsted acid-assisted Brønsted acid" concept,[51] in our case, the coordination of the diphenyl phosphoric acid to the salicylaldehyde could make the hydroxylic proton acidic enough to protonate the sulfoxonium ylide **2** generating intermediate **VII** and the corresponding phenolate, capable to displace DMSO forming the alkylated intermediate **XI**, which could then evolve to the ultimate product via the pathway shown or alternative ones.




*Scheme 4.11. Possible pathway involving insertion of the ylide 2 into the O-H bond.*

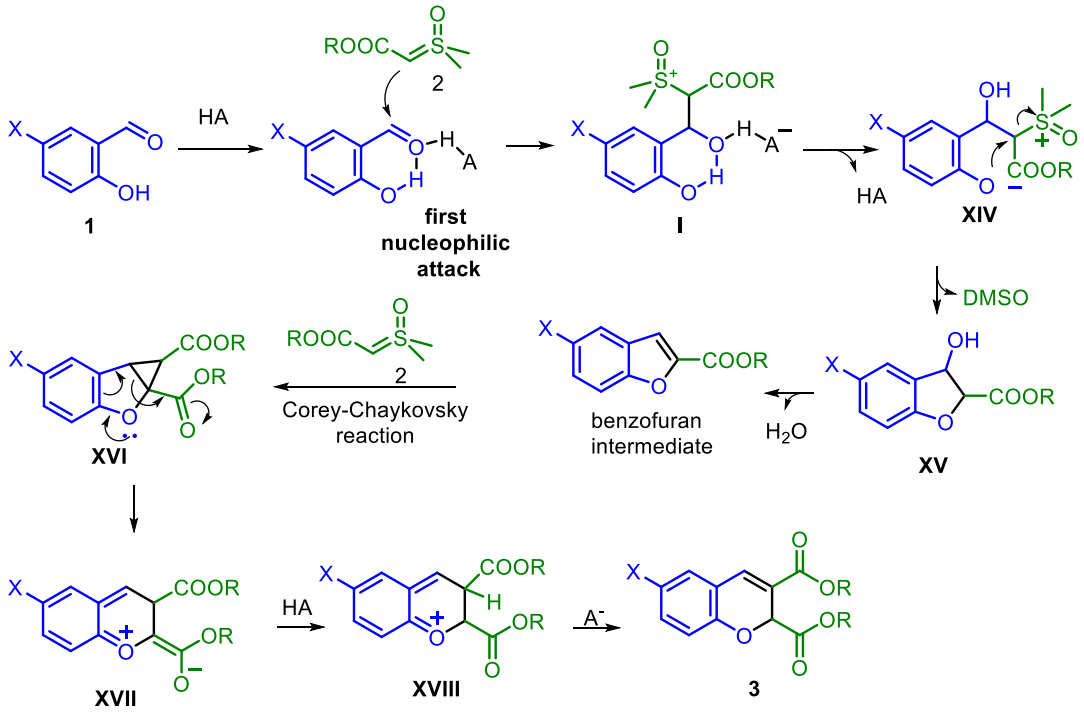
This pathway was excluded by the control experiment reported in *Scheme 4.12*. Indeed, running the reaction with a beforehand prepared (by alkylation of salicylaldehyde with bromoacetate) putative intermediate **XI** no traces of product **3aa** were observed, only the starting materials being present in the reaction mixture.

51 a) H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924-1942; b) M. R. Monaco, D. Fazzi, N. Tsuji, M. Leutzsch, S. Liao, W. Thiel, B. List, *J. Am. Chem. Soc.* **2016**, *138*, 14740-14749.




*Scheme 4.12. Control experiment excluding O-H insertion pathway.*

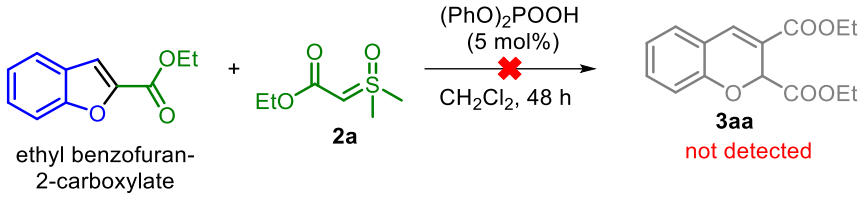
3. Benzofuran formation: another possible reaction pathway involves a benzofuran intermediate. Benzofurans are the ultimate products in the reaction between the unstabilized sulfoxonium ylide and salicylaldehydes.[52] The formation of this putative intermediate might involve a ring-closure step (**XIV** → **XV**) followed by dehydration (*Scheme 4.13*). At this point, a Corey-Chaykovsky cyclopropanation can occur forming intermediate **XVI** which evolves into oxonium ylide **XVII** through a rearrangement. Subsequent protonation and deprotonation steps can deliver product **3**.




*Scheme 4.13. Possible pathway involving a benzofuran intermediate.*

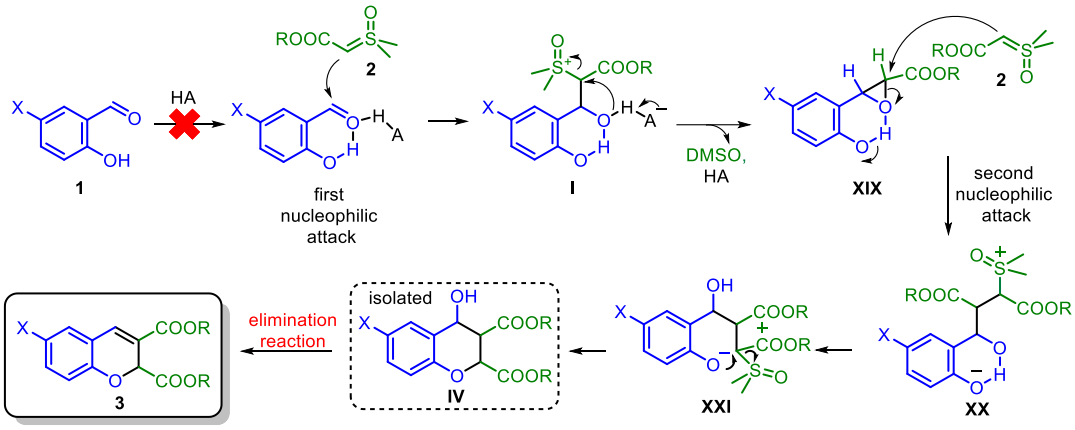
52 B. Holt, P. A. Lowe, *Tetrahedron Lett*. **1966**, *7*, 683-686.

Also this reaction pathway could be excluded. Indeed, performing the reaction with the ethyl benzofuran-2-carboxylate instead of salicylaldehyde **1a** (*Scheme 4.14*), only starting materials were present in the reaction mixture.



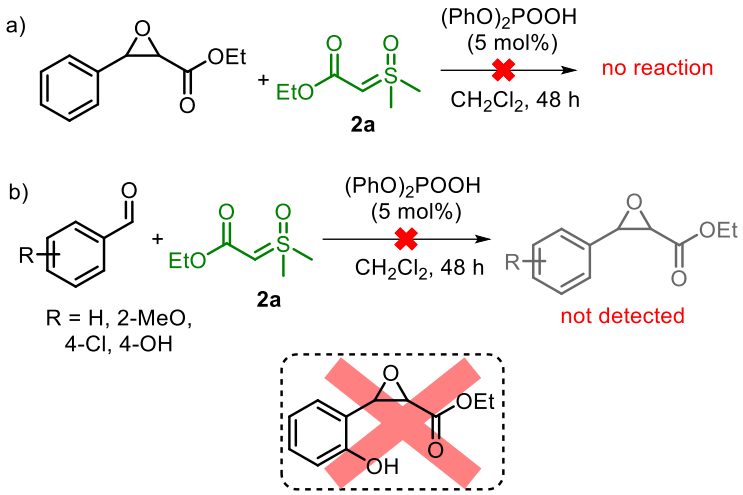

*Scheme 4.14. Control experiment excluding benzofurans from the reaction pathway.*

4. Formation of an oxirane motif: a variation in the plausible pathway involves the formation of epoxide **XIX** as intermediate via a Corey-Chaykovsky epoxidation reaction (*Scheme 4.15*). A nucleophilic attack by an ylide can open the oxirane **XIX** generating intermediate **XX** and then **XXI**, which via ring-closure evolve to **IV** and then to product **3**.




*Scheme 4.15. Possible pathway involving the formation of an oxirane.*

Unfortunately, we were unable to prepare epoxides derived from salicylaldehydes, like **XIX**. However, a weak evidence of its exclusion from the pathway was collected by noticing that: i) a cinnamate epoxide does not give any reaction when treated with ylide **2a**, and that ii) benzaldehydes showed either decomposition or no reactivity with the same ylide; in any case epoxide formation was observed (*Scheme 4.16*).

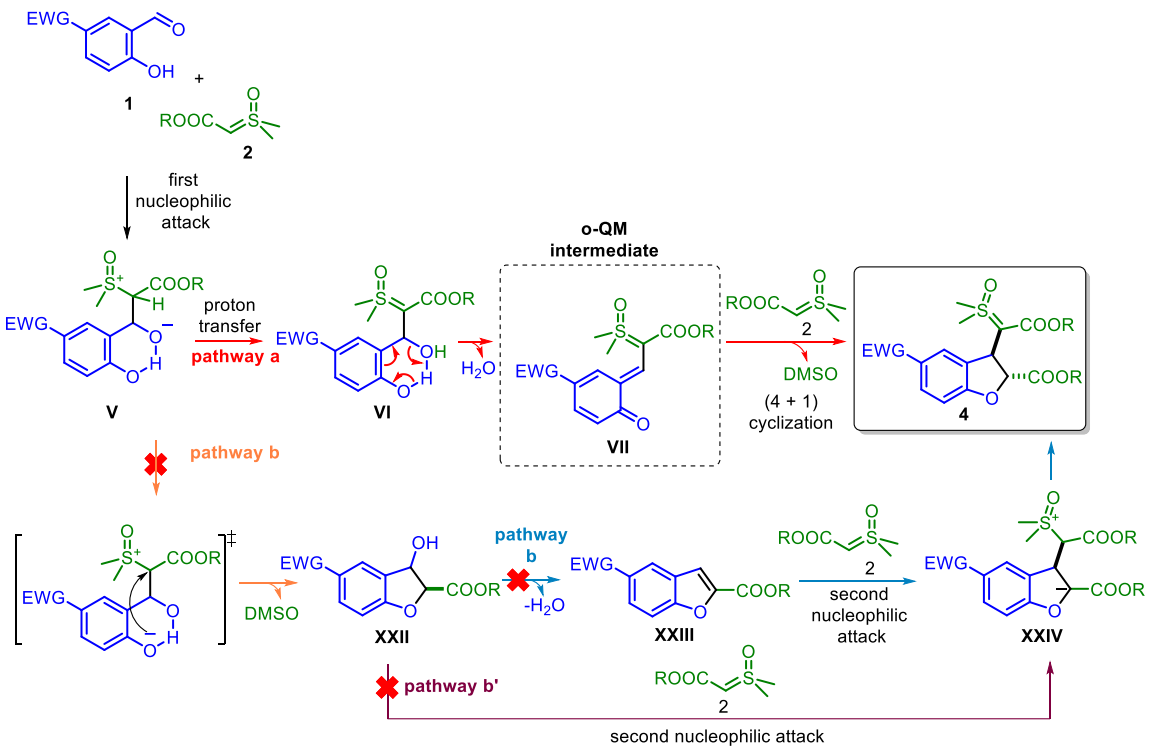



*Scheme 4.16. Control experiments suggesting that epoxides are not reaction intermediates.*

### 4.2.4 Proposed reaction pathway for product 4

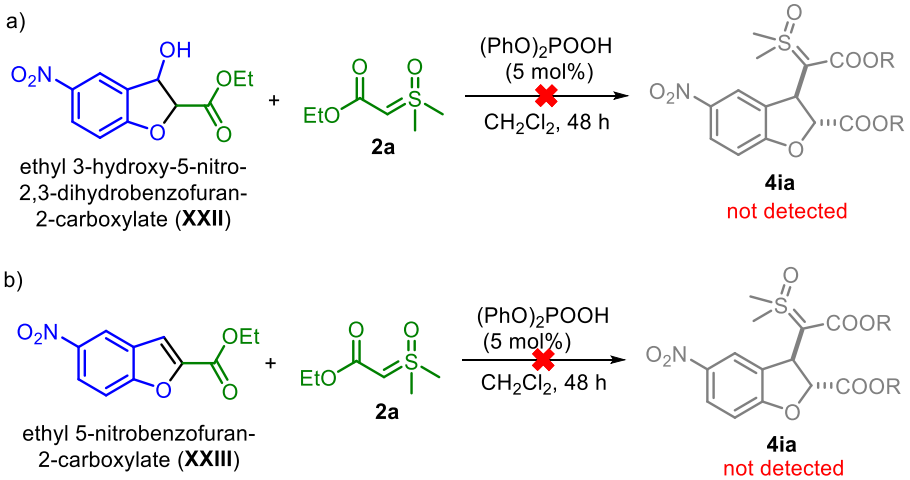
Regarding the formation of products **4**, mainly three different reaction pathways are conceivable (*Scheme 4.17*). First of all, a nucleophilic attack by ylide **2** to the formylic carbon can occur, forming intermediate **V**. Following *pathway a*, intermediate **V** evolves into intermediate **VI** after a proton transfer. At this point, the loss of one water molecule generates an *ortho*-quinone methide (*o*-QM) intermediate[53] **VII** which undergoes a formal (4+1) cyclization reaction forming directly product **4**. An additional possible pathway, *pathway b*, can occur if intermediate **V** evolves into **XXII** via ring closure (similarly to the reaction with the unstabilised ylide). This intermediate **XXII** generates via dehydration the electron poor benzofuran derivative **XXIII**, which suffers the nucleophilic attack of a second molecule of ylide **2** forming **XXIV**. At this point, a proton-transfer process delivers product **4**. In a related alternative *pathway b'*, intermediate **XXII** undergoes directly a substitution reaction, possibly assisted by the phenolic oxygen, forming **XXIV** and then product **4**.

53 a) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu, T. R. R. Pettus, *Acc. Chem. Res.* **2014**, *47*, 3655. b) L. Caruana, M. Fochi, L. Bernardi, *Molecules* **2015**, *20*, 11733. c) M. T. Richers, M. Breugst, A. Yu. Platonova, A. Ullrich, A. Dieckmann, K. N. Houk, D. Seidel, *J. Am. Chem. Soc.* **2014**, *136*, 6123. d) L. Xu, F. Liu, L.-W. Xu, Z. Gao, Y.-M. Zhao, *Org. Lett.* **2016**, *18*, 3698. e) M. Suleman, Z. Li, P. Lu, Y. Wang, *Eur. J. Org. Chem*. **2019**, 4447.




*Scheme 4.17. Possible reaction pathways a, b and b' for the formation of products* ***4***

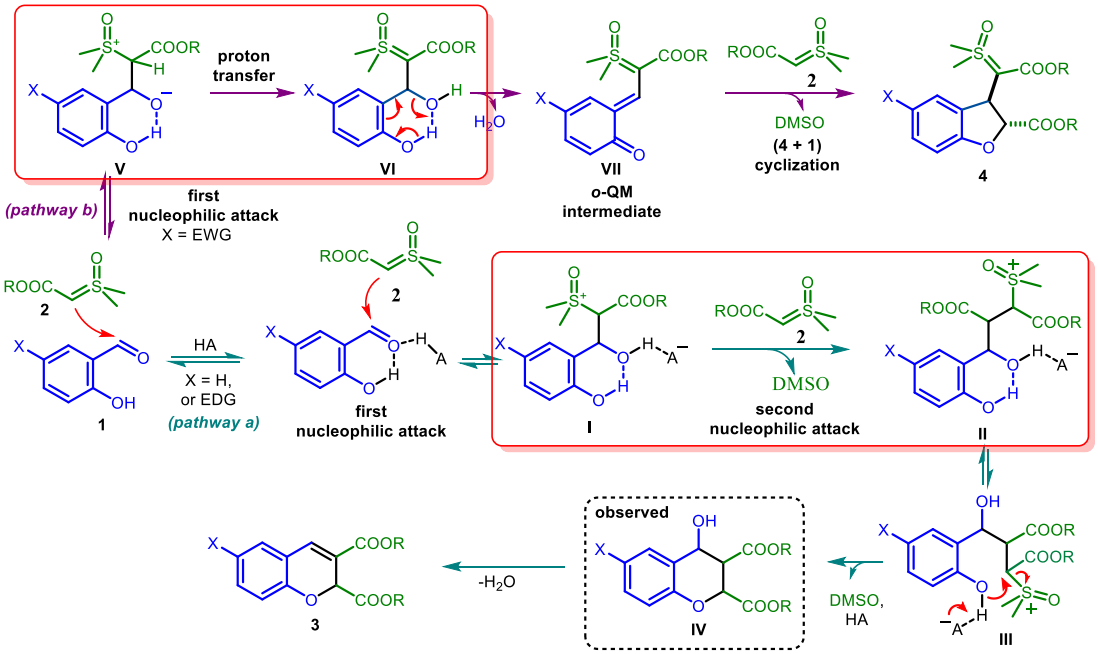
Pathways b and b' were safely excluded, thanks to the control experiments reported in *Scheme 4.18*. Running the reaction with ethyl 3-hydroxy-5-nitro-2,3-dihydrobenzofuran-2-carboxylate (**XXII**) and ethyl 5-nitrobenzofuran-2-carboxylate (**XXIII**) under the standard reaction condition, product **4ia** was not detected in the reaction mixture, only starting materials were present. Therefore, it can be concluded that pathway a is the most likely for this reaction.




*Scheme 4.18. Control experiments excluding pathways b and b'.*

### 4.2.5 Additional experiments on the modulation of the chemoselectivity by using sulfonium ylides vs sulfoxonium ylides

A comparison between the plausible reaction pathways leading to 2*H*-chromenes **3** and dihydrobenzofurans **4** (*Scheme 4.19*) highlights that the factors affecting the chemoselectivity of the reaction (i.e. formation of **3** *vs* **4**) are the presence of the catalytic species, as well as the competition between the nucleophilic addition of ylide to catalyst bound intermediate **I** *vs* the proton transfer from the sulfoxonium carbon to the benzylic, negatively charged, oxygen in a catalyst-free intermediate **V** closely related to **I**. Thus, it can be surmised that the chemoselectivity of the reaction can be at least in part controlled by the amount of catalyst employed, and by modulating the nucleophilic properties of the ylides, as well as the acidity of the parent salt.

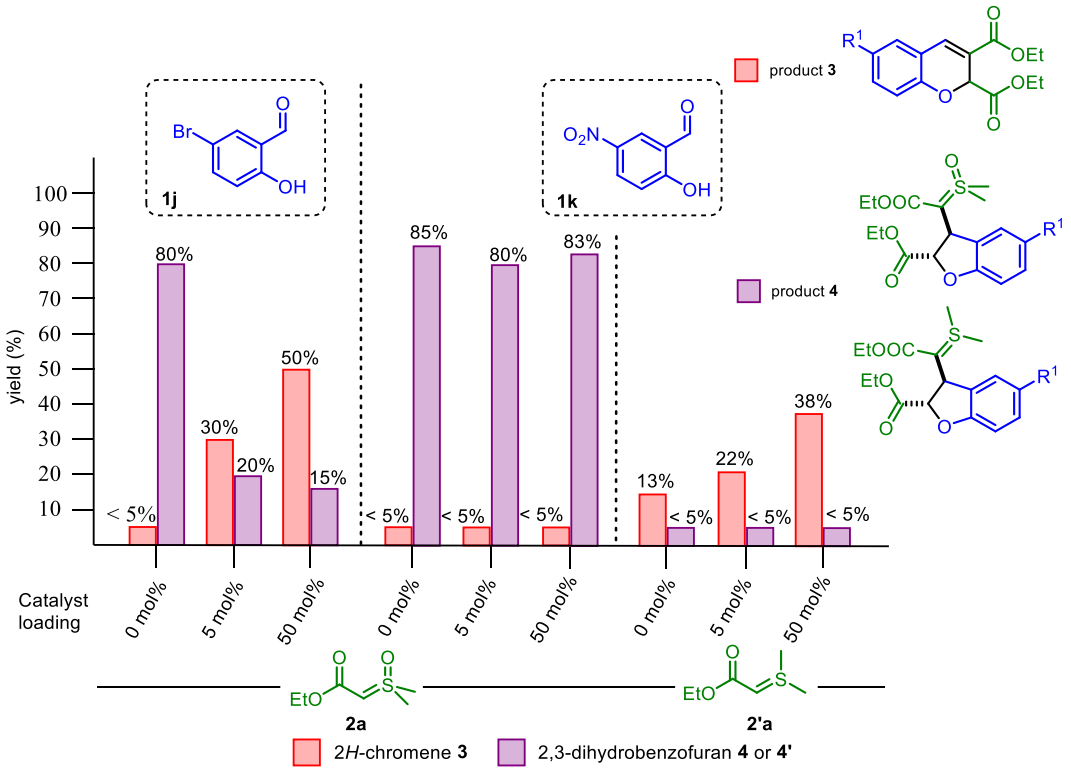



*Scheme 4.19. Possible reaction pathways accounting for the formation of products **3** and **4**.*

It is known that sulfonium ylides are more nucleophilic than sulfoxonium ones. Furthermore, sulfonium salts are less acidic than sulfoxonium ones. Thus, in comparison with sulfoxonium ylides, sulfonium ones should have a greater tendency to enter the pathway leading to **3**, which involves a second nucleophilic addition, compared to the pathway leading to compounds **4'**, which requires a proton-transfer from a sulfonium C-H (vs sulfoxonium C-H, **V** → **VI**).

To validate this hypothesis, and consequently the proposed pathways, two different sets of experiments with increasing amounts of catalyst and using aldehydes **1j** and **1k** were performed and the results are reported in *Scheme 4.20*. Performing the reaction between aldehyde **1j** and sulfoxonium ylide **2a**, without catalyst or with a large amount of it

(50 mol%), an inversion of the selectivity in favor of **4ja** or **3ja**, respectively, was in fact observed (*Scheme 4.20*, left). Besides, the yield of **3ja** increased slightly by moving from the standard 5 mol% to the high 50 mol% catalyst loading. On the contrary, the more acidic/reactive salicylaldehyde **1k** led to the exclusive formation of product **4ka**, irrespective of the amount of catalyst employed (*Scheme 4.20*, middle). Thus, to reverse the selectivity of the reaction with **1k**, we considered the use of an ylide species more nucleophilic than sulfoxonium ylide **2a**, such as the corresponding sulfonium derivative **2'a**. In fact, according to *Scheme 4.19*, a more nucleophilic sulfonium ylide may favor a second nucleophilic attack to a catalyst-bound intermediate **I'**. Furthermore, the less acidic nature of sulfonium *vs* sulfoxonium salts could hinder the proton-transfer step in intermediate **V'**. Both factors should combine towards channeling the reaction through the pathway leading to 2*H*-chromene **3ka**. Indeed, performing the reaction between aldehyde **1k** and sulfonium ylide **2'a**, we were delighted to observe that only product **3ka** was present in the reaction mixture, with no traces of the corresponding 2,3-dihydrobenzofuran derivative **4'ka** (Figure 1, right). The yield of **3ka** could be even increased to a moderate level, by using a larger amount of catalyst. In contrast with sulfoxonium ylides, which do not form products **3** in the absence of catalyst, sulfonium ylide **2'a** could deliver small amounts of **3ka** even without catalyst being present. On the other hand, the reaction of ylide **2'a** with the electron neutral neutral salicylaldehyde **1a** was found to give the product **3aa** in low yield (17%), possibly due to the poor stability of this ylide under the reaction conditions.




*Scheme 4.20. Catalyst- and ylide- controlled chemoselectivity switch.*

## 4.3 Conclusions

In conclusion, we have optimized a chemodivergent reaction between salicylaldehydes **1** and stabilized sulfoxonium ylides **2**, leading to 2*H*-chromenes **3** or *trans*-2,3 dihydrobenzofurans **4** embedding a disubstituted sulfoxonium ylide moiety. The chemoselectivity of the reaction depends on a combination of catalyst activation and substitution pattern on the salicylaldehyde aromatic ring. In more detail, the use of a Brønsted acid catalyst steers the reaction towards the formation of 2*H*-chromene structures **3**, while electron-withdrawing groups on the aldehyde allow the reactions to proceed without catalyst, leading to the 2,3-dihydrobenzofuran counterparts **4**. Two competing reaction pathways accounting for the formation of these structures were proposed. In these pathways, the chemoselectivity derives from a competition between a proton-transfer step, favoured in the absence of catalyst and leading to 2,3-dihydrobenzofurans **4**, *vs* a nucleophilic addition of a second ylide to a reaction intermediate, which ultimately delivers 2*H*-chromenes **3**. These hypotheses were validated by reversing the chemoselectivity of the reaction, at least in some cases, through the modulation of the catalyst loading and the nucleophilicity of the sulfur ylide. In general terms, the

results herein reported introduce a new entry in the multifarious, and sometimes surprising, reactivity of sulfoxonium ylides with polyfunctional substrates. Besides, the capability of a catalyst to steer the reaction towards the formation of 2*H*-chromenes **3**, *vs* benzofurans **4** obtained without catalyst, highlights the competency of catalytic species in outcompeting innate reaction pathways and reactivities. [54] (*Figure 4.1*)

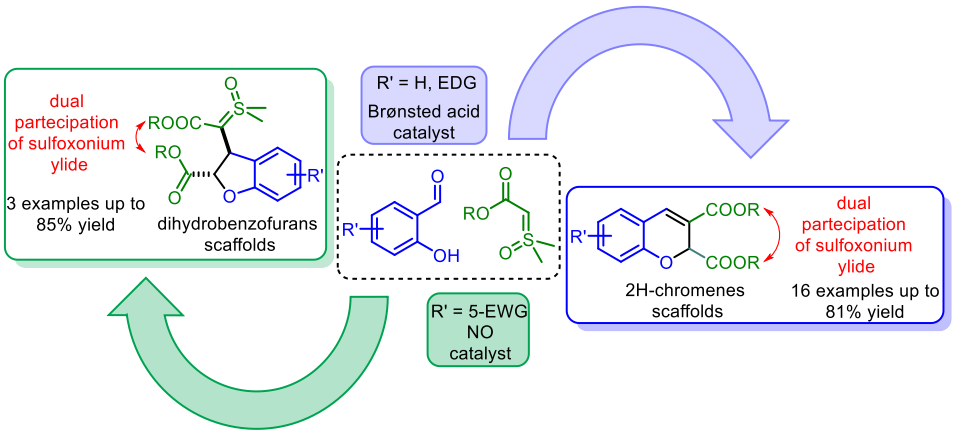



*Figure 4.1. Summary of the project*

54 J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 10954.

## 4.4 Experimental section

### General methods and materials

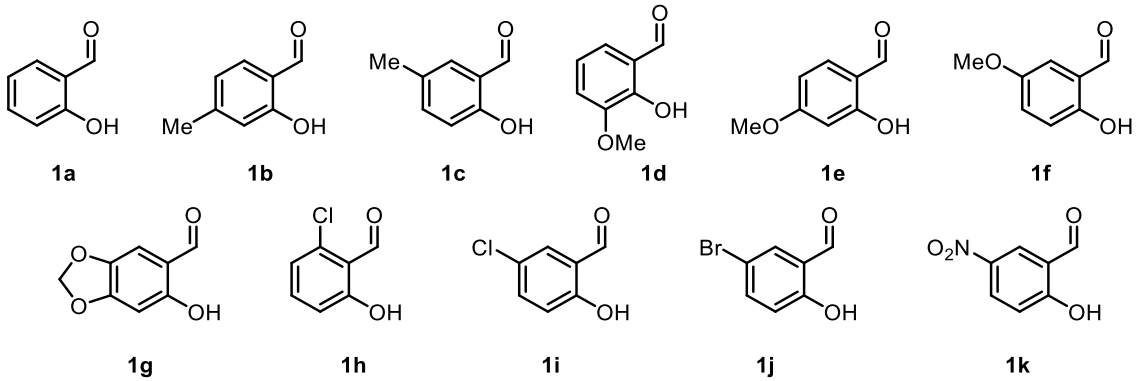
**General Methods**. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Inova 300 or Mercury 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvents signals[55] for $^{1}H$ and $^{13}C$ NMR. Signal patterns are indicated as follows: bs, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in Hertz (Hz). $^{13}C$ NMR were acquired with $^{1}H$ broad-band decoupled mode. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionization techniques or on a FOCUS/DSQ using electron impact (EI) ionization techniques (relative intensities are given in brackets). High Resolution Mass Spectra (HRMS) were recorded on a Waters Xevo Q-TOF spectrometer.

**Materials**. Analytical grade solvents and commercially available reagents were used as received, unless otherwise noted.

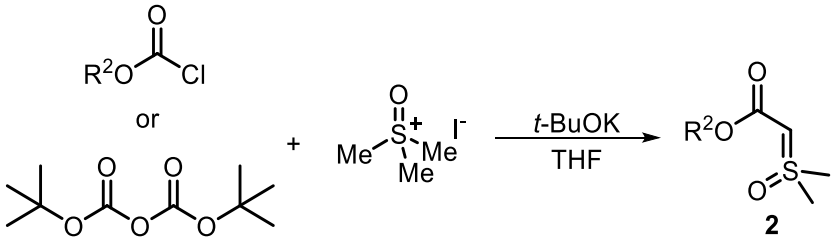
### Preparation of starting materials

Salicylaldehydes **1**

Salicylaldehydes **1a**-**f** and **1h**-**k**, reported below, are commercially available compounds. Aldehyde **1g** was prepared according to literature procedure.[56]




Sulfoxonium ylides **2**

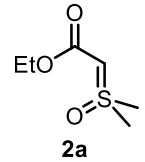



To a stirred suspension of *t*-BuOK (10 mmol, 4 equiv) in anhydrous THF (12 mL), trimethylsulfoxonium iodide (7.5 mmol, 3 equiv.) was added. The resulting suspension was refluxed for 1 h. Then, the reaction mixture was cooled to 0 °C and a solution of 2.5 mmol (1 equiv.) of the opportune chloroformate (or di-*tert*-butyl dicarbonate) in 2 mL of THF was added dropwise. After 1 h, the suspension was filtered over a short plug of Celite®. The organic phase

55 H. E. Gottlieb, V. Kottlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.
56 B. Zhang, C. Lv, W. Li, Z. Cui, D. Chen, F. Cao, F. Miao, L. Zhou, *Chem. Pharm. Bull.* **2015**, *63*, 255.

was evaporated under reduced pressure, and the crude was purified by column chromatography on silica gel ($CH_2Cl_2$:MeOH = 95:5).

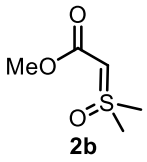
**Ethyl 2-(dimethyl(oxo)-λ$^6$-sulfaneylidene)acetate (2a)**



**2a**

Following the model procedure with ethyl chloroformate, compound **2a** was obtained in 98% yield, as a yellow oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 4.09 (q, J = 7.1 Hz, 2H), 3.93 (s, 1H), 3.38 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H).

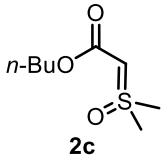
**Methyl 2-(dimethyl(oxo)-λ$^6$-sulfaneylidene)acetate (2b)**



**2b**

Following the model procedure with methyl chloroformate, compound **2b** was obtained in 71% yield, as a white solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 3.93 (s, 1H), 3.62 (s, 3H), 3.38 (s, 6H).

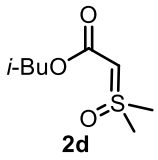
**Butyl 2-(dimethyl(oxo)-λ$^6$-sulfaneylidene)acetate (2c)**



**2c**

Following the model procedure with *n*-butyl chloroformate, compound **2c** was obtained in 67% yield, as a colourless oil. **$^1$H NMR** (300 MHz, DMSO-$d_6$) δ = 4.15 (s, 1H), 3.98 – 3.77 (m, 2H), 3.40 (s, 6H), 1.57 – 1.40 (m, 2H), 1.40 – 1.19 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

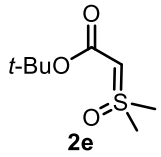
***Iso*-butyl 2-(dimethyl(oxo)-λ$^6$-sulfaneylidene)acetate (2d)**



**2d**

Following the model procedure with *i*-butyl chloroformate, compound **2d** was obtained in 88% yield, as a white solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 3.94 (s, 1H), 3.81 (d, *J* = 6.3 Hz, 2H), 3.38 (s, 6H), 1.93-1.88 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 6H).

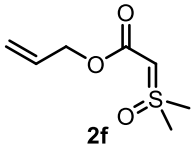
***Tert*-butyl 2-(dimethyl(oxo)-λ$^6$-sulfaneylidene)acetate (2e)**



**2e**

Following the model procedure with di-*tert*-butyl dicarbonate, compound **2e** was obtained in 75% yield, as a white solid. **$^1$H NMR** (300 MHz, DMSO-$d_6$) δ = 3.99 (s, 1H), 3.36 (s, 6H), 1.36 (s, 9H).

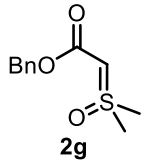
**Allyl 2-(dimethyl(oxo)-λ$^6$-sulfaneylidene)acetate (2f)**



**2f**

Following the model procedure with allyl chloroformate, compound **2f** was obtained in 45% yield, as a colourless oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.03-5.83 (m, 1H), 5.39-5.25 (m, 1H), 5.13-5.03 (m, 1H), 4.55 (d, *J* = 5.6 Hz, 2H), 3.97 (s, 1H), 3.38 (s, 6H).

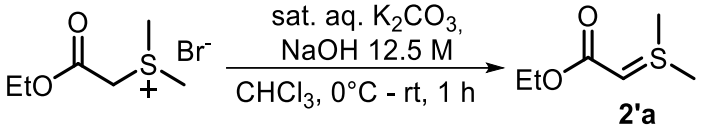
**Benzyl 2-(dimethyl(oxo)-λ$^6$-sulfaneylidene)acetate (2g)**



**2g**

Following the model procedure with benzyl chloroformate, compound **2g** was obtained in 43% yield, as a yellow oil. **$^1$H NMR** (300 MHz, DMSO-$d_6$) δ = 7.44 – 7.12 (m, 5H), 4.96 (s, 2H), 4.23 (s, 1H), 3.43 (s, 6H).

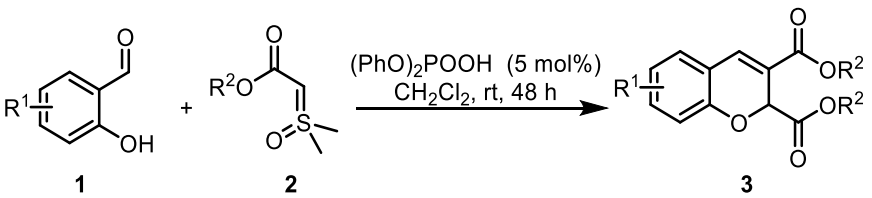
## Synthesis of sulfonium ylide 2'a



**2'a**

A saturated aqueous solution of $K_2CO_3$ (3.75 mL) and an aqueous solution of NaOH (800 µL, 12.5 M) were added to a solution of (2-ethoxy-2-oxoethyl)dimethylsulfonium bromide (7.5 mmol, 1.1 g) in $CHCl_3$ (7.5 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 10 minutes. After that, the reaction mixture was allowed to stir at room temperature for 1 h. The crude mixture was then filtered through a pad of Celite ® and washed with $CH_2Cl_2$. The combined organic phases were then concentrated in vacuo in order to obtain the crude sulfonium ylide **2'a** used in the next step without further purification. **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 4.06 (q, J = 7.1 Hz, 2H), 2.93 (s, 1H), 2.76 (s, 6H), 1.23 (t, J = 7.1 Hz, 3H).

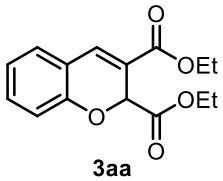
## General Procedure for the synthesis of products 3



**1** **2** **3**

In a small vial equipped with a magnetic stirring bar, salicylaldehyde **1** (1.0 equiv., 0.25 mmol) sulfoxonium ylide **2** (2.5 equiv., 0.62 mmol), $CH_2Cl_2$ (500 µL) and catalyst $(PhO)_2POOH$ (3.12 mg, 0.013 mmol, 5 mol% in two portions, the first one immediately and the second one after 8 h) were added. The resulting solution was stirred for 48 h at room temperature and then directly purified by column chromatography on silica gel, to afford the desired compound **3** as a solid.

**Diethyl 2*H*-chromene-2,3-dicarboxylate (3aa)**[57]



**3aa**

Following the general procedure using salicylaldehyde **1a** and sulfoxonium ylide **2a**, product **3aa** was obtained as white solid in 72% yield (49.7 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1).**$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 0.7 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.17 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.99 (ddd, *J* = 8.2, 1.3, 0.6 Hz, 1H), 6.94 (m, 1H), 5.78 (s, 1H), 4.36 – 4.24 (m, 2H), 4.20 – 4.05 (m, 2H), 1.34 (t, *J* = 7.4, 3H), 1.18 (t, *J* = 7.1, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.1, 164.4, 153.8, 133.4, 132.4, 129.1, 122.2, 121.4, 119.8, 116.5, 71.8, 61.6, 61.1, 14.2, 14.0. **EI-MS** (m/z, relative intensity): 276 ($M^+$, 2%), 203 ($M^+$ -$CO_2Et$, 100%).

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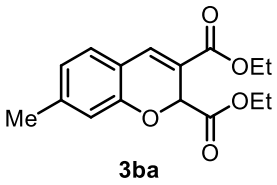
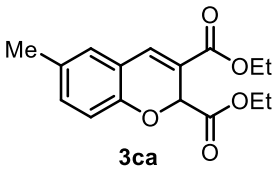
**Diethyl 7-methyl-2*H*-chromene-2,3-dicarboxylate (3ba)**



**3ba**

Following the general procedure using salicylaldehyde **1b** and sulfoxonium ylide **2a**, product **3ba** was obtained as white solid in 60% yield (43.5 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 0.8 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 6.76 (dd, *J* = 7.7, 1.6, Hz, 1H), 5.76 (s, 1H), 4.36 – 4.24 (m, 2H), 4.19 – 4.06 (m, 2H), 2.32 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) = δ 169.3, 164.5, 153.8, 143.5, 133.5, 128.9, 123.2, 120.1, 117.2, 117.0, 71.8, 61.6, 60.9, 21.8, 14.3, 14.0. **EI-MS** (m/z, relative intensity): 290 ($M^+$, 3%), 217 ($M^+$ -$CO_2$Et, 100%).

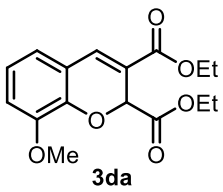
**Diethyl 6-methyl-2*H*-chromene-2,3-dicarboxylate (3ca)**



**3ca**

Following the general procedure using salicylaldehyde **1c** and sulfoxonium ylide **2a**, product **3ca** was obtained as pale-yellow solid in 63% yield (45.7 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.48 (s, 1H), 7.08 (ddd, *J* = 8.2, 2.2, 0.7 Hz, 1H), 6.97 (s, 1H), 6.90 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.75 (s, 1H), 4.36 – 4.24 (m, 2H), 4.19 – 4.05 (m, 2H), 2.26 (d, *J* = 0.7 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.2, 164.4, 151.7, 133.6, 133.1, 131.5, 129.3, 121.3, 119.6, 116.2, 71.7, 61.6, 61.0, 20.4, 14.3, 14.0. **EI-MS** (m/z, relative intensity): 290 ($M^+$, 3%), 217 ($M^+$ -$CO_2$Et, 100%).

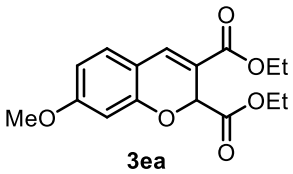
**Diethyl 8-methoxy-2*H*-chromene-2,3-dicarboxylate (3da)**



**3da**

Following the general procedure using salicylaldehyde **1d** and sulfoxonium ylide **2a**, product **3da** was obtained as white solid in 81% yield (62.1 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 3:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 0.4 Hz, 1H), 6.96 – 6.86 (m, 2H), 6.81 (dd, *J* = 6.8, 2.4 Hz, 1H), 5.87 (s, 1H), 4.37 – 4.25 (m, 2H), 4.20 – 4.03 (m, 2H), 3.92 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.0, 164.3, 148.2, 143.2, 133.3, 122.0, 121.6, 121.1, 120.6, 115.3, 71.7, 61.6, 61.1, 56.4, 14.3, 13.9. **EI-MS** (m/z, relative intensity): 306 ($M^+$, 3%), 233 ($M^+$ -$CO_2$Et, 100%).

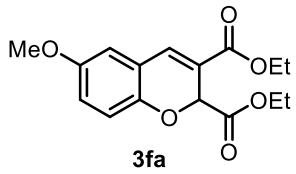
**Diethyl 7-methoxy-2*H*-chromene-2,3-dicarboxylate (3ea)**



**3ea**

Following the general procedure using salicylaldehyde **1e** and sulfoxonium ylide **2a**, product **3ea** was obtained as white solid in 41% yield (31.7 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 3:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 0.8 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 2.4, Hz, 1H), 6.51 (dd, *J* = 8.4, 2.4, Hz, 1H), 5.77 (s, 1H), 4.36 – 4.26 (m, 2H), 4.21 – 4.06 (m, 2H), 3.80 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.3, 164.6, 163.4, 155.6, 133.5, 130.2, 117.9, 113.0, 109.1, 101.6, 71.9, 61.6, 60.8, 55.5, 14.3, 14.0. **EI-MS** (m/z, relative intensity): 306 ($M^+$, 3%), 233 ($M^+$ -$CO_2$Et, 100%).

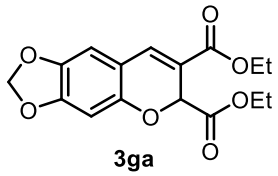
**Diethyl 6-methoxy-2*H*-chromene-2,3-dicarboxylate (3fa)**



**3fa**

Following the general procedure using salicylaldehyde **1f** and sulfoxonium ylide **2a**, product **3fa** was obtained as white solid in 74% yield (56.6 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 3:1).**$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.48 (d, *J* = 0.7 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.71 (d, *J* = 2.9 Hz, 1H), 5.73 (s, 1H), 4.34 – 4.26 (m, 2H), 4.19 – 4.06 (m, 2H), 3.76 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.3, 164.4, 154.5, 147.8, 133.3, 122.2, 120.2, 118.4, 117.3, 113.1, 71.7, 61.6, 61.1, 55.7, 14.3, 14.0. **EI-MS** (m/z, relative intensity): 306 ($M^+$, 7%), 233 ($M^+$ -$CO_2Et$, 100%).

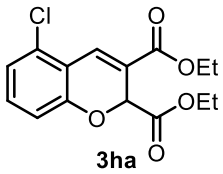
**Diethyl 6*H*-[1,3]dioxolo[4,5-*g*]chromene-6,7-dicarboxylate (3ga)**



**3ga**

Following the general procedure using salicylaldehyde **1g** and sulfoxonium ylide **2a**, product **3ga** was obtained as white solid in 65% yield (52.3 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 4:1).**$^1$H NMR (**400 MHz, $CDCl_3$) δ = 7.41 (s, 1H), 6.61 (s, 1H), 6.58 (s, 1H), 5.96 (apparent singlet, 1H), 5.94 (apparent singlet, 1H), 5.73 (s, 1H), 4.34 – 4.26 (m, 2H), 4.25 – 4.05 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.4, 164.5, 150.9, 150.5, 142.9, 133.5, 118.2, 112.8, 107.2, 101.7, 98.9, 71.7, 61.6, 60.9, 14.3, 14.0. **HRMS** calculated for [$C_{16}H_{16}O_7$ + $Na^+$]: 343.0794; found 343.0793.

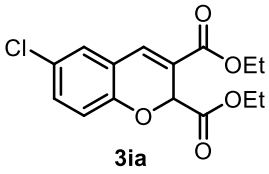
**Diethyl 5-chloro-2*H*-chromene-2,3-dicarboxylate (3ha)**



**3ha**

Following the general procedure using salicylaldehyde **1h** and sulfoxonium ylide **2a**, product **3ha** was obtained as pale-yellow solid in 45% yield (34.9 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 6:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.83 (s, 1H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.00 (dd, J = 8.0, 1.1 Hz, 1H), 6.97 – 6.87 (m, 1H), 5.75 (s, 1H), 4.34 – 4.26 (m, 2H), 4.22 – 4.06 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.7, 164.1, 155.0, 133.7, 132.3, 129.4, 123.0, 122.4, 118.5, 115.3, 71.4, 61.8, 61.3, 14.3, 14.0. **HRMS** calculated for [$C_{15}H_{15}ClO_5$ + $Na^+$]: 333.0506; found 333.0507.

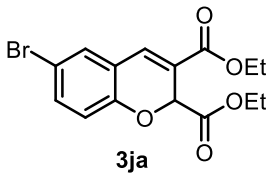
**Diethyl 6-chloro-2*H*-chromene-2,3-dicarboxylate (3ia)**



**3ia**

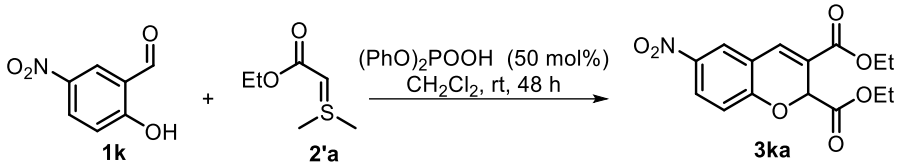
Following the general procedure using salicylaldehyde **1i** and sulfoxonium ylide **2a**, product **3ia** was obtained as pale-yellow solid in 40% yield (31.3 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). Using 50 mol% catalyst loading, the product **3ia** was obtained in 45% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 0.7 Hz, 1H), 7.22 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 8.6, 0.8 Hz, 1H), 5.78 (s, 1H), 4.46 – 4.22 (m, 2H), 4.19 – 4.07 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.7, 164.0, 152.4, 132.1, 131.9, 128.4, 127.1, 122.7, 121.0, 117.9, 71.9, 61.8, 61.3, 14.2, 14.0. **EI-MS** (m/z, relative intensity): 312 ($M^+$,$^{37}$Cl 1%), 310 ($M^+$,$^{35}$Cl 3%), 239 ($M^+$,$^{37}$Cl -$CO_2Et$ 33%), 237 ($M^+$ -$CO_2Et$, 100%).

**Diethyl 6-bromo-2*H*-chromene-2,3-dicarboxylate (3ja)**[58]



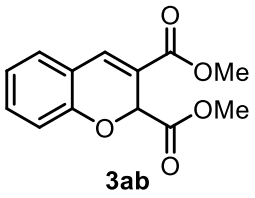

Following the general procedure using salicylaldehyde **1j** and sulfoxonium ylide **2a**, product **3ja** was obtained as pale-yellow solid in 30% yield (26.6 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). Using 50 mol% catalyst loading, the product **3ja** was obtained in 50% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.42 (s, 1H), 7.36 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 6.89 (dd, *J* = 8.6, 0.7 Hz, 1H), 5.78 (s, 1H), 4.46 – 4.22 (m, 2H), 4.19 – 4.07 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.7, 164.0, 152.9, 134.8, 132.0, 131.3, 122.6, 121.6, 118.3, 114.3, 71.8, 61.8, 61.3, 14.2, 14.0. **EI-MS** (m/z, relative intensity): 356 ($M^+$,$^{81}$Br 3.5%), 354 ($M^+$,$^{79}$Br 4%), 283 ($M^+$,$^{81}$Br -$CO_2Et$, 100%), 281 ($M^+$, $^{79}$Br -$CO_2Et$, 100%).

**Diethyl 6-nitro-2*H*-chromene-2,3-dicarboxylate (3ka)**




In a small vial equipped with a magnetic stirring bar, salicylaldehyde **1k** (1.0 equiv., 0.25 mmol) sulfonium ylide **2'a** (2.5 equiv., 0.62 mmol), $CH_2Cl_2$ (500 µL) and catalyst $(PhO)_2POOH$ (32.5 mg, 0.13 mmol, 50 mol%) were added. The resulting solution was stirred for 8 h at room temperature. Product **3ka** was obtained as white solid in 38% yield (determined by $^1$H NMR using bibenzyl as internal standard). Product **3ka** was isolated with 90% of purity after two purifications by column chromatography on silica gel, the first one in DCM as mobile phase and the second one using (PhMe:DCM = 1:1). Its structure was determined by analogy with products **3** and thanks to HRMS reported below. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.19 (dd, *J* = 9.0, 2.7 Hz, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 7.53 (s, 1H), 7.10 (d, *J* = 9.0, 1H) 5.91 (s, 1H), 4.39 – 4.30 (m, 2H), 4.20 – 4.12 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.0, 163.5, 158.8, 142.6, 131.4, 127.8, 124.6, 123.5, 119.8, 117.1, 72.7, 62.2, 61.6, 14.2, 14.0. **HRMS** calculated for [$C_{15}H_{15}NO_7$ + $Na^+$]: 344.0746; found 344.0744.

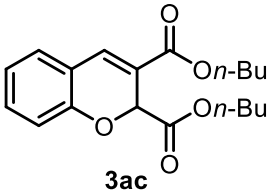
**Dimethyl 2*H*-chromene-2,3-dicarboxylate (3ab)**[58]




Following the general procedure using salicylaldehyde **1a** and sulfoxonium ylide **2b**, product **3ab** was obtained as white solid in 70% yield (43.4 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 0.8 Hz, 1H), 7.38 – 7.24 (m, 1H), 7.18 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.07 – 6.90 (m, 2H), 5.81 (s, 1H), 3.85 (s, 3H), 3.69 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.5, 164.7, 153.8, 133.8, 132.6, 129.2, 122.3, 120.7, 119.7, 116.6, 71.6, 52.6, 52.2. **EI-MS** (m/z, relative intensity): 248 ($M^+$, 3%), 189 ($M^+$ -$CO_2Me$, 100%).

58 A. Ramazania, Y. Ahmadia, H. Aghahosseinia, S. W. Joo, *Phosphorus Sulfur Silicon Relat. Elem.*, 2016, **191**, 354-358.

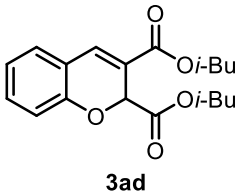
**Dibutyl 2*H*-chromene-2,3-dicarboxylate (3ac)**



**3ac**

Following the general procedure using salicylaldehyde **1a** and sulfoxonium ylide **2c**, product **3ac** was obtained as white solid in 64% yield (53.1 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 0.8 Hz, 1H), 7.28 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 7.17 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.03 – 6.98 (m, 1H), 6.96 – 6.94 (m, 1H), 5.79 (s, 1H), 4.25 (t, *J* = 6.6 Hz, 2H), 4.16 – 3.97 (m, 2H), 1.77 – 1.61 (m, 2H), 1.59 – 1.37 (m, 4H), 1.31 – 1.17 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.1, 164.4, 153.9, 133.3, 132.4, 129.1, 122.2, 121.5, 119.8, 116.5, 71.7, 65.4, 64.9, 30.7, 30.4, 19.2, 18.8, 13.7, 13.5. **EI-MS** (m/z, relative intensity): 332 ($M^+$, 1%), 231 ($M^+$ -$CO_2$*n*-Bu, 100%).

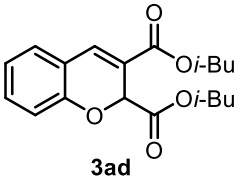
**Di-*iso*-butyl 2*H*-chromene-2,3-dicarboxylate (3ad)**



**3ad**

Following the general procedure using salicylaldehyde **1a** and sulfoxonium ylide **2d**, product **3ad** was obtained as white solid in 75% yield (62.3 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1).**$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 0.8 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.19 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.97 – 6,93 (m, 1H), 5.82 (s, 1H), 4.04 (d, *J* = 6.6 Hz, 2H), 3.87 (d, *J* = 6.4 Hz, 2H), 2.03 (hept, *J* = 6.4 Hz, 1H), 1.83 (hept, *J* = 6.6 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 6H), 0.81 (d, *J* = 6.7 Hz, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.1, 164.4, 153.9, 133.3, 132.4, 129.1, 122.2, 121.5, 119.8, 116.6, 71.7, 71.5, 71.1, 27.8, 27.6, 19.1 (2C), 18.75, 18.72. **EI-MS** (m/z, relative intensity): 332 ($M^+$, 1%), 231 ($M^+$ -$CO_2$*i*-Bu, 100%).

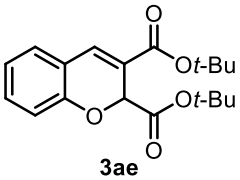
**Di-*tert*-butyl 2*H*-chromene-2,3-dicarboxylate (3ae)**



**3ad**

Following the general procedure using salicylaldehyde **1a** and sulfoxonium ylide **2e**, product **3ae** was obtained as white solid in 62% yield (51.5 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 0.7 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.15 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.97 – 6.85 (m, 1H), 6.94 – 6.90 (m, 1H), 5.64 (s, 1H), 1.55 (s, 9H), 1.37 (s, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.2, 163.6, 154.1, 132.1, 132.0, 128.9, 123.3, 121.9, 120.0, 116.3, 82.4, 81.3, 72.1, 28.1 (3C), 27.9 (3C). **HRMS** calculated for [$C_{19}H_{24}O_5$ + $Na^+$]: 355.1521; found 355.1517.

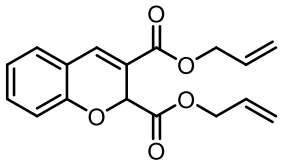
**Diallyl 2*H*-chromene-2,3-dicarboxylate (3af)**



**3ae**

Following the general procedure using salicylaldehyde **1a** and sulfoxonium ylide **2f**, product **3af** was obtained as white solid in 60% yield (45.2 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 0.8 Hz, 1H), 7.37 – 7.25 (m, 1H), 7.19 (dd, *J* = 7.6, 1.7, Hz, 1H), 7.10 – 6.93 (m, 2H), 5.99 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.86 (s, 1H), 5.85 – 5.75 (m, 1H), 5.41-5.39 (m, 1H), 5.32-5.25 (m, 1H), 5.24 – 5.14 (m, 2H), 4.79-4.67 (m, 2H), 4.59 (tt, *J* = 5.6, 1.5 Hz, 2H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.7, 163.9, 153.9, 134.0, 132.6, 131.9, 131.2, 129.3, 122.3, 120.8, 119.7, 118.5, 118.2, 116.6, 71.7, 65.9, 65.7. **EI-MS** (m/z, relative intensity): 300 ($M^+$, 1%), 215 ($M^+$ -$CO_2$allyl, 100%).

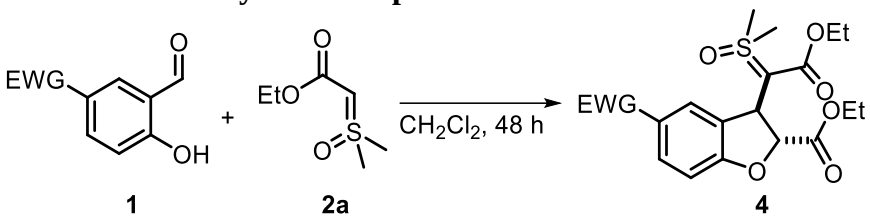
**Dibenzyl 2*H*-chromene-2,3-dicarboxylate (3ag)**




**3af**

Following the general procedure using salicylaldehyde **1a** and sulfoxonium ylide **2g**, product **3ag** was obtained as white solid in 30% yield (30.1 mg) after column chromatography on silica gel (*n*-hexane/$Et_2O$ = 5:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 0.7 Hz, 1H), 7.41 – 7.24 (m, 9H), 7.21 – 7.13 (m, 3H), 7.05 – 7.02 (m, 1H), 6.97 – 6.95 (m, 1H), 5.89 (s, 1H), 5.24 (s, 2H), 5.14 (d, *J* = 12.5 Hz, 1H), 5.06 (d, *J* = 12.5 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.9, 164.2, 153.9, 135.6, 135.2, 134.1, 132.6, 129.3, 128.6, 128.5, 128.4, 128.27, 128.24, 127.7, 122.4, 120.8, 119.7, 116.6, 71.7, 67.1, 66.9. **HRMS** calculated for [$C_{25}H_{20}O_5$ + $Na^+$]: 423.1208; found 423.1206.

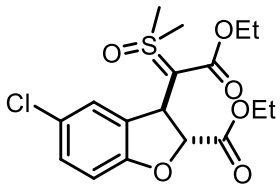
## General procedure for the synthesis of product 4




**1** **2a** **4**

In a small vial equipped with a magnetic stirring bar, salicylaldehyde **1** (1.0 equiv, 0.25 mmol) and sulfoxonium ylide **2a** (2.5 equiv., 0.62 mmol) were dissolved in 500 µL of $CH_2Cl_2$. The resulting solution was stirred for 18 h at room temperature and then directly purified by column chromatography on silica gel to afford compounds **4**.

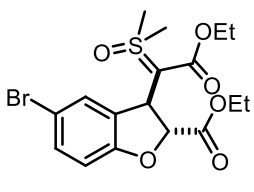
**Ethyl-5-chloro-3-(1-(dimethyl(oxo)-λ$^6$-sulfaneylidene)-2-ethoxy-2-oxoethyl)-2,3-dihydrobenzofuran-2-carboxylate (4ia)**




**4ia**

Following the general procedure using salicylaldehyde **1i** and sulfoxonium ylide **2a**, product **4ia** was obtained as white solid in 87% yield (84.6 mg) after column chromatography on silica gel (EtOAc). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.04 (dd, *J* = 8.4, 2.3, Hz, 1H), 6.92 (dd, *J* = 2.3, 1.3 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 5.08 (d, *J* = 9.0 Hz, 1H), 4.59 (d, *J* = 8.9 Hz, 1H), 4.32-4.46 (m, 2H), 3.99-3.80 (m, 2H), 3.52 (s, 3H), 3.41 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.87 (bt, *J* = 7.1, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 171.3, 157.6, 132.0, 127.5, 125.5, 123.2, 110.3, 85.6, 61.6, 59.4, 58.6, 44.8, 43.4, 42.4, 14.3, 14.0. **ESI-MS** = 388 [M($^{35}$Cl) + $Na^+$], 290 [M($^{37}$Cl) + $Na^+$].

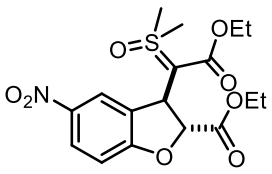
**Ethyl-5-bromo-3-(1-(dimethyl(oxo)-λ$^6$-sulfaneylidene)-2-ethoxy-2-oxoethyl)-2,3-dihydrobenzofuran-2-carboxylate (4ja)**




**4ja**

Following the general procedure using salicylaldehyde **1j** and sulfoxonium ylide **2a**, product **4ja** was obtained as white solid in 80% yield (86.5 mg) after column chromatography on silica gel (EtOAc). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.19 (dd, *J* = 8.5, 2.2, Hz, 1H), 7.12 – 7.04 (m, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 5.09 (d, *J* = 8.9 Hz, 1H), 4.60 (d, *J* = 8.9 Hz, 1H), 4.38 – 4.25 (m, 2H), 4.01 – 3.77 (m, 2H), 3.54 (s, 3H), 3.42 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.6, 3H).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 171.2, 158.1, 132.5, 130.5, 126.1, 112.6, 111.0, 85.5, 61.6, 59.4, 58.6, 44.9, 43.5, 42.4, 14.2, 14.1. **HRMS** calculated for [$C_{17}H_{21}BrO_6S$ + $H^+$]: 433.0337 [M($^{79}$Br) + $Na^+$], 434.0177 [M($^{81}$Br) +.$Na^+$]; found 433.0320.

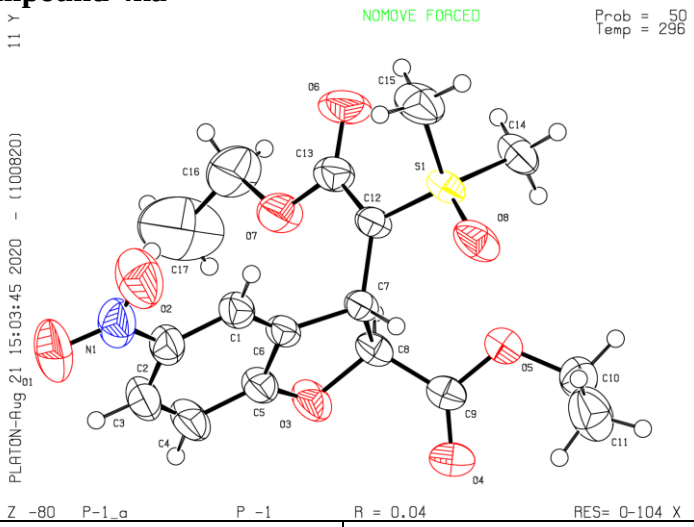
**Ethyl-3-(1-(dimethyl(oxo)-λ$^6$-sulfaneylidene)-2-ethoxy-2-oxoethyl)-5-nitro-2,3-dihydrobenzofuran-2-carboxylate (4ka)**




**4ja**

Following the general procedure using salicylaldehyde **1k** and sulfoxonium ylide **2a**, product **4ka** was obtained as white solid in 85% yield (84.8 mg) after column chromatography on silica gel (EtOAc). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.11 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.89 (dd, *J* = 2.5, 1.4 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 8.7 Hz, 1H), 4.64 (d, *J* = 8.6 Hz, 1H), 4.37 – 4.25 (m, 2H), 4.02 – 3.77 (m, 2H), 3.58 (s, 3H), 3.44 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.85 (bt, *J* = 6.81, 3H). **$^{13}$C NMR** (400 MHz, $CDCl_3$) δ = 170.4, 164.2, 142.5, 132.0, 125.4, 119.6, 109.3, 86.8, 61.9, 59.3, 58.7, 44.9, 43.5, 41.7, 14.2, 14.0. **ESI-MS** = 367 [M + $Na^+$].

## X-ray data of compound 4ka[59]




| | |
|---|---|
| Molecular Formula | $C_{17}H_{21}NO_8S$ |
| Formula Weight | 399.41 |
| Crystal System | triclinic |
| Space Group | *P*-1 |
| a (Å) | 8.8970(4) |
| b (Å) | 8.9808(4) |
| c (Å) | 12.6218(7) |
| α (deg) | 87.967(2) |
| β (deg) | 81.060(2) |
| γ (deg) | 80.6680 |
| Volume (Å$^3$) | 983.02(8) |
| Z | 2 |
| $\rho$ (g/cm$^3$) | 1.349 |
| T (K) | 296(2) |
| $\mu$ (mm$^{-1}$) | 0.208 |
| *F*(000) | 420 |
| $\theta$ limits (deg) | 2.298 - 24.997 |
| Index Ranges | $-10 \leq h \leq 10, -10 \leq k \leq 10, -14 \leq l \leq 14$ |
| Reflections Collected | 12025 |
| Independent Reflections | 3350 [*R*(int) = 0.0205] |
| Completeness to $\theta$ max | 96.7% |
| Data / Restraints / Parameters | 3350/ 3/ 248 |
| Goodness-of-fit | 1.046 |
| $R_1$ (I > 2σ (I)) | 0.0432 |
| $wR_2$ (all data) | 0.1203 |
| Largest difference peak and hole, e Å$^{-3}$ | 0.237 and –0.223 |

59 CCDC2043727 (for **4ka**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

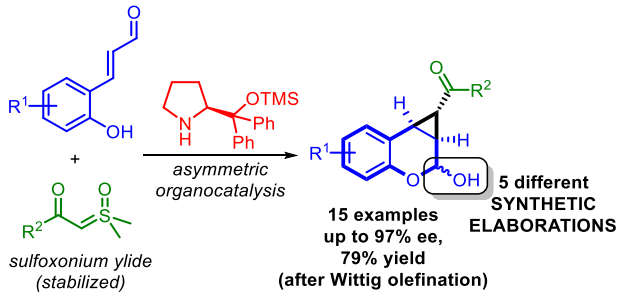
# 5 Sulfoxonium Ylides in Aminocatalysis: An Enantioselective Entry to Cyclopropane-Fused Chromanol Structures

The procedures and results here described are part of- and can be found in-:

- G. D. Bisag, P. Pecchini, M. Mancinelli, M. Fochi, L. Bernardi. *Org. Lett.* 2022, 24, 29, 5468–5473

ABSTRACT

The 1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene, arising from fusion of chromane and cyclopropane rings, is the core of medicinally relevant compounds. Engaging for the first time sulfoxonium ylides in enantioselective aminocatalytic reactions, a convenient entry to this scaffold is presented. Several ring-fused derivatives were obtained in moderate-to-good yields and enantioselectivites, and with perfect diastereoselectivity at the cyclopropane, using an α,α-diphenyl prolinol aminocatalyst. The versatility of the hemiacetal moiety in the products was leveraged to effect various synthetic manipulations.




## 5.1 Background

The cyclopropane ring is present in numerous pharmacologically active compounds. The fame of this ring in medicinal chemistry is not only due to the strain of the cycle, which reserves a reactivity somewhat similar to an olefin, but also to the presence of C-H bonds shorter and stronger than those of common alkanes. Furthermore, the coplanarity of the three carbon atoms makes the reactivity displayed by cyclopropane truly unique.[60] In this context, the specific tricyclic 1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene framework, arising from the fusion of chromane and cyclopropane rings, is the core of several medicinally relevant compounds (*Figure 5.1a*). Examples include 8-carboxy-7-

60 T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712.

sulfonamido derivatives **I**, which activity against methionyl aminopeptidase suggests their use in the treatment of liver disorders and obesity,[61] urea **II** (MIV-160), a reverse transcriptase inhibitor studied for anti-HIV therapy,[62] and carboxylic acid **III**, member of a series of fused cyclopropane derivatives agonists of G-protein coupled receptor 40 (GP40), and potentially useful in the treatment of type 2 diabetes.[63] Furthermore, "cyclopropanochroman" natural products, such as radulanins I-K (**IV-VI**), have been isolated from liverworts extracts in racemic or enantiopure form.[64] Radulanin K from *Radula javanica* has shown to inhibit the release of superoxide anion radical from guinea pig macrophage.[65] This backbone can be obtained exploiting an asymmetric Corey-Chaykovsky-type cyclopropanation[66] of 2'-hydroxycinnamaldehydes **1** with stabilized sulfoxonium ylides **2** (*Figure 5.1b*). Aminocatalytic cyclopropanation reactions of other α,β-unsaturated aldehydes have been reported. In this context, examples of Corey-Chaykovsky-type reactions are relatively rare, and restricted to α-keto sulfonium ylides, [67] while cyclopropanations with α-halo(di)carbonyl compounds, 1-bromonitroalkanes and activated benzyl halides (*e.g.* 2,4-dinitrobenzyl chloride), are more abundant.[68] The latter group of reactions is generally performed with Jørgensen-Hayashi type catalysts,[69] which simplest congener proved to be effective in our case too (*Figure 5.1b*). This reaction represents the first example of utilization of sulfoxonium ylides in asymmetric aminocatalysis,[70] and affords the tricyclic ring-fused derivatives **3** with very good stereocontrol. Importantly, the connectivity and relative stereochemistry of these compounds match the core of GP40 agonist **III** (*Figure 5.1a*). Lastly, besides providing an alternative, and enantioselective, approach to this scaffold, this methodology affords

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69 a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2005**, *44*, 794.
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adducts (**3**) carrying a hemiacetal functionality, which can be leveraged as a synthetic handle enabling access to a variety of compounds.

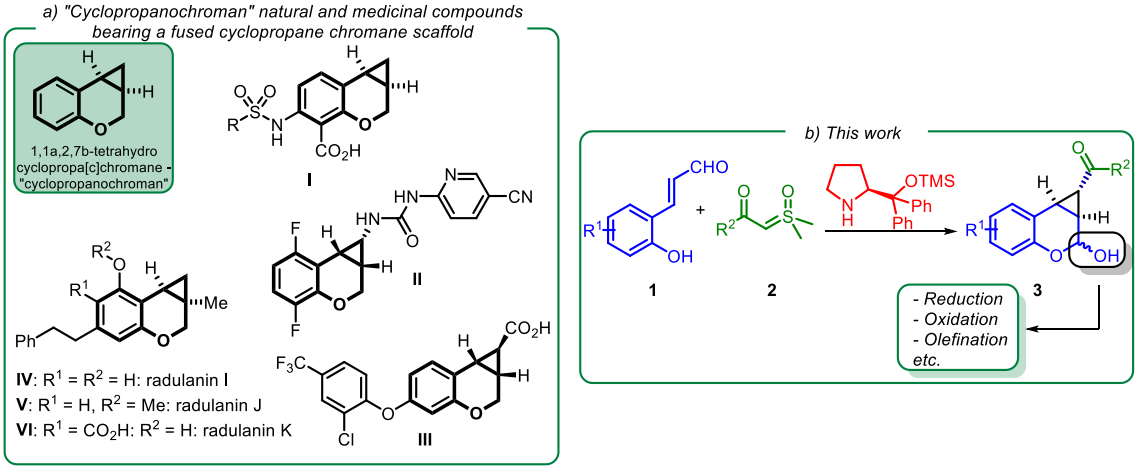


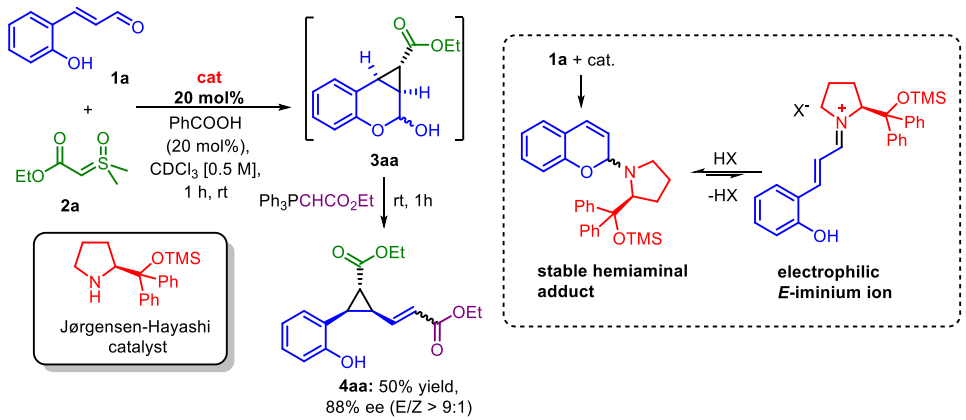

*Figure 5.1. a) Natural and medicinally relevant compounds embedding the 1,1a,2,7b-TH-cyclopropa[c]chromene framework; b) This work: enantioselective access to this scaffold via aminocata-lytic cyclopropanation of enals 1 with sulfoxonium ylides 2*

## 5.2 Results and discussion

### 5.2.1 Optimization of the reaction conditions

During our initial studies on the reaction between 2'-hydroxycinnamaldehyde **1a** and sulfoxonium ylide **2a** under the promotion of a common Jørgensen-Hayashi catalyst, we noticed an immediate color change by mixing aldehyde **1a** with the secondary amine catalyst in $CDCl_3$ (*Scheme 5.1*). Such color change can be attributed to the formation of a stable and nucleophilic hemiaminal adduct.[71] To revert this hemiaminal to an electrophilic iminium ion species, presumably *E*-configured 20 mol% of benzoic acid co-catalyst was added followed by the nucleophilic sulfoxonium ylide **2a**. To our delight, we observed the formation of the desired chromanol derivative **3aa**, which was derivatized by Wittig olefination into the corresponding **4aa**, obtained as a highly prevalent E-isomer, for isolation and determination of the enantiomeric excess. Immediately, we understood that the reaction was characterized by promising results in terms of yield and enantioselectivity. Indeed, performing the reaction under these standard conditions, 50% yield and 88% enantioselectivity were achieved. Furthermore, regarding the chirality centers of the cyclopropane ring, the diastereoselectivity of the reaction appeared complete.

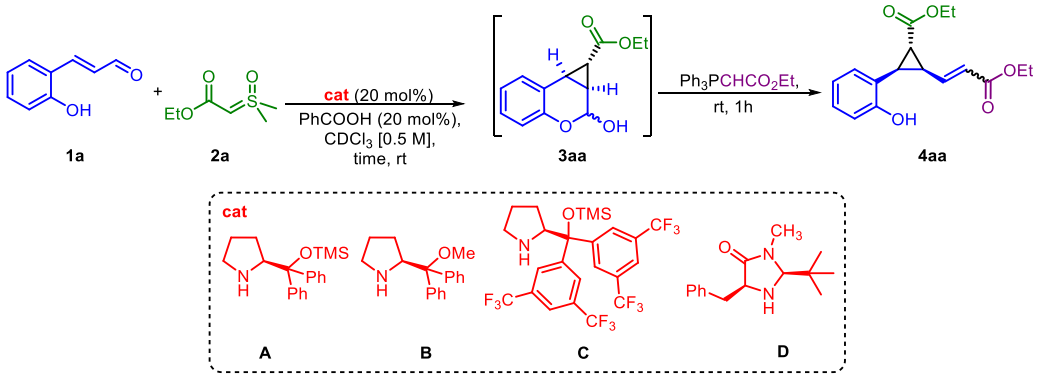
71 a) L. Zu, S. Zhang, H. Xie, W. Wang, *Org. Lett.* **2009,** *11*, 1627. b) D. B. Ramachary, M. S. Prasad, S. V. Laxmi, R. Madhavachary, *Org. Biomol. Chem.* **2014**, *12*, 574.




*Scheme 5.1. Reactivity of 2-hytroxycinnamaldehyde an stabilized sulfoxonium ylides*

Different catalysts were tested in the reaction between 2'-hydroxy cinnamaldehyde **1a** and stabilized sulfoxonium ylide **2a** and the results are reported in *Table 5.1*. Only the reaction performed with catalyst **A** gives product **4aa** with promising results in terms of yield and enantioselectivity (entry 1). Indeed, a little change on the catalyst's backbone such as a methyl as O-protecting group or 3,5-$CF_3$ as substituents on the two aromatic rings leads to obtaining product **4aa** with a lower value of yield and enantioselection (entries 2 and 3). While, performing the reaction with imidazolidinone **D** as catalyst, product **4aa** was present in the reaction mixture only in traces and in a racemic form.

*Table 5.1. Catalyst screening*



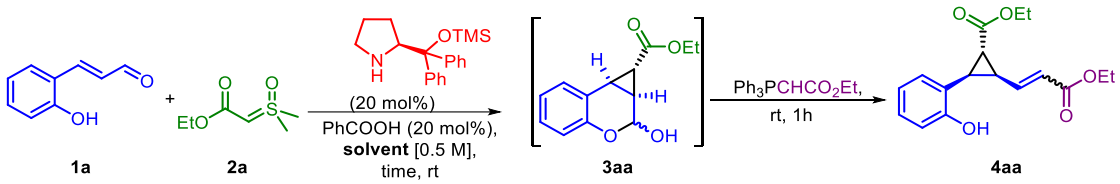

| entryentry[a] | cat | ee [%][b] | Yield [%][c] | Time [h] |
|---|---|---|---|---|
| **1** | A | 88 | 50 | 1 |
| **2** | B | 7 | 27 | 12 |
| **3** | C | 52 | 22 | 12 |
| **4** | D | *rac* | 9 | 12 |

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2a** (0.15 mmol, 1.5 equiv.), PhCOOH (0.02 mmol, 20 mol%) catalyst **A-D** (0.02 mmol, 20 mol%) and $CDCl_3$ (200 µL), rt, 1-12 h. [b] Enantiomeric excess determined by CSP-HPLC. [c] Yield determined after chromatographic column on silica gel.

Once the right catalyst for the reaction was identified, a solvent screening was performed and the results are reported in *Table 5.2*. Numerous solvents were tested, but product **4aa**

was obtained only by performing the reaction in toluene or in halogenated solvents (entries 1-3). Indeed, performing the reaction in THF, MTBE or EtOAc only starting materials were present in the reaction mixture without traces of product **4aa** (entries 4-6). Performing the reaction in toluene (entry 2) product **4aa** was obtained with a lower value of yield and enantiomeric excess, compared to $CDCl_3$. While using dichloromethane, comparable results in terms of yield and enantio-selection were obtained (entry 3). Given the convenience of using a deuterated solvent during the optimization process, and the good results obtained, we decided to use deuterated chloroform as solvent for the next screening.

*Table 5.2. Solvent screening*

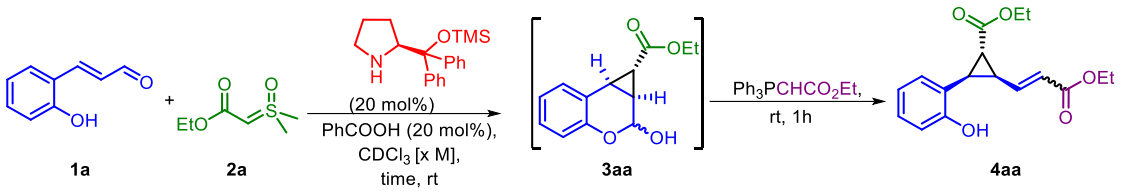



| entryentry[a] | solvent | ee [%][b] | Yield [%][c] | Time [h] |
|---|---|---|---|---|
| **1** | $CDCl_3$ | 88 | 50 | 1 |
| **2** | PhMe | 63 | 37 | 12 |
| **3** | DCM | 85 | 50 | 1.5. |
| **4** | THF | / | / | 12 |
| **5** | MTBE | / | / | 12 |
| **6** | EtOAc | / | / | 12 |

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2a** (0.15 mmol, 1.5 equiv.), PhCOOH (0.02 mmol, 20 mol%) catalyst **A** (0.02 mmol, 20 mol%) and solvent (200 µL), rt, 1-12 h. [b] Enantiomeric excess determined by CSP-HPLC. [c] Yield determined after chromatographic column on silica gel.

To improve both the enantiomeric excess and the yield of the product **4aa** we investigated the dilution of the reaction (*Table 5.3*). We found that performing a more diluted reaction (0.1 M, entry 2 instead of 0.5 M entry 1), product **4aa** can be obtained with higher values of both yield and enantio-selection.

*Table 5.3. Concentration*

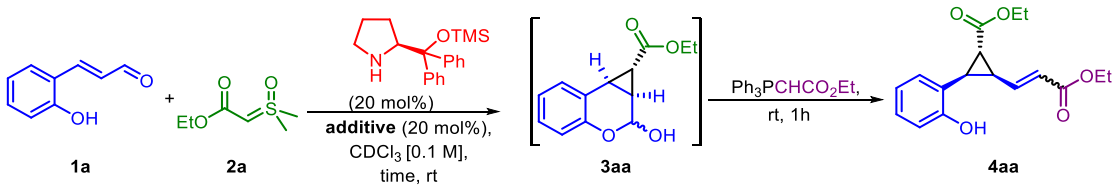



| entryentry[a] | Concentration [M] | ee [%][b] | Yield [%][c] | Time [h] |
|---|---|---|---|---|
| **1** | 0.5 | 88 | 50 | 1 |
| **2** | 0.1 | 95 | 57 | 2 |

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2a** (0.15 mmol, 1.5 equiv.), PhCOOH (0.02 mmol, 20 mol%) catalyst **A** (0.02 mmol, 20 mol%) and $CDCl_3$ (200 or 1000 µL), rt, 1-2 h. [b] Enantiomeric excess determined by CSP-HPLC. [c] Yield determined after chromatographic column on silica gel.

Then, we moved to evaluate the influence of the additives as co-catalysts in the reaction between aldehyde **1a** and sulfoxonium ylide **2a** (*Table 5.4*). We found that performing the reaction with CSA as additive, product **4aa** can be obtained with a very high value of enantiomeric excess but a lower yield (entry 2). Moving on to evaluate the different acidity of benzoic acid derivatives, we understood that performing the reaction with a rather acidic benzoic acid, *p*-$NO_2$-benzoic acid, it is possible to improve the yield of product **4aa**, compared to the simple benzoic acid, while the enantiomeric excess experiences a considerable decrease (entry 3). Performing the reaction with a less acidic benzoic acid, *p*-MeO-benzoic acid, both the value of yield and enantioselectivity remain unchanged (entry 4). In the end, we decided to test an aliphatic acid (AcOH) but no variation of the yield or enantiomeric excess was verified (entry 5). Taking into consideration the achieved result, but considering that the acidity of the additive could compromise the stability of the sulfoxonium ylide **2a** we decided to perform the same experiment but using sodium acetate as additive. In this case, an increase of yield was observed (entry 6). The beneficial effect of sodium acetate on the yield of the reaction was confirmed by an experiment performed without additives (entry 7). We then tried alternative bases, such as tertiary amines, as additives in the reaction. As shown in entries 8-11, use of these bases in either catalytic or stoichiometric amounts led to poorer results, so sodium acetate was chosen as co-catalyst for further optimization.

*Table 5.4. Additives screening*

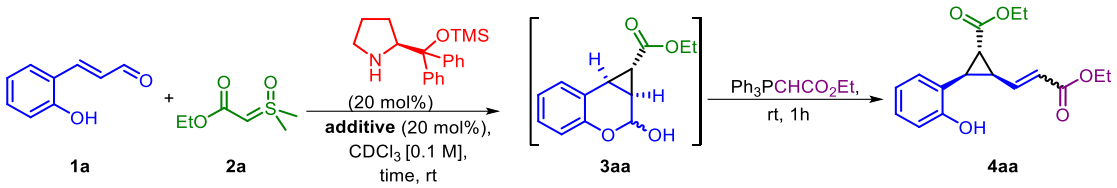



| entryentry[a] | additive | ee [%][b] | Yield [%][c] | Time [h] |
|---|---|---|---|---|
| **1** | PhCOOH | 95 | 57 | 2 |
| **2** | CSA | 98 | 36 | 1 |
| **3** | p-$NO_2$ benzoic acid | *72* | 63 | 2 |
| **4** | p-MeO benzoic acid | 96 | 50 | 12 |
| **5** | AcOH | 96 | 52 | 12 |
| **6** | AcONa | 96 | 67 | 12 |
| **7** | - | 96 | 41 | 12 |
| **8** | $Et_3N$ | 97 | 42 | 12 |
| **9** | $Et_3N$ (1 equiv.) | 97 | 29 | 12 |
| **10** | *i*-$Pr_2EtN$ | 93 | 40 | 12 |
| **11** | *i*-$Pr_2EtN$ (1 equiv.) | 94 | 25 | 12 |

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2a** (0.15 mmol, 1.5 equiv.), additive (0.02 mmol, 20 mol%) catalyst **A** (0.02 mmol, 20 mol%) and $CDCl_3$ (1000 µL), rt, 1-12 h. [b] Enantiomeric excess determined by CSP-HPLC. [c] Yield determined after chromatographic column on silica gel.

Finally, we decided to explore the buffer system AcONa/AcOH (*Table 5.5*). Performing the reaction with AcOH as additive, as previously mentioned a high value of enantiomeric excess but a lower yield was obtained (entry 1). Performing the same reaction but using AcONa as additive high value of yield and enantioselectivity were obtained (entry 5). At this point different different mixture of the system AcONa/AcOH were tested. Performing the reaction with equal amounts of acetic acid and sodium acetate, an increment of the yield was achieved, while the enantioselectivity decreased (entry 2). Then, performing the reaction with different relative amounts of the acid and its conjugate base, two different behaviors were observed. With an excess of sodium acetate, the yield of product **4aa** decreased again while its enantiomeric excess raised slightly (entry 3). Running the reaction with more acetic acid than sodium acetate the yield improved, but the enantioselectivity dropped (entry 4). On the basis of this results we chose AcONa as the only additive for the catalytic reaction (entry 5).

*Table 5.5. Buffer system as additive*

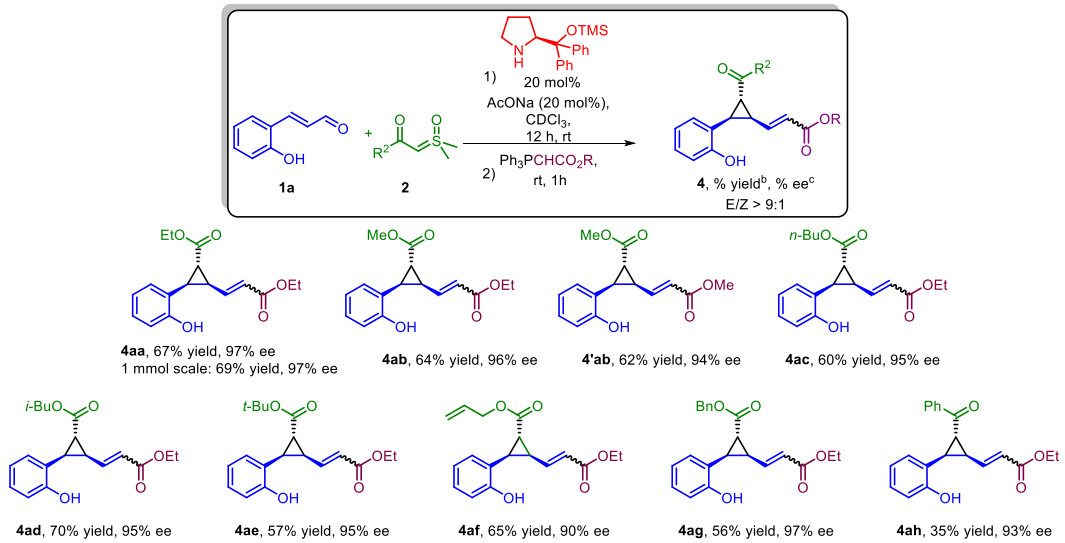



| entryentry[a] | additive | ee [%][b] | Yield [%][c] | Time [h] |
|---|---|---|---|---|
| **1** | AcOH [20] | 96 | 52 | 12 |
| **2** | AcONa [20] + AcOH [20] | 79 | 74 | 12 |
| **3** | AcONa [20] + AcOH [10] | 82 | 65 | 12 |
| **4** | AcONa [10] + AcOH [20] | 74 | 75 | 12 |
| **5** | AcONa [20] | 97 | 67 | 12 |

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2a** (0.15 mmol, 1.5 equiv.), additive (0.02 mmol, 20 mol%) catalyst **A** (0.02 mmol, 20 mol%) and $CDCl_3$ (1000 µL), rt, 1-12 h. [b] Enantiomeric excess determined by CSP-HPLC. [c] Yield determined after chromatographic column on silica gel.

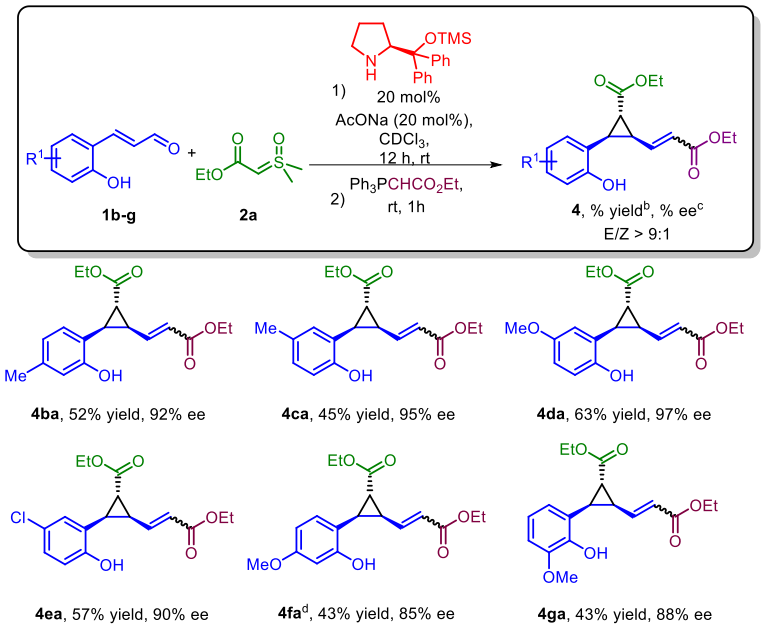
### 5.2.2 Scope of the reaction

We then moved to evaluate the generality of the reaction, after having verified that the reaction can be carried out with similar results on a 1 mmol scale (*Scheme 5.2*). The variation of the sulfoxonium ylide **2** reported in *Scheme 5.2* showed that both short chain and long chain ester substituents are very well tolerated giving products **4ab** and **4ac** with comparable results in terms of yield, and very good enantioselectivity. Also, bulky substituents such as the *iso*-butyl or the *tert*-butyl group on the ester moiety give products **4ad** and **4ae** respectively in good yields and with high enantiomeric excesses. Similarly, the use of an allylic or a benzylic ester did not significantly affect either the yield or the enantioenrichment of products **4af** and **4ag**. Next, the sulfoxonium ylide **2h** with a ketone instead of an ester substituent was tested. Product **4ah** was obtained in a lower yield, possibly due to the less nucleophilic nature of this ylide, but with high enantiomeric excess. Finally, using a different phosphorous ylide, compound **4'ab** with two methyl esters was prepared, and its relative and absolute configurations determined as 1R,2R,3S by means of NOESY-1D NMR and Electronic Circular Dichroism (ECD) method (see next paragraph). This assignment, was extended by analogy to all products **4**.




*Scheme 5.2. Sulfoxonium ylide 2 substrate scope*

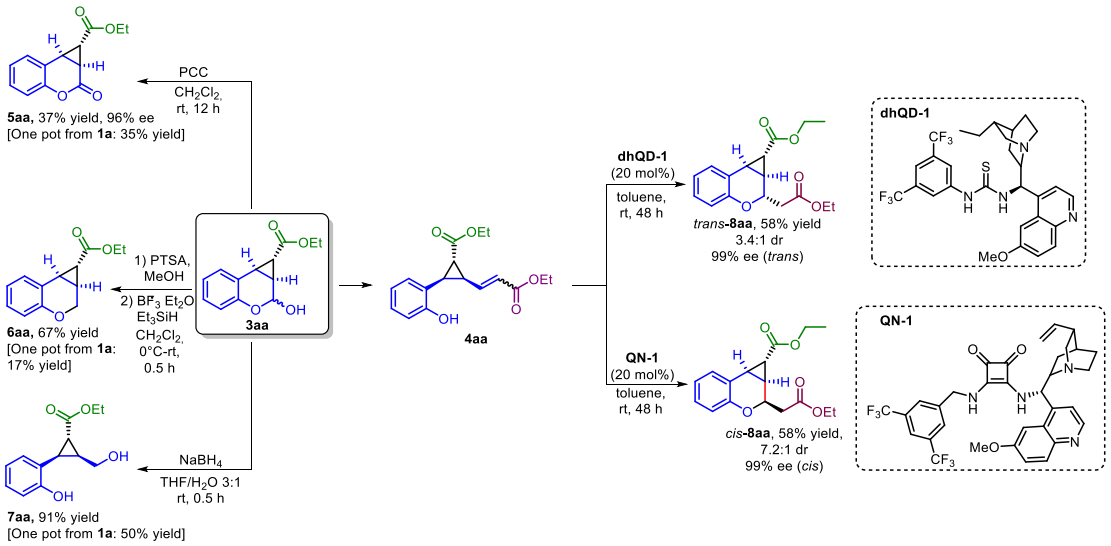
We then explored the reactivity of sulfoxonium ylide **2a** with different 2'-hydroxycinnamaldehydes **1b-g** and the results are reported in *Scheme 5.3*. A 4'-methyl substituent gave product **4ba** in good yield and high enantiomeric excess, while the same group at the 5' position led to product **4ca** in a lower yield but still high enantioselectivity. A more electron-donating substituent like a methoxy group at different positions was also tolerated, delivering products **4da**, **4fa** and **4ga** in moderate to good yields and good enantiomeric excesses. Interestingly, product **4fa** bears an oxygenated substituent at the same position of the aryloxygroup of GP40 agonist **III** (*Figure 5.1*). Finally, using an electron-withdrawing substituent like a chlorine atom, led to the corresponding product **4ea** with good results.




*Scheme 5.3. 2'-Hydroxycinnamaldehyde 1 substrate scope*

### 5.2.3 Synthetic elaborations

As previously mentioned, the backbone of the catalytic products is present in numerous natural and medicinal compounds. For this reason, we moved to explore their synthetic versatility (*Scheme 5.4*). Treating **3aa** with PCC, the hemiacetal group could be oxidized delivering coumarin **5aa** in moderate yield. The readily obtained methyl acetal of **3aa** could be smoothly reduced to the corresponding chromane **6aa** using triethylsilane in the presence of $BF_3 \cdot OEt$. Using sodium borohydride, the fleeting aldehydic function could instead be converted into a primary alcohol, obtaining product **7aa** in very good yield. Protocols combining the catalytic reaction and these reductions or oxidation in one pot fashion were also implemented. Using these streamlined and convenient methods product **5aa** was obtained with comparable yield, while **6aa** and **7aa** were afforded with lower yield values. Product **4aa** resulting from Wittig olefination of **3aa** was subjected to an intramolecular diastereodivergent oxa-Michael reaction. Performing the reaction with bifunctional catalysts derived from pseudo-enantiomeric *Cinchona* alkaloids, it was possible to direct the diastereoselectivity of the reaction either towards the *cis*-**8aa** or the *trans*-**8aa** derivative. The intrinsic diastereomeric relationship between the transitions states leading to the *cis*-**8aa** and to the *trans*-**8aa** isomer justifies the requirement of different (*i.e.* not enantiomeric) catalytic structures for the two reactions.

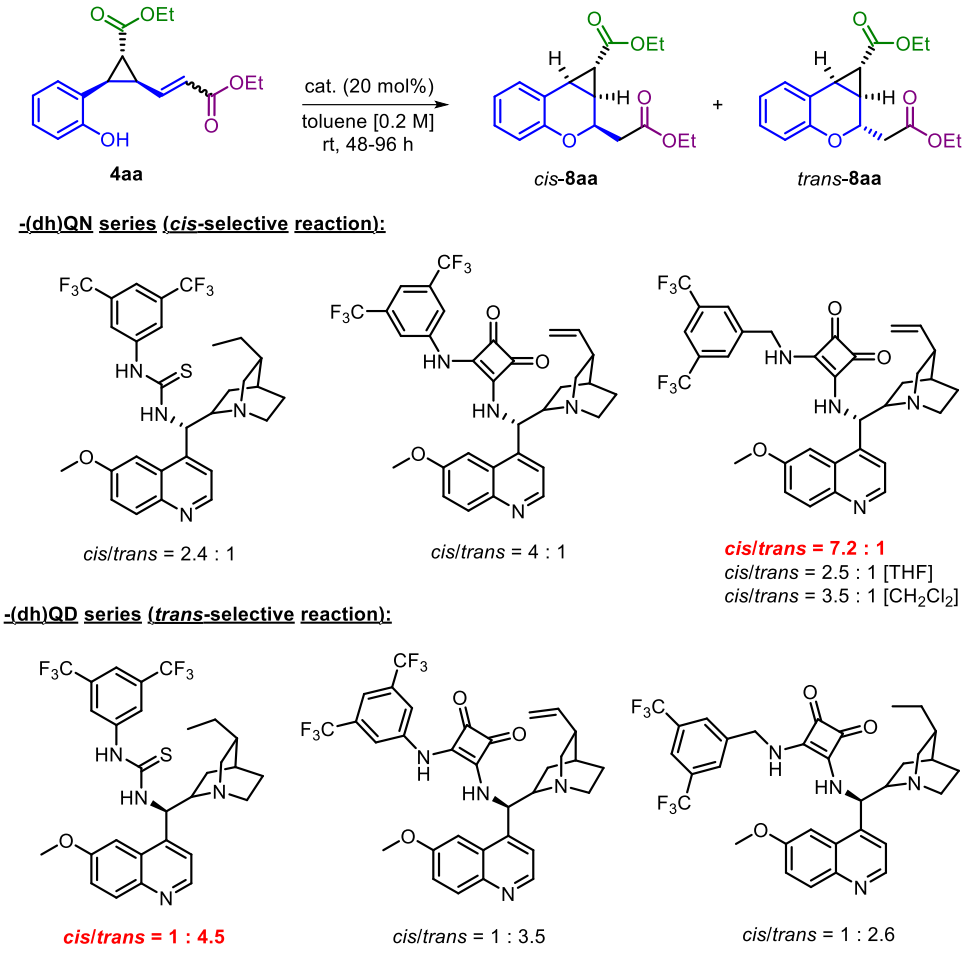



*Scheme 5.4. Synthetic elaborations*

**Synthetic elaborations additional results**

The intramolecular oxa-Michael reaction delivering **8aa** from **4aa** was found to proceed smoothly under basic promotion. Since an achiral catalyst/promoter such as $Et_3N$ delivered the product with low diastereomeric ratio (1.5 : 1 favoring *trans*-**8aa**), few chiral bifunctional catalysts derived from *Cinchona* alkaloids were tried in the reaction in toluene at room temperature (*Scheme 5.5*), in order to develop a selective, and possibly diastereo-divergent, process. This class of catalysts is known to be very effective in a related oxa-Michael reaction.[72] Catalysts from the quinine series were found to promote the selective formation of the *cis*-**8aa** isomer, with a benzylic squaramide derivative outperforming other structures. Solvents other than toluene did not provide any improvement. Quinidine derived catalysts were indeed able to steer the reaction towards the *trans*-**8aa** isomer. However, in this case the catalyst providing the best result was found to be a thiourea derivative. The requirement of non-pseudoenantiomeric catalysts for a diastereo-divergent process of this type can be rationalized considering that the transition states leading to *cis*-**8aa** and *trans*-**8aa** are intrinsically diastereomeric, and thus do not necessarily require enantiomeric catalysts for their stabilization/promotion.[73]

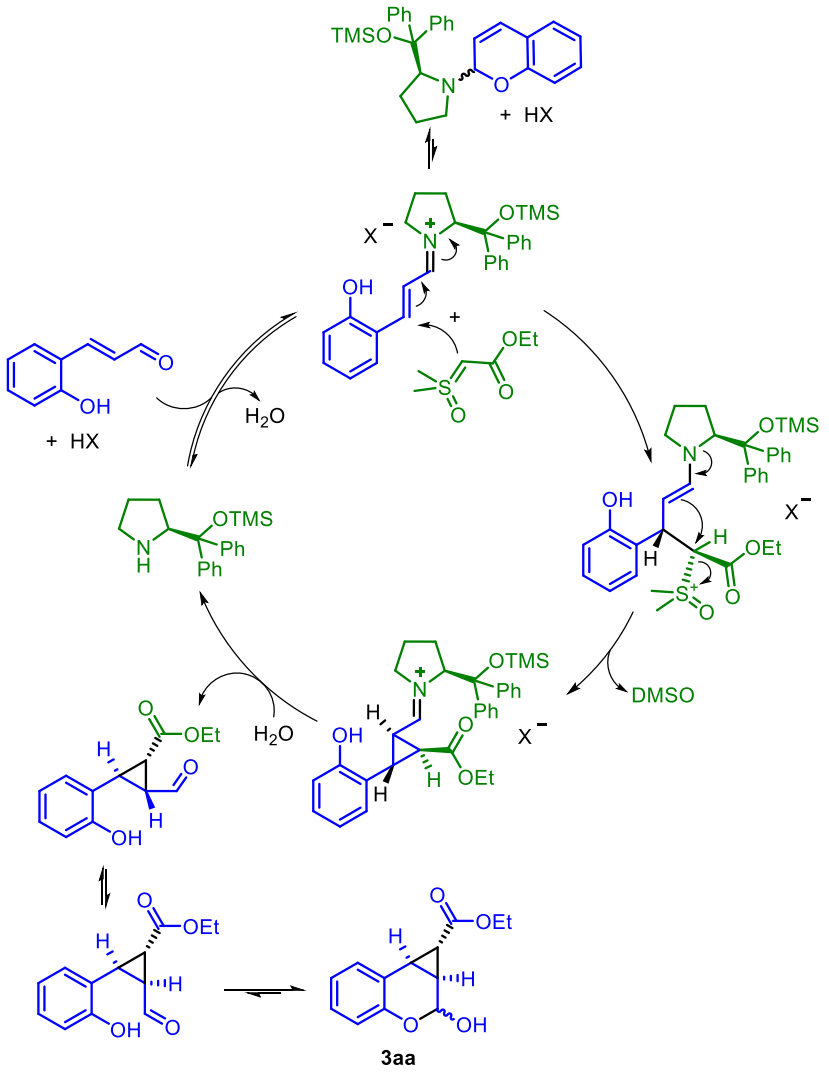
72 Zhu, D.-X.; Liu, J.-G.; Xu, M.-H. *J. Am. Chem. Soc.* **2021**, *143*, 8583.
73 a) Lotter, D.; Castrogiovanni, A.; Neuburger, M.; Sparr, C. *ACS Cent. Sci.* **2018**, *4*, 656. b) Corti, V.; Riccioli, R.; Martinelli, A.; Sandri, S.; Fochi, M.; Bernardi, L. *Chem. Sci.* **2021**, *12*, 10233.




*Scheme 5.5. Screening catalyst for the oxa-Michael reaction*

### 5.2.4 Proposed reaction pathway

In *Scheme 5.6* is summarized our current hypothesis on the reaction pathway. Condensation of the cinnamaldehyde with the catalyst, under acidic conditions, affords a reactive iminium ion in equilibrium with its more stable (and unreactive) hemiaminal form. Attack of the sulfoxonium ylide on the less hindered rear face of the iminium ion results in an enamine intermediate. The enamine can displace DMSO by attacking with its rear face in a $S_N2$-like reaction. The perfect diastereoselectivity observed in all cases can be ascribed either to a highly diastereoselective attack of the ylide to the imium ion, or to a reversible attack to the iminium ion followed by a selectivity determining DMSO displacement step. Hydrolysis releases the catalyst and an aldehyde product with 2,3-*trans* configuration. Epimerization α to the aldehyde function can be expected to be facile in this species. Hemiacetalization traps the *cis*-isomer giving stable compound **3aa**.




*Scheme 5.6. Proposed reaction pathway*

### 5.2.5 Determination of the relative configuration of 4'ab and 3ab

Compound **4'ab** was selected for the assignment of the relative disposition of cyclopropane protons. Full assignment of $^{1}$H NMR signals was preliminarily determined by J-coupling and HSQC and HMBC bidimensional sequences. The $^{1}$H NMR spectrum shows that the $H_3$ signal is coupled with the $H_1$, $H_2$ and $H_{1E}$ giving a ddd signal. The J constant $H_3$-$H_{1E}$ ($J$ = 9.5 Hz) is easily confirmed by the $H_{1E}$ signal at 6.22 ppm. The large value of J coupling constant with the cyclopropane $H_2$ ($J$ = 9.7 Hz) and the smaller J constant with the last cyclopropane $H_1$ ($J$ = 4.3 Hz) suggests that $H_3$ is cis and trans, respectively, to these protons. To confirm the 1R*,2R*,3S* relative configuration, NOESY-1D spectra were acquired (*Figure 5.2*).

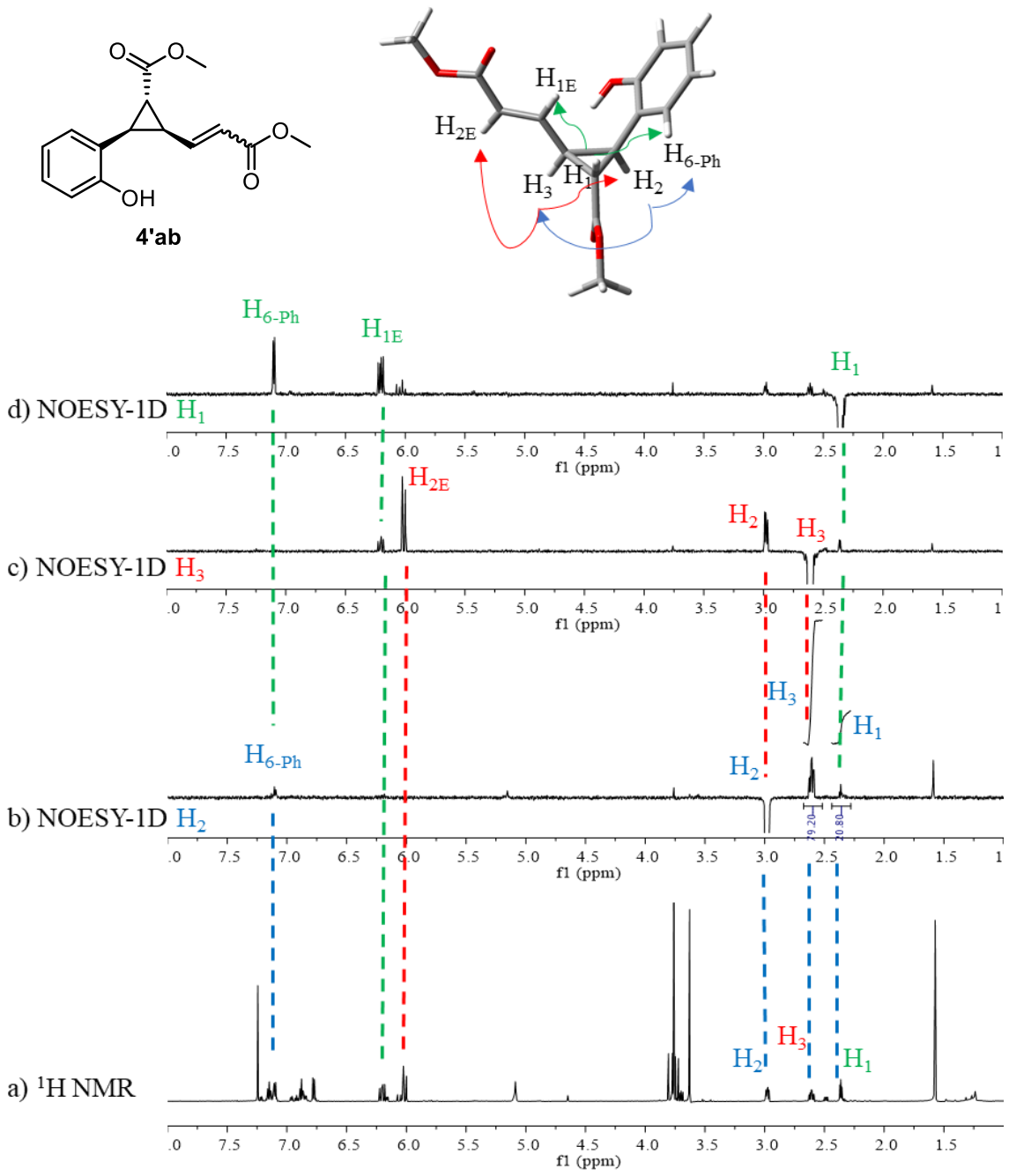
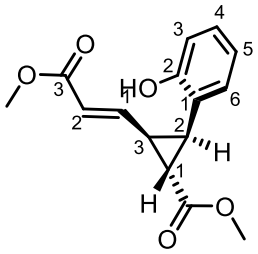



*Figure 5.2 DPFGSE-NOE spectra of 4'ab (600 MHz in $CDCl_3$, T = 25 °C); a) control $^1$H-NMR spectrum; b) saturation of cyclopropane $H_2$ signal; c) saturation of cyclopropane $H_3$ signal; d) saturation of cyclopropane $H_1$ signal.*

On saturation of the proton in position 2 of the cyclopropane ($H_2$), strong NOE effect is generated on the $H_3$ hydrogen (79.2%), smaller on the $H_1$ (20.8%) and $H_{6\text{-Ph}}$ signals (***Figure 5.2*** trace b). If the protons were in the same side, a 50% of NOE effect should occur. When $H_3$ is saturated only $H_2$ and $H_{2E}$ give strong NOE effect. Finally, on saturation of the $H_1$, strong NOE effect is generated on the $H_{1E}$ and $H_{6\text{-Ph}}$ signals confirming that the substituents of the cyclopropane are in the same side of $H_1$.

These results indicate that cyclopropane has a 1R*,2R*,3S* relative configuration.



methyl (1*R*,2*R*,3*S*)-2-(2-hydroxyphenyl)-3-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)cyclopropane-1-carboxylate

Having in hand the relative configuration of compound **4'ab**, the relative assignment of the cyclopropyl ring in both major and minor products of compound **3ab** was done. The two diastereoisomers differ for the configuration of the hemiacetal carbon 2 (*Figure 5.3* up). Keeping in mind the C.I.P. priority groups, the relative configuration is 1S*,1aS*,2*,7bR*. To assign the relative configuration of the two isomers, NOESY-1D experiments were acquired (*Figure 5.3*).

On saturation of the aromatic proton $H_7$, NOE effect is generated on the $H_{7b}$ cyclopropane proton (Figure 2, trace b). When hemiacetal proton of major diastereosiomer ($H_{2maj}$) is saturated, both $H_1$ and $H_{1a}$ give strong NOE effect (Figure S2, trace c), suggesting its disposition in the same side (3D structure in Figure S2, major). Vice versa, $H_1$ does not give NOE effect on saturation of hemiacetal proton of minor diastereosiomer ($H_{2min}$) (trace d) confirming their opposite side (3D structure in Figure S2, minor).

In conclusion, the relative configuration of the major diastereoisomer of **3ab** is 1S*,1aS*,2R*,7bR* and the minor diastereoisomer of **3ab** is 1S*,1aS*,2S*,7bR*.

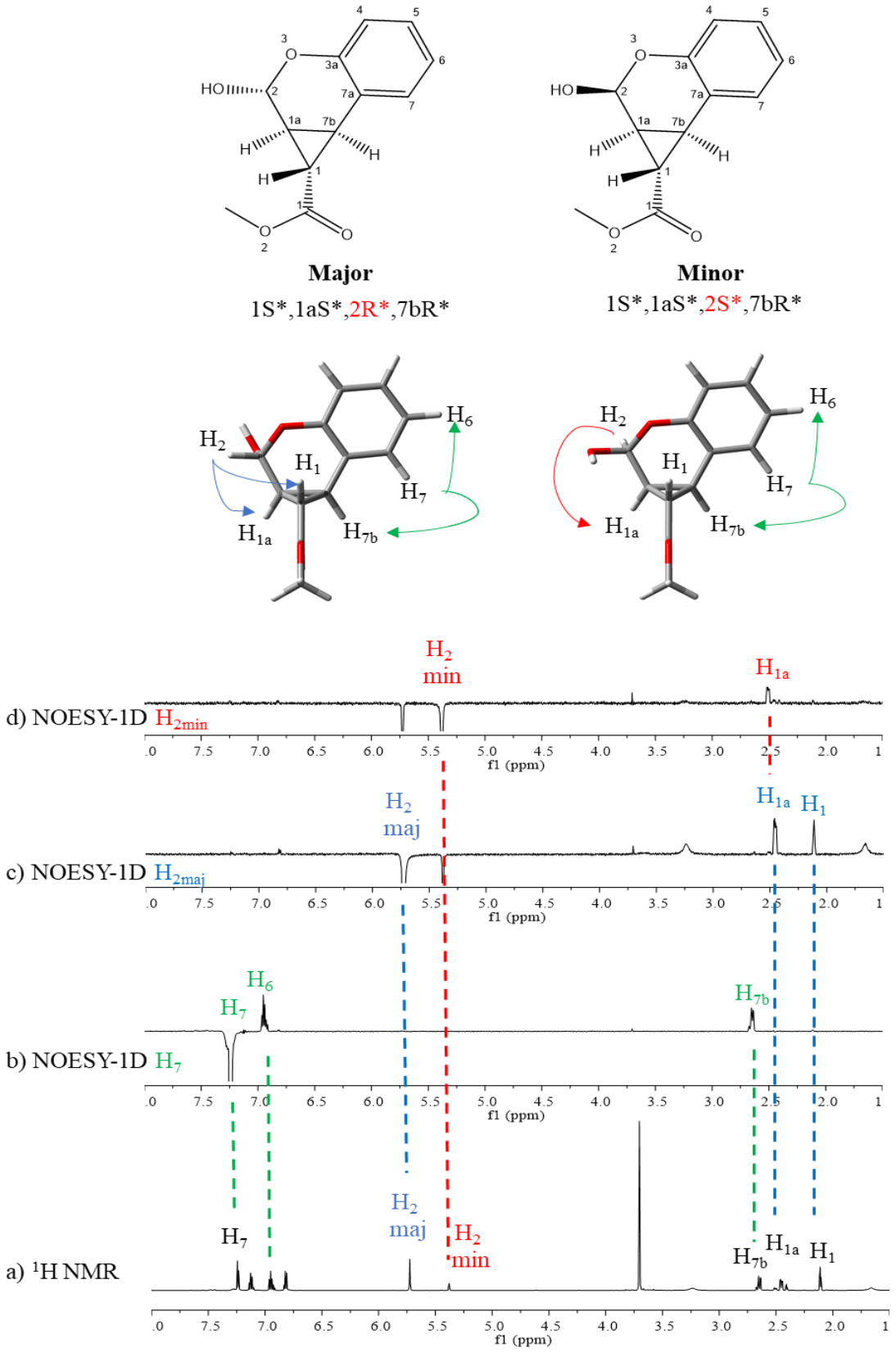
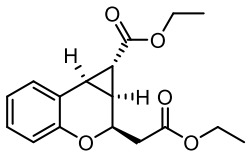
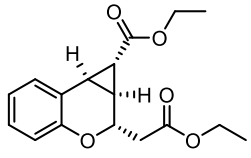



*Figure 5.3 DPFGSE-NOE spectra of* ***3ab*** *(600 MHz in $CDCl_3$, T = 25 °C); a) control $^1$H-NMR spectrum; b) saturation of $H_7$ aromatic signal; c) saturation of $H_{2maj}$ major signal of hemiacetal; d) saturation of $H_{2min}$ minor signal of hemiacetal.*

### 5.2.6 Determination of the relative configuration of cis-8aa and trans-8aa



1a,2-*cis*-**8aa**



1a,2-*trans*-**8aa**

To determine the relative configuration between the C1a and C2 chirality centers of compounds *cis*-and *trans*-**8aa**, NOESY-1D experiments were performed on a mixture enriched in the *trans*-**8aa** isomer (*Figure **5.4***). Irradiation of the aromatic signal corresponding to $H_7$ at 7.22 ppm (dd, *J* = 7.5, 1.5 Hz, 1H) gave a NOE effect on the signal at 6.92 ppm (td, *J* = 7.4, 1.0 Hz, 1H), assigned to $H_6$, and on the signal at 2.56 ppm (dd, *J* = 8.8, 5.2 Hz, 1H) (*Figure **5.4***, trace b). The latter signal could thus be assigned to $H_{7b}$. Such assignment was confirmed by irradiating the signal at 6.75 ppm (br d, *J* = 8.1 Hz, 1H, $H_4$), which gave NOE effect only on the aromatic signal at 7.11 ppm (td, *J* = 7.8, 1.6 Hz, 1H, $H_5$) (not shown). Irradiating the signal at 4.91 ppm (br t, *J* = 6.9 Hz, 1H), assigned to $H_2$ based on its chemical shift, gave NOE effect on the two cyclopropanic proton signals at 2.28 ppm (br t, J = 4.0 Hz, 1H), and 2.27-2.24 ppm (m, 1H) (*Figure 5.4*, trace c). Irrespective of the assignment of these signals to $H_1$ and $H_{1a}$, this result indicates a *cis*-relationship between $H_2$ and $H_1$ and thus, ultimately, a 1a,2-*trans* relationship.

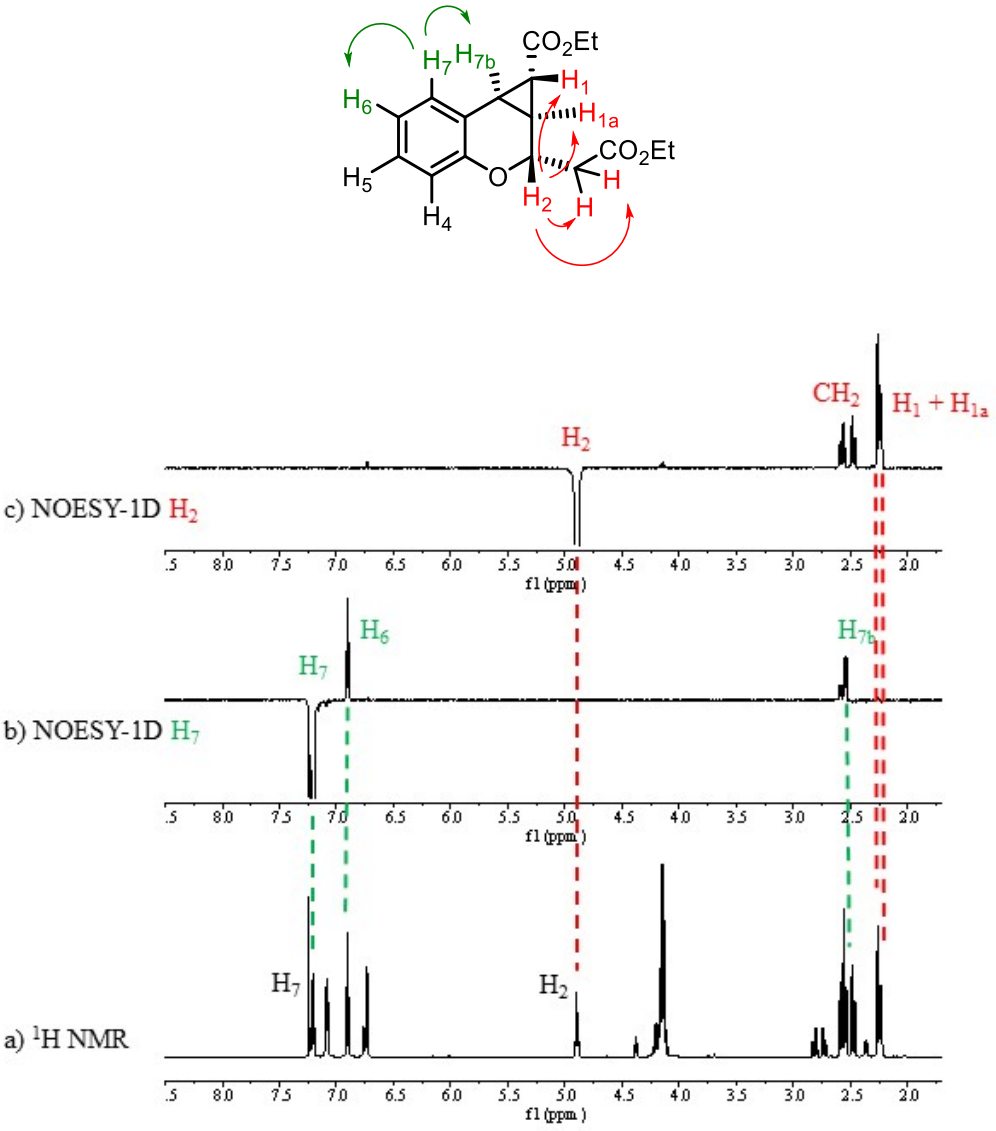



*Figure 5.4. DPFGSE-NOE spectra of* ***8aa****, predominantly 1a,2-trans (600 MHz in $CDCl_3$, T = 25 °C); a) control $^1$H-NMR spectrum; b) saturation of $H_7$ aromatic signal; c) saturation of $H_2$.*

### 5.2.7 Determination of the absolute configuration of compounds 4'ab and 3ab

The determination of the absolute configuration (AC) of these products using X-Ray diffractometer was unfeasible because good crystals were not obtained. Therefore, the electronic circular dichroism (ECD) method was selected for the absolute configuration assignment.

**Absolute Configuration of Compound 4'ab**

The experimental ECD spectrum of compound **4'ab** was acquired in the 195-400 nm region using a JASCO J-810 spectropolarimeter in HPLC-grade acetonitrile solution. Concentration was about $2 \cdot 10^{-4}$ M, optimized in order to have a maximum absorbance less

than 1, with a cell path of 0.1 cm. The spectrum was obtained by the average of 6 scans at 50 nm·min$^{-1}$ scan rate.

The ECD spectrum for compound **4'ab** shows a large negative band at 280 nm and a positive one at 220 nm (vide infra).

For compound **4'ab**, two ground state geometries, within less than 1 kcal/mol, were found and optimized at the B3LYP/6-31G(d,p) level of theory (*Figure 5.5*), and validated by frequency analysis (no imaginary frequency was observed). The two geometries differ in the dihedral angle of the *o*-phenol, which can be -145.4° (73.3%) or +58.7° (26.7%).

The ECD spectra have been calculated in the gas phase for the two conformations with 1*R*,2*R*,2*S* absolute configuration using TD-DFT. Four different hybrid functionals (BH&HLYP[74] and M06-2X,[75] ώB97-XD[76] and CAM-B3LYP[77]) and the basis set (6-311++G(2d,p) were employed (*Figure 5.5*).

74 In Gaussian 16 the BH&HLYP functional has the form: $0.5*E^{EXHF} + 0.5*E^{EXLSDA} + 0.5*\Delta E X^{Becke88} + E C^{LYP}$

75 Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.

76 Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615. Iikura, H.; Tsuneda, T.; Yanai, T.; Hirao, K. *J. Chem. Phys.* **2001**, *115*, 3540.

77 Yanai, T.; Tew, D.; Handy, N. *Chem. Phys. Lett.* **2004**, *393*, 51.

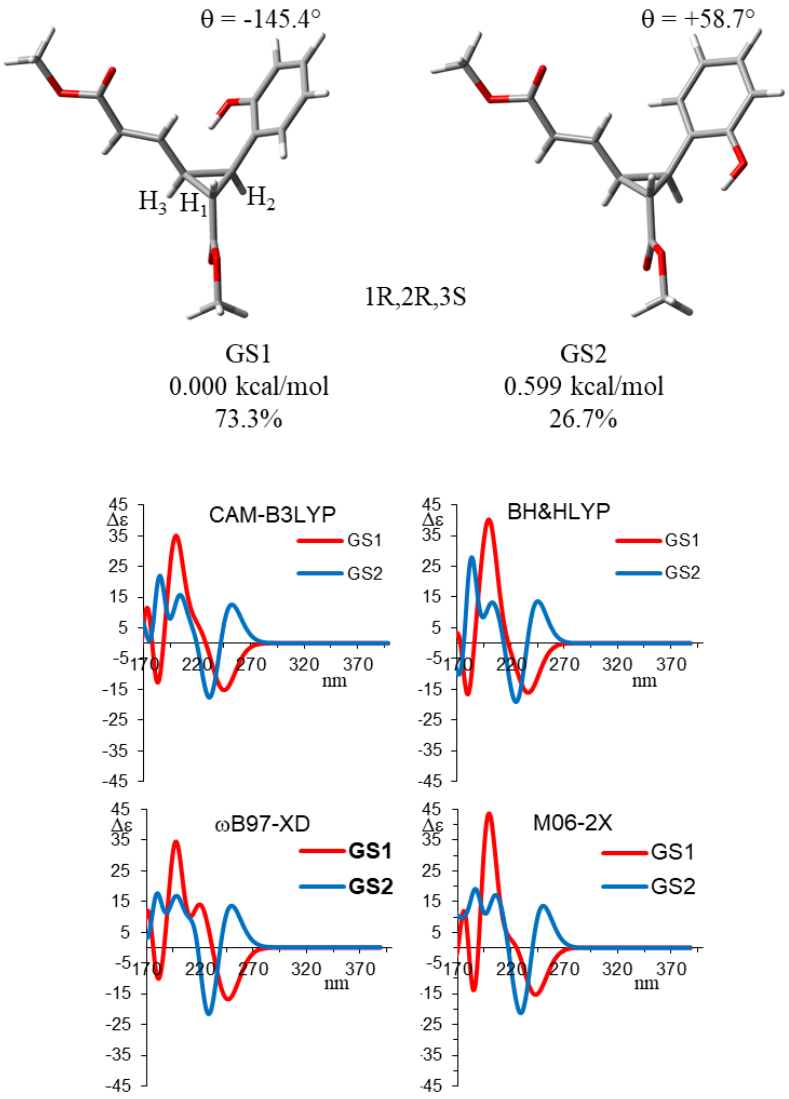



*Figure 5.5. Top: Ground state geometries of **4'ab** with 1R,2R,3S absolute configuration. Bottom: calculated ECD spectra*

The calculated spectra for the two geometries are quite different (*Figure 5.5*), therefore the weighted sum was done and compared with the experimental ECD spectrum (Figure 5.6). The simulated spectra were vertically scaled and red-shifted to get the best match with the experimental spectrum. A very good overlap with the experimental ECD spectrum permits to assign the 1*R*,2*R*,2*S* absolute configuration to compound **4'ab**.

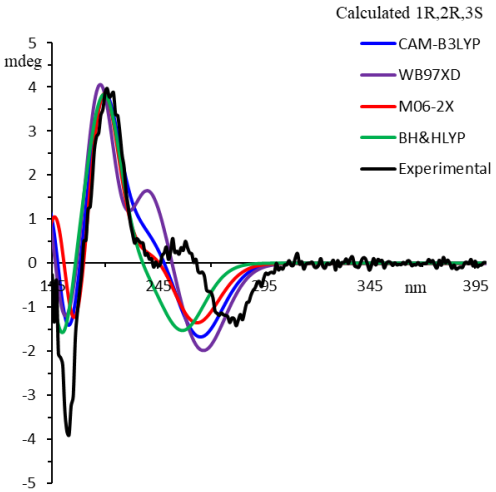



Figure 5.6. Overlap of calculated and experimental (black line) ECD spectra for compound (1*R*,2*R*,2*S*)-**4'ab**.

## Absolute Configuration of Compound 3ab

For compound **3ab**, two diastereomeric geometries were found. Starting from relative configuration, 1*S*,1a*S*,2*R*,7b*R* geometry was calculated for the major diastereoisomer (78% by NMR) and 1*S*,1a*S*,2*S*,7b*R* geometry was calculated for the minor diastereoisomer (22% by NMR).

The ECD spectra have been calculated in the gas phase using TD-DFT, such as for compound **4'ab**. Both calculated spectra for the two diastereoisomers have a good overlap with the experimental ECD of the mixture, meaning that the hemiacetal chiral carbon does not influence the biggest band at 230 nm, that is mainly due to the chromophores tetrahydrocyclopropa[*c*]chromene (*Figure 5.7* and *Figure 5.8*). However, the weighted sum of the two diastereoisomers was done and compared with the experimental ECD spectrum (*Figure 5.9*). The simulated spectra were vertically scaled and red-shifted to get the best match with the experimental spectrum. A very good overlap with the experimental ECD spectrum permits to assign the 1*S*,1a*S*,2*R*,7b*R* A.C. to the major diastereosiomer and 1*S*,1a*S*,2*S*,7b*R* A.C. to the minor diastereoisomer, thus confirming the correctness of the assignment previously done on **4'ab**.

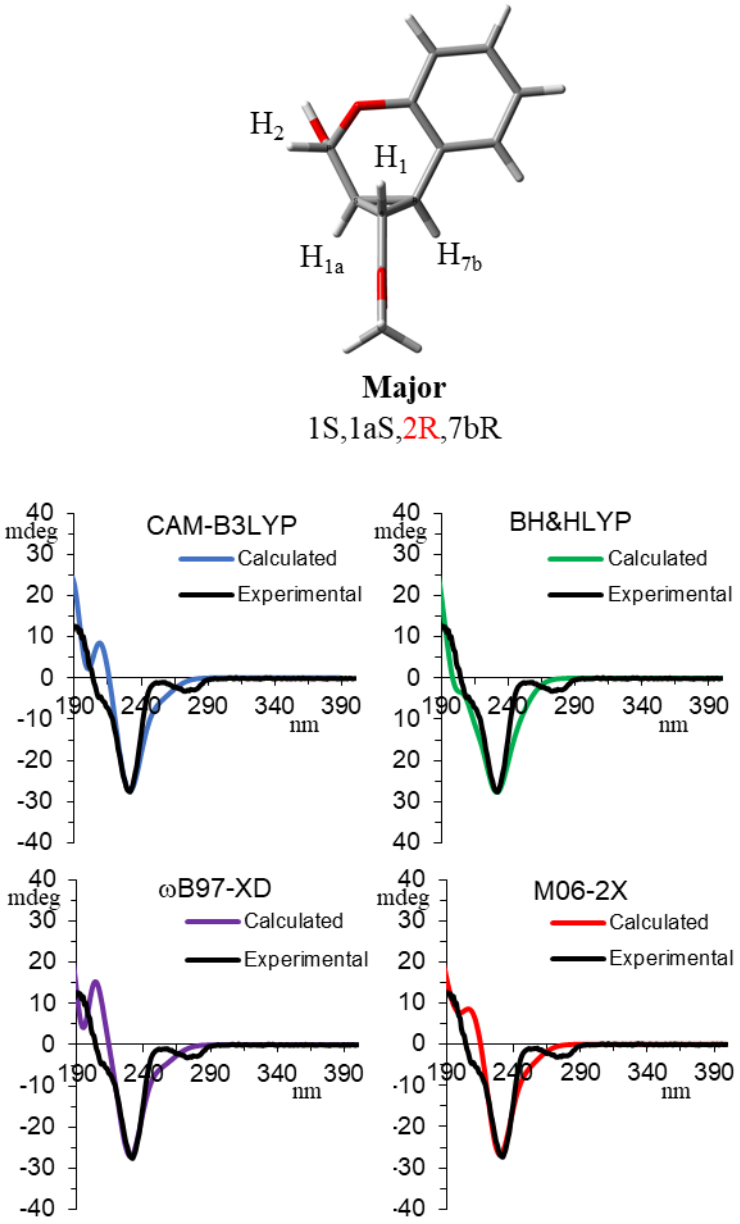



*Figure 5.7. Overlap of calculated ECD spectra for the major diastereoisomer of **3ab**, and the experimental ECD of the diastereomeric mixture.*

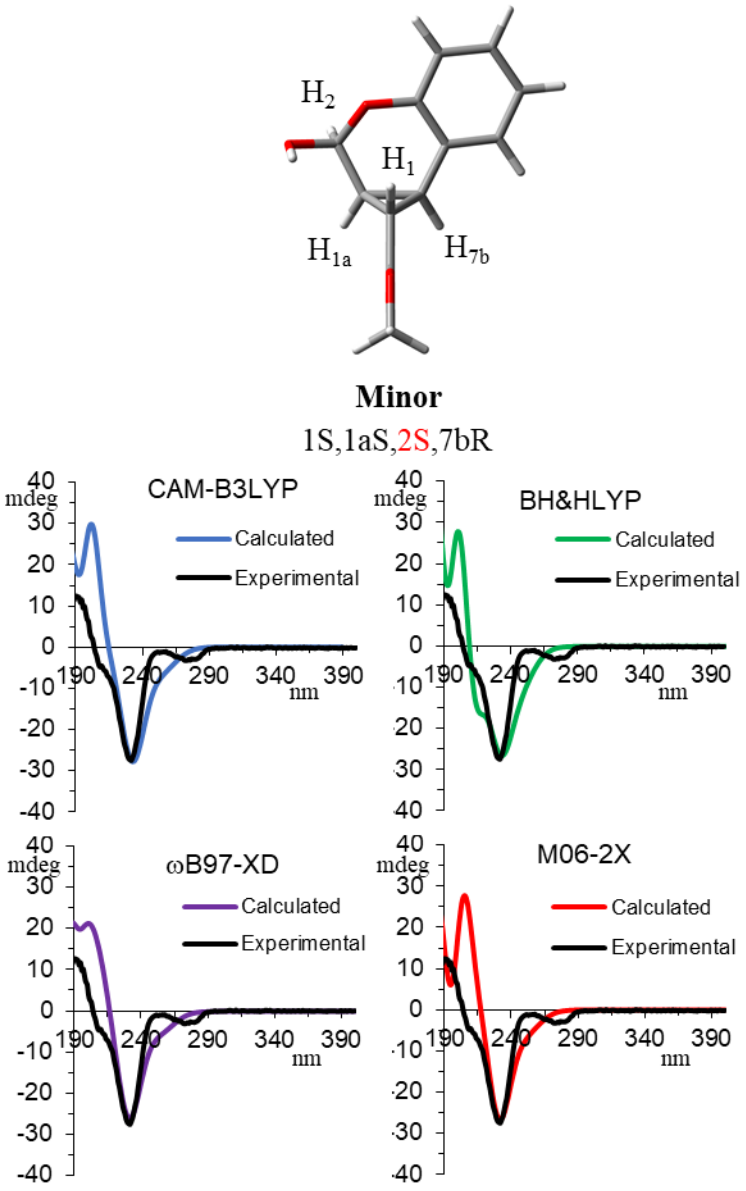



*Figure 5.8. Overlap of calculated ECD spectra for the minor diastereoisomer of* ***3ab****, and the experimental ECD of the diastereomeric mixture*

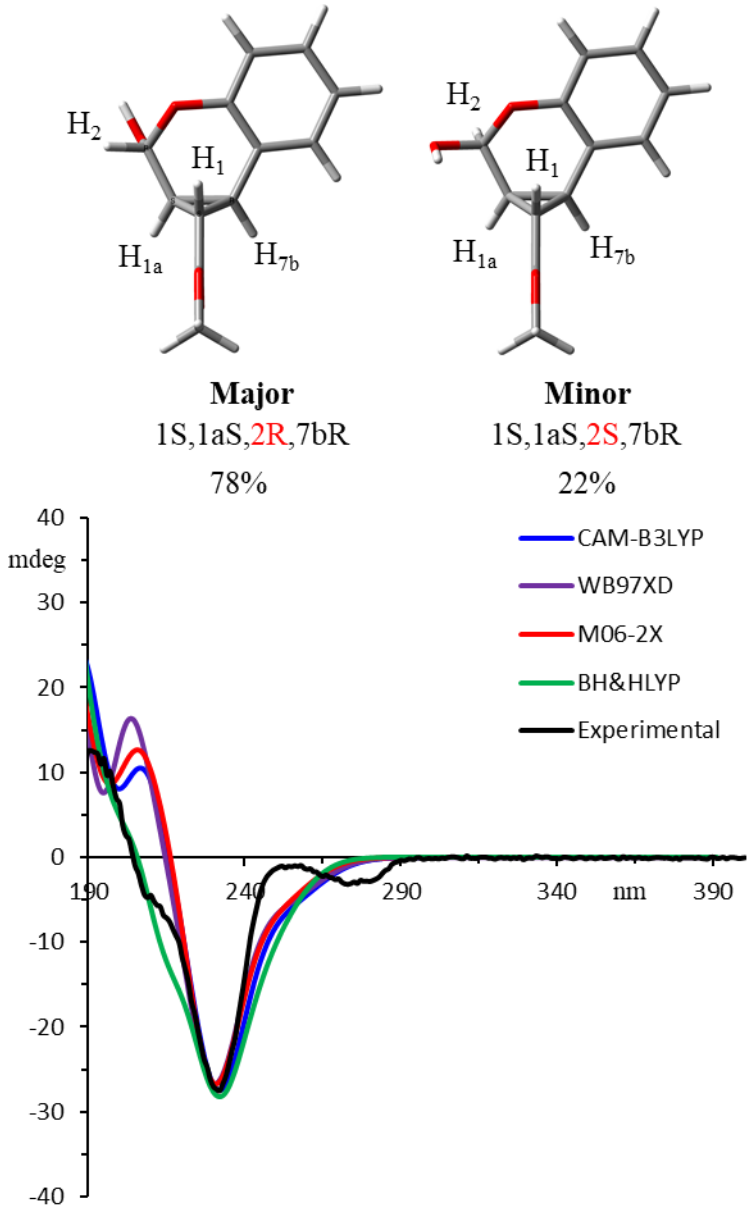



*Figure 5.9. Overlap of calculated, the weighted sum of the two diastereoisomers of **3ab**, and experimental (black line) ECD spectra.*

## 5.3 Conclusions

In conclusion, we have developed the catalytic enantioselective reaction between 2'-hydroxycinnamaldehydes **1** and stabilized sulfoxonium ylides **2**, affording cyclopropane-fused chromane derivatives **3** in moderate yields and excellent enantioselectivites. Besides the evident relevance of the scaffold of these products in medicinal compounds, the presence of a versatile hemiacetal moiety allowed to perform various synthetic elaborations. Disclosing the first utilization of sulfoxonium ylides under aminocatalytic

conditions, these results add an important piece to the still poorly disclosed puzzle of asymmetric organocatalysis with sulfoxonium ylides substrates *Figure 5.10*).

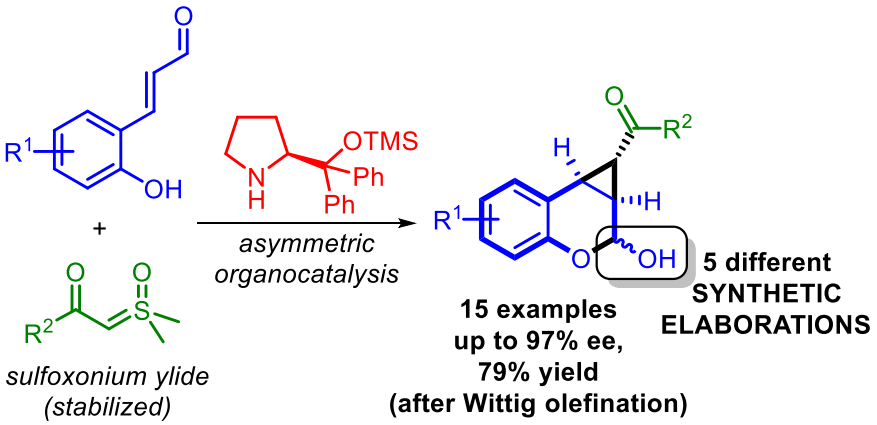



*Figure 5.10. Summary of the project*

## 5.4 Experimental section

**General Methods**. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Mercury 300, 400 or Inova 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvents signals for $^{1}H$ and $^{13}C$ NMR.[78] $^{13}C$ NMR were acquired with $^{1}H$ broad-band decoupled mode. NOE spectra were recorded using the DPFGSE-NOE sequence,[79] using a mixing time of 2.80 s and "rsnob" 50 Hz wide selective pulses. ECD spectra were recorded on a Jasco J-810 instrument. High Resolution Mass Spectra (HRMS) were recorded on a Waters Xevo Q-TOF spectrometer. ESI spectra were recorded on a micromass LCT spectrometer using electrospray (ESI) ionization technique. Compounds **4ba-ga** are rather unstable and could not be subjected to HRMS analysis, but only to ESI (faster access). Optical rotations were measured on a Perkin Elmer 241 Polarimeter provided with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\,(^{\circ}C)}$ (c = g/100 mL, solvent). The enantiomeric excess of the products (ee) were determined by chiral stationary phase HPLC (Daicel Chiralpak OJ-H or AD-H or IC columns), using a UV detector operating at 254 nm. Infrared (ATR) spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer equipped with an ATR probe. Signals are reported as strong (s), medium (m), and weak (w). Melting points (uncorrected) were determined with a Stuart Scientific SMP3 apparatus. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) or by gravimetric chromatography using 70-230 mesh silica. The absolute and relative configuration of the products was determined on compounds **4'ab** and **3ab** (see dedicated section), and assigned by analogy to the remaining compounds. The relative configuration at the cyclopropane of known compound **6aa**, derived from **3aa**, is in line with this assignment.

**Materials**. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Catalyst **A** was purchased from Fluorochem and used as received. Reference racemic products **4** for CSP HPLC analysis were prepared using an equimolar mixture of (*R*)-**A** and (*S*)-**A** as catalyst. Catalysts **QN-1** and **dhQD-1** were prepared according to the literature.[80]

78 Gottlieb, H. E.; Kottlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.

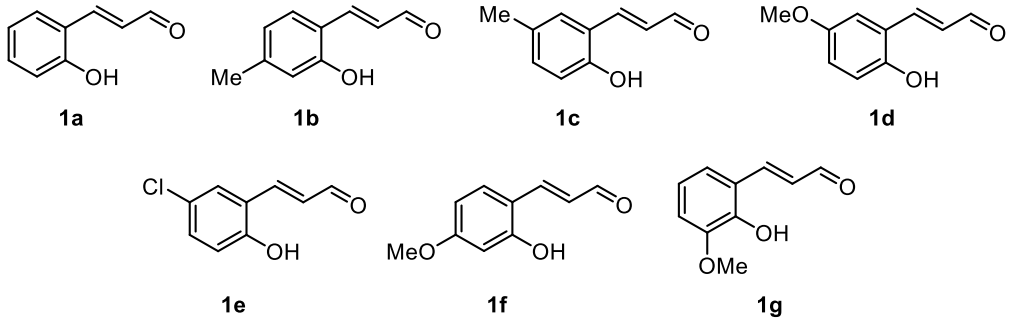
79 a) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037. b) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. c) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302. d) Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Reson.* **1999**, *141*, 191.

80 a) Wang, Y.; Milikiewicz, K. L.; Kaufman, M. L.; He, L.; Landmesser, N. G.; Levy, D. V.; Allwein, S. P.; Christie, M. A.; Olsen, M. A.; Nelville, C. J.; Muthukumaran, K. *Org. Process Res. Dev.* **2017**, *21*, 408. b) Cassani, C; Martín-Rapún, R.; Arceo, E.; Bravo, F.; Melchiorre, P. *Nat. Protoc.* **2013**, *8*, 325. c) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

**Starting Materials**

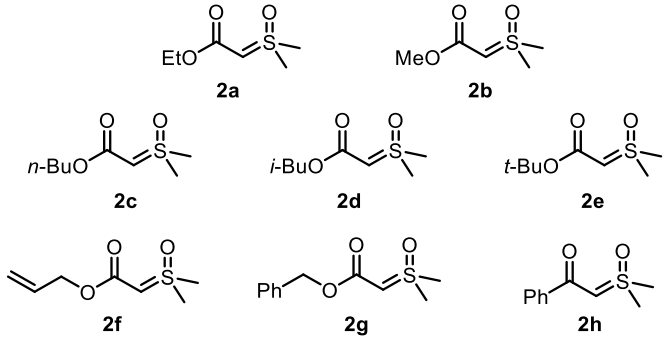
**2'-hydroxycinnamaldehydes 1**

2'-hydroxycinnamaldehydes **1**, reported below, were prepared according to literature procedure.[81]

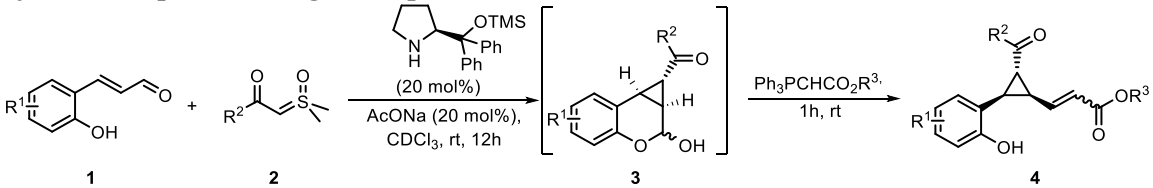



**Sulfoxonium ylides 2**

Sulfoxonium ylides **2**, reported below, were prepared according to literature procedure.[82]




**Synthesis of products 4: general procedure and characterization**

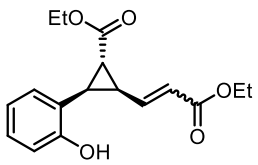



In a small vial equipped with a magnetic stirring bar, aldehyde **1** (0.1 mmol, 1 equiv.) and sulfoxonium ylide **2** (0.15 mmol, 1.5 equiv.) were added to a $CDCl_3$ (1 mL) solution of catalyst (*S*)-**A** (0.02 mmol, 0.20 equiv., 6.5 mg) and AcONa (0.02 mmol, 0.20 equiv., 1.6 mg). The resulting mixture was stirred at room temperature for 12 h. Subsequently, the appropriate phosphorous ylide (0.3 mmol, 3 equiv.) was added and the resulting mixture was stirred at room temperature for 1 h. Next, the solvent was eliminated under vacuum and directly purified by flash column chromatography on silica gel affording compounds **4** as E/Z mixtures. In some cases, a fraction containing compounds **4** as single E-isomers was collected and used for the characterization. In all cases, the E-**4** isomer was highly prevalent over its Z-**4** counterpart (estimated ratio in the crude >9:1).

81 Ackrill, T. D.; Sparkes, H. A.; Wills, C. L. *Org. Lett.* **2015**, *17*, 3884-3887.

82 Bisag, G. D.; Ruggieri, S.; Fochi, M.; Bernardi, L. *Adv. Synth. Catal.* **2021**, *363*, 3053-3059.

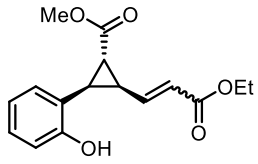
**Ethyl (1*R*,2*S*,3*R*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxyphenyl)cyclopropane-1-carboxylate 4aa**




**4aa**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2a**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4aa** as E/Z mixture, and a fraction containing pure E-**4aa** as colorless oils (overall 67% yield, 20.4 mg). Performing the reaction on 1 mmol scale, that is, using 148.2 mg of substrate **1a** (1.0 mmol), 246.3 mg of ylide **2a** (1.5 mmol), 65.1 mg of catalyst (*S*)-**A** (0.20 mmol), 16.4 mg of sodium acetate (0.20 mmol) in 10 mL of $CDCl_3$ as solvent for the catalytic reaction, and 1.045 g of phosphorous ylide (3 mmol) for the Wittig reaction, product **4aa** was obtained in 69% overall yield (210.0 mg, 0.69 mmol) and 97% ee. E-**4aa** isomer: $[\alpha]_D^{25}$ = +20 (c = 0.5, $CH_2Cl_2$) for 97% ee. **IR** (ATR) ν(max) =3408 (br, m) 2981 (m) 1717 (s) 1697 (s) 1176 (s) $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$, +25 °C) δ = 7.18 – 7.07 (m, 2H), 6.88 (t, J = 7.5 Hz, 1H), 6.78 (dd, J = 8.0, 1.2 Hz, 1H), 6.22 (dd, J = 15.5, 10.3 Hz, 1H), 6.02 (d, J = 15.5 Hz, 1H), 5.35 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 2.98 (dd, J = 9.2, 5.7 Hz, 1H), 2.61 (ddd, J = 10.4, 9.2, 4.4 Hz, 1H), 2.37 (dd, J = 5.7, 4.3 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 172.0, 166.0, 155.0, 144.9, 129.8, 128.9, 122.7, 120.9, 120.7, 115.5, 61.3, 60.3, 30.4, 28.4, 27.8, 14.25, 14.21. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}O_5Na$ 327.1203; Found 327.1196. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min) $t_{min}$ = 15.1, min, $t_{maj}$ = 17.9 min.

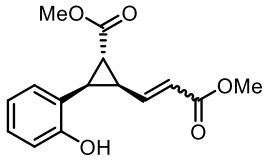
**Methyl (1*R*,2*S*,3*R*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxyphenyl)cyclopropane-1-carboxylate 4ab**




**4ab**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2b**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing E/Z mixture of **4ab** as colorless oil (64% yield, 18.6 mg) with 96% ee. E/Z-**4ab**: **IR** (ATR) ν(max) =3392 (br, m) 1710 (s) 1691 (s) 1248 (s) 1167 (s) 1139 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 7.14 (ddd, J = 8.1, 7.4, 1.7, Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.20 (dd, J = 15.5, 10.4 Hz, 1H), 6.01 (d, J = 15.5 Hz, 1H), 5.12 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 2.97 (dd, J = 9.1, 5.7 Hz, 1H), 2.61 (ddd, J = 10.3, 9.2, 4.3 Hz, 1H), 2.36 (dd, J = 5.7, 4.4 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 172.4, 165.9, 154.9, 144.7, 129.8, 128.9, 122.8, 120.8, 120.7, 115.5, 60.3, 52.3, 30.4, 28.4, 27.5, 14.2 **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{18}O_5Na$ 313.1046; Found 313.1043; $[M + K]^+$ Calcd for $C_{16}H_{18}KO_5$ 329.0786; Found 329.0780. **HPLC**: IC (*n*-hexane/*i*-PrOH 80:20, 1 mL/min) E-isomer: $t_{min}$ = 7.7 min, $t_{maj}$ = 9.4 min.

**Methyl (1*R*,2*R*,3*S*)-2-(2-hydroxyphenyl)-3-(3-methoxy-3-oxoprop-1-en-1-yl)cyclopropane-1-carboxylate 4'ab**

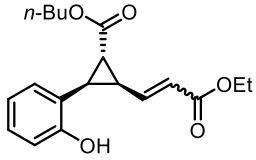



**4'ab**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2b,** and methyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing E/Z mixture of **4'ab** as colorless oil in 62% yield (17.1 mg) with 94% ee. E/Z-**4'ab**: **IR** (ATR) ν(max) =3392 ( br, m) 1710 (s) 1691 (s) 1248 (s) 1167 (s) 1139 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 7.15 (td, *J* = 7.8, 1.6 Hz, 1H), 7.10 (dd, *J* = 6.3, 4.8 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.78 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.20 (dd, *J* = 15.5, 10.4 Hz, 1H), 6.01 (d, *J* = 15.4 Hz, 1H), 5.09 (s, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 3.01 – 2.94 (m, 1H), 2.61 (ddd, *J* = 10.2, 9.1, 4.3 Hz, 1H), 2.36 (dd, *J* = 5.7, 4.4 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 172.3, 166.3, 154.9, 145.0, 129.9, 128.9, 122.4, 120.83, 120.81, 115.5, 52.3, 51.5, 30.4, 28.5, 27.6. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}O_5Na$ 299.0890;

Found 299.0886; $[M + K]^+$ Calcd for $C_{15}H_{16}KO_5$ 315.0629; Found 315.0637. **HPLC**: ADH (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min) E-isomer: $t_{maj}$ = 18.2 min, $t_{min}$ = 19.6 min.

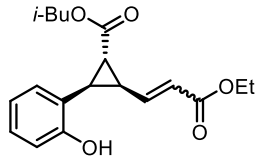
**Butyl (1*R*,2*S*,3*R*)-2-(-3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxyphenyl)cyclopropane-1-carboxylatecarboxylate 4ac**




**4ac**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2c,** and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4ac** as E/Z mixture, and a fraction containing pure E-**4ac** as colorless oils (overall 60% yield, 19.9 mg) with 95% ee. E-**4ac** isomer: $[\alpha]_D^{25}$ = +28 (c = 0.5, $CH_2Cl_2$) for 95% ee. **IR** (ATR) ν(max) =3398 (br, m) 1718 (s) 1693 (s) 1248 (s) 1168 (s) 1139 (s) $cm^{-1}$.**$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) δ = 7.17 – 7.06 (m, 2H), 6.87 (td, J = 7.5, 1.2 Hz, 1H), 6.77 (dd, J = 8.1, 1.2 Hz, 1H), 6.21 (dd, J = 15.5, 10.4 Hz, 1H), 6.01 (d, J = 15.4 Hz, 1H), 5.29 (s, 1H), 4.15 (t, J = 6.7 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 2.96 (dd, J = 9.1, 5.7 Hz, 1H), 2.60 (ddd, J = 10.3, 9.1, 4.3 Hz, 1H), 2.36 (dd, J = 5.7, 4.3 Hz, 1H), 1.72 – 1.56 (m, 2H), 1.46 – 1.34 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 172.1, 166.0, 155.0, 144.9, 129.8, 128.9, 122.7, 120.9, 120.7, 115.5, 65.2, 60.3, 30.6, 30.3, 28.4, 27.8, 19.1, 14.1, 13.7. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{24}O_5Na$ 355.1516; Found 355.1508. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min) $t_{min}$ = 10.6 min, $t_{maj}$ = 12.4 min.

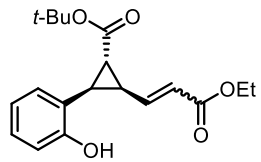
**Isobutyl (1*R*,2*S*,3*R*)-2-(-3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxyphenyl)cyclopropane-1-carboxylate 4ad**




**4ad**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2d**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4ad** as E/Z mixture, and a fraction containing pure E-**4ad** as colorless oils (overall 70% yield, 23.2 mg) with 95% ee. E-**4ad** isomer: $[\alpha]_D^{25}$ = +27 (c = 0.5, $CH_2Cl_2$) for 95% ee. **IR** (ATR) ν(max) =3396 (br, m) 1718 (s) 1693 (s) 1247 (s) 1163 (s) 1139 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) δ = 7.17 – 7.05 (m, 2H), 6.87 (td, J = 7.5, 1.2 Hz, 1H), 6.77 (dd, J = 8.1, 1.2 Hz, 1H), 6.22 (dd, J = 15.5, 10.4 Hz, 1H), 6.01 (d, J = 15.4 Hz, 1H), 5.30 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.93 (d, J = 6.6 Hz, 2H), 2.97 (dd, J = 9.2, 5.7 Hz, 1H), 2.61 (ddd, J = 10.4, 9.1, 4.4 Hz, 1H), 2.37 (dd, J = 5.7, 4.4 Hz, 1H), 2.01-1.97 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.7 Hz, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 172.0, 166.0, 155.0, 144.9, 129.8, 128.9, 122.7, 120.9, 120.7, 115.5, 71.4, 60.3, 30.3, 28.4, 27.8, 27.7, 19.1, 14.1. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{24}O_5Na$ 355.1516; Found 355.1515. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min) $t_{min}$ = 8.9 min, $t_{maj}$ = 10.0 min.

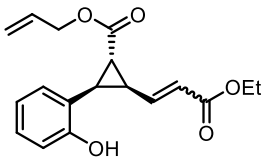
***tert*-Butyl (1*R*,2*S*,3*R*)-2-(-3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxyphenyl)cyclopropane-1-carboxylate 4ae**




**4ae**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2e**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4ae** as E/Z mixture, and a fraction containing pure E-**4ae** as colorless oils (overall 57% yield, 19.0 mg) with 95% ee. E-**4ae** isomer: $[\alpha]_D^{25}$ = +25 (c = 0.4, $CH_2Cl_2$) for 95% ee. **IR** (ATR) ν(max) =3423 (br, m) 1710 (s) 1698 (s) 1254 (s) 1141 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) δ = 7.17 – 7.06 (m, 2H), 6.87 (td, *J* = 7.5, 1.2 Hz, 1H), 6.78 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.20 (dd, *J* = 15.5, 10.4 Hz, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 5.29 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.89 (dd, *J* = 9.1, 5.7 Hz, 1H), 2.53 (ddd, *J* = 10.4, 9.2, 4.4 Hz, 1H), 2.28 (dd, *J* = 5.8, 4.4 Hz, 1H), 1.48 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 171.0, 166.0, 155.0, 145.1, 129.8, 128.8, 122.6, 121.0, 120.6, 115.5, 81.6, 60.2, 30.0, 28.8, 28.1, 28.0, 14.2. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{24}O_5Na$ 355.1516; Found 355.1514. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min) $t_{min}$ = 7.1 min, $t_{maj}$ = 7.8 min.

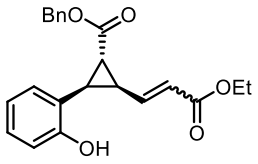
**Allyl (1*R*,2*S*,3*R*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxyphenyl)cyclopropane-1-carboxylate 4af**



**4af**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2f**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4af** as E/Z mixture, and a fraction containing pure E-**4af** as colorless oils (overall 65% yield, 20.5 mg) with 90% ee. E-**4af** isomer: $[\alpha]_D^{25}$ +31 (c = 0.3, $CH_2Cl_2$) for 90% ee. **IR** (ATR) ν(max) =3393 (br, m) 1712 (s) 1692 (s) 1249 (s) 1160 (s) 1139 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) δ = 7.19 – 7.06 (m, 2H), 6.87 (td, *J* = 7.5, 1.2 Hz, 1H), 6.77 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.21 (dd, *J* = 15.5, 10.3 Hz, 1H), 6.01 (d, *J* = 15.5 Hz, 1H), 5.94 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.39 – 5.31 (m, 1H), 5.27 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.23 (s, 1H), 4.65 (dt, *J* = 5.9, 1.4 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.99 (dd, *J* = 9.2, 5.7 Hz, 1H), 2.62 (ddd, *J* = 10.3, 9.1, 4.3 Hz, 1H), 2.39 (dd, *J* = 5.7, 4.4 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 171.7, 165.9, 154.9, 144.7, 131.8, 129.8, 128.9, 122.8, 120.8, 120.7, 118.7, 115.5, 65.9, 60.3, 30.5, 28.5, 27.7, 14.1. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{20}O_5Na$ 339.1203; Found 339.1210. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min) $t_{min}$ = 15.3 min, $t_{maj}$ = 19.1 min.

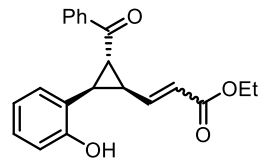
**Benzyl (1*R*,2*S*,3*R*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxyphenyl)cyclopropane-1-carboxylate 4ag**



**4ag**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2g** and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4ag** as E/Z mixture, and a fraction containing pure E-**4ag** as colorless oils (overall 56% yield, 10.5 mg) with 97% ee. E-**4ag** isomer: $[\alpha]_D^{25}$ = +11 (c = 0.4, $CH_2Cl_2$) for 97% ee. **IR** (ATR) ν(max) =3388 (br, m) 1714 (s) 1690 (s) 1248 (s) 1161 (s) 1138 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) δ = 7.41 – 7.29 (m, 5H), 7.17 – 7.06 (m, 2H), 6.86 (td, *J* = 7.5, 1.2 Hz, 1H), 6.76 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.20 (dd, *J* = 15.5, 10.3 Hz, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 5.19 (br s, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.00 (dd, *J* = 9.2, 5.7 Hz, 1H), 2.63 (ddd, *J* = 10.4, 9.2, 4.3 Hz, 1H), 2.42 (dd, *J* = 5.7, 4.3 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 171.8, 165.9, 154.9, 144.7, 135.5, 129.8, 128.9, 128.6, 128.4, 128.3, 122.9, 120.8, 120.7, 115.5, 67.1, 60.3, 30.5, 28.6, 27.7, 14.1. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{22}O_5Na$ 389.1359; Found 389.1357. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min) $t_{min}$ = 27.3 min, $t_{maj}$ = 38.7 min.

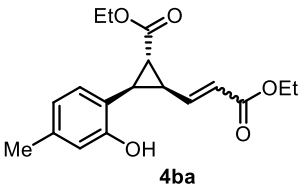
**Ethyl 3-((1*S*,2*R*,3*R*)-2-benzoyl-3-(2-hydroxyphenyl)cyclopropyl)acrylateacrylate 4ah**



**4ah**

The general procedure was followed using aldehyde **1a**, sulfoxonium ylide **2h**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4ah** as E/Z mixture as colorless oil (35% yield, 12.4 mg) with 93% ee. E/Z-**4ah** mixture: **IR** (ATR) ν(max) =3431 (br, m) 1700 (s) 1661 (s) 1253 (s) 1140 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 8.09 – 8.05 (m, 2H), 7.65 – 7.57 (m, 1H), 7.55 – 7.48 (m, 2H), 7.20-7.17 (m, 2H), 6.91 (td, *J* = 7.5, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.5, 1.2 Hz, 1H), 6.41 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.06 (d, *J* = 15.5 Hz, 1H), 5.24 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.38 (dd, *J* = 5.6, 4.2 Hz, 1H), 3.23 (dd, *J* = 8.9, 5.6 Hz, 1H), 2.81 (ddd, *J* = 10.6, 8.9, 4.2 Hz, 1H), 1.29 – 1.15 (m, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 197.1, 166.1, 155.0, 145.2, 137.3, 133.4, 130.0, 129.0, 128.8, 128.3, 122.7, 121.3, 120.8, 115.7, 60.3, 33.5, 32.2, 30.7, 14.2. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{20}O_4Na$ 359.1254; Found 359.1253. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min, E-isomer) $t_{min}$ = 30.7 min, $t_{maj}$ = 42.6 min.

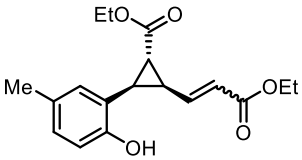
**Ethyl (1*R*,2*S*,3*R*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxy-4-methylphenyl)cyclopropane-1-carboxylate 4ba**



**4ba**

The general procedure was followed using aldehyde **1b**, sulfoxonium ylide **2a**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4ba** as E/Z mixture, and a fraction containing pure E-**4ba** as colorless oils (overall 52% yield, 16.5 mg) with 92% ee. E-**4ba** isomer: $[\alpha]_D^{25}$ +38 (c = 0.3, $CH_2Cl_2$) for 92% ee. **IR** (ATR) ν(max) =3396 (br, m) 1715 (s) 1693 (s) 1251 (s) 1173 (s) 1139 (s) $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$, +25 °C) δ = 7.02 – 6.93 (m, 1H), 6.69 (dt, *J* = 7.7, 1.1 Hz, 1H), 6.61 (s, 1H), 6.22 (dd, *J* = 15.5, 10.4 Hz, 1H), 6.02 (d, *J* = 15.5 Hz, 1H), 5.06 (s, 1H), 4.28 – 4.18 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.93 (dd, *J* = 9.1, 5.6 Hz, 1H), 2.58 (ddd, *J* = 10.4, 9.1, 4.3 Hz, 1H), 2.33 (dd, *J* = 5.7, 4.3 Hz, 1H), 2.28 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 172.0, 166.0, 154.7, 145.0, 139.1, 129.6, 122.7, 121.5, 117.7, 116.2, 61.3, 60.2, 30.4, 28.2, 27.8, 21.1, 14.25, 14.22. **MS** (ESI) m/z: $[M + Na]^+$ 341. **HPLC**: IC (*n*-hexane/*i*-PrOH 80:20, 1 mL/min) $t_{min}$ = 7.1 min, $t_{maj}$ = 8.8 min.

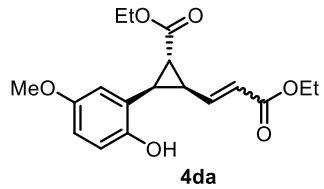
**Ethyl (1*R*,2*S*,3*R*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxy-5-methylphenyl)cyclopropane-1-carboxylate 4ca**



**4ca**

The general procedure was followed using aldehyde **1c**, sulfoxonium ylide **2a**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing E/Z mixture of **4ca** as colorless oil (overall 45% yield, 14.3 mg) and 95% ee. E/Z-**4ca**: **IR** (ATR) ν(max) =3433 (br, m) 1703 (s) 1700 (s) 1251 (s) 1180 (s) 1138 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 6.98 – 6.86 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.20 (dd, *J* = 15.5, 10.4 Hz, 1H), 6.03 (dd, *J* = 23.6, 15.5 Hz, 1H), 4.94 (s, 1H), 4.26 – 4.15 (m, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.00 – 2.89 (m, 1H), 2.58 (ddd, *J* = 10.5, 9.1, 4.3 Hz, 1H), 2.35 (dd, *J* = 5.7, 4.3 Hz, 1H), 2.24 (s, 3H), 1.33 – 1.26 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 172.0, 165.9, 152.6, 144.9, 130.3, 129.9, 129.3, 122.7, 115.4, 61.3, 60.2, 30.4, 28.5, 27.7, 20.5, 14.27, 14.23. **MS** (ESI) m/z: $[M + Na]^+$ 341. **HPLC**: IC (*n*-hexane/*i*-PrOH 80:20, 1 mL/min) E-isomer: $t_{min}$ = 6.9 min, $t_{maj}$ = 8.6 min.

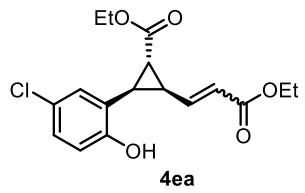
**Ethyl (1*R*,2*S*,3*R*)-2-(-3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxy-5-methoxyphenyl)cyclopropane-1-carboxylate 4da**



**4da**

The general procedure was followed using aldehyde **1d**, sulfoxonium ylide **2a**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing E/Z mixture of **4da** as colorless oil (overall 63% yield, 21.1 mg), and 97% ee. E/Z-**4da**: **IR** (ATR) ν(max) =3409 (br, m) 1714 (s) 1695 (s) 1251 (s) 1199 (s) 1176 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 6.80 – 6.60 (m, 3H), 6.23 (dd, *J* = 15.5, 10.3 Hz, 1H), 6.03 (d, *J* = 15.5 Hz, 1H), 4.82 (s, 1H), 4.22 (qd, *J* = 7.2, 0.6 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 2.99 – 2.93 (m, 1H), 2.60 (ddd, *J* = 10.4, 9.2, 4.3 Hz, 1H), 2.34 (dd, *J* = 5.7, 4.4 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 171.8, 165.9, 153.5, 148.9, 144.7, 122.9, 121.9, 116.3, 115.6, 113.8, 61.3, 60.3, 55.8, 30.3, 28.6, 27.8, 14.25, 14.22. **MS** (ESI) m/z: $[M + Na]^+$ 357. **HPLC**: IC (*n*-hexane/*i*-PrOH 80:20, 1 mL/min) E-isomer: $t_{min}$ = 10.2 min, $t_{maj}$ = 11.7 min.

**Ethyl (1*R*,2*R*,3*S*)-2-(5-chloro-2-hydroxyphenyl)-3-(-3-ethoxy-3-oxoprop-1-en-1-yl)cyclopropane-1-carboxylate 4ea**

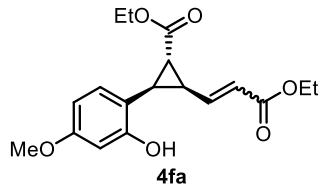


**4ea**

The general procedure was followed using aldehyde **1e**, sulfoxonium ylide **2a**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing **4ea** as E/Z mixture, and a fraction containing pure E-**4ea** as pale yellow oils (overall 57% yield, 19.3 mg) with 90% ee. E-**4ea**: $[\alpha]_D^{25}$ = +38 (c = 0.3, $CH_2Cl_2$) for 90% ee**. IR** (ATR) ν(max) = 3389 (br, m) 1734 (s) 1723 (s) 1231 (s) 1208 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 7.15 – 7.04 (m, 2H), 6.73 – 6.66 (m, 1H), 6.17 (dd, *J* = 15.4, 10.3 Hz, 1H), 6.01 (d, *J* = 15.5 Hz, 1H), 5.50 (s, 1H), 4.25-4.19 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.92 (dd, *J* = 9.2, 5.7 Hz, 1H), 2.59 (ddd, *J* = 10.3, 9.1, 4.4 Hz, 1H), 2.34 (dd, *J* = 5.7, 4.4 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 171.7, 166.0, 153.7, 144.2, 129.7, 128.7, 125.3, 123.2, 122.8, 116.8, 61.5, 60.4, 30.2, 28.1, 27.5, 14.2, 14.1. **MS** (ESI) m/z: $[M(^{35}Cl) + Na]^+$ 361, $[M(^{37}Cl) + Na]^+$ 363. **HPLC**: IC (*n*-hexane/*i*-PrOH 80:20, 1 mL/min) E-isomer: $t_{min}$ = 5.1 min, $t_{maj}$ = 5.9 min.

**Ethyl (1R,2S,3R)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxy-4-methoxyphenyl)cyclopropane-1-carboxylate 4fa**

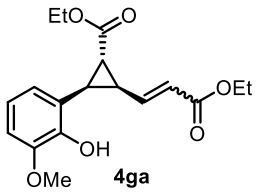
**4fa**



**4fa**

The general procedure was followed using aldehyde **1f**, sulfoxonium ylide **2b** and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate and 1 equiv. of NaOAc (8.2 mg). Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing E/Z mixture of **4fa** as yellow oil (43% yield, 14.4 mg), and 85% ee . E-**4fa**: $[\alpha]_D^{25}$ = +23 (c = 0.4, $CH_2Cl_2$) for 85% ee. **IR** (ATR) ν(max) = 3393 (br, m) 1715 (s) 1695 (s) 1162 (s) $cm^{-1}$. **$^1$H NMR** (300 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 7.01 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.44 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 6.23 (dd, *J* = 15.5, 10.3 Hz, 1H), 6.02 (d, *J* = 15.5 Hz, 1H), 4.26 – 4.16 (m, 2H), 4.16 – 4.06 (m, 2H), 3.76 (s, 2H), 2.88 (dd, *J* = 8.9, 5.5 Hz, 1H), 2.57 (ddd, *J* = 10.4, 9.0, 4.3 Hz, 1H), 2.31 (dd, *J* = 5.6, 4.3 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 171.9, 165.9, 160.3, 155.8, 144.8, 130.6, 122.7, 113.0, 106.2, 101.7, 61.3, 60.2, 55.3, 30.2, 27.9, 27.8, 14.2, 14.2. **MS** (ESI) m/z: $[M + Na]^+$ 357. **HPLC**: AJ-H (*n*-hexane/*i*-PrOH 90:10, 1 mL/min) E-isomer: $t_{maj}$ = 16.7 min, $t_{min}$ = 22.8 min.

**Ethyl (1*R*,2*S*,3*R*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(2-hydroxy-3-methoxyphenyl)cyclopropane-1-carboxylate 4ga**



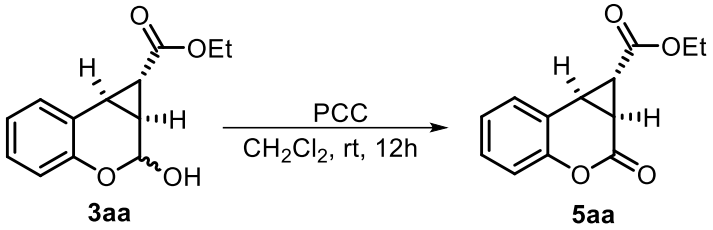
**4ga**

The general procedure was followed using aldehyde **1g**, sulfoxonium ylide **2a**, and ethyl 2-(triphenyl-$\lambda^5$-phosphaneylidene)acetate. Flash column chromatography ($CH_2Cl_2$/Acetone = 200:1) afforded a fraction containing E/Z mixture of **4ga** as colorless oil (overall 43% yield 14.4 mg) and 88% ee. E/Z-**4ga**: **IR** (ATR) ν(max) = 3427 (br, m) 1711 (s) 1272 (s) 1176 (s) $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 6.81 – 6.73 (m, 2H), 6.73 – 6.66 (m, 1H), 6.26 (dd, *J* = 15.5, 10.4 Hz, 1H), 5.99 (d, *J* = 15.4 Hz, 1H), 5.74 (s, 1H), 4.21 – 4.15 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.06 (dd, *J* = 9.3, 5.8 Hz, 1H), 2.58 (ddd, *J* = 10.5, 9.4, 4.4 Hz, 1H), 2.38 (dd, *J* = 5.8, 4.4 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$, +25 °C) [signals of the E-isomer] δ = 172.1, 166.1, 146.4, 145.6, 145.0, 122.3, 121.4, 120.7, 119.3, 109.8, 61.1, 60.1, 56.0, 30.7, 28.6, 27.7, 14.22, 14.20. **MS** (ESI) m/z: $[M + Na]^+$ 357. **HPLC**: IC (*n*-hexane/*i*-PrOH 80:20, 1 mL/min) E-isomer: $t_{maj}$ = 12.5 min, $t_{min}$ = 15.2 min.

**Synthetic elaborations**

Synthetic elaboration on **3aa** were performed using freshly prepared **3aa**, isolated by a fast flash column chromatography using 3:1 hexane/acetone from catalytic crude, or using the one pot protocols detailed below.

**Ethyl (1*S*,1a*S*,7b*S*)-2-oxo-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene-1-carboxylate 5aa**



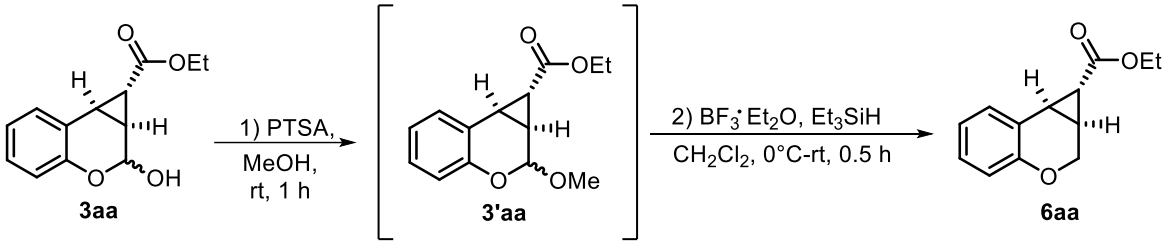

**3aa** **5aa**

In a small vial equipped with a magnetic stirring bar, PCC (0.2 mmol, 2 equiv., 43 mg) was added to a solution of cyclopropanchromanol **3aa** (0.1 mmol, 1 equiv., 23 mg), in $CH_2Cl_2$ (0.5 mL). The resulting solution was stirred at room temperature for 12 h and then poured into an aq. solution of $Na_2SO_3$ (3 M), and extracted with DCM (3 x). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (*n*-hexane/$Et_2O$ = 3:1) affording product **5aa** as a white solid in 37% yield (8.6 mg)

*One pot protocol:* In a small vial equipped with a magnetic stirring bar, aldehyde **1a** (0.1 mmol, 1 equiv., 14.8 mg) and sulfoxonium ylide **2a** (0.15 mmol, 1.5 equiv., 25.2 mg) were added to a $CDCl_3$ (1 mL) solution of catalyst (*S*)-**A** (0.02 mmol, 0.20 equiv., 6.5 mg) and AcONa (0.02 mmol, 0.20 equiv., 1.6 mg). The resulting mixture was stirred at room temperature for 12 h, then treated directly with PCC (0.3 mmol, 3 equiv., 65 mg). Work-up and purification as above afforded compound **5aa** as a white solid in 35% yield (8.1 mg).

m.p. = 77-80 °C. $[\alpha]_D^{25}$ +7.2 (c = 0.25, $CH_2Cl_2$) for 96% ee. **IR** (ATR) ν(max) =1754 (s) 1722 (s) 1172 (s) 1076 (s) $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$, +25 °C) δ = 7.39 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.13 (td, *J* = 7.5, 1.2 Hz, 1H), 7.05 – 6.98 (m, 1H), 4.26-4.21 (m, 2H), 3.04 (dd, *J* = 8.1, 4.2 Hz, 1H), 2.85 (dd, *J* = 8.1, 4.1 Hz, 1H), 2.07 (t, *J* = 4.1 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 169.9, 163.9, 150.0, 128.7, 128.2, 124.7, 119.0, 117.4, 62.0, 27.5, 27.0, 25.2, 14.1. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{12}O_4Na$ 255.0628; Found 255.0633. **HPLC**: AD-H (*n*-hexane/*i*-PrOH 90:10, 0.75 mL/min) $t_{maj}$ = 11.4 min, $t_{min}$ = 15.7 min.

**Ethyl (1*S*,1a*S*,7b*R*)-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene-1-carboxylate 6aa**



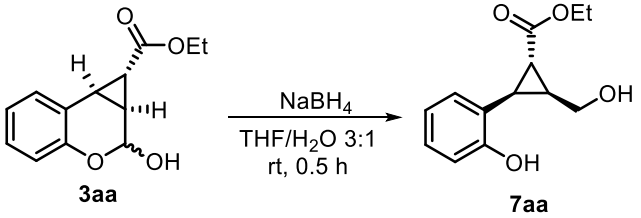

**3aa** **3'aa** **6aa**

In a small vial equipped with a magnetic stirring bar, PTSA·$H_2O$ (0.1 mmol, 1 equiv., 95.1 mg) was added to a solution of cyclopropanchromanol **3aa** (0.1 mmol, 1 equiv., 23 mg) in 2.5 mL of MeOH. The reaction was stirred at rt for 1 h and then the desired intermediate **3'aa** was purified by a short plug on silica gel using DCM as eluent. Intermediate **3'aa** was then dissolved in 1 mL of DCM and cooled to 0 °C, then $BF_3$·$Et_2O$ (0.3 mmol, 3 equiv., 42.5 mg, 37 μL) and $Et_3SiH$ (0.3 mmol, 3 equiv., 34.9 mg, 48 μL) were added and the reaction was stirred at rt for 30 min. The mixture was then poured into a solution of $NaHCO_{3(sat)}$ and extracted with DCM (3x). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (DCM/*n*-hexane = 1:1) affording product **6aa**[83] as an oil in 67% yield (14.6 mg).

83 Racemic **6aa**: Ye, L.-W.; Sun, X.-L.; Li, C.-Y.; Tang, Y. *J. Org. Chem.* **2007**, *72*, 1335.

*One pot protocol:* In a small vial equipped with a magnetic stirring bar, aldehyde **1a** (0.1 mmol, 1 equiv., 14.8 mg) and sulfoxonium ylide **2a** (0.15 mmol, 1.5 equiv., 25.2 mg) were added to a $CDCl_3$ (1 mL) solution of catalyst (*S*)-**A** (0.02 mmol, 0.20 equiv., 6.5 mg) and AcONa (0.02 mmol, 0.20 equiv., 1.6 mg). The resulting mixture was stirred at room temperature for 12 h, then evaporated to dryness (replacing residual $CDCl_3$ with MeOH portions). The residue was dissolved in MeOH (1 mL), and treated with $PTSA{\cdot}H_2O$ (0.1 mmol, 1 equiv., 95.1 mg). The reaction was stirred at rt for 1 h, then evaporated to dryness. The mixture containing intermediate **3'aa** was then dissolved in 1 mL of DCM and cooled to 0 °C, then $BF_3{\cdot}Et_2O$ (0.3 mmol, 3 equiv., 42.5 mg, 37 µL) and $Et_3SiH$ (0.3 mmol, 3 equiv., 34.9 mg, 48 µL) were added and the reaction was stirred at rt for 30 min. Work-up and purification as above afforded compound **6aa** as an oil in 17% yield (3.7 mg). $[\alpha]_D^{25}$ -104.5 (c = 0.32, $CH_2Cl_2$) **IR** (ATR) ν(max) =1721 (s) 1582 (s) 1491 (m) 1433 (m) $cm^{-1}$. **$^1$H NMR** (300 MHz, $CDCl_3$, +25 °C) δ = 7.24 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.10 (ddd, *J* = 1.6, 7.5, 8.0 Hz, 1H), 6.91 (ddd, *J* = 1.2, 7.5, 8.0 Hz, 1H), 6.8 (dd, *J* = 1.0, 8.1 Hz, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.91 (dd, *J* = 10.7, 0.8 Hz, 1H), 2.57 (dd, *J* = 4.4, 8.4 Hz, 1H), 2.37-2.28 (m, 2H) 1.27 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$, +25 °C) δ = 172.2, 152.7, 128.7, 127.3, 124.0, 121.8, 117.3, 61.6, 60.8, 26.9, 24.4, 22.7, 14.2. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{14}O_3Na$ 241.0835; Found 241.0841.

**Ethyl (1*S*,2*S*,3*R*)-2-(hydroxymethyl)-3-(2-hydroxyphenyl)cyclopropane-1-carboxylate 7aa**

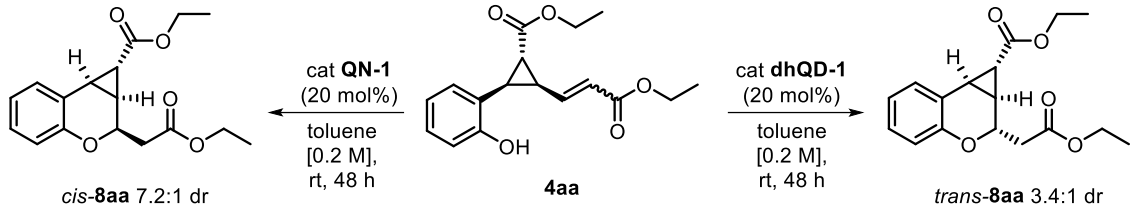


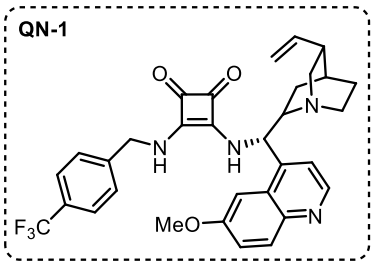

In a small vial equipped with a magnetic stirring bar $NaBH_4$ (0.225 mmol, 1.5 equiv., 8.5 mg) was added to a cooled (0 °C) solution of cyclopropanchromanol **3aa** (0.15 mmol, 35.1 mg) in a 3:1 $THF/H_2O$ mixture (1.5 mL). After 30 minutes stirring at 0 °C, the mixture was poured into a solution of $NH_4Cl_{(sat)}$ and extracted with DCM. The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*n*-hexane/acetone = 5:1) affording product **7aa** as a yellow oil in 91% yield (32.5 mg).

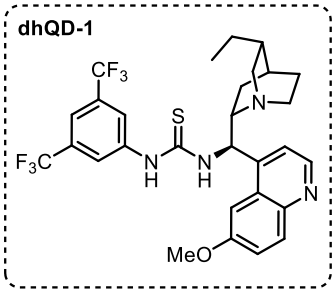
*One pot protocol:* In a small vial equipped with a magnetic stirring bar, aldehyde **1a** (0.1 mmol, 1 equiv., 14.8 mg) and sulfoxonium ylide **2a** (0.15 mmol, 1.5 equiv., 25.2 mg) were added to a $CDCl_3$ (1 mL) solution of catalyst (*S*)-**A** (0.02 mmol, 0.20 equiv., 6.5 mg) and AcONa (0.02 mmol, 0.20 equiv., 1.6 mg). The resulting mixture was stirred at room temperature for 12 h, then evaporated to dryness (replacing residual $CDCl_3$ with THF portions). The residue was dissolved in a 3:1 $THF/H_2O$ mixture (1.5 mL), cooled to 0 °C, and treated with $NaBH_4$ (0.225 mmol, 1.5 equiv., 8.5 mg). After 1.5 h, additional $NaBH_4$ (0.225 mmol, 1.5 equiv., 8.5 mg) was added. The mixture was stirred at 0 °C for an additional 30 minutes. Work-up and purification as described above afforded compound **7aa** as a yellow oil in 50% yield (11.8 mg).

$[\alpha]_D^{25}$ -18.0 (c = 0.5, $CH_2Cl_2$). **IR** (ATR) ν(max) =3452 (w, br) 3165 (w, br) 1724 (s) 1701 (s) 1188 (s) 1018 (s) $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$, +25 °C) δ = 7.20-7.15 (m, 2H), 6.90-6.85 (m, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.90 (dd, *J* = 11.2, 4.3 Hz, 1H), 2.85 (t, *J* = 10.6 Hz, 1H), 2.7 (dd, *J* = 5.0, 9.1 Hz, 1H), 2.25-2.20 (m, 1H), 1.91 (t, *J* = 4.9 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, +25 °C) δ = 173.1, 154.9, 131.3, 128.8, 122.8, 121.1, 116.7, 61.5, 61.1, 29.1, 26.6, 22.9, 14.2. **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{16}O_4Na$ 259.0941; Found 259.0946.

**Ethyl (1*S*,1a*S*,2*R*,7b*R*)-2-(2-ethoxy-2-oxoethyl)-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene-1-carboxylate and Ethyl (1*S*,1a*S*,2*S*,7b*R*)-2-(2-ethoxy-2-oxoethyl)-1,1a,2,7b-tetrahydro cyclopropa[*c*]chromene-1-carboxylate 8aa**




***cis*-8aa-selective reaction (QN-1 catalyzed):**

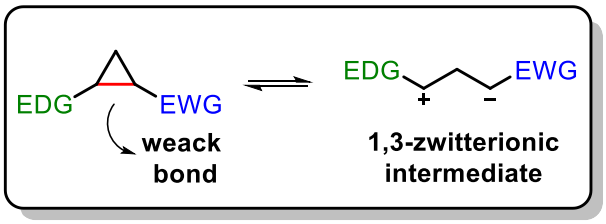
In a small vial equipped with a magnetic stirring bar catalyst **QN-1** (0.02 mmol, 0.2 equiv., 11.3 mg) was added to a solution of **4aa** (0.1 mmol, 1 equiv., 30.4 mg) in toluene (0.5 mL). The reaction was stirred 48 h at rt, then the catalyst was removed by a short plug of silica gel using $Et_2O$ as eluent. After evaporation of the solvents, the residue was analyzed by $^1$H NMR spectroscopy indicating a 7.2:1 diastereomeric ratio favoring the *cis*-**8aa** isomer. Subsequently, the crude residue was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt = 14:1) affording product **8aa** as a diastereomeric mixture in 58% yield (17.6 mg) and 99% ee for the *cis*-**8aa** isomer. *Cis*/*trans*-**8aa**: **IR** (ATR) ν(max) =1720 (s) 1263 (s) 1172 (s) cm$^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the *cis*-isomer] δ = 7.25 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.10 (td, *J* = 7.7, 1.6 Hz, 1H), 6.92 (td, *J* = 7.4, 1.0 Hz, 1H), 6.78 (br d, *J* = 8.1 Hz, 1H), 4.39 (br t, *J* = 6.5 Hz, 1H), 4.26-4.19 (m, 2H), 4.19-4.12 (m, 2H), 2.83 (dd, *J* = 15.5, 7.5 Hz, 1H), 2.75 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.61 (dd, *J* = 9.2, 3.5 Hz, 1H), 2.38 (ddd, *J* = 9.2, 4.4, 1.4 Hz, 1H), 2.25 (br t, *J* = 4.0 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$, +25 °C) [signals of the *cis*-isomer] δ = 171.9, 170.2, 152.5, 128.4, 127.4, 123.6, 122.0, 117.4, 68.0, 60.9, 60.8, 40.4, 30.6, 23.7, 23.1, 14.23, 14.21. **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}O_5$ 305.1389; Found 305.1389. **HPLC**: IC (*n*-hexane/*i*-PrOH 95:5, 0.75 mL/min) *cis*-**8aa** isomer: $t_{min}$ = 18.5 min, $t_{maj}$ = 30.8 min.

***trans*-8aa-selective reaction (dhQD-1 catalyzed):**

In a small vial equipped with a magnetic stirring bar catalyst **dhQD-1** (0.02 mmol, 0.2 equiv., 12.0 mg) was added to a solution of **4aa** (0.1 mmol, 1 equiv., 30.4 mg) in toluene (0.5 mL). The reaction was stirred 48 h at rt, then the catalyst was removed by a short plug of silica gel using $Et_2O$ as eluent. After evaporation of the solvents, the residue was analyzed by $^1$H NMR spectroscopy indicating a 3.4:1 diastereomeric ratio favoring the *trans*-**8aa** isomer. Subsequently the crude residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 14:1) affording product **8aa** as a diastereomeric mixture in 58% yield (17.5 mg) and 99% ee for the *trans*-**8aa** isomer. **$^1$H NMR** (600 MHz, $CDCl_3$, +25 °C) [signals of the *trans*-isomer] δ = 7.22 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.11 (td, *J* = 7.8, 1.6 Hz, 1H), 6.92 (td, *J* = 7.4, 1.0 Hz, 1H), 6.75 (br d, *J* = 8.1 Hz, 1H), 4.91 (br t, *J* = 6.9 Hz, 1H), 4.19-4.13 (m, 4H), 2.59 (d, *J* = 15.4, 7.9 Hz, 1H), 2.56 (dd, *J* = 8.8, 5.2 Hz, 1H), 2.49 (dd, *J* = 15.4, 5.8 Hz, 1H), 2.28 (br t, *J* = 4.0 Hz, 1H), 2.27-2.24 (m, 1H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$, +25 °C) [signals of the *trans*-isomer] δ = 171.9, 170.3, 149.5, 128.5, 127.8, 123.7, 122.1, 118.4, 67.6, 60.9, 60.8, 38.4, 29.6, 25.5, 22.2, 14.23, 14.18. **HPLC**: IC (*n*-hexane/*i*-PrOH 95:5, 0.75 mL/min) *trans*-**8aa** isomer: $t_{min}$ = 23.2 min $t_{maj}$ = 34.1 min.

# 6 LiteratureDonor-Acceptor cyclopropane: literature background and preliminary investigations

The cyclopropane is the smallest possible saturated ring, only three carbon atoms. The $sp^3$ hybridization of each carbon in a such small cycle, makes this structure extremely tensioned accompanied by unique chemical and elecronical properties. The chemical reactivity of the cyclopropyl ring is similar to an olefinic double bond. Indeed, the coplanarity of the three carbon atoms gives to the C-C bonds a p-character, while the C-H bonds are characterized by a more accentuated s-character.[84] Despite the cyclopropanes are characterized by an extremely tensioned structure and therefore by a relevant thermodynamic instability, these structures require high activation energy, and this aspect limits their use in organic synthesis.[85] To overcome this limitation different activation strategies have been developed. One of these methodologies is the installation of donor and acceptor substituents in strategic positions of the cycle. In particular, the presence of an electron-donating group (EDG) and an electron-withdrawing group as substituents of two vicinal carbon of the three-membered ringsring significantly increases the reactivity of this structure and consequently their use in organic synthesis. The presence of donor (EDG) and acceptor (EWG) substituents of two vicinal carbon weakens considerably the C-C bond of the cycle, promoting the formation of a 1,3-zwitterionic intermediate (*Scheme 6.1*). Moreover, the positive and the negative charge are respectively stabilized by the donor and acceptor substituents.




*Scheme 6.1. Generic structure of donor-acceptor cyclopropane*

The most common electron-withdrawing groups are carbonyl compounds such as ketones, esters, amides, or nitrile groups. Generally, two acceptor groups in a geminal position, that guarantee a better activation, are employed. Regarding the electron-donating groups, the

84 T. T. Talele, *J. Med. Chem.*, **2016**, *59*, 8712.
85 A. De Meijere, *Angew. Chem. Int. Ed.*, **1979**, *18*, 809.

choice may fall on heteroatoms (OR, SR, $NR_2$, etc.) or, more often, on aromatic substituents

To quantify the polarizing effect of the electron-withdrawing and the electron-donating substituents, Wertz and coworkers[86] conducted a systematic theoretical investigation by calculating the activation barrier of different donor-acceptor cyclopropane. In *Scheme 6.2*In *Figure 6.1* are reported the results of this study. On the basis of this table is possible to modulate the push-pull effect of the substituents modulating at the same time the reactivity of the cyclopropyl substrate.

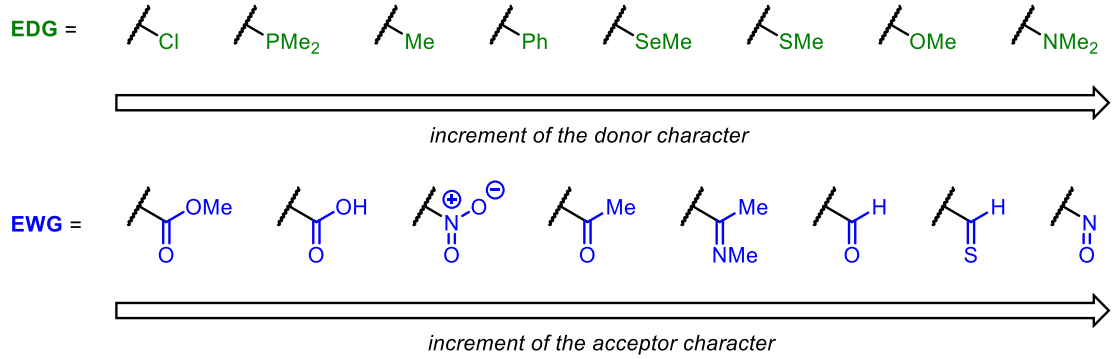
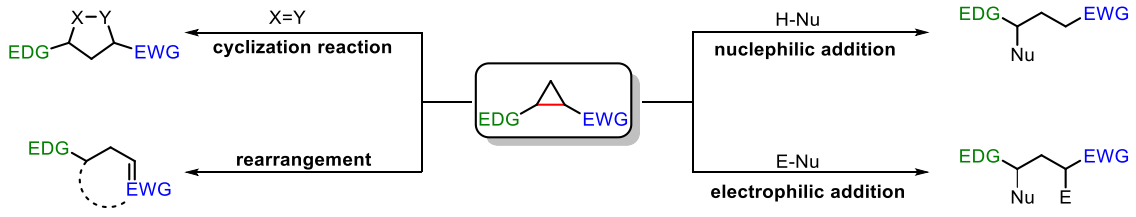



*Figure 6.1. Acceptor and donor characteristics of the main functional groups*

*Scheme 6.2. Acceptor and donor characteristics of the main functional groups*

## 6.1 Reactivity

The most common reactions of donor-acceptor cyclopropane generally are nucleophilic/electrophilic addition with subsequent ring-opening reactions, cyclization reactions, and rearrangements (*Scheme 6.3*). [87]

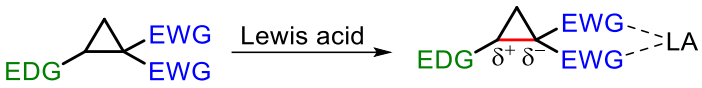



*Scheme 6.3. Reactivity of donor-acceptor cyclopropane*

The typical activation mode of donor-acceptor cyclopropane is Lewis acid catalysis. The Lewis acid, generally a transition metal, coordinates one or both the electron-withdrawing

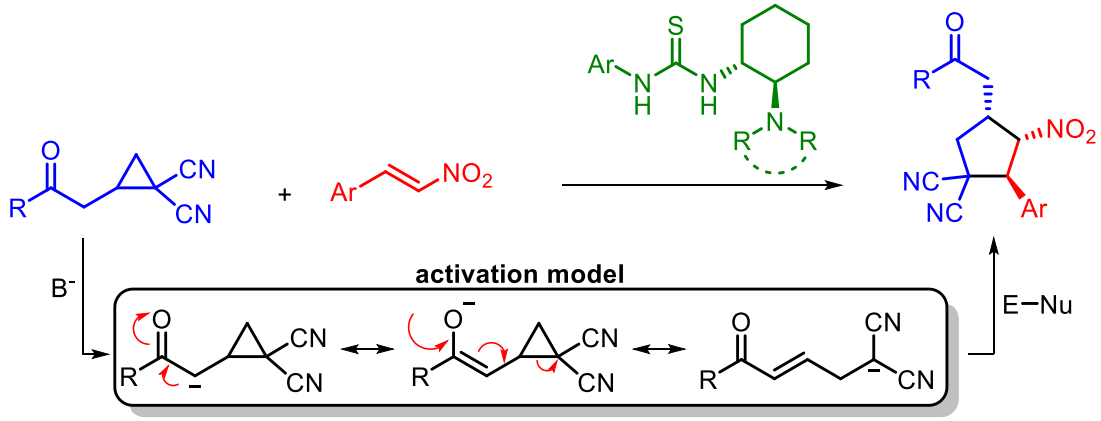
86 a) T. F. Schneider, D. B. Werz, *Org. Lett.*, **2011**, *13*, 1848. b) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.*, **2014**, *43*, 804.
87 T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.*, **2014**, *53*, 5504.

groups further weakening the C-C bond of the cycle and allowing the formation of a partial negative charge, stabilized by the electron-withdrawing substituents, and the formation of a partial positive charge, stabilized by the electron-donating group. Using a chiral and enantiopure ligand for the transition metal is possible to control the absolute and the relative configuration of the new chiral centers formed during the reaction.[88]




*Scheme 6.4. Polarization of the C-C bond in the presence of a Lewis acid as catalyst*

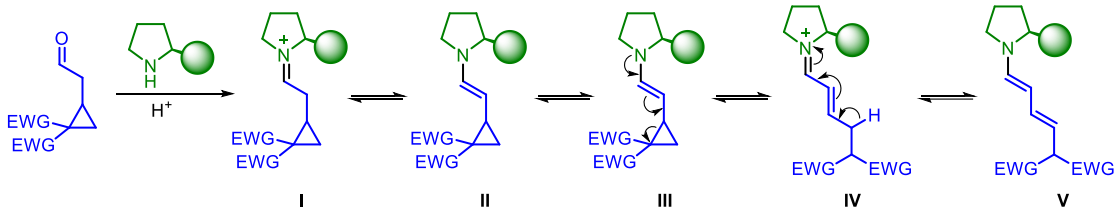
An alternative activation mode reckonis based on the formation, *in situ*, of a strong donor functionality. This activation mode can be effectuated using two different classes of catalyst and the opportune donor-acceptor cyclopropane. The first methodology taken into consideration is the formation of an enolate as donor functionality (*Scheme 6.5*).[89] In this case, a chiral and enantiopure base, a Takemoto's type thiourea, is used for the deprotonation of the enolizable carbonyl compounds. Once formed the donor enolate functionality, one of the possible resonance forms of the molecule is a linear chain with the negative charge stabilized by the two electron-withdrawing groups. Then, the Takemoto's type thiourea coordinates the reagent partner forming the cyclic product in an enantioselective fashion.




*Scheme 6.5. Enolate as donor functionality*

88 Y. Xia, X. Liu, X. Feng, *Angew. Chem. Int. Ed.*, **2021**, 60, *9192*.
89 a) J. Blom, A. Vidal-Albalat, J. Jørgensen, C. L. Barløse, K. S. Jessen, M. V. Iversen, K. A. Jørgensen, *Angew. Chem. Int. Ed.*, **2017**, *56*, 11831. b) D. A. McLeod, M. K. Thøgersen, C. L. Barløse, M. L. Skipper, E. B. Obregón, K. A. Jørgensen, *Angew. Chem. Int. Ed.*, **2022**, *61*, e2022060.

The formation of an enamine (*Scheme **6.6***) using, also in this case, an enolizable carbonyl compound (preferably an aldehyde) and a prolinol derivative as catalyst[90] represents an alternative activation model. In this case, the first step is the condensation reaction between the aldehydic substrates and the catalyst directly forming the iminium ion intermediate **I**. Subsequently, the acidic condition required for this type of reaction promotes the tautomerism imine/enamine with the formation of enamine **II**. Then, the presence of an aliphatic ring in α-position of the enamine and the acidic condition allows the ring-opening reaction to form iminium ion **IV** which evolves into intermediate **V** after a proton shift. At this point, the conjugated enamine **V** is prone to react with an opportune reagent partner.




*Scheme 6.6. Enamine formation and ring-opening reaction*

### 6.1.1 Nucleophilic/electrophilic addition

The most common reaction of donor-acceptor cyclopropane is its transformation into an open chain product through a nucleophilic or an electrophilic addition reaction. These types of reactions are generally conducted under Lewis acid catalysis.[91]

Substitution reactions with the formation of open chain products are fully developed under both asymmetric and racemic conditions. The most popular additions are the nucleophilic substitution reactions using as nucleophiles indoles,[92] thiols,[93] naphthols[94] or amine derivatives[95] (*Figure 6.2*). The resulting products of nucleophilic substitution reactions are open chain molecules with a substituent in 3-position with respect to the two carbonyl compounds. To catalyze these types of reactions, generally, Lewis acids are employed. In function of the nature of the electron-donating group and the nature of the nucleophile, a

90 K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.*, **2015**, *137*, 1685.
91 W. Luo, Z. Sun, E. H. N Fernando, V. N. Nesterov, T. R. Cundari, H. Wang, *ACS Catal.*, **2019**, 9, 8285.
92 a) L. C. Irwin, C. R. Renwick, Michael A. Kerr, *J. Org. Chem.*, **2018**, 83, 6235. b) P. Harrington, M. A. Kerr, *Tetrahedron Lett.*, **1997**, *38*, 5949. c) M. R. Emmett, M. A. Kerr, *Org. Lett.*, **2011**, *13*, 4180.
93 Y. Xia, L. L. Lin, F. Z. Chang, X. Fu, X. H. Liu, X. M. Feng, *Angew. Chem. Int. Ed.*, **2015**, *54*, 13748.
94 Y. Xia, F. Z. Chang, L. L. Lin, Y. L. Xu, X. H. Liu, X. M. Feng, *Org. Chem. Front.*, **2018**, *5*, 1293.
95 a) S. Liao, X. -L. Sun, Y. Tang, *Acc. Chem. Res.*, **2014**, *47*, 2260. b) W. Luo, Z. Sun, E. H. N. Fernando, V. N. Nesterov, T. R. Cundari, H. Wang, *ACS Catal.*, **2019**, *9*, 8285.

chiral center is installed on the product's backbone. So, employing a chiral and enantiopure catalyst, is possible to control the absolute configuration of the chiral center.

Regarding the electrophilic substitution reaction, this topic is less studied but nevertheless, some examples of racemic and enantioselective methodologies are reported.[96] In these cases, the product of the reaction has not only a functionalization in 3-position to the two carbonyl compounds but also in α-position.

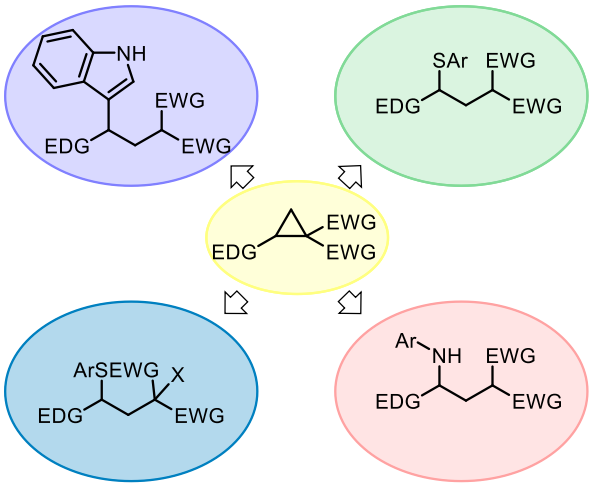



*Figure 6.2. Nucleophilic/Electrophilic substitution reaction of donor acceptor cyclopropane*

### 6.1.2 Cyclization reaction

Donor acceptor cyclopropanes in combination with a wide range of reaction partners are perfect substrates for the synthesis of five-,[97] six-[98] or seven-membered[99] rings (*Figure 6.3*). Donor acceptor cyclopropane reacts in the 1,3-zwitterionic form with carbonyl compounds such as aldehydes or ketones to give directly tetrahydrofurans. Using imines as reagent partners, pyrrolidine cycles are the main products of the reaction. With activated double bonds and conjugated ones (both electron-rich or electron-poor), five or seven membered carbocycles were obtained. Finally, using nitrons or nitrile derivatives, saturated heterocycles or pirrols derivatives arewere respectively obtained.

96 a) A. U. Augustin, P. G. Jones, D. B. Werz, *Chem. Eur. J.*, **2019**, *25*, 11620. b) C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.*, **2011**, *50*, 8391. c) J. Wallbaum, L. K. B. Garve, P. G. Jones, D. B. Werz, *Org. Lett.* **2017**, *19*, 98. d) S. Das, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.*, **2017**, *56*, 11554.

97 a) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.*, **2009**, *131*, 3122. b) H. .Xu, J.-P. Qu, S. Liao, H. Xiong, Y. Tang, *Angew. Chem. Int. Ed.*, **2013**, *52*, 4004. c) J. Sabbatani, N. Maulide, *Angew. Chem. Int. Ed.*, **2016**, *55*, 6780.

98 a) A. O. Chagarovskiy, V. S. Vasin, V. V. Kuznetsov, O. A. Ivanova, V. B. Rybakov, A. N. Shumsky, N. N. Makhova, I. V. Trushkov., *Angew. Chem. Int. Ed.*, **2018**, *57*, 10338. b) M. Petzold, P. G. Jones, D. B. Werz, *Angew. Chem. Int. Ed.*, **2019**, *58*, 6225. c) .K. Varshnaya, P. Banerjee, *J. Org. Chem.*, **2019**, *84*, 1614.

99 a) O. A. Ivanova, E. M. Budynina, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Angew. Chem. Int. Ed.*, **2008**, *47*, 1107. b) .Xu, J. -L. Hu, L. Wang, S. Liao, Y. Tang, *J. Am. Chem. Soc.*,**2015**, *137*, 8006.

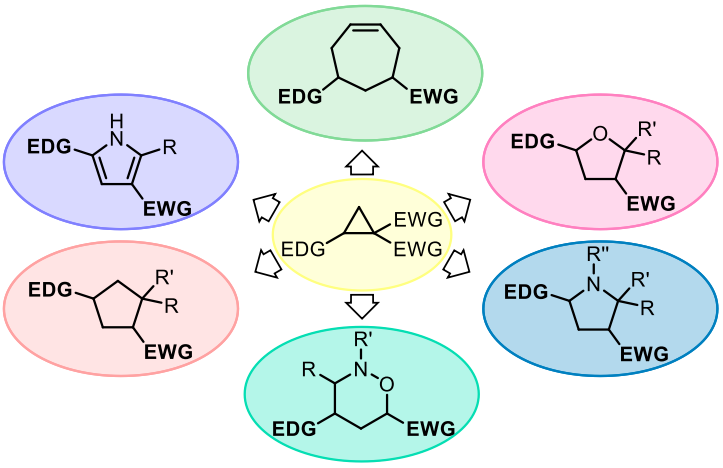
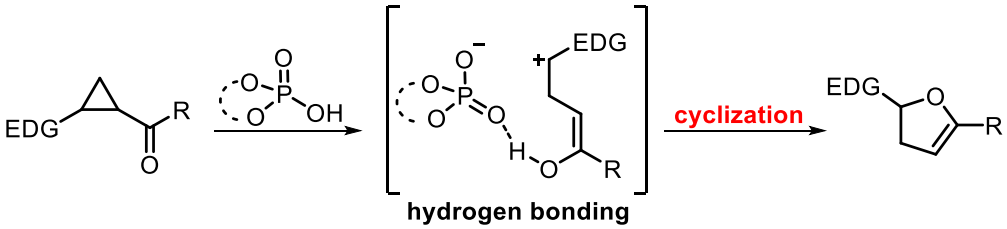



*Figure 6.3. Cycloaddition reaction with donor-acceptor cyclopropane*

### 6.1.3 Rearrangements

There are only a few examples of rearrangement employing donor-acceptor cyclopropanes and the most important is reported by Vicario and coworkers.[100] This methodology not only set the stage for an important class of reactions with donor-acceptor cyclopropane but is also actually the only example regarding the use of chiral phosphoric acids as catalysts (*Scheme 6.7*). In this case, the coordination of the phosphoric acid promotes the ring-opening reaction with subsequent formation of the enol reported below, characterized by the positive charge stabilized not only by the electron-donating group but also by the catalyst. Subsequently, the enol oxygen undergoes a ring closure reaction generating a chiral dihydrofuran as product.



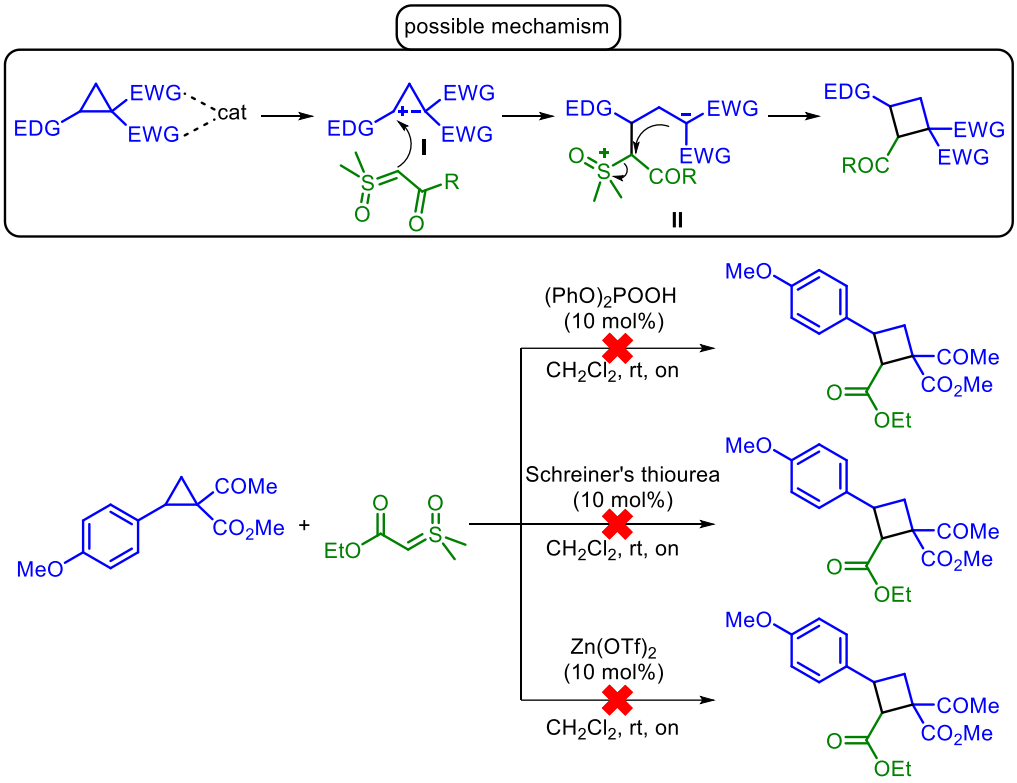

*Scheme 6.7. Cloke-Wilson rearrangement*

100 A. Ortega, R. Manzano, U. Uria, L. Carrillo, E. Reyes, T. Tejero, P. Merino, J. L. Vicario, *Angew. Chem. Int. Ed.* **2018**, 57, 8225.

## 6.2 Experimental evolution

In the previous paragraphs, the reactivity of donor-acceptor cyclopropane was quickly summarized. Donor-acceptor cyclopropanes can undergo a wide range of reactions, generating an even larger quantity of product. This versatility fueled our curiosity to study and better know the reactivity and the behavior of these substrates with different reaction partners. Among all the reactions tested, the most interesting will be discussed in this section.

The first reactions tested, try to merge the reactivity of the previously discussed sulfoxonium ylides with donor-acceptor cyclopropanes under different reaction conditions. The aim of this methodology was the synthesis of a cyclobutane ringsring exploiting the typical reactivity of both sulfoxonium ylides and donor-acceptor. cyclopropane. A possible mechanism is shown in *Scheme 6.8*. The acidic catalyst coordinates the donor-acceptor cyclopropane generating the opened 1,3-zwiterionic intermediate **I** which rapidly undergoes a nucleophilic attack by the sulfoxonium ylide. Once formed intermediate **II**, a ring closure reaction can occur generating the four-membered ring product. The reaction was conducted under different catalysis conditions, in particular, Brønsted acid catalysis, H-bond catalysis, and Lewis acid catalysis but unfortunately the cyclobutane product was never detected in the reaction mixtures (*Scheme 6.8*).

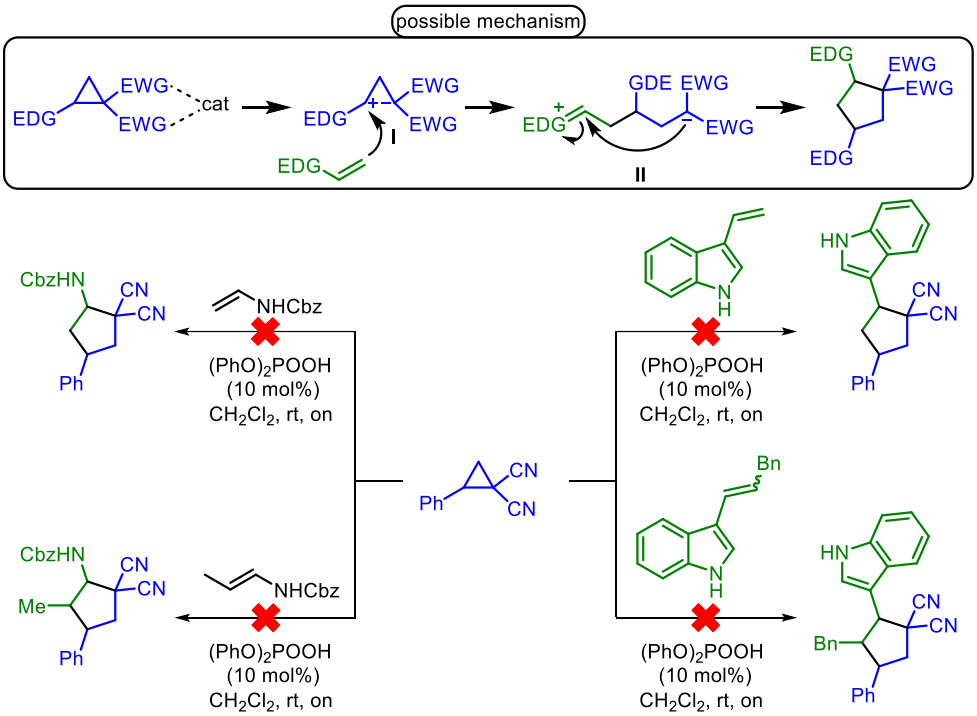



*Scheme 6.8. Reactions between sulfoxonium ylides and donor-acceptor cyclopropane*

Subsequently, we move to analyze another cycloaddition reaction using activated olefins as reagent partners. Different electron-rich olefins were employed and the possible mechanism, the olefins employed, and the reaction conditions are shown in *Scheme 6.9*. Regarding the possible mechanism, after the formation of intermediate **I** assisted by the catalyst coordination, the electron-rich double bond undergoes a nucleophilic attack forming the zwitterionic intermediate **II**. Then, an intramolecular ring closure reaction generates the substituted cyclopentane product, restoring the neutrality of the entire molecule.

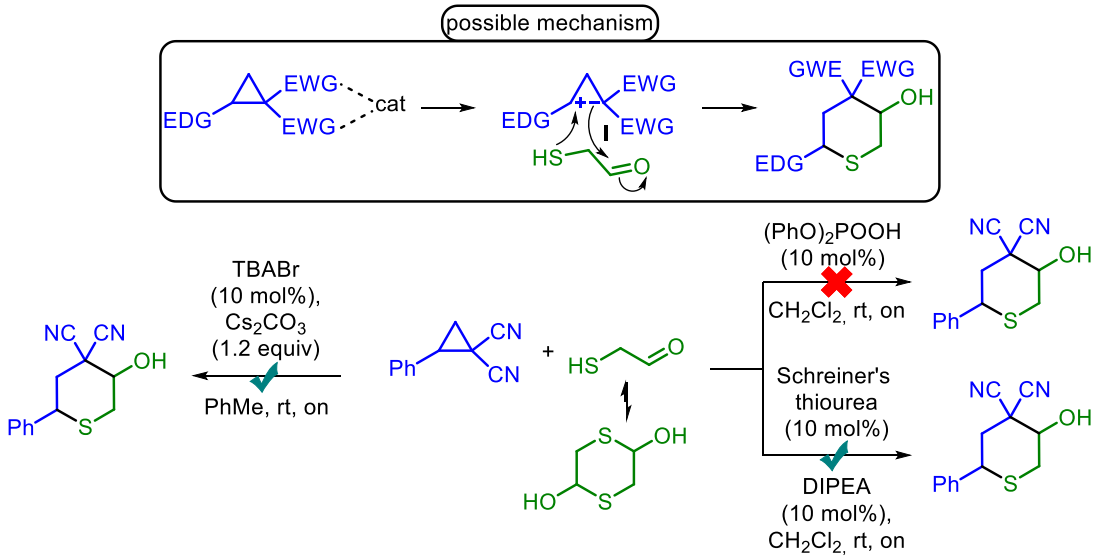
Due to the low reactivity observed in the previous reactions, we chose to use a more reactive donor-acceptor cyclopropane. In this case, the two electron-withdrawing groups, cyano groups, have a more accentuated electron-withdrawing character, facilitating the breaking of C-C bond of the cyclopropyl ring (*Scheme 6.9*). All the reactions are conducted under Brønsted acid catalyst, and the electron-rich olefins employed have different natures. First of all, unsubstituted 3-vinylindol was tested as reaction partner, but only the decomposition of the olefin was observed in the crude mixture. Subsequently, we try to use a more stable vinylindol derivative, characterized by a benzylic group as substituent of the double bond. In this case, less decomposition was observed, but no traces of the

cyclopentane product were detected. Also carbamate derivatives were employed as reaction partners, but no reactivity was detected using unsubstituted carbamate derivative nor using the more stable methyl subtituted one.



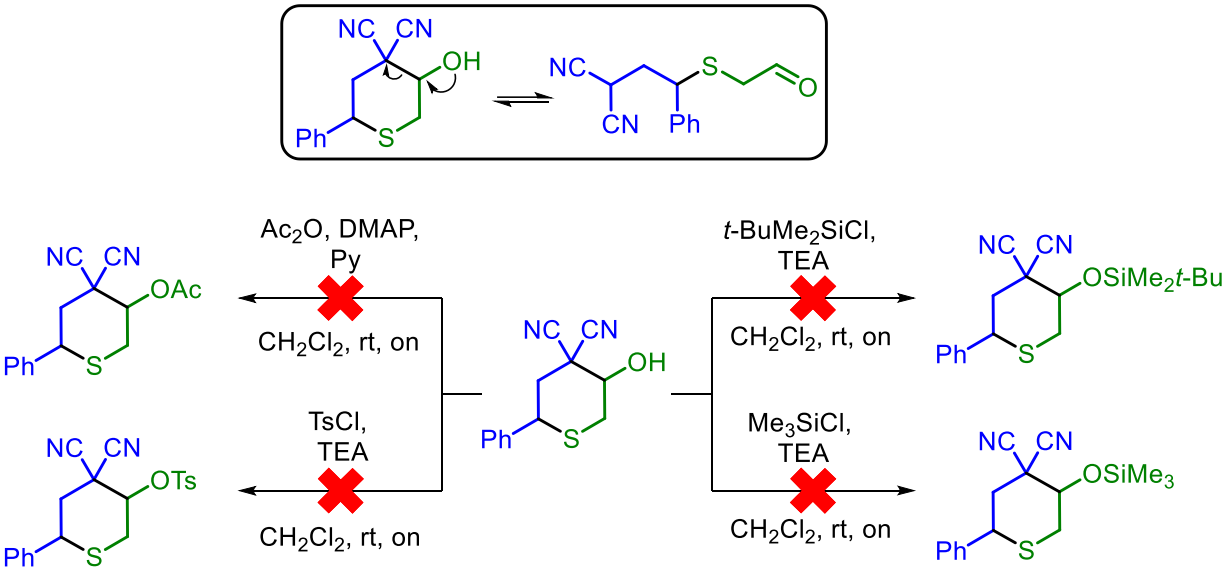

*Scheme 6.9. Reactions between donor-acceptor cyclopropane and electron-rich olefins*

Another cycloaddition tested involves 1,4-dithiane-2,5-diol as reaction partner and a possible mechanism is reported in *Scheme 6.10*. After the ring-opening reaction and formation of intermediate **I** the nucleophilic sulfur attacks the positive charge of zwitterion **I** and, simultaneously the carbanion attacks the aldehydic moiety generating a six-membered heterocycle as product. Different reaction conditions were tested: performing the reaction under Brønsted acid conditions any reactivity was observed, while moving towards basic conditions a great reactivity was detected. Indeed, performing the reaction with Schreiner's thiourea as catalyst and DIPEA as co-catalyst or under phase transfer conditions complete conversion was observed.



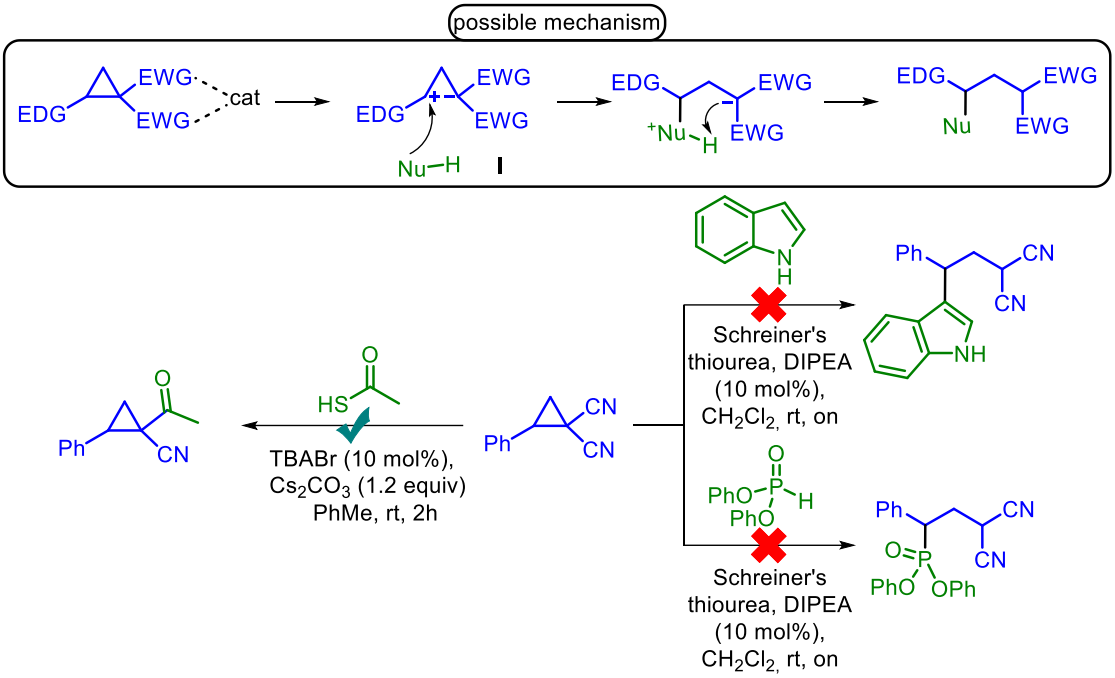

*Scheme 6.10. Reaction between donor-acceptor cyclopropane and 1,4-dithiane-2,5-diol*

The main goal of this methodology is to obtain the six-membered heterocycle product in an enantioselective fashion. Unfortunately, the HPLC chromatogram of the racemic product suggests that it is involved in an internal equilibrium, (possible formation of the open chain product) (*Scheme 6.11*). For this reason, it is necessary to stabilize the obtained product trying to prevent the formation of the open chain one. Different attempts to protect the hydroxylic functionality were undertaken using silicon derivatives, tosyl chloride, and acetic anhydride, but none of them gave satisfying results (*Scheme 6.11*)).



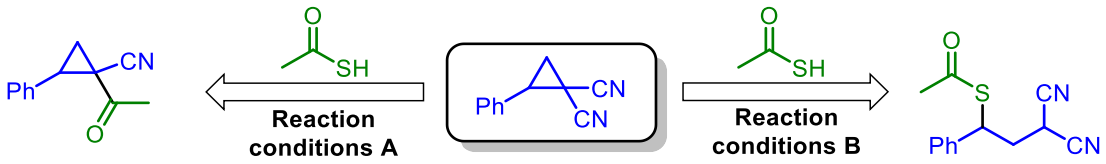

*Scheme 6.11. Protecting reaction to stabilize the product*

Subsequently, we move on to the study of nucleophilic substitution reactions. Nucleophiles such as indole or diphenylphosphite, which exhibits a good reactivity with nitrolefins, under H-bond catalysis showed no reactivity.[101]




*Scheme 6.12. Nucleophilic addition to donor-acceptor cyclopropane*

Surprisingly, using thioacetic acid as nucleophile, under phase transfer conditions, an unexpected product was isolated. The obtained product is itself a donor-acceptor cyclopropane, but one of the cyano groups was replaced by an acetyl moiety. Further investigation allowed us to understand that a little change in reaction conditions permits to obtainedobtain two different products (*Scheme 6.13*). Due to the interesting behavior, this methodology will be analyzed in detail in the following chapter.



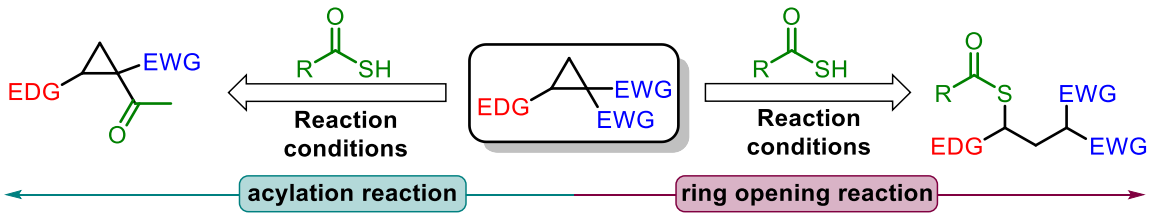

*Scheme 6.13. Chemodivergent reaction of donor-acceptor cyclopropane*

101 Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.*, **2010**, *49*, 153.

# 7 Organocatalytic chemodivergent reaction between donor-acceptor cyclopropane and thioacetic acid

ABSTRACT

Donor-acceptor cyclopropanes are key building blocks until now exploited under acidic conditions for the synthesis of a great variety of heterocycle or open chain products. Herein a new organocatalytic chemodivergent protocol, under basic phase transfer catalysis, involving donor-acceptor cyclopropane is described. This protocol exploits not only the natural reactivity of donor-acceptor cyclopropane but, modulating the reaction conditions, it is possible to give rise to an unusual non-reductive decyanation reaction.




## 7.1 Background

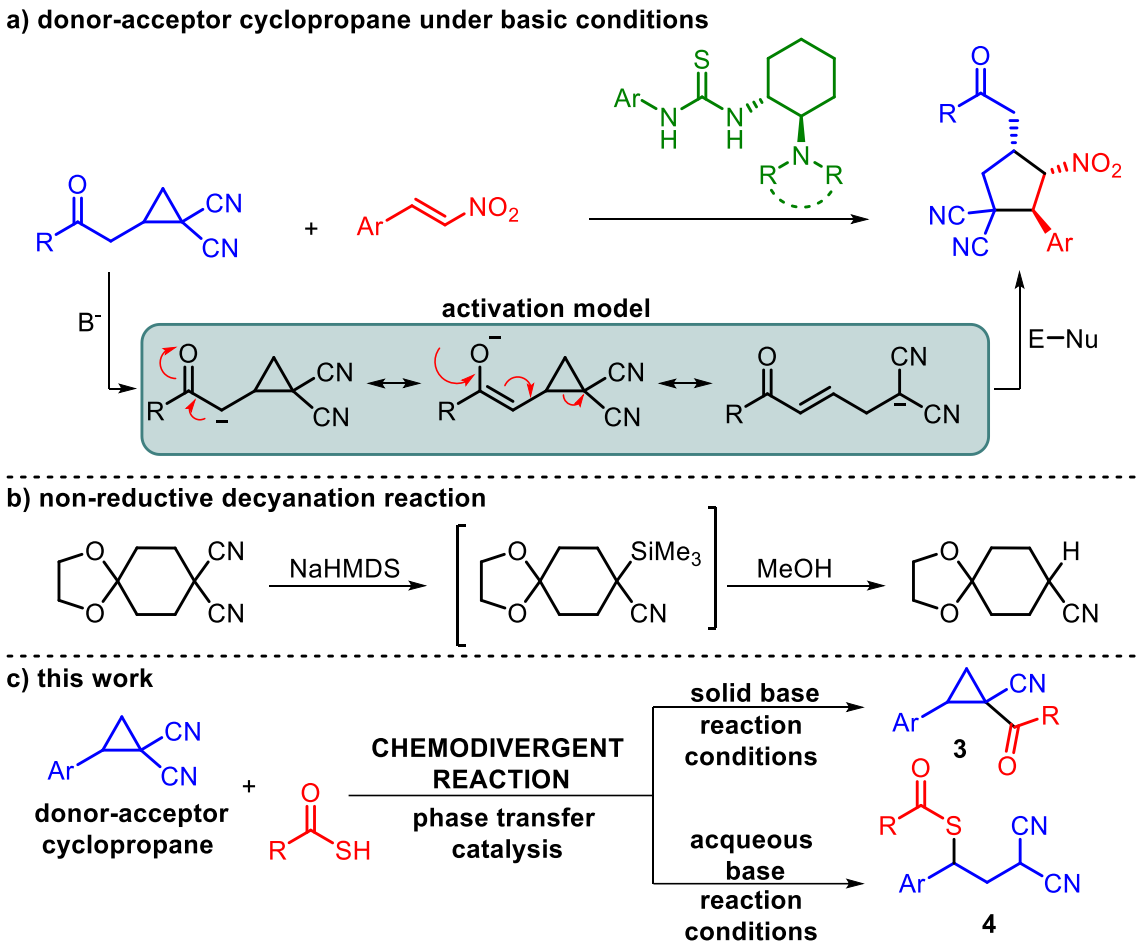
Donor-acceptor cyclopropanes are three-membered constricted rings characterized by at least two substituents on two adjacent carbon atoms, an electron-withdrawing group (EWG) and an electron donating group (EDG). The presence of these two substituents characterized by significant electronic properties, leads to a weakening in the C-C bond of the cyclopropane, facilitating the formation of an open chain product or a ring expansion reaction.[102]

The reactivity of donor-acceptor cyclopropane has been extensively developed under both racemic[103] and asymmetric[104] reaction conditions, but in all cases, an acidic catalyst

102 a) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504. b) K. Ghosh, S. Das, *Org. Biomol. Chem.*, **2021**, *19*, 965. c) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.*, **2015**, *13*, 655. d) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.*, **2014**, *43*, 804. e) O. A. Ivanova, I. V. Trushkov, *Chem. Rec.* **2019**, *19*, 2189.
103 a) S. S. So, T. J. Auvil, V. J. Garza, A. E. Mattson, *Org. Lett.*, **2012**, *14*, 3792. b) S. Sathishkannan, K. Srinivasan, *Org. Biomol. Chem.*, **2013**, *11*, 5793. c) A. Ghosh, A. K. Pandey, P. Banerjee, *J. Org. Chem.* **2015**, *80*, 7235.
104 a) L. Li, Z. Li, Q. Wang, Synlett. 2009, 1830. b) G. Dickmeiss, V. De Sio, J. Udmark, T. B. Poulsen, V. Marcos, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2009**, *48*, 6650. c) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.* **2015**, *137*, 1685. d) J. Wallbaum, L. K. B. Garve, P. G. Jones, D. B. Werz, *Chem. Eur. J.*, **2016**, *22*, 18756.

(Brønsted[105] or Lewis acid[106]) able to activate the donor-acceptor cyclopropane ring was employed. Only one example of donor-acceptor cyclopropane under basic conditions is reported[107] (*Scheme 7.1a*) but in this case, the asymmetric basic catalyst, in addition to donate enantioinduction to the reaction, generates also the electron donation functionality. Herein, the reactivity of donor-acceptor cyclopropane under phase transfer catalysis is described. The novelty of this methodology is based on the activation mode of the reagents. Thus, the catalyst is not acting via activation of the cyclopropanic substrate but activate the nucleophilic reaction partner, namely the thioacetic acid. Performing the reaction under phase transfer reaction conditions, we quickly realized that the employed donor-acceptor cyclopropane generates two different products, an open chain product **3**, in line with the ordinary reactivity of this kind of substates, and a different donor-acceptor cyclopropane, product **4**, derived from the unusual non-reductive decyanation reaction of substates **1**. Decyanation reactions are a powerful toll in organic synthesis because the transformation of the nitrile functionality permits to obtain numerous functional groups such as primary ammine, aldehydes or alcohols, but often these transformations follow a radical mechanism[108] or required reductive conditions.[109] To the best of our knowledge, only an example of non-reductive decyanation reactions has been reported[110] (*Scheme 7.1b*), replacing one of the two nitrile groups with a hydrogen atom, due to the use of sodium bis(trimethylsilyl)amide (NaHMDS) and methanol as reagents. Herein, one of the nitrile groups of the cyclopropane is replaced by an acetyl functionality, thanks to the presence of the thioacetic acid as unusual acetylating agent.

105 a) A. Ortega, R. Manzano, U. Uria, L. Carrillo, E. Reyes, T. Tejero, P. Merino, Jose L. Vicario, *Angew. Chem. Int. Ed.* **2018**, *57*, 8225. b) A. Ortega, U. Uria, T. Tejero, L. Prieto, E. Reyes, P. Merino, J. L. Vicario, *Org. Lett.* **2021**, *23*, 2326. c) E. Richmond, V. D. Vuković, J. Moran, *Org. Lett.*, **2018**, *20*, 574.
106 a) A. U. Augustin, M. Busse, P. G. Jones, D. B. Werz, *Org. Lett.*, **2018**, *20*, 820. b) A. F. G. Goldberg, N. R. O'Connor, R. A. Craig, B. M. Stoltz., *Org. Lett.*, **2012**, *14*, 5314.
107 J. Blom, A. Vidal-Albalat, J. Jørgensen, C. L. Barløse, K. S. Jessen, M. V. Iversen, K. A. Jørgensen, *Angew. Chem. Int. Ed.*, **2017**, *56*, 11831.
108 T. Kawamoto, K. Oritani, D. P. Curran, A. Kamimura, *Org. Lett.*, **2018**, *20*, 2084.
109 J. -M. R. Mattalia, *Beilstein J. Org. Chem*., **2017**, *13*, 267.
110 D. Domon , M. Iwakura, K. Tanino, *Tetrahedron Lett.*, **2017**, *58*, 1957.

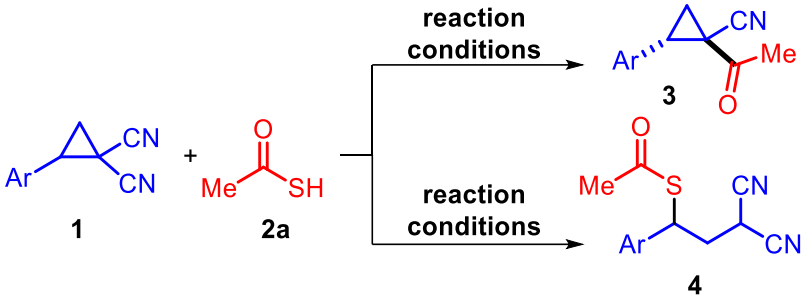



*Scheme 7.1. Enantioselective ring opening reaction under basic reaction conditions; b) non-reductive decyanation reaction c) this work*

## 7.2 Results and discussion

At the outset of this work, we started our investigation by reacting the donor-acceptor cyclopropane **1a** and the thioacetic acid **2a** under phase transfer catalysis (PTC) in presence of an inorganic base. From these preliminary experiments we realized that, depending the reaction conditions, two completely different products, **3aa** and **4aa**, can be obtained (*Scheme 7.2*). Product **3aa** is itself a donor-acceptor cyclopropane, due to the presence of an electron donating group (the phenyl ring) and two electron-withdrawing groups (the nitrile and the acetyl groups) in a vicinal position. Compound **3aa** is indeed, the product of a non-reductive decyanation reaction, one of the two nitrile groups of the substrate **1a** is replaced by the acetyl moiety, so the conducted reaction does not affect the cyclopropane ring but one of the nitrile groups present on the substrate backbone. Regarding product **4aa**, the normal reactivity of the donor-acceptor cyclopropane is verified, indeed an open

chain product **4aa** is obtained. Taking into consideration the two observed reaction pathway, we started two different optimization processes to increment the yield and the selectivity for both products **3aa** and **4aa**.

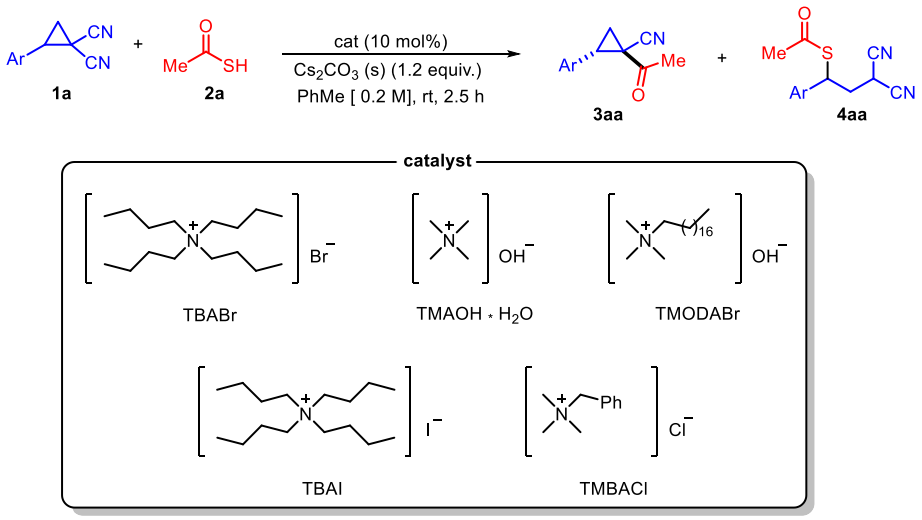



*Scheme 7.2. Reaction between cyclopropane **1** and thioacetic acid **2a** using a solid base or an aqueous base solution*

### 7.2.1 Optimization of product 3aa

We started our investigation by performing a catalyst screening and the results are reported in *Table 7.1*. Performing the rection with tetrabutylammonium bromide (TBABr) as catalyst promising results in terms of yield and very good selectivity in favor of product **3aa** were obtained (entry 1). Performing the reaction with tetramethylammonium hydroxide hydrate (TMAOH $*$ $5H_2O$) only traces of product **3aa** or **4aa** were present in the reaction mixture, both with or without additional base (entries 3 and 7). Performing the reaction with tetramethylammonium hydroxide hydrate (TMAOH $*$ $5H_2O$) only traces of product **3aa** or **4aa** were present in the reaction mixture, both with or without additional base with an additional base (entries 3 and 7). Promising results were obtained performing the reaction with catalysts such as tetrabutylammonium iodide (TBAI), trimethyloctadecylammonium bromide (TMODABr), or timethylbenzylammonium chloride (TMBACl), (entries 4-6). TMODABr gives a slight lower degree of selection between products **3aa** and **4aa** (entry 5), but the higher yield value obtained encouraged us to choose it as a catalyst for subsequent screening.

*Table 7.1. Catalyst screening*

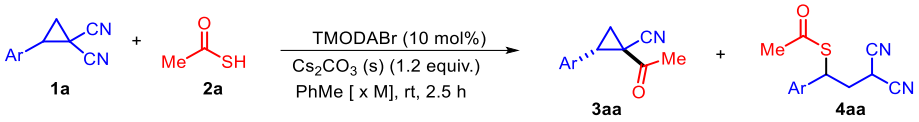



| entry[a] | Catalyst | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|
| **1** | **TBABr** | 32 | 27 | 11:1 |
| **2** | / | 2 | nd | > 20:1 |
| **3** | **TMAOH • 5H$_2$O** | 0 | nd | - |
| **4** | **TBAI** | 34 | nd | 17:1 |
| **5** | **TMODABr** | 46 | nd | 14:1 |
| **6** | **TMBACl** | 10 | nd | > 20:1 |
| **7** | **TMAOH • 5H$_2$O** | 4 | nd | 14:1 |

[a] reaction conditions: **1a** (0.1 mmol), 2a (0.15 mmol), cat. (10 mol%), $Cs_2CO_3$ (0.12 mmol) in PhMe (500 µL), rt, 2.5 h. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel

Subsequently, we move to analyze the concentration of the solvent medium (*Table 7.2*). Performing the reaction in a more concentrated solvent medium (compare entries 1 and 2) lower values of both yield and selection were achieved. Performing the reaction with a lower concentration (entry 3) the yield of the reaction drops, while the selectivity between products **3aa** and **4aa** was still higher. Due to the better yield and the good selectivity obtained performing the reaction at a concentration of 0.2 M, this value was chosen for further implementation.

*Table 7.2. Concentration*

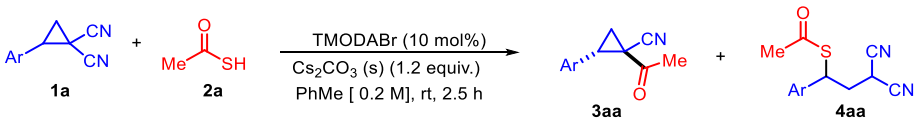



| entry[a] | concentration | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|
| **1** | **0.2** | 46 | nd | 14:1 |
| **2** | **0.4** | 19 | nd | 10:1 |
| **3** | **0.1** | 31 | nd | >20:1 |

[a] reaction conditions: **1a** (0.1 mmol), 2a (0.15 mmol), cat. (10 mol%), $Cs_2CO_3$ (0.12 mmol) in PhMe (x µL), rt, 2.5 h. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

Then, we focus our attention on the stoichiometry of the reaction. In particular, increasing amounts of substrate **1a** were tested and the results are reported in *Table 7.3*. Performing the reaction with a slight excess of substrate **1a** (entry 2) an increase in the yield and a better selectivity were obtained (compare entries 1 and 2). To evaluate if a grate excess of substrate **1a** could further increase the yield of product **3aa** more, an experiment with 2.5 equiv. of **1a** was set up (entry 3) but in this case, a decrement of the yield was observed. Consequently, we decided to use a slight excess of substrate **1a** for the next tests.

*Table 7.3. Equivalents of **1a***



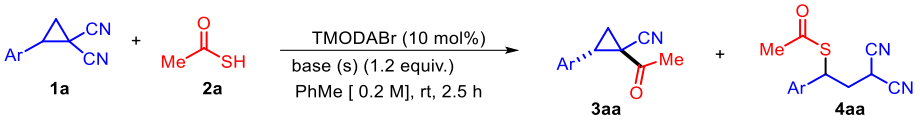

| entry[a] | equiv. 1a | equiv 2a | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|---|
| **1** | **1** | 1.5 | 46 | nd | 14:1 |
| **2** | **1.5** | 1 | 52 | nd | >20:1 |
| **3** | **2.5** | 1 | 42 | nd | >20:1 |

[a] reaction conditions: **1a** (x mmol), **2a** (x mmol), cat. (10 mol%), $Cs_2CO_3$ (0.12 mmol) in PhMe (500 µL), rt, 2.5 h. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

Following, a base screening was carried out and the results are reported in *Table 7.4*. Performing the reaction with phosphate derivatives (entries 6-10) any reactivity or only traces of product **3aa** was observed.low reactivity was observed. On the contrary, performing the reaction with more strong bases such as carbonates derivatives, different yields were observed. In particular, with $NaHCO_3$ (a very weak base) no reactivity was observed (entry 5) while performing the reaction with a stronger base such as $Na_2CO_3$ product **3aa** was obtained in low yield. We then move to change the cation of the base. Performing the reaction with $KHCO_3$ product **3aa** was obtained in very low yield while

increasing the basicity of the additive, so performing the reaction with $K_2CO_3$ the yield is more than duplicate (entry 2). In any case, the best results were obtained with $Cs_2CO_3$ as base (entry 1).

*Table 7.4. Bases screening*

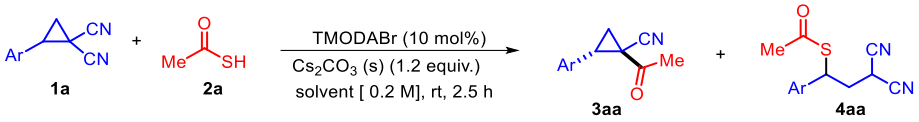



| entry[a] | base | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|
| **1** | $Cs_2CO_3$ | 52 | nd | >20:1 |
| **2** | $K_2CO_3$ | 19 | nd | >20:1 |
| **3** | $KHCO_3$ | 7 | nd | >20:1 |
| **4** | $Na_2CO_3$ | 14 | nd | >20:1 |
| **5** | $NaHCO_3$ | traces | nd | nd |
| **6** | $K_3PO_4$ | 29 | nd | >20:1 |
| **7** | $K_2HPO_4 * 3H_2O$ | 7 | nd | >20:1 |
| **8** | $KH_2PO_4$ | traces | nd | nd |
| **9** | $Na_2HPO_4$ | traces | nd | nd |
| **10** | $NaH_2PO_4 * 3H_2O$ | traces | nd | nd |

[a] reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), cat. (10 mol%), base (0.12 mmol) in PhMe (500 µL), rt, 2.5 h. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

Once individuated the correct base, we move to analyze different solvent medium (*Table **7.5***).*Table 7.5*). Good reactivity and very good selectivity were achieved performing the reaction in polar solvents such as EtOAc (entry 3). Moreover, comparable results in terms of yield and selectivity were obtained performing the reaction in apolar or halogenated solvents such as PhMe and $CH_2Cl_2$ (entries 1 and 2). Interesting results in terms of yield were observed performing the reaction in ethereal solvents. In particular, performing the reaction in $Et_2O$ or MTBE (entries 4 and 5) lower values of yield were achieved (compare the results with the standard ones (entry 1). Surprisingly, performing the reaction in THF, an increment of the yield value was obtained (entry 6). For this reason, we continue our screening by employing a more hindered ethereal solvent, the 2-Me-THF, but in this case, a decrement of the yield was observed. Taking into consideration all the results obtained we select THF as solvent medium for future investigations (entry 6).

*Table 7.5. Solvent screening*

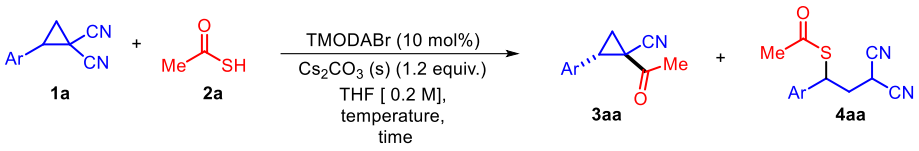



| entry[a] | solvent | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|
| **1** | PhMe | 52 | nd | >20:1 |
| **2** | $CH_2Cl_2$ | 50 | 47 | >20:1 |
| **3** | EtOAc | 39 | 31 | >20:1 |
| **4** | $Et_2O$ | 28 | 23 | >20:1 |
| **5** | MTBE | 43 | 40 | >20:1 |
| **6** | THF | 69 | 61 | >20:1 |
| **7** | 2-Me-THF | 46 | 39 | >20:1 |

[a] reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), cat. (10 mol%), $Cs_2CO_3$ (0.12 mmol) in solvent (500 µL), rt, 2.5 h. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

The last parameters analyzed are time and temperature and the results are reported in *Table 7.6*. Performing the reaction for a longer period of time with respect to the standard reaction conditions (compare entries 1 and 2) a decrement of the yield value was observed, probably because the strongly basic conditions deteriorate the reaction yield. At this point the temperature of the reaction was evaluated, but as you can see any increment of the reaction yield was observed neither increasing nor decreasing the temperature (compare entries 1, 3 and 4). So, the best reaction condition identified for the synthesis of product **3aa** are reported in entry 1.

*Table 7.6. Temperature and time investigation*




| entry[a] | T | time | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|---|
| **1** | rt | 2.5 h | 69 | 61 | >20:1 |
| **2** | rt | 19 h | nd | 25 | >20:1 |
| **3** | 60 °C | 2.5 h | nd | 23 | >20:1 |
| **4** | 0 °C | 19 h | 60 | nd | >20:1 |

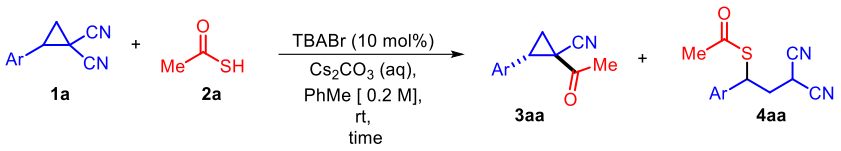
[a] reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), cat. (10 mol%), $Cs_2CO_3$ (0.12 mmol) in THF (500 µL), temperature, time. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

### 7.2.2 Optimization of product 4aa

Regarding the optimization of product **4aa** more aimed screenings were carried out and the results of the catalysts tested are reported below. We started our investigation by testing

the temperature and the time of the reaction and the results are reported in *Table 7.7*. Performing the reaction at room temperature (entry 2)), promising results in terms of yield and very good selectivity in favor of product **4aa** were achieved. To increase the yield value, we decided to test the temperature. Increasing the temperature of the reaction (entry 3) only product **3aa** was present in the reaction mixture while performing the reaction at 0°C the desired product **4aa** was obtained in higher yield with respect to the reaction carried out at room temperature (compare entries 1 and 2). Due to the impact of the temperature on both the selectivity and the yield of the reaction, we decided to further decrease the temperature (entries4entries 4 and 5) but in this case, a poor reactivity was observed also performing the reaction for a longer period of time. So, we decided to continue our investigation according to the conditions reported in entry 1.

*Table 7.7 Temperature and time investigation*

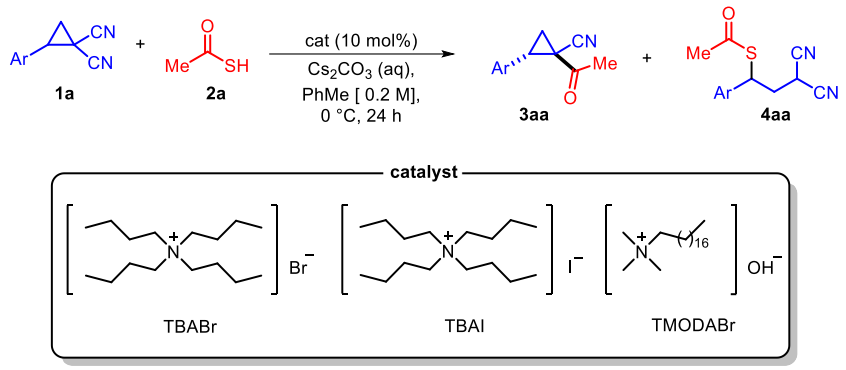



| entry[a] | T | Time | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|---|
| **1** | 0 °C | 24 h | 43 | 42 | 1:20 |
| **2** | rt | 2.5 h | 26 | 24 | 1:20 |
| **3** | 45 °C | 2.5 h | - | - | 20:1 |
| **4** | - 20 °C | 24 h | 5 | nd | 1:20 |
| **5** | - 20 °C | 48 h | 6 | nd | - |

[a] reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), TBABr (10 mol%), $Cs_2CO_3$ (aq 10 w/w, 250 µL) in toluene (500 µL), temperature, time. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

We continue the optimization of the reaction by testing different catalysts and the results are reported in *Table 7.8*. Performing the reaction with TBABr and TBAI similar results in terms of yield and enantioselectivity were obtained (compare entries 1 and 3) while performing the reaction with TMODABr (best catalyst for the synthesis of products **3**) very low yield and poor selectivity were observed.

*Table 7.8. Catalyst screening*

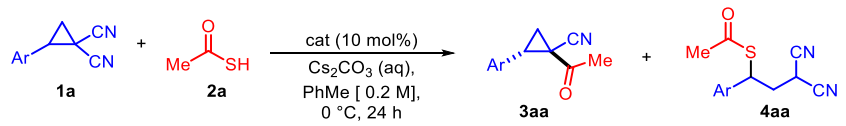



| entry[a] | catalyst | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|
| **1** | TBABr | 43 | nd | 1:20 |
| **2** | TMODABr | 7 | nd | 1:1 |
| **3** | TBAI | 44 | nd | 1:20 |

[a] reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), cat (10 mol%), $Cs_2CO_3$ (aq 10 w/w, 250 µL) in toluene (500 µL), 0°C, 24 h. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

We continue our investigation by testing the amount of base necessary for the reaction and the results are reported in *Table 7.9*. Performing the reaction with a more concentrated base solution (entry 2) a lower reactivity and very poor selectivity was observed (compare entries 1 and 2). Therefore, we maintain the conditions of entry 1 for further implementation.

*Table 7.9. Amount of base*



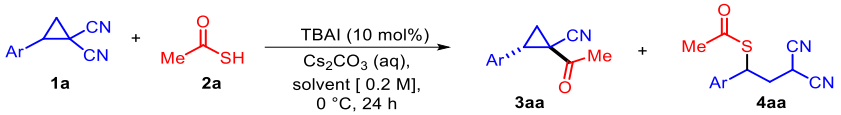

| entry[a] | base | $^1$H NMR yield[b] | Yield[c] | 3aa/4aa |
|---|---|---|---|---|
| **1** | $Cs_2CO_3$ (aq 10 w/w) | 44 | nd | 20:1 |
| **2** | $Cs_2CO_3$ (aq 20 w/w) | 7 | nd | 5:1 |

[a] reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), cat (10 mol%), $Cs_2CO_3$ (aq X w/w, 250 µL) in toluene (500 µL), 0°C, 24 h. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

At this point, a solvents screening was carried out and the results are reported in *Table **7.10***. Performing the reaction in halogenated solvents such as $CH_2Cl_2$ a lower reactivity and a very poor selectivity was observed (entry 2). Regarding the ethereal solvents, different behaviors were observed. Performing the reaction in THF only product **3aa** was present in the reaction mixture (entry 3) while performing the reaction in MTBE and 2-Me-THF low reactivity and poor selectivity were observed (4 and 5). Performing the

reaction in $Et_2O$ sloppy reactivity but very good selectivity were detected. More polar solvents such as EtOAc furnish good results in terms of yield and very good selectivity (entry 7). Moreover, by increasing the reaction time, from 24 to 48 h (compare entries 7 and 9) an increment of the yield value was verified. Due to the similar reactivity observed in toluene and EtOAc in the reaction performed for 24 h (compare entries 1 and 7), another experiment in PhMe increasing the reaction time was carried out but in this case, a decrement of the yield value was observed. Taking into consideration all the experiments carried out the best results are reported in entry 9.

*Table 7.10. Solvent screening*

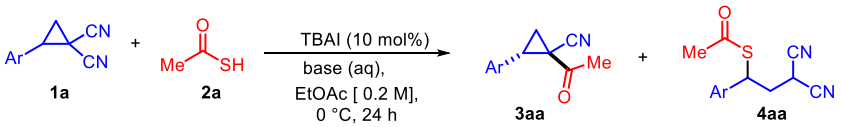



| entry[a] | solvent | time | $^1$H NMR yield[b] | Yield[c] | 4aa/3aa |
|---|---|---|---|---|---|
| **1** | PhMe | 24 h | 44 | nd | > 20:1 |
| **2** | $CH_2Cl_2$ | 24 h | 31 | nd | 1:1 |
| **3** | THF | 24 h | - | - | 1:20 |
| **4** | MTBE | 24 h | 25 | nd | 4:1 |
| **5** | 2-Me-THF | 24 h | 46 | 20 | 2:1 |
| **6** | $Et_2O$ | 24 h | low | nd | > 20:1 |
| **7** | EtOAc | 24 h | 46 | 38 | > 20:1 |
| **8** | PhMe | 48 h | 34 | nd | 4:1 |
| **9** | EtOAc | 48 h | 57 | 53 | > 20:1 |

[a] reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), cat (10 mol%), $Cs_2CO_3$ (aq 10 w/w, 250 µL) in solvent (500 µL), 0 °C, time. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

Subsequently, the nature of the base was evaluated and the results are reported in *Table **7.11***. Performing the reaction with $K_2CO_3$ only product **3aa** was present in the reaction mixture (entry 2), so the conditions reported in entry 1 are the best for the synthesis of product **4aa**.

*Table 7.11. Base screening*

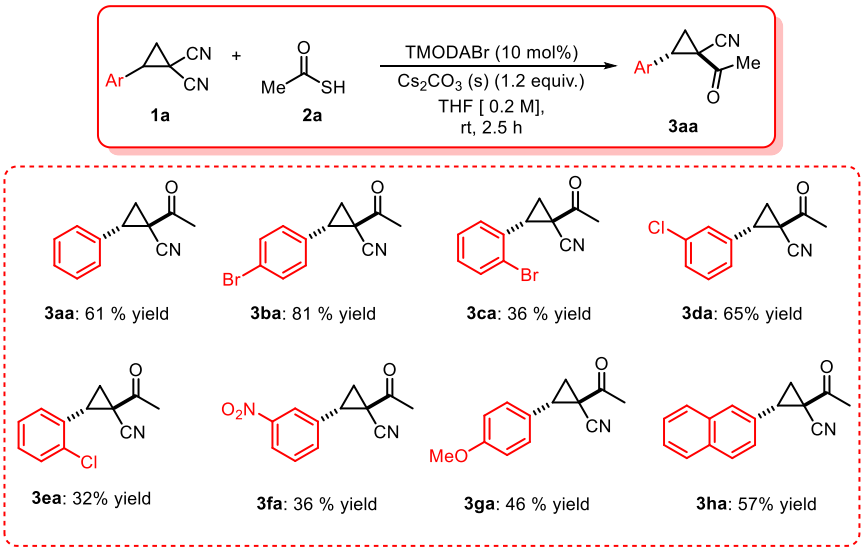



| entry[a] | base | $^1$H NMR yield[b] | Yield[c] | 4aa/3aa |
|---|---|---|---|---|
| **1** | $Cs_2CO_3$ (10% w/w) | 57 | 53 | > 20:1 |
| **2** | $K_2CO_3$ (10% w/w) | - | - | 1:20 |

[a] reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), cat (10 mol%), base (aq 10 w/w, 250 µL) in solvent (500 µL), 0 °C, 48. [b] determined using *m*-dinitrobenzene as internal standard. [c] determined after chromatographic column on silica gel.

## 7.3 Scope of the reaction

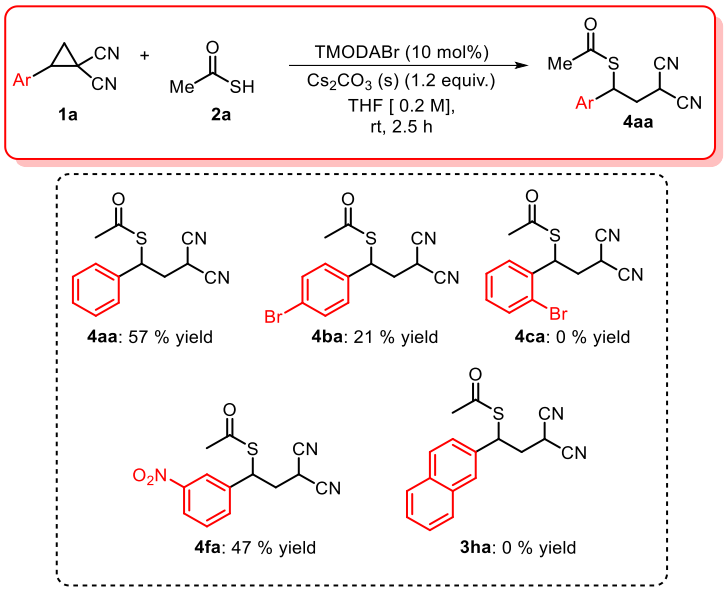
Once identified the best reaction conditions for the synthesis of products **3** and **4** we begin to evaluate the scope of the reactions. Regarding products **3** a preliminary analysis variating the substituent present on the aromatic ring of the cyclopropane derivative was effectuated (*Scheme 7.3*). Good results in terms of yield were achieved introducing a halogen atom inat the *para* or *meta* position of the aromatic ring (products **3ba** and **3da** respectively), while performing the reaction with a halogen atom inat the *ortho* position of the aromatic ring (products **3ca** and **3ea)** a sloppy reactivity was observed regardless of the steric hindrance of the halogen atom. Performing the reaction with electron-rich or electron-poor substituents such as a nitro substituent inat the *meta* position or a methoxy inat *para* position, moderate reactivity was obtained (products **3fa** and **3ga)**. Finally, we tested the reactivity of 2-naphthalene as substituent and product **3ha** was obtained in good yield.




*Scheme 7.3. Substrate scope of products **3***

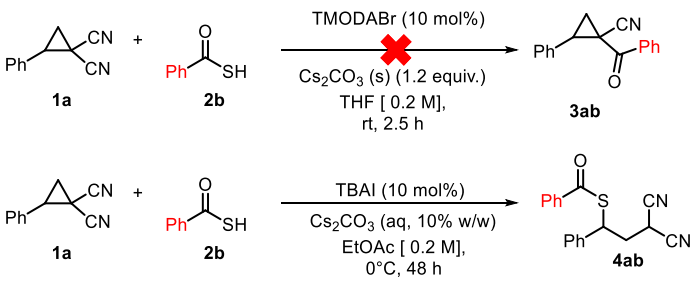
At the same time, a short evaluation of the generality of products **4** was carried out (*Scheme 7.4*). Performing the reaction with a halogen atom in the *para* position of the aromatic ring, substrate **1b** product **4ba** was obtained in low yields.yield. Moreover, performing the reaction with substrate **1c**, any reactivity was observed, probably because a bromine atom in the *ortho* position of the aromatic ring makes the cyclopropylic carbon too hindered for a nucleophilic attack. An enhance of the reactivity was observed performing the reaction with substrate **1f** characterized by a nitro group in the *meta* position of the aromatic ring

of the cyclopropane and product **4fa** was obtained in good yield. Substrate **1h** with a 2-naphthalene group instead of a simple aromatic ring, didn't show reactivity: probably also in this case the cyclopropylic carbon is too hindered to accommodate another substituent.




*Scheme 7.4. Substrate scope of products **4***

Subsequently, we move on to analyze the reactivity of the reaction by changing the acidic nucleophile. We try to perform the same reaction using thiobenzoic acid and the results are reported in *Scheme 7.5*. Performing the reaction with TMODABr as catalyst and solid base, product **3ab** was not detected in the crude mixture. While the reaction performed with TBAI and aqueous base, product **4ab** was obtained in good yield. This result opens the door to a more thorough evaluation of the generality of the reaction.

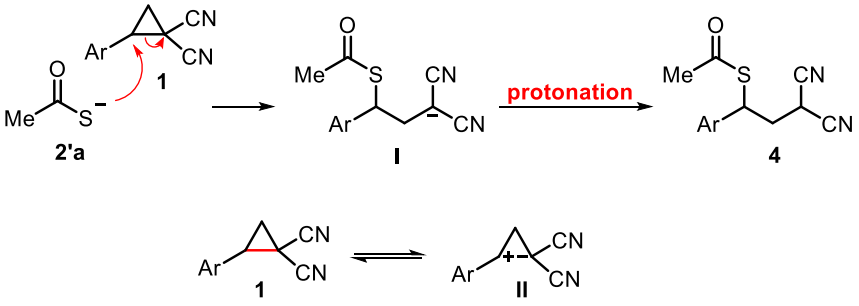



*Scheme 7.5. Experiments with thiobenzoic acid*

## 7.4 Reactions mechanisms

The reaction mechanisms still need to be thoroughly investigated but, taking into consideration some literature reports it is possible to hypothesize a reaction pathway for each product.

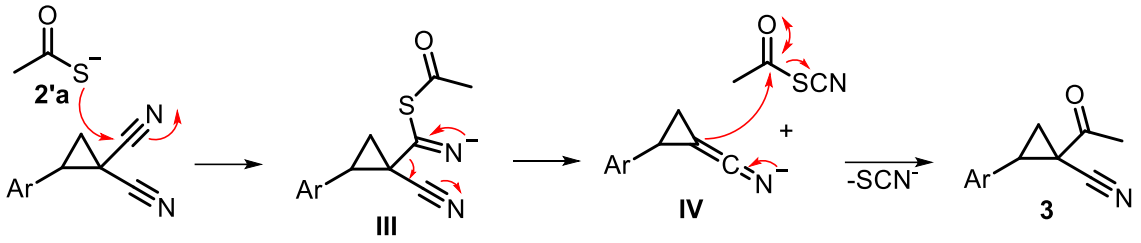
Regarding products **4** first of all an acid-base reaction between the thioacetic acid and the base occur, generating the thiolate **2'a** which can act as a nucleophile on the electrophilic carbon of the cyclopropane producing the anionic intermediate **I** (*Scheme 7.6*). At this point, the aqueous conditions favor a rapid protonation of intermediate **I** to generate products **4**. The nucleophilic attack of thiolate **2'a** can occur through an $S_N2$ or an $S_N1$ substitution reaction because substrates **1** are in equilibrium with the zwitterionic form, intermediate **II**. In particular, the presence of an electron donating group and two electron-withdrawing groups as substituents of vicinal carbons makes the bond between these carbons (highlighted in red in *Scheme 7.6*) weak enough to allow the equilibrium with the open zwitterionic form intermediate **II**.




*Scheme 7.6. Possible mechanism for product **4***

A completely different mechanism based on the work of Tanino et al.[111] can be supposed for products **3** (*Scheme 7.7*). Also in this case, the first step is an acid-base reaction between thioacetic acid and the base to generate thiolate **2'a**. Thiolate **2'a** produces a nucleophilic attack on the electrophilic carbon of one of the two cyan group with subsequent formation of intermediate **III**. Then, an intramolecular rearrangement with consequent formation of intermediate **IV** and acetyl thiocyanate can occur. Subsequently, intermediate **IV** undergoes a nucleophilic attack on the electrophilic carbon of the acetyl thiocyanate with the rapid formation of product **3** and simultaneous release of thiocyanate ion.

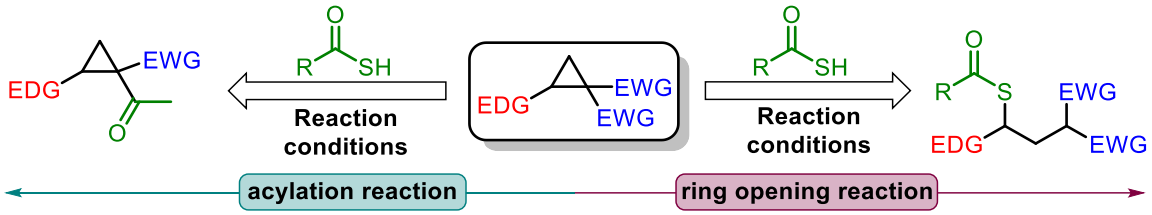
111 D. Domon , M. Iwakura, K. Tanino, *Tetrahedron Lett.* **2017**, *58*, 1957




*Scheme 7.7. Possible mechanism for product **3***

## 7.5 Conclusions and future prospect

In conclusion, a chemodivergent reaction depending on the reaction conditions was developed. The divergent methodology exploits two different reactive sites of the cyclopropylic substrate. The two protocols are based on a ring opening reaction exploiting the classical reactivity of donor -acceptor cyclopropane and on a non-reductive decyanation reaction. These methodologies were developed under basic phase transfer catalysis, an unconventional mode of activation of donor-acceptor cyclopropane. Moreover, once identified the best reaction conditions for both products, a short evaluation of the generality of the reaction was carried out. In the future, the generality of the reaction will be studied by testing different donor-acceptor cyclopropane and different thiocarboxylic acids. Moreover, it will be carried out a thorough investigation of the mechanisms of the reaction.



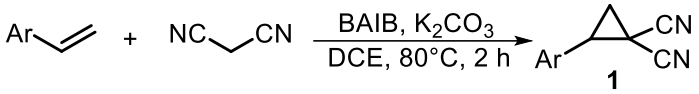
## 7.6 Experimental section

**General methods and materials**

**General Methods**. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Inova 300 or Mercury 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvents signals[112] for $^{1}H$ and $^{13}C$ NMR. Signal patterns are indicated as follows: bs, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in Hertz (Hz). $^{13}C$ NMR were acquired with $^{1}H$ broad-band decoupled mode. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionization techniques or on a FOCUS/DSQ using electron impact (EI) ionization techniques (relative intensities are given in brackets).

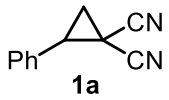
**Materials**. Analytical grade solvents and commercially available reagents were used as received, unless otherwise noted.

**Preparation cyclopropane 1**



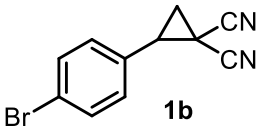

To a solution of malononitrile in DCE (20 mL), the corresponding styrene (1 equiv. 5 mmol), $K_2CO_3$ (2.2 equiv., 11 mmol, 1.52 g) and bisacetoxyiodobenzene (2.2 equiv. 11 mmol, 3.55 g) were added. The suspension was stirred at 80°C for 1h. Then, the reaction mixture was cooled to room temperature, filtered through a short plug of Celite ® and then extracted with water. The combined organic phases were evaporated under reduced pressure, and the crude was purified by column chromatography on silica gel using 5:1 = *n*-hexane: EtOAc as eluent.

**2-phenylcyclopropane-1,1-dicarbonitrile 1a**



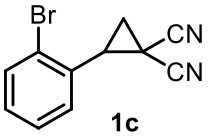

Following the model procedure with styrene, product **1a** was obtained in 67% yield as pale yellow solid. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ = 7.47 – 7.39 (m, 3H), 7.33 – 7.27 (m, 2H), 3.30 (t, J = 9.0 Hz, 1H), 2.26 (d, J = 9.0, 1.4 Hz, 2H).

**2-(4-bromophenyl)cyclopropane-1,1-dicarbonitrile 1b**




Following the model procedure with *p*-Br styrene, product **1b** was obtained in 29% yield as pale yellow solid. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ = 7.61 – 7.51 (m, 2H), 7.22 – 7.12 (m, 2H), 3.24 (t, J = 9.0 Hz, 1H), 2.24 (dd, J = 9.0, 7.1 Hz, 2H).

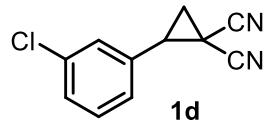
**2-(2-bromophenyl)cyclopropane-1,1-dicarbonitrile 1c**




Following the model procedure with *o*-Br styrene, product **1c** was obtained in 22% yield as pale yellow solid. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ = 7.69 (d, J = 7.5, 1H), 7.38 – 7.24 (m, 2H), 7.13 (d, J = 7.5, 1H), 3.28 (t, J = 9.0 Hz, 1H), 2.27 (dq, J = 9.0, 6.4 Hz, 2H).

[112] H. E. Gottlieb, V. Kottlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.

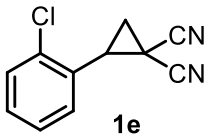
**2-(3-chlorophenyl)cyclopropane-1,1-dicarbonitrile 1d**



**1d**

Following the model procedure with *m*-Cl styrene, product **1d** was obtained in 32% yield as pale yellow solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.19 (s, 1H), 7.54 – 7.63 (m, 3H), 7.71 (s, 1H).

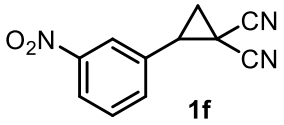
**2-(2-chlorophenyl)cyclopropane-1,1-dicarbonitrile 1e**



**1e**

Following the model procedure with *o*-Cl styrene, product **1e** was obtained in 35% yield as pale yellow solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.57 – 7.49 (m, 1H), 7.39 (tdd, J = 8.0, 1.7, 0.6 Hz, 1H), 7.32 (tdd, J = 7.5, 1.4, 0.4 Hz, 1H), 7.21 – 7.14 (m, 1H), 3.38 – 3.31 (m, 1H), 2.35 – 2.23 (m, 2H).

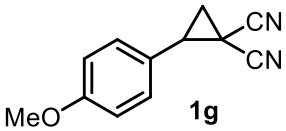
**2-(3-nitrophenyl)cyclopropane-1,1-dicarbonitrile 1f**



**1f**

Following the model procedure with *m*-$NO_2$ styrene, product **1f** was obtained in 22% yield as yellow solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.34 – 8.24 (m, 1H), 8.21 – 8.16 (m, 1H), 7.73 – 7.57 (m, 2H), 3.40 (t, J = 9.0 Hz, 1H), 2.44 – 2.29 (m, 2H).

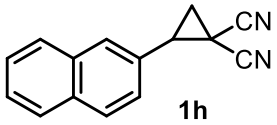
**2-(4-methoxyphenyl)cyclopropane-1,1-dicarbonitrile 1g**



**1g**

Following the model procedure with *m*-$NO_2$ styrene, product **1g** was obtained in 53% yield as pale yellow solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.25 – 7.19 (m, 2H), 6.97 – 6.91 (m, 2H), 3.82 (s, 3H), 3.27 (t, *J* = 9.1 Hz, 1H), 2.22 (d, *J* = 9.1 Hz, 2H).

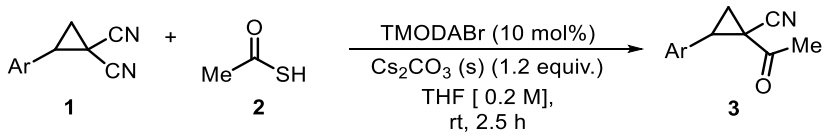
**2-(naphthalen-2-yl)cyclopropane-1,1-dicarbonitrile**



**1h**

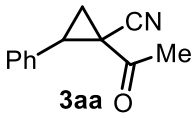
Following the model procedure with 2-vinylnaphthalene, product **1h** was obtained in 15% yield as pale yellow solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.80 (m, 3H), 7.72 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.39 (dd, *J* = 8.5, 1.9 Hz, 1H), 3.41 (td, *J* = 9.3, 0.8 Hz, 1H), 2.35 (dd, *J* = 8.7, 6.4 Hz, 1H), 2.23 (dd, *J* = 9.3, 6.4 Hz, 1H).

## General Procedure for the synthesis of products 3




In a small 4 mL vial equipped with a magnetic stirring bar, salicylaldehyde cyclopropane **1** (1.5 equiv., 0.15 mmol), TMODABr (0.01 mmol), thioacetic acid and $Cs_2CO_3$ are dissolved in 500 µL of THF. The resulting suspension was stirred for 2.5 h at room temperature and then directly pre-purified by a short plug on silica gel using DCM and $Et_2O$ as eluent. After evaporation of solvent the crude product was purified through chromatography on silica gel, to afford the desired compound **3** as oils.

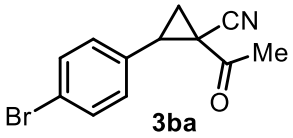
**1-acetyl-2-phenylcyclopropane-1-carbonitrile 3aa**



**3aa**

Following the model procedure using substrate **1a**, product **3aa** was obtained in 61% yield after chromatographic purification on silica gel using 3:1 = DCM: *n*-hexane as eluent. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 7.44 – 7.31 (m, 3H), 7.30 – 7.18 (m, 2H), 3.12 (t, J = 9.1 Hz, 1H), 2.58 (s, 3H), 2.21 (dd, J = 9.1, 4.9 Hz, 1H), 2.11 (dd, J = 8.4, 4.9 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 198.6, 133.1, 128.8 (2C), 128.6, 128.2 (2C), 118.3, 38.4, 30.3, 29.4, 24.7.

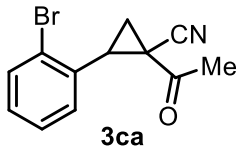
**1-acetyl-2-(4-bromophenyl)cyclopropane-1-carbonitrile 3ba**



**3ba**

Following the model procedure using substrate **1b**, product **3ba** was obtained in 81% yield after chromatographic purification on silica gel using 2:1 = DCM: *n*-hexane as eluent. **$^{1}$H NMR** (600 MHz, $CDCl_3$) δ = 7.50 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.05 (t, J = 8.7 Hz, 1H), 2.56 (s, 3H), 2.17 (dd, J = 9.1, 5.0 Hz, 1H), 2.03 (dd, J = 9.1, 5.0 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ = 198.2, 132.2, 131.9 (2C), 129.8 (2C), 122.7, 118.1, 37.4, 30.1, 29.4, 24.7.

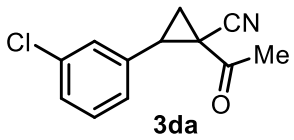
**1-acetyl-2-(2-bromophenyl)cyclopropane-1-carbonitrile 3ca**



**3ca**

Following the model procedure using substrate **1c**, product **3ca** was obtained in 36% yield after chromatographic purification on silica gel using 3:1 = DCM: *n*-hexane as eluent. **$^{1}$H NMR** (600 MHz, $CDCl_3$) δ = 7.65 (dd, J = 8.0, 1.2 Hz, 1H), 7.33 (td, J = 7.5, 1.2 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.17 (dt, J = 7.6, 1.3 Hz, 1H), 3.08 (t, J = 8.6 Hz, 1H), 2.63 (s, 3H), 2.26 (dd, J = 8.8, 4.9 Hz, 1H), 2.10 (dd, J = 8.5, 5.0 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ = 198.6, 133.5, 133.0, 130.3, 129.2, 127.8, 126.9, 117.9, 39.4, 29.3, 29.3, 24.3.

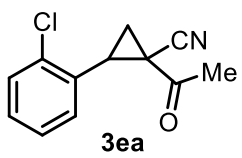
**1-acetyl-2-(3-chlorophenyl)cyclopropane-1-carbonitrile 3da**



**3da**

Following the model procedure using substrate **1d**, product **3da** was obtained in 65% yield after chromatographic purification on silica gel using 3:1 = DCM: *n*-hexane as eluent. **$^{1}$H NMR** (600 MHz, $CDCl_3$) δ = 7.47 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.30 (dtd, *J* = 19.2, 7.5, 1.7 Hz, 2H), 7.18 (dd, *J* = 7.4, 1.8 Hz, 1H), 3.10 (t, *J* = 8.6 Hz, 1H), 2.62 (s, 3H), 2.26 (dd, *J* = 8.9, 4.9 Hz, 1H), 2.09 (dd, *J* = 8.4, 4.9 Hz, 1H).

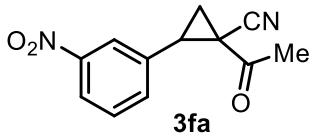
**1-acetyl-2-(2-chlorophenyl)cyclopropane-1-carbonitrile 3ea**



**3ea**

Following the model procedure using substrate **1e**, product **3ea** was obtained in 32% yield after chromatographic purification on silica gel using 3:1 = DCM: *n*-hexane as eluent. **$^{1}$H NMR** (600 MHz, $CDCl_3$) δ = 7.33 – 7.30 (m, 2H), 7.26 – 7.23 (m, 1H) 7.13 – 7.10 (m, 1H), 3.10 – 3.02 (m, 1H), 2.58 (s, 3H), 2.17 (dd, *J* = 9.1, 5.0 Hz, 1H), 2.06 (dd, *J* = 8.3, 5.0 Hz, 1H).

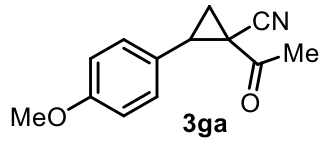
**1-acetyl-2-(3-nitrophenyl)cyclopropane-1-carbonitrile 3fa**




**3fa**

Following the model procedure using substrate **1f**, product **3fa** was obtained in 36% yield after chromatographic purification on silica gel using 4:1 = *n*-hexane: EtOAc as eluent. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.26 – 8.20 (m, 1H), 8.17 – 8.13 (m, 1H), 7.62 – 7.57 (m, 2H), 3.22 (t, J = 8.7 Hz, 1H), 2.62 (s, 3H), 2.25 (dd, J = 9.1, 5.2 Hz, 1H), 2.16 (dd, J = 8.2, 5.2 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 197.8, 148.4, 135.5, 134.0, 129.9, 123.6, 123.5, 117.6, 36.4, 29.9, 29.5, 24.6.

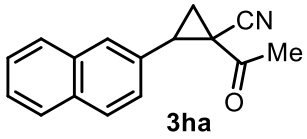
**1-acetyl-2-(4-methoxyphenyl)cyclopropane-1-carbonitrile 3ga**




**3ga**

Following the model procedure using substrate **1g**, product **3ga** was obtained in 46% yield after chromatographic purification on silica gel using 3:1 = *n*-hexane: EtOAc as eluent. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.21 – 7.15 (m, 2H), 6.94 – 6.87 (m, 2H), 3.81 (s, 3H), 3.08 (dd, J = 9.1, 8.4 Hz, 1H), 2.57 (s, 3H), 2.20 (dd, J = 9.2, 4.9 Hz, 1H), 2.09 – 2.02 (m, 1H).

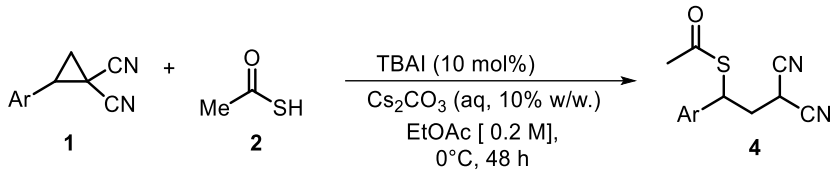
**1-acetyl-2-(naphthalen-2-yl)cyclopropane-1-carbonitrile 3ha**




**3ha**

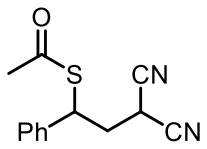
Following the model procedure using substrate **1e**, product **3ea** was obtained in 32% yield after chromatographic purification on silica gel using 3:1 = DCM: *n*-hexane as eluent. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.93 – 7.76 (m, 4H), 7.76 – 7.69 (m, 1H), 7.57 – 7.44 (m, 2H), 7.36 (dd, *J* = 8.5, 1.9 Hz, 1H), 3.29 (t, *J* = 8.7 Hz, 1H), 2.61 (s, 3H), 2.33 – 2.22 (m, 3H).

**General procedure for the synthesis of products 4**




In a small 4 mL vial equipped with a magnetic stirring bar, cyclopropane **1** (1.5 equiv., 0.15 mmol), TBAI (0.01 mmol), thioacetic acid (1.5 equiv ) and $Cs_2CO_3$ (aq, 10% w/w, 250 µL) are dissolved in 500 µL of EtOAc. The resulting suspension was stirred for 48 h at 0°C and then directly pre-purified by a short plug on silica gel using DCM and $Et_2O$ as eluent. After evaporation of solvent the crude product was purified through chromatography on silica gel, to afford the desired compound **4** as oils.

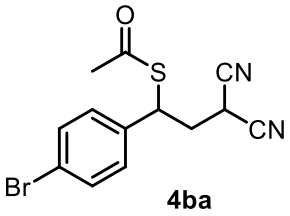
**(3,3-dicyano-1-phenylpropyl) ethanethioate 4aa**




**4aa**

Following the model procedure using substrate **1a**, product **4aa** was obtained in 53% yield after chromatographic purification on silica gel using 3:1 = DCM: *n*-hexane as eluent. **$^1$H NMR** (600 MHz, $CDCl_3$) δ = 7.42 – 7.32 (m, 3H), 7.31 – 7.27 (m, 2H), 4.73 (dd, J = 9.3, 6.6 Hz, 1H), 3.53 (dd, J = 9.0, 6.4 Hz, 1H), 2.71 (ddd, J = 13.8, 9.0, 6.6 Hz, 1H), 2.58 (ddd, J = 13.8, 9.4, 6.4 Hz, 1H), 2.35 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ = 193.5, 136.9, 129.5, 128.9, 127.6, 111.9, 111.6, 44.8, 37.1, 30.4, 20.9.

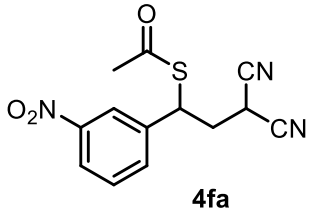
**(1-(4-bromophenyl)-3,3-dicyanopropyl) ethanethioate 4ba**




**4ba**

Following the model procedure using substrate **1b**, product **4ba** was obtained in 21% yield after chromatographic purification on silica gel using 3:1 = DCM: *n*-hexane as eluent. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 4.70 (dd, J = 8.9, 7.1 Hz, 1H), 3.59 (dd, J = 8.6, 6.9 Hz, 1H), 2.69 (ddd, J = 13.9, 8.6, 7.1 Hz, 1H), 2.56 (ddd, J = 13.9, 8.9, 6.9 Hz, 1H), 2.36 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 193.0, 136.4, 132.6, 129.3, 122.9, 111.7, 111.4, 44.2, 36.7, 30.4, 20.9.

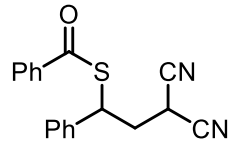
**(3,3-dicyano-1-(3-nitrophenyl)propyl) ethanethioate 4fa**




**4fa**

Following the model procedure using substrate **1f**, product **4fa** was obtained in 36% yield after chromatographic purification on silica gel using 4:1 = *n*-hexane: EtOAc as eluent. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.26 – 8.18 (m, 2H), 7.73 – 7.68 (m, 1H), 7.63 – 7.57 (m, 1H), 4.87 (t, J = 8.0 Hz, 1H), 3.76 (t, J = 7.5 Hz, 1H), 2.82 – 2.64 (m, 2H), 2.39 (s, 3H).

**(3,3-dicyano-1-phenylpropyl) benzothioate 4ab**

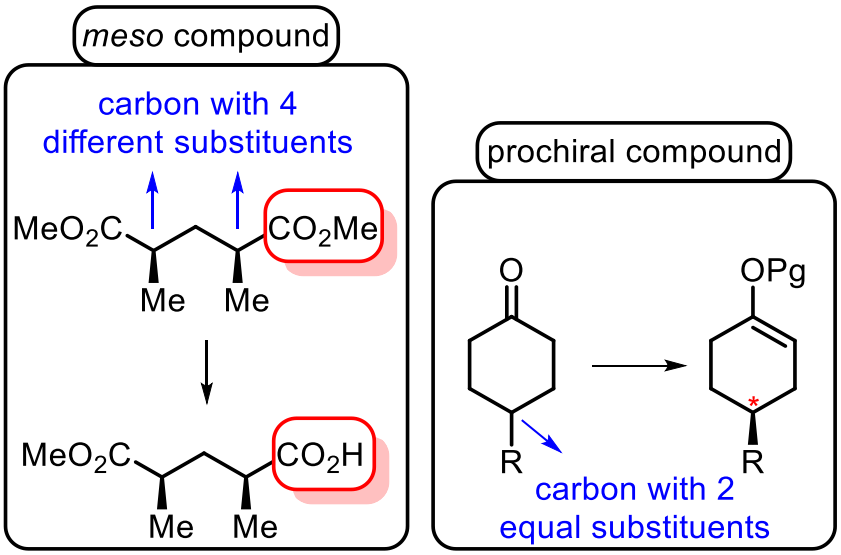



**4ab**

Following the model procedure using substrate **1f** and thiobenzoic acid, product **4ab** was obtained in 72 % yield after chromatographic purification on silica gel using 2:1 = DCM: *n*-hexane as eluent. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.97 – 7.90 (m, 2H), 7.64 – 7.56 (m, 1H), 7.53 – 7.31 (m, 7H), 4.97 (dd, J = 9.4, 6.5 Hz, 1H), 3.62 (dd, J = 9.0, 6.5 Hz, 1H), 2.86 (ddd, J = 13.8, 8.9, 6.5 Hz, 1H), 2.69 (ddd, J = 13.8, 9.4, 6.5 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 189.6, 137.0, 135.9, 134.1, 129.64, 129.61, 128.8, 127.8, 127.5, 112.0, 111.6, 44.8, 37.4, 21.0.

# 8 LiteratureDesymmetrization reactions: literature background and preliminary investigations

The desymmetrization reactions determine the loss of one or more symmetry elements.[113] This loss allows to obtain a chiral product, starting from an achiral starting material. The desymmetrization methodologies can be divided into two main categories. The desymmetrization of prochiral molecules, and the desymmetrization of *meso* compounds (*Scheme 8.1*). The desymmetrization of prochiral molecules is based on the creation of the stereochemical information, while the desymmetrization of *meso* compounds reveals the already existing stereochemistry.[114] Taking into consideration the examples reported below (*Scheme 8.1*), regarding the desymmetrization of *meso* compounds, after the saponification of one of the esters groups, the substrate goes from a *meso* to an asymmetric form. Regarding the desymmetrization of prochiral compounds, the substrate is characterized by a tertiary carbon with two equal substituents. After the desymmetrization reaction, one of the two substituents increases its priority due to the formation of the enolate group.




*Scheme 8.1. Prochiral and meso compounds*

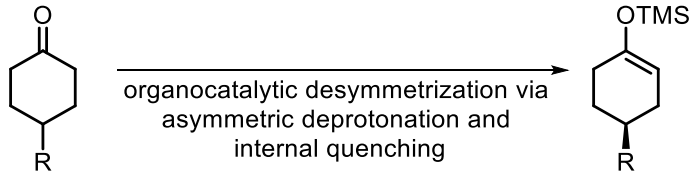
The organocatalytic approach for the desymmetrization methodologies has become in the last years a great challenge, but also an invaluable opportunity, for the synthesis of chiral and enantiopure structures. Generally, the most exploited desymmetrization reactions are

113 G. P. Moss, *Pure Appl. Chem.*, **1996**, *68*, 2193.
114 J. Mèrad, M. Candy, J. -M. Pons, C. Bressy, *Synthesis*, **2017**, *49*, 1938.

the desymmetrization of *meso* compounds because they give an easy access to molecules containing multiple stereogenic elements in one symmetry-breaking operation.[115]

To develop a desymmetrization process, is possible to exploit an infinity of chemical transformations such as Wittig olefination, nucleophilic/electrophilic additions, deprotonation reactions, coupling reactions etc.[116] Once the reaction to be exploited has been individuated is necessary to identify the right class of catalyst which permits an enantioselective development.

One of the simplest reactions exploited for a desymmetrization process is the formation of an enantioenriched enolate starting from a symmetric ketone (*Scheme 8.2*).



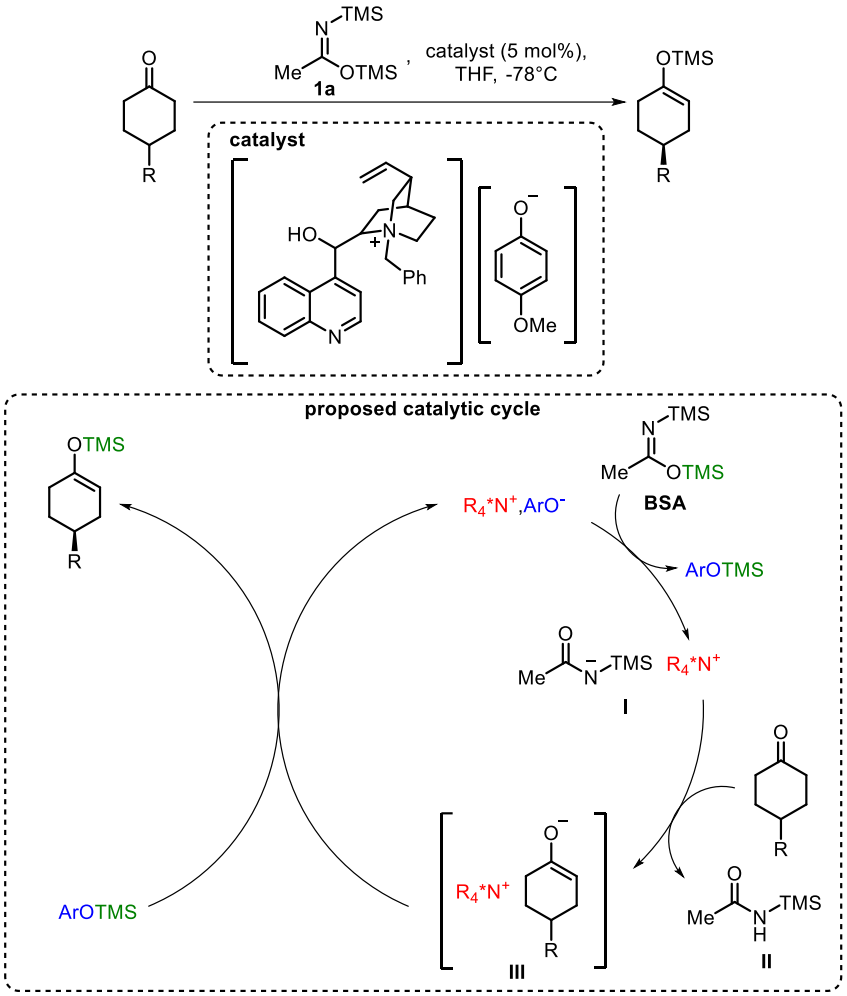

*Scheme 8.2. Desymmetrization process: synthesis of chiral silyl enol ethers*

In this work,[117] the authors take advantage of the ketone deprotonation by the chiral quaternary ammonium amide salt, and then, the resulting enolate is trapped by the ArOTMS generated during the catalytic cycle forming a stable, chiral, and enantioenriched silyl enol ethers as product (*Scheme 8.3*). In particular, the first interaction occurs between the ammonium salt catalyst and bis(trimethylsilyl)acetamide (BSA) with the rapid formation of ArOTMS as the effective silylating species, and ammonium salt **I** which has undergone an anion exchange. Then, the anion of intermediate **I** acts as a base desymmetrizing the ketone by deprotonation, and forming salt **III**. The anion of **III** is immediately captured by ArOTMS, forming the silyl enol ether product.

115 a) R. S. Ward, *Chem. Soc. Rev*., **1990**, *19*, 1. b) M. C. J. Willis, *Chem. Soc. Perkin Trans*., **1999**, *1*, 1765. c) I. M. Pastor, M. Yus, *Curr. Org. Chem*., **2005**, *9*, 1.

116 a) X.-P. Zeng, Z. -Y. Cao, Y. -H. Wang, F. Zhou, J. Zhou, Chem. Rev., **2016**, *116*, 7330. b) N. Di Iorio, S. Crotti, G. Bencivenni, *Chem. Rec.*, **2019**, *19*, 2095. c) T. Shu, J. Cossy, *Chem. Soc. Rev.*, **2021**, *50*, 658. d) T. Suzuki, / *Tetrahedron Letters*, **2017**, *58* 4731. e) Y. -X. Ding, Z. -H. Zhu, C. -B. Yu, Y. -G. Zhou, *Asian J. Org. Chem.*, **2020**, *9*, 1942.

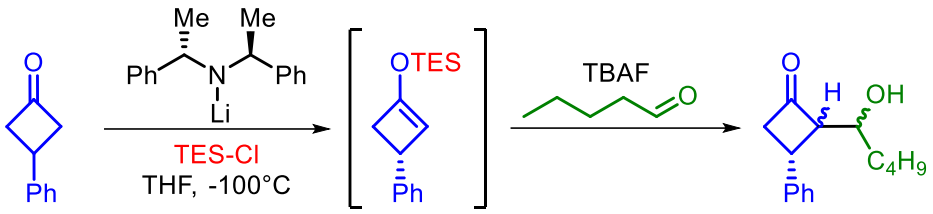
117 A. Claraz, S. Oudeyer, V. Levacher, *Tetrah. Asymm.*, **2013**, *24*, 764.




*Scheme 8.3. Desymmetrization of symmetric ketone: reaction conditions and possible catalytic cycle*

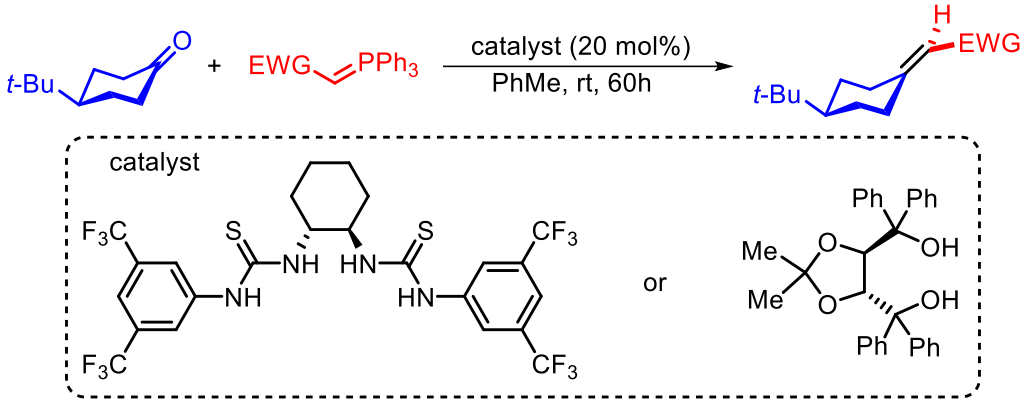
This work was inspired by earlier achievements by Honda and coworkers. (*Scheme 8.4*).[118] In this case, the chiral inducing agent is not a catalyst. Instead, stoichiometric amount of a chiral base is used. Moreover, the chiral and enantioenriched silyl enol ether intermediate is subsequently trapped by the valeraldehyde restoring the ketonic functionality and desymmetrizing the substrate due to the presence of a substituent in the α-position of the ketone.

118 a) T. Honda, N. Kimura, M. Tsubuki, *Tetrahedron Asymmetry* **1993**, *4*, 1475. b) T.Honda, N. Kimura, *J. Chem. Soc. Chem. Commun.* **1994**, 77. c) T. Honda, N. Kimura, S. Sato, D. Kato, H. Tominaga, J. Chem. Soc. *Perkin Trans. 1*, **1994**, 1043.




*Scheme 8.4. Desymmetrization of cyclobutanones*

Another important example of a desymmetrization process is reported below. This example from our laboratory exploits an asymmetric Wittig olefination for the desymmetrization of an asymmetrica cyclic ketone (*Scheme 8.5*). [119]




*Scheme 8.5. Desymmetrization process exploiting the Wittig olefination*

Is important to observe that the three examples previously reported employ similar ketones as substrates, but the authors use completely different methodologies for the desymmetrization approach. Moreover, the methodologies employed, yield products characterized by two different types of chirality. The silyl enol ether and the α-substituted ketone are characterized by central chirality, while the Wittig adduct is characterized by axial chirality.

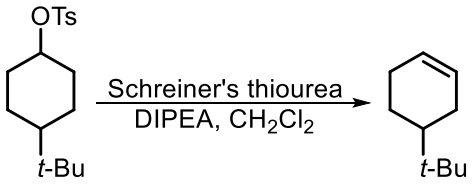
## 8.1 Experimental evolution

The main features of the desymmetrization approach and some examples, useful to understand the breadth of this methodology, have been rapidly summarized in the previous paragraph. In particular, it was highlighted the versatility of this approach. Starting from similar substrates, symmetric ketones, is possible to desymmetrize them using different

119 L. Gramigna, S. Duce, G. Filippini, M. Fochi, M. Comes Franchini, Luca Bernardi, *Synlett.*, **2011**, *18*, 2745.

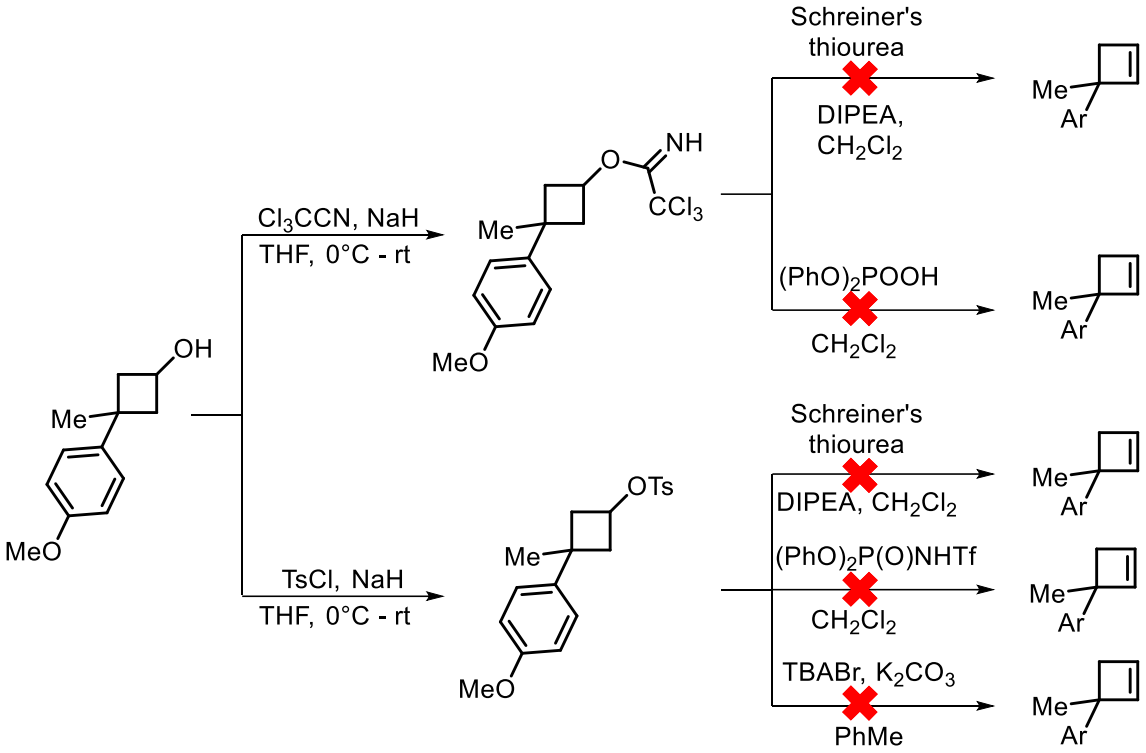
methodologies to obtain enantioenriched products characterized by different types of chirality. During my period abroad, the principal goal was to desymmetrize symmetric alcohols through an enantioselective elimination reaction. A summary of the substrate search and the catalytic methodologies tested are reported below.

One of the methodologies which was first planned is based on the elimination reaction of activated alcohols under basic catalysis (*Scheme 8.6*). The first substrate synthesized is a six-membered ring O-Ts alcohol, but unfortunately, its purification turned out to be quite complicated. Numerous crystallization and chromatographic purification were attempted. However, the substrate was never obtained with an acceptable degree of purity. Due to the presence of traces of tosyl chloride, the catalytic reactions were not tested because this impurity can interact with the catalyst influencing, in an uncontrolled manner, its activity and selectivity.



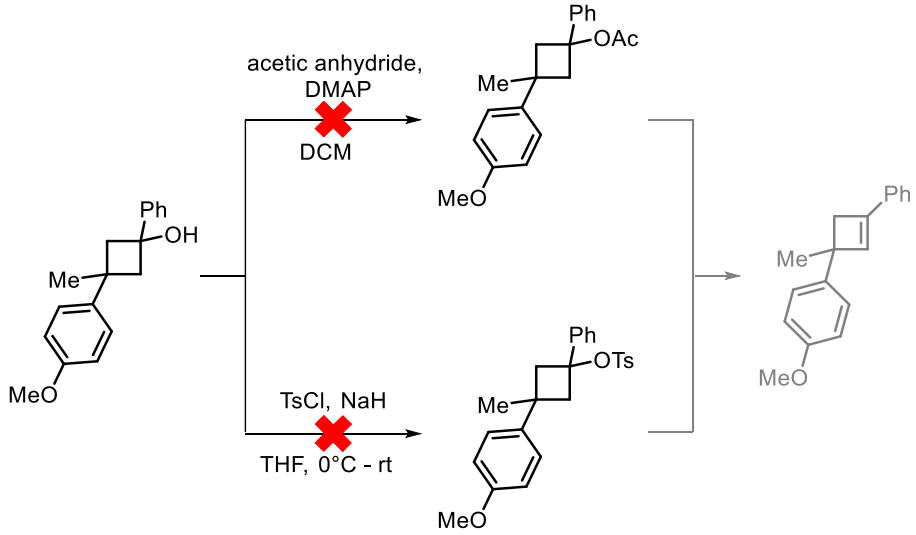

*Scheme 8.6. Elimination reaction of a six-membered ring O-Ts protected alcohols*

Due to the difficult purification of the previously synthesized substrate, we decided to synthesize more polar and interesting substrates. We decided to start with the synthesis of a 3-subtituted cyclobutanol, instead of six-membered ring alcohol, because more appealing molecules often difficul to obtain in an enantioselective manner under mild rearction conditions. As is possible to observe in *Scheme 8.7*, two different O-protected cyclobutanols were synthesized and tested under different reaction conditions, but no reactivity was observed.



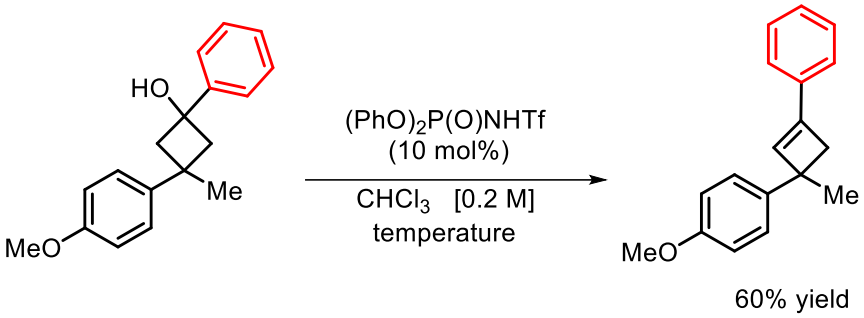

*Scheme 8.7. Reaction tested*

Subsequently, we decide to continue our attempt to desymmetrize such type of molecule by synthesizing tertiary alcohol derivatives, to facilitate the formation of the double bond through the formation of a stable carbocation (E1 mechanism). Unfortunately, the cyclobutanol turned out to be too much hindered for a possible functionalization reaction. Indeed, the protected products were not detected in the reaction mixture. (*Scheme 8.8*)




*Scheme 8.8. Attempted synthesis of hindered substrates*

Finally, we decided to test the non-protected cyclobutanol previously prepared, under acidic catalytic conditions. Surprisingly, using ((trifluoromethyl)sulfonyl)phosphonate as catalyst the cyclobutene product was obtained in 60% yield (*Scheme 8.9*). Due to the promising reactivity shown under racemic conditions, we decided to begin an enantioselective study of this reaction. All the synthetic development will be reported in the next chapter.

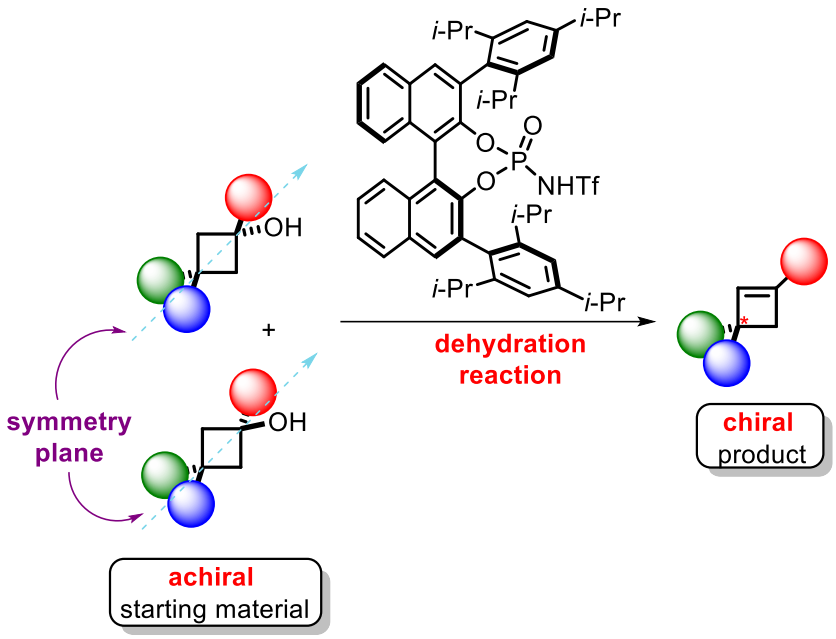



*Scheme 8.9. Catalytic desymmetrization of a cyclobutanol*

# 9 Desymmetrization reaction of cyclobutanols

ABSTRACT

In the last years, the desymmetrization reactions have become a challenging object of study in asymmetric organic synthesis. Herein, is reported a preliminary study of the desymmetrization reaction of cyclobutanols under asymmetric acidic catalysis. An asymmetric elimination reaction is exploited for this methodology. The main aspect considered is the search for a productive substrate. Moreover, an overview of the possible mechanisms involved will be discussed.




## 9.1 Background

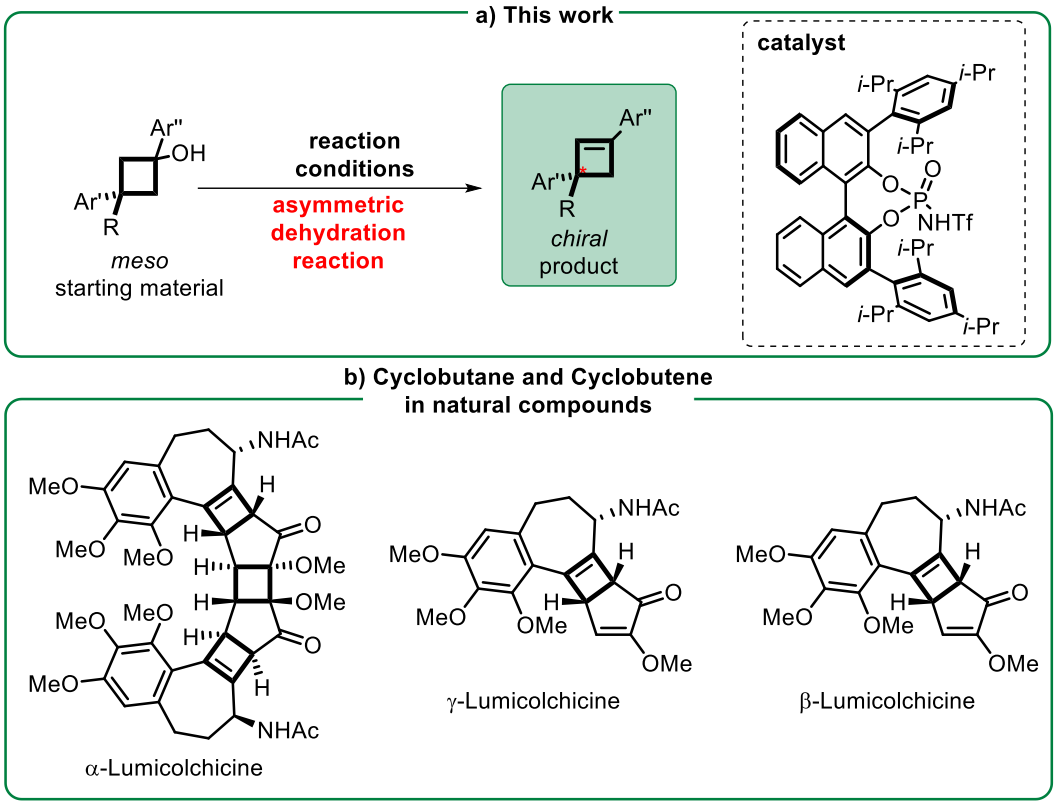
Desymmetrization reactions are a powerful tool exploited in asymmetric synthesis to easily obtain chiral and enantioenriched molecules starting from prochiral or *meso* compounds.[120] Moreover, this methodology could be a promising and attractive route for easy access to quaternary carbon stereocenters,[121] often challenging to obtain with a more classical methodology. This protocol generally based on a single synthetic step permits the installation of multiple stereogenic elements exploiting the appropriate combination

120 G. 120. G. Dickmeiss, V. De Sio, J. Udmark, T. B. Poulsen, V. Marcos, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2009**, *48*, 6650. C. Nájera, F. Foubelo, J. M. Sansano, M. Yusa, *Tetrahedron*, **2022,** 132629. N. Di Iorio, S. Crotti, G. Bencivenni, *Chem. Rec.*, **2019**, *19*, 2095.
121 X.-P. Zeng, Z.-Y. Cao, Y.-H- Wang, F. Zhou, J. Zhou, *Chem. Rev.* **2016**, *116*, 7330.

between substrate and catalyst. This aspect is important especially in the total synthesis of natural compounds[122] because it allows a decrease in the numerous synthetic steps generally involved. Herein, the application of this methodology in the synthesis of cyclobutenes exploiting an asymmetric dehydration reaction of the corresponding cyclobutanol under asymmetric acidic catalysis will be described (*Scheme 9.1* top).

Cyclobutane and cyclobutene are very important constricted rings that often occur in natural products, such as plant and marine species.[123] Moreover, these structures found application in medicinal chemistry.[124] Examples include compounds known for their antimicrobial or anti-inflammatory properties, but also the colchicine derivatives reported below, named lumicolchicines and containing both a cyclobutane and a cyclobutene ring, are studied for their antitumor activities.[125](*Scheme 9.1*Examples include compounds known for their antimicrobial or anti-inflammatory properties, but also the colchicine derivatives reported below, named lumicolchicines and containing both a cyclobutane and a cyclobutene ring, which are studied for their antitumor activities.[126](*Scheme 9.1* bottom)

122 J. Merad, M. Candy, J. -M. Pons, C. Bressy, *Synthesis*, **2017**, *49*, 1938.
123 V. M. Dembitsky, *J. Nat. Med.* **2008**, *62*.
124 M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes, D. Blanco-Ania, *Chem Med. Chem*. **2022**, *17*, e202200020
125 B. Singh, A. Kumar, P. Joshi, S. K. Guru, S. Kumar, Z. A. W. G. Mahajan, A. Hussain, A. K. Qazi, A. Kumar, S. S. Bharate, B. D. Gupta, P. R. Sharma, A. Hamid, A. K. Saxena, D. M. Mondhe, S. Bhushan, S. B. Bharate, R. A. Vishwakarma, *Org. Biomol. Chem.*, **2015**,*13*, 5674.
126 B. Singh, A. Kumar, P. Joshi, S. K. Guru, S. Kumar, Z. A. W. G. Mahajan, A. Hussain, A. K. Qazi, A. Kumar, S. S. Bharate, B. D. Gupta, P. R. Sharma, A. Hamid, A. K. Saxena, D. M. Mondhe, S. Bhushan, S. B. Bharate, R. A. Vishwakarma, *Org. Biomol. Chem.*, **2015**,*13*, 5674.




*Scheme 9.1. a) Natural relevant compounds embedding cyclobutane and cyclobutene ring. b) Enantioselective desymmetrization reaction of cyclobutanols*

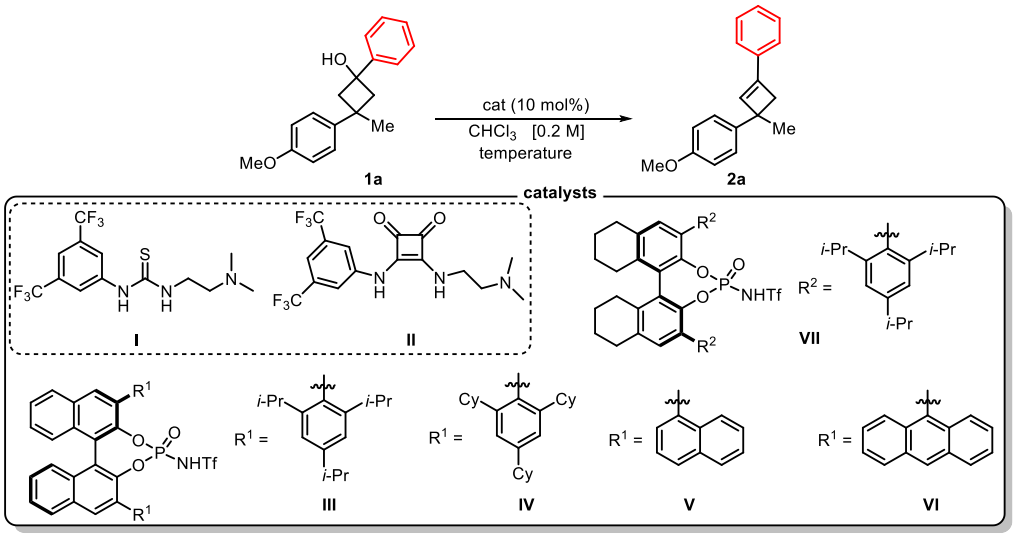
## 9.2 Results and Discussion

### 9.2.1 Optimization of the reaction conditions

We started our investigation by performing the dehydration reaction of substrate **1a** (*cis*, *trans* mixure) under both acidic and basic conditions. (*Table 9.1*) Performing the reaction under quite basic conditions, using Takemoto type thiourea and squaramide (catalyst **I** and **II** respectively), product **2a** is not detected in the reaction mixture, not even performing the reaction at 50 °C (entries 1 and 2). On the contrary, performing the reaction under acidic conditions, using catalyst **III** product **2a** was obtained with promising results in terms of yield and enantioselectivity (entry 3). Once identified the nature of the catalyst, a catalyst screening was performed and both the geometry of the catalyst and the steric hindrance of the substituents in 3 and 3' position of the binol core were evaluated. Conducting the reaction with a more hindered catalyst **IV** no product was observed in the reaction mixture, neither performing it at 50 °C (entry 4). We moved then towards catalysts with entirely aromatic substituents, that is, catalysts **V** and **VI**. Carrying out the reaction with catalyst **V**, an increase of the yield was observed but, unfortunately, product **2a** was

obtained in racemic form. While performing the reaction with catalyst **VI**, no reactivity was observed (entry 6). To conclude this preliminary catalyst screening, catalyst **VII** related to **III** but with a slightly different geometry was employed, but also in this case any reactivity was observed neither at room temperature nor at 50 °C (entry 7).

*Table 9.1. Catalyst screening*



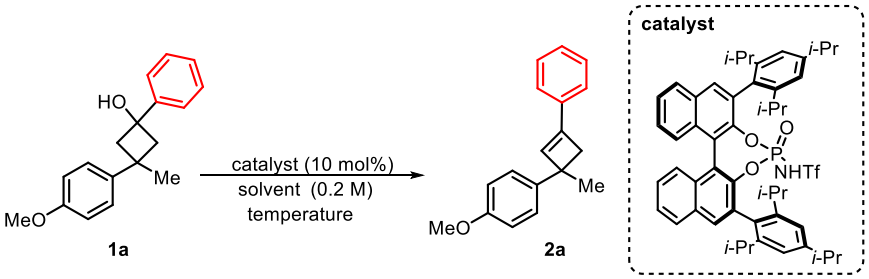

| Entry[a] | cat | temperature | Time h | Y % 2a[b] | ee 2a[c] |
|---|---|---|---|---|---|
| **1** | **I** | rt – 50°C | 32 | <5 | - |
| **2** | **II** | rt – 50°C | 32 | <5 | - |
| **3** | **III** | rt | 16 | 17 | 40 |
| **4** | **IV** | rt – 50°C | 32 | <5 | - |
| **5** | **V** | rt – 50°C | 12 | 48 | *rac* |
| **6** | **VI** | rt | 12 | <5 | - |
| **7** | **VII** | rt – 50°C | 32 | <5 | - |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), cat (10 mol%), $CHCl_3$ (0.25 mL), temperature, time. [b] Determined after column chromatography on silica gel. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

Once identified the catalyst superacid **III** as the best catalyst for the asymmetric dehydration reaction (*Table 9.1*) we moved to analyze the solvent medium. (*Table 9.2*) Performing the reaction in polar solvents such as EtOAc, $CH_3CN$, or THF (entries 3, 10 and 12) lower values of enantiomeric excess in combination with lower reactivity or no reactivity were obtained. Carrying out the reaction in apolar solvents such as toluene and increasing the temperature at 50°C to facilitate the solubility of the substrate **1a** (entry 2), product **2a** was obtained in higher yields but with a lower enantiomeric excess compared with the results obtained in chloroform (entry 4). Since the halogenated solvents seem to be the best medium for the asymmetric desymmetrization reaction, different halogenated

solvents were tested (entries 1, 4-9, and 11). The best ones were found to be $CH_2Cl_2$ and $CHCl_3$.

*Table 9.2. Solvents screening*

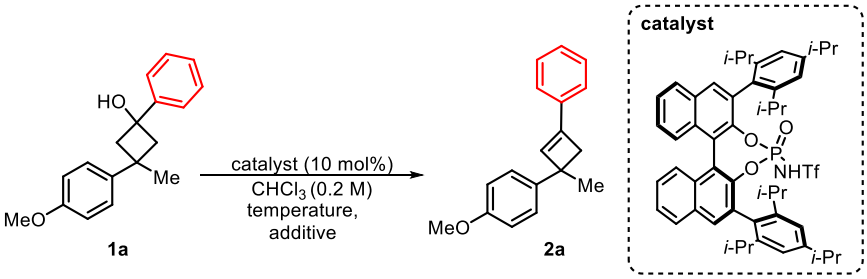



| entry[a] | solvent | temperature | Time h | Y % 2a[b] | ee 2a[c] |
|---|---|---|---|---|---|
| **1** | $CH_2Cl_2$ | rt | 16 | 25 | 30 |
| **2** | PhMe | 50 °C | 16 | 60 | 20 |
| **3** | THF | rt | 16 | <5 | / |
| **4** | $CHCl_3$ | rt | 16 | 17 | 40 |
| **5** | DCE | rt | 16 | 12 | 33 |
| **6** | PhCl | 50 °C | 16 | 70 | 5 |
| **7** | $PhCF_3$ | 50 °C | 16 | 66 | 10 |
| **8** | $CHCl_3$ | rt | ow | 30 | 36 |
| **9** | PhF | 50 °C | 16 | 40 | rac |
| **10** | EtOAc | rt – 50°C | 16 | 56 | 10 |
| **11** | $CCl_4$ | 50°C | 16 | 88 | 30 |
| **12** | $CH_3CN$ | 50°C | 16 | 35 | 13 |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), cat (10 mol%), solvent (0.25 mL), temperature, time. [b] Determined after column chromatography on silica gel. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

We then move to understand if the addition of additives could influence both the reactivity and the enantioselectivity. As is possible to observe in *Table 9.3*, performing the reaction in the presence of molecular sieves no improvement of the enantioselectivity was observed (entry 1) while, performing the reaction in the presence of 1 equiv. of acetic acid, product **2a** was not detected in the reaction mixture (entry 2).

*Table 9.3. Additives screening*




| entry[a] | additive | temperature | Time h | Y % 2a[b] | ee 2a[c] |
|---|---|---|---|---|---|
| **1** | 4Å MS | rt | 16 | n.d. | 40 |
| **2** | AcOH (1 equiv) | rt | 64 | - | - |

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), cat (10 mol%), solvent (0.25 mL), temperature, time. [b] Determined after column chromatography on silica gel. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

## 9.2.2 4.2.2 Search of substrate requirements

Due to the poor reactivity and enantioselectivity shown by substrate **1a,** we move to design other substrates focusing the attention on the geometry and the electronic properties of the substituent on the quaternary carbon bearing the hydroxylic moiety. In particular, different substrates characterized by electron-rich or electron-poor aromatic rings, heteroaromatic rings, aliphatic and alkyne substituents were synthesized (*Figure 9.1*) and the results are reported in the next paragraph.

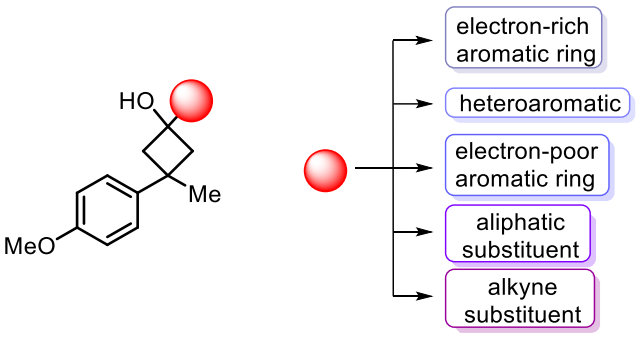



*Figure 9.1. Substrate variety*

To stabilize the positive charge formed after the elimination of the hydroxylic moiety, hypothesizing that the reaction follows an E1 pathway, a substrate characterized by an electron-rich aromatic ring on the same carbon was synthesized. In contrast with **1a**, it was possible to separate the two diastereoisomers of substrate **1b** featuring a *p*-MeO group on

the aromatic ring by purification on flash silica gel. Thus, in this case the two diastereoisomers were individually tested in the catalytic reactions.

Regarding the relative configuration of the two diastereoisomers, is possible to assign preliminarily the *cis*/*trans* configuration considering the shape of the $CH_2$ signals and comparing it with similar compounds present in literature.[127] Regarding the $CH_2$ signals, they converge with a more significant roof effect in the *cis* configuration (see product *cis*-**A**, *Figure 9.2*), while in the case of trans configuration they appear more separated and the roof effect is less market (see product *trans*-**B**). The same behavior could be observed also for products **1b**. In the first case, the $CH_2$ signals are very close together with a clear roof effect, and for this reason, this diastereoisomer was preliminarily assigned as substrate *cis*-**1b**. As expected, the $CH_2$ signals of the other diastereoisomer appear more dislocated with a less pronounced roof effect; due to the great similarity with the shape of signals of product *trans*-**B**, this diastereoisomer was preliminarily assigned as substrate *trans*-**1b**.

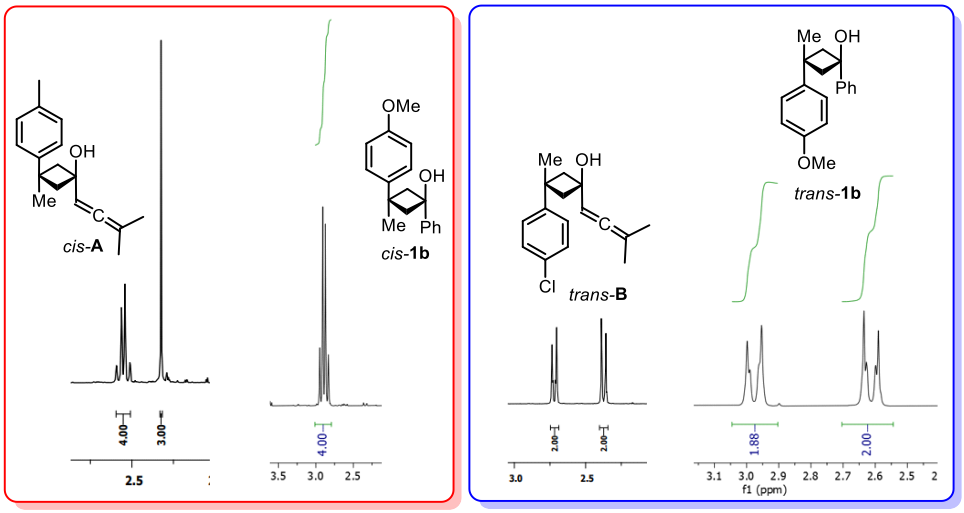



*Figure 9.2. cis-trans configuration, a preliminary assignment*

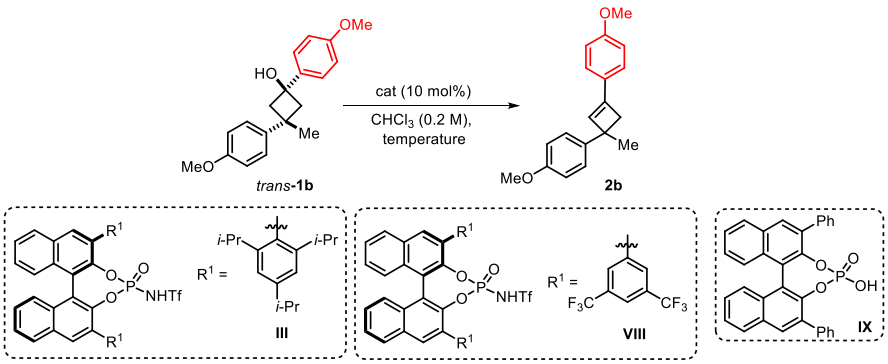
Regarding diastereoisomer *trans*-**1b**, a good enhancement of the reactivity was observed compared to **1a**. Indeed, complete conversion of the reaction was detected after only few minutes. Moreover, an equilibrium in the reaction medium between the two diastereoisomer *cis*-**1b** and *trans*-**1b** was also observed. In particular, starting from one single diastereoisomer, and checking the reaction at a very short reaction time, both diastereoisomers were present in the reaction medium. It means that with substrates **1b** an

127 S. Matsumura, Y. Maeda, T. Nishimura, S. Uemura, *J. Am. Chem. Soc.*, **2003**, *125*, 8862.

equilibrium between an intermediate carbocation species and the substrates is established under acidic reaction conditions.

Performing the reaction with substrate *trans*-**1b** and with catalyst **III** at room temperature (*Table 9.4*, entry 1), a great reactivity was observed but unfortunately product **2b** was obtained in a racemic form. Due to the great reactivity with type **III** catalysts, to decrease the kinetics of the reaction and therefore try to increase at the same time the enantioselectivity, some experiments with catalysts **III** and the less hindered catalyst **VIII**, which can increase the coordination with the substrates, thanks to the absence of hindered aliphatic substituents in 3(entries 2 and 3' positions of the catalyst core, were conducted at 0°C (entries 2 and 3).3). Unfortunately, decreasing the temperature of the reaction, only a lower reactivity was observed and product **2b** was still obtained in a racemic form.

*Table 9.4. Miscellaneus informations subsrate trans-**1b***



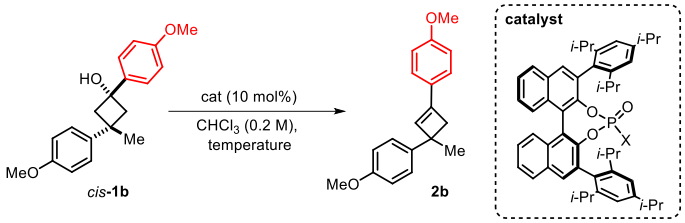

| entry[a] | catalyst | temperature | Time h | Y % 2a[b] | ee 2a[c] |
|---|---|---|---|---|---|
| **1** | **III**, X = NHTf | rt | 10 min | 65 | *rac* |
| **2** | **III**, X = NHTf | 0°C | 5 min | 51% | *rac* |
| **3** | **VIII**, X = NHTf | 0°C | 16 | 10 | *rac* |
| **4** | **IX** | rt | 16 | - | - |

[a] Reaction conditions: *trans*-**1b** (0.1 mmol, 1.0 equiv.), cat (10 mol%), solvent (0.25 mL), temperature, time. [b] Determined after column chromatography on silica gel. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

Similar tests were performed also using diastereoisomer *cis*-**1b** and the results are reported in *Table 9.5***.** Performing the reaction in the presence of 10 mol% of (*S*)-TRIP phosphoric acid (entry 1) no reactivity was observed, while using the corresponding phosphoric super acid **III** (NHTf, entry 2), the reaction shows complete conversion in few minutes, obtaining product **2b** in very good yield but unfortunately also in this case in a racemic form. Performing the reaction in the presence of 10 mol% of (*S*)-TRIP phosphoric acid (entry 1) no reactivity was observed, while using the corresponding phosphoric super acid **III**

(NHTf, entry 2), the reaction shows complete conversion in a few minutes, obtaining product **2b** in very good yield but unfortunately also in this case in a racemic form.

*Table 9.5. Miscellaneus informations subsrate cis-**1b***

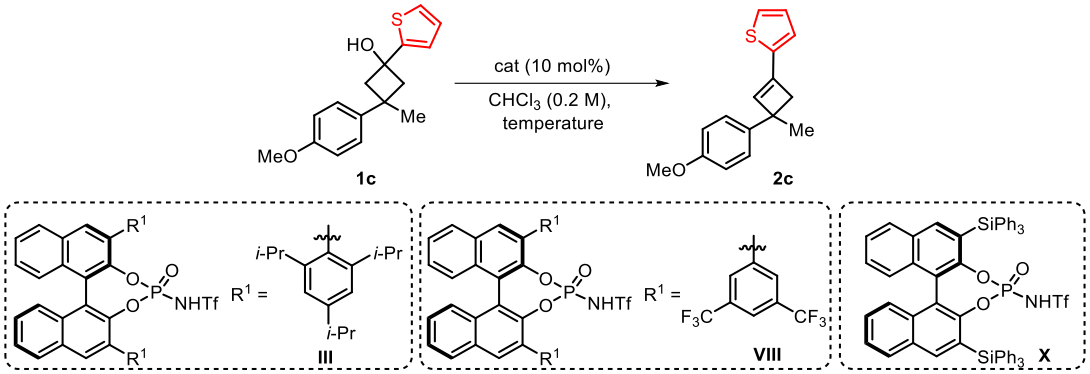



| entry[a] | catalyst | temperature | Time h | Y % 2a[b] | ee 2a[c] |
|---|---|---|---|---|---|
| **1** | X = OH | 10 | 48 h | - | - |
| **2** | X = NHTf | 10 | 5 min | 91 | *rac* |

[a] Reaction conditions: *cis*-**1b** (0.1 mmol, 1.0 equiv.), cat (10 mol%), solvent (0.25 mL), temperature, time. [b] Determined after column chromatography on silica gel. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

Subsequently, we decided to exploit the information that electron rich aryls provide good reactivity by designing a new substrate with a heteroaromatic electron-rich aromatic ring, instead of the substituted phenyl, to install on the reagent an extra coordination site for the catalyst and enhance in this way the enantioselectivity of the reaction. The alcohol taken into consideration is alcohol **1c** characterized by thiophene as a substituent of the quaternary carbon, on which the positive charge will form after the release of the hydroxylic moiety. Unfortunately, as it is possible to observe in *Table 9.6*, inafter a short catalysts screening product **2c** was always obtained in good yields but in a racemic form.

*Table 9.6. Miscelaneus informations about substate **1c***



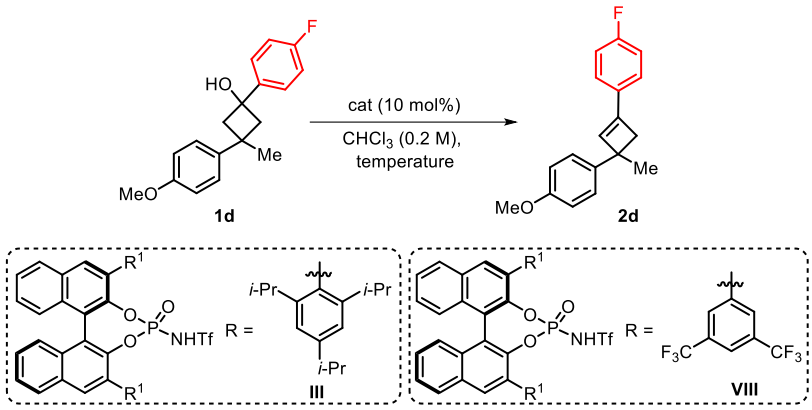

| entry[a] | catalyst | temperature | Time h | Y % 2a[b] | ee 2a[c] |
|---|---|---|---|---|---|
| **1** | **III** | rt | 16 | 45 | *rac* |
| **2** | **VIII** | rt | 16 | 22 | *rac* |
| **3** | **X** | rt | 16 | 64 | *rac* |

[a] Reaction conditions: **1c** (0.1 mmol, 1.0 equiv.), cat (10 mol%), solvent (0.25 mL), temperature, time. [b] Determined after column chromatography on silica gel. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

At this point, we decided to force the route of the reaction towards an E2 elimination pathway, instead of the E1 which was thought to be operative at least for substrates **1b** and **1c**. To promote the E2 elimination reaction, it is necessary to destabilize the positive charge localized on the carbon bearing the hydroxylic group. For this reason, two different substrates were synthesized. One carries an electron-poor aromatic ring and the other one with an aliphatic substituent, a methyl group, instead of the phenyl ring.

Regarding substrate **1d** characterized by an electron-poor aromatic ring, due to the presence of a fluorine atom in the *para* position of the aromatic ring, as substituent of the carbon bearing the hydroxylic moiety, the results of the catalytic reactions are reported in *Table 9.7*. Performing the desymmetrization reaction in the presence of catalyst **III** comparable results in terms of yield and enantioselectivity with substate **1a** were obtained (entry 1) while performing the reaction with a different catalyst, catalyst **VIII**, lower values of yield and enantiomeric excess were achieved (entry 2).

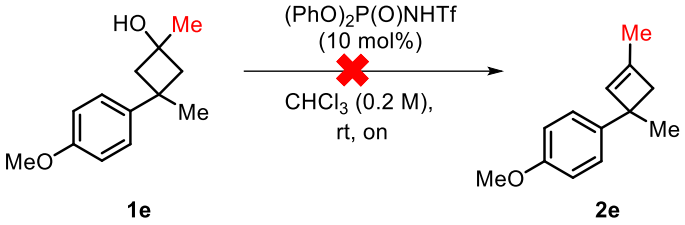
*Table 9.7. Miscellaneous information about substate **1d***




| entry[a] | catalyst | temperature | Time h | Y % 2a[b] | ee 2a[c] |
|---|---|---|---|---|---|
| **1** | **III** | rt | 16 | 20 | 40 |
| **2** | **VIII** | rt | 16 | 50 | 10 |

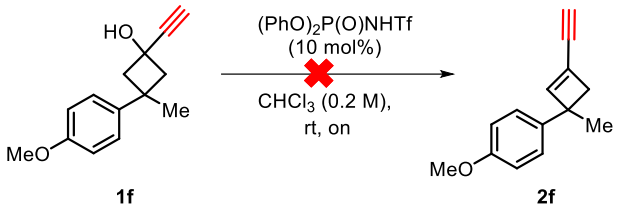
[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), cat (10 mol%), solvent (0.25 mL), temperature, time. [b] Determined after column chromatography on silica gel. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

Moving on to analyze the substates with an aliphatic substituent instead of the aromatic one, substrate **1e**, any reactivity was observed performing the reaction with an achiral ((trifluoromethyl)sulfonyl)phosphonate catalyst (*Scheme 9.2*). Due to the absence of reactivity of substate **1e** in the presence of the acidic catalyst, the experiments with the chiral and enantiopure catalysts have not been carried out. Due to the absence of reactivity of substate **1e** in the presence of the acidic catalyst which permits to obtain the racemic version of product **2**, the experiments with the chiral and enantiopure catalysts have not been carried out.




*Scheme 9.2. Catalytic reaction with substrate **1e***

Regarding the manipulation of this part of the substrate, the last product tested is substrate **1f** characterized by an alkyne substituent instead of the aromatic ring, and the results are reported below (*Scheme 9.3*). Also in this case, performing the reaction with ((trifluoromethyl)sulfonyl)phosphonate as catalyst, no reactivity was observed.




*Scheme 9.3. Catalytic reaction with substrate **1f***

At this point, we completely change the approach regarding the design of the substrates. Until now, all the manipulation regarding the geometry and the electronic proprieties were effectuated on the substituents of the carbon carrying the hydroxylic moiety. Now, we try to design other substrates, changing the skeleton and the electronic properties of the substituents in $C_3$ position with respect of the carbon bearing the leaving group. (*Figure 9.3*)

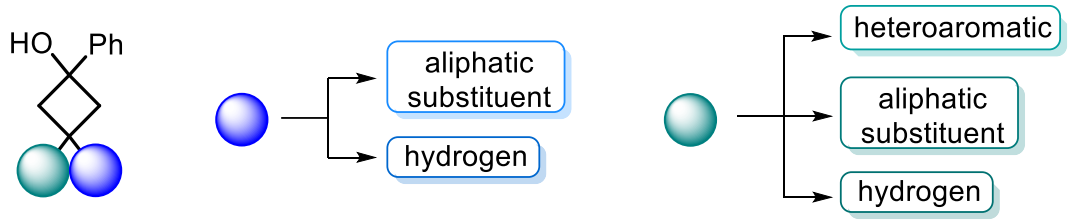
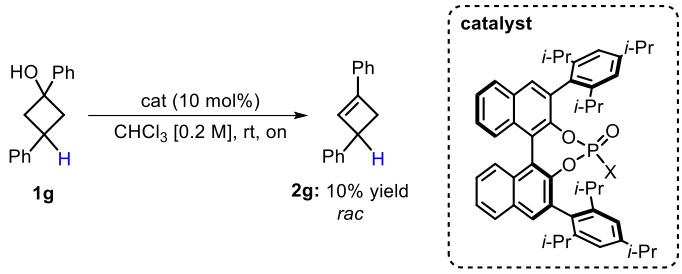



*Figure 9.3. Substrate design by modification at C3*

First of all, substrate **1g** bearing only a phenyl as substituent on the $C_3$ carbon of the cyclobutanol was synthesized. Unfortunately, as shown in *Scheme 9.4* product **2g** was obtained in a low yield and in a racemic form in the presence of catalyst **III**.

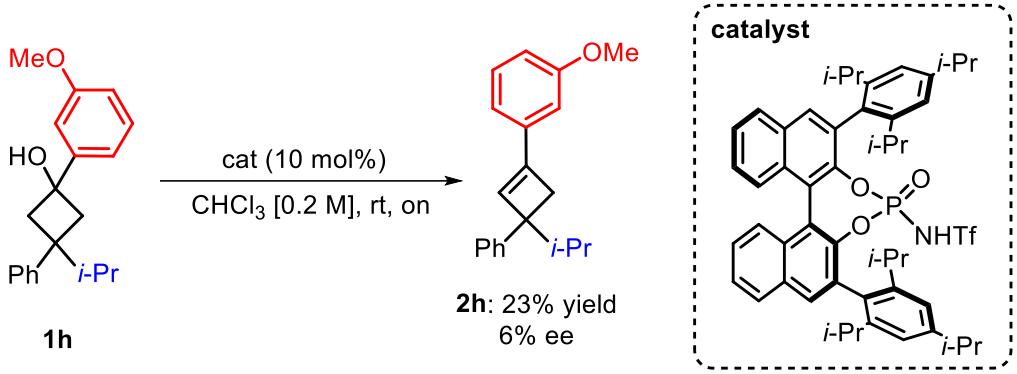



*Scheme 9.4. Catalytic reaction with substate **1g***

Subsequently, we have synthesized also substrate **1h** with a more hindered $C_3$ carbon, in particular with an *i*-Pr group, instead of methyl or simple hydrogen. Moreover, having understood from the previous study that an electron donating substituents is necessary to enhance the reactivity, but at the same time the presence of an electron-poor aromatic ring is important for the enantioselectivity of the reaction, substrate **1h** is not characterized only

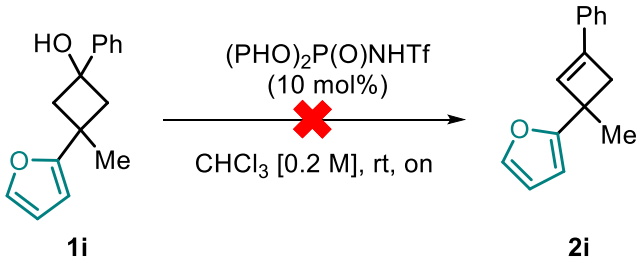
by a hindered substituent in C3 position, but also by a *m*-MeO substituent, an electron donating group in a deactivating position of the aromatic ring.

Unfortunately, also in this case, the results are not satisfactory (*Scheme 9.5*), indeed product **2h** was obtained in low yield and with very poor enantioselectivity. An important aspect understood by these experiments is that the presence of a methyl group as substituents of the $C_3$ carbon provides better results.




*Scheme 9.5. Catalytic reaction with substrate **1h***

Then, we move on to changing the nature of the aromatic ring in $C_3$ position to the hydroxylic moiety. First of all, instead of an unsubstituted or a substituted phenyl as substituents in 3 position of cyclobutanols **1**, a heteroaromatic ring - a furan - was installed on the substrate backbone, and the results are reported in *Scheme 9.6*. Performing the reaction with substrate **1i** no reactivity was observed under standard racemic conditions, probably due to the presence of basic oxygen which quenches the acidity of the catalyst.




*Scheme 9.6. Catalytic reaction with substate **1i***

Subsequently, substrate **1l** was synthesized hoping that the presence of an aliphatic chain installed on the cyclobutanol ring could better accommodate the reaction intermediates into the chiral pocket of the catalyst, increasing at the same time the catalyst coordination and subsequently the enantiomeric excess. The reactivity of substate **1l** was checked performing the reaction in the presence of an achiral ((trifluoromethyl)sulfonyl)phosphonate catalyst (*Figure 9.4*). Unfortunately, product **2l**

could not be separated in the chiral stationary phases tested. Therefore, it was decided to prepare an analogous of **1l** but slightly more polar.

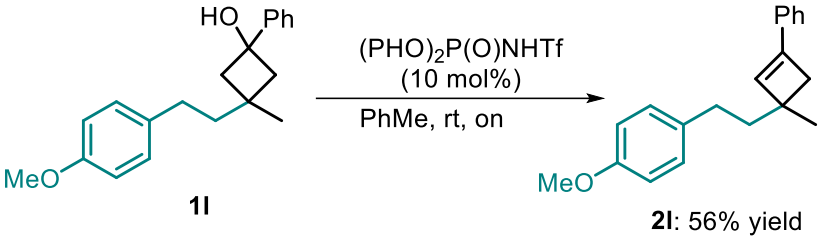



*Figure 9.4. Catalytic reaction with substate **1l***

The more polar substrate to test the behavior of an aliphatic chain in $C_3$ position is substrate **1m**. Alcohol **1m** is characterized not only by the presence of the aliphatic chain in $C_3$ position but also by the *m*-MeO substituent on the aromatic ring next to the hydroxylic group. Performing the catalytic reaction under asymmetric catalytic conditions product **2m** was disappointingly obtained in low yield and very low enantiomeric excess (*Figure 9.5*).

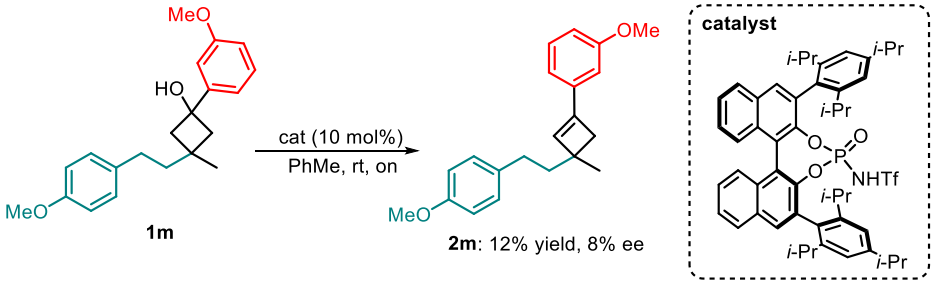



*Figure 9.5 Catalytic reaction with substrate **1m***

Finally, we try to follow the same methodology previously mentioned subjecting substrate **1n** under the standard reaction conditions. Alcohol **1n** is characterized by an aliphatic chain instead of an aromatic ring and by the presence of a heteroatom able to coordinate the catalyst, hoping to enhance in this wasway the enantioselectivity of the reaction. Performing the reaction with substrate **1n** under the standard racemic conditions, no reactivity was observed (*Figure 9.6*) probably due to the presence of the basic oxygen which quenches the acidity of the catalyst suppressing the dehydration reaction.

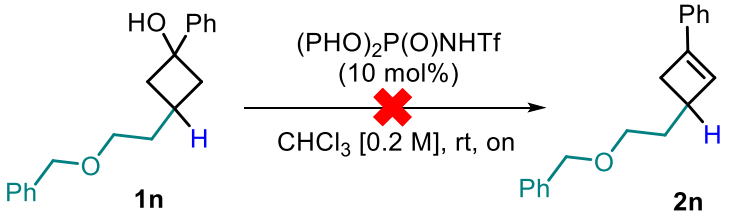
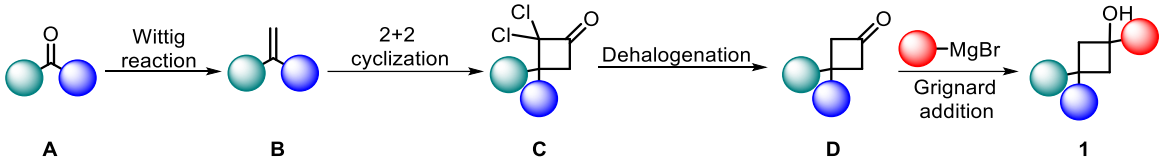



*Figure 9.6. Catalytic reaction with substate **1n***

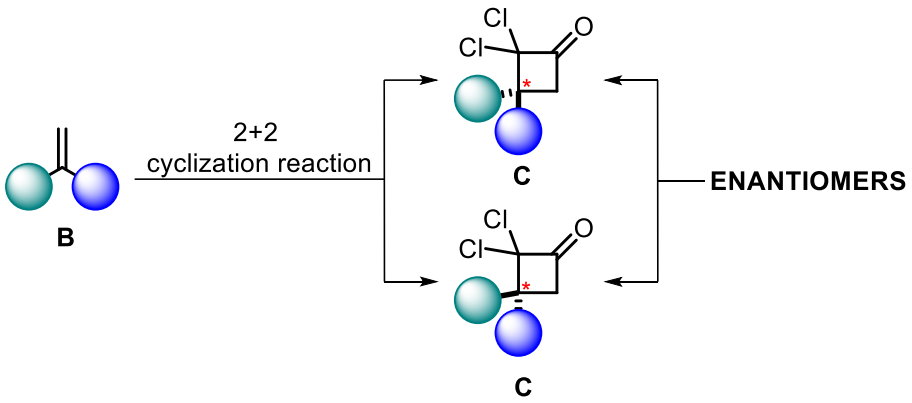
### 9.2.3 Symmetry elements during the formation of the starting materials

Before we start talking about the possible mechanisms for the synthesis of products **2** it is necessary to analyze the synthesis of starting materials **1** and, in particular, the symmetry elements acquired and lost during the different synthetic steps**.** The synthesis of starting material **1a-m** is based on four synthetic steps (*Scheme 9.7*), a Wittig olefination starting from the corresponding ketones **A** to form olefines **B**, a 2 + 2 cyclization reaction to generate intermediates **C**, a dehalogenation reaction to obtain cyclobutanones **D** and a Grignard addition reaction which generates the final substrates **1**.



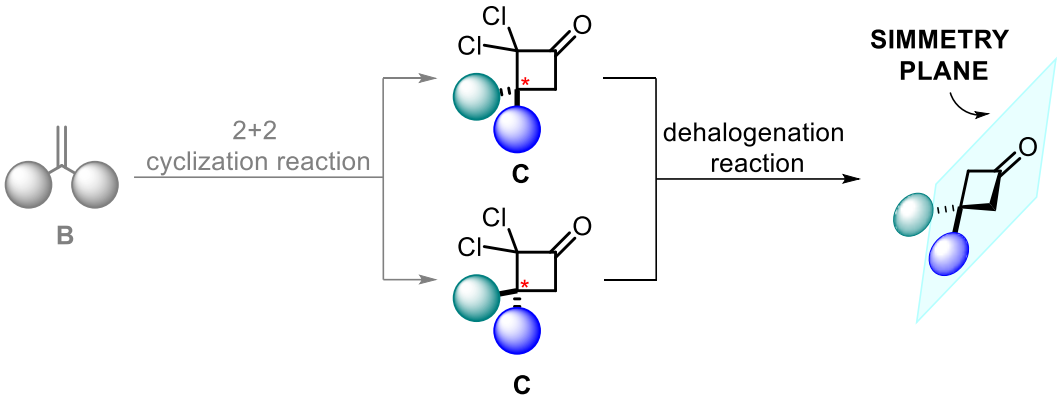

*Scheme 9.7. Synthesis of the starting materials*

The first synthetic step is a Wittig olefination starting from the prochiral ketone **A** to generate the prochiral olefin **B**. At this point, the 2 + 2 cyclization reaction generates intermediate **C**. The 2 + 2 cyclization reaction takes place in achiral conditions, moreover, intermediate **C** is a chiral compound with a stereogenic center in the β position of the carbonyl, so the product **C** is obtained in a racemic form. (*Scheme 9.8*)



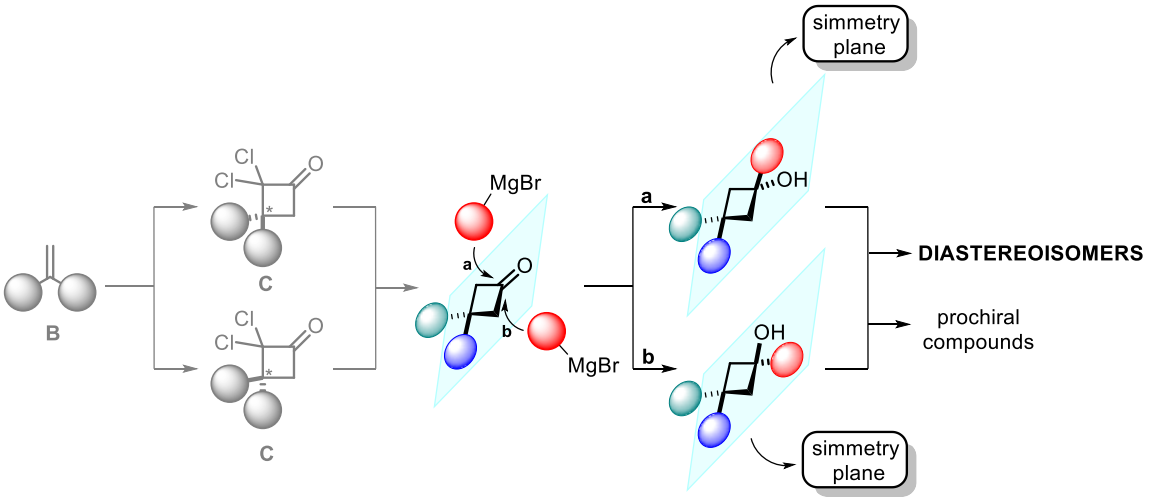

*Scheme 9.8. 2 + 2 cyclization reaction*

The dehalogenation reaction that follows is apt to eliminate the two chlorine atoms from the cyclic structure adding at the same time a symmetry plane cyclobutanone **D** (*Scheme 9.9*). The dehalogenation reaction that follows is apt to eliminate the two chlorine atoms from the cyclic structure adding at the same time a symmetry plane cyclobutanone **D** and consequently removing the asymmetry from the compound (*Scheme 9.9*).



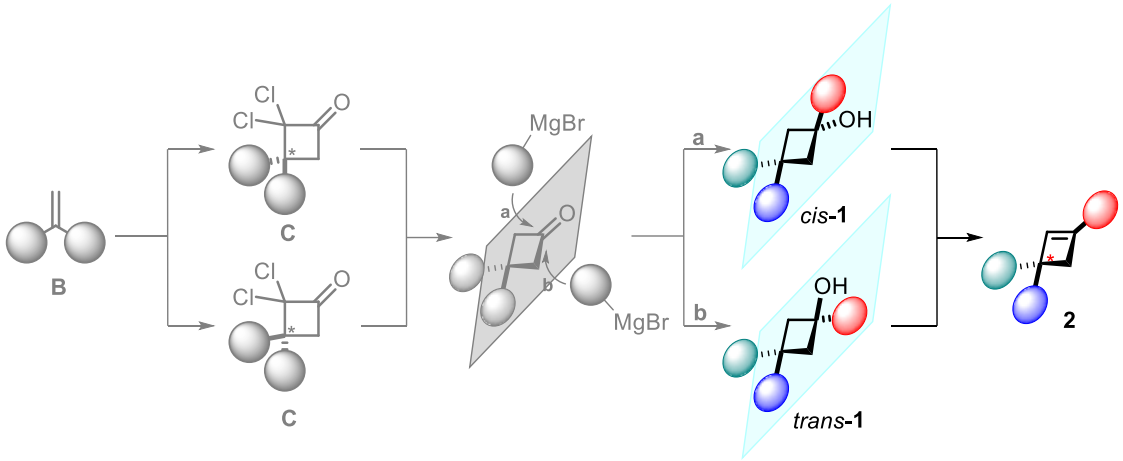

*Scheme 9.9. Dehalogenation reaction*

The last synthetic step is the Grignard addition to the cyclobutanone **D** to generate the alcohols **1**. A nucleophilic addition on a generic ketonic carbonyl can occur on both faces of the carbonyl, forming a tetrasubstituted tetrahedral carbon. In this case, the nucleophilic addition of the Grignard reagent on the ketonic carbonyl generates two different diastereoisomers, because of the presence of another tetrasubstituted tetrahedral carbon (*Scheme 9.10*).




*Scheme 9.10. Grignard addition*

The two different diastereoisomers of substrate **1** are generally obtained as inseparable mixtures but during the dehydration reaction both of them generate the same product. The presence of the double bond inside the cycle and the presence of tetrasubstituted carbon carrying four different substituents make product **2** a chiral compound, thanks to the breaking of the symmetry of the entire molecule. The two diastereoisomers having different chemical and physical properties in the asymmetric dehydration reaction can be characterized by different reactivity.




*Scheme 9.11. Dehydration reaction*

The dehydration reaction, formally an elimination reaction, can undergo two different mechanisms; a two-step unimolecular elimination reaction (E1), and a single-step bimolecular elimination reaction (E2). Both possible mechanisms will be discussed in the following paragraphs, paying particular attention to the stereochemistry of the product and the enantioselectivity of the reaction.

1. Unimolecular elimination reaction (E1): one of the possible reaction mechanisms could be represented by an E1 elimination reaction. In this model, the presence of the two diastereoisomers does not influence the enantioselectivity of the reaction because both diastereoisomers give the same carbocationic intermediate, characterized by a single tetrahedral carbon. Indeed, this model is based on two different steps, with the formation of a carbocation as intermediate. First, the loss of one water molecule after the protonation of the hydroxylic group with subsequent formation of a carbocation, then, the abstraction of one of the hydrogen atoms in the α position of the thus formed cation, with subsequent formation of the double bond, by the conjugated base of the catalyst.

   The four hydrogen atoms in the α position of the carbocation are two by two chemically equivalent, as shown below. So, using for example an achiral catalyst the two enantiotopic Ha's will be removed at the same rate, and the same will happen for the two enantiotopic $H_b$'s, resulting in an equimolar amount of the two enantiomers (racemic mixture). (

   *Scheme **9.12***)The four hydrogen atoms in the α position of the carbocation are two by two chemically equivalent, as shown in *Scheme 9.12*. So, using for example an achiral catalyst the two enantiotopic Ha's will be removed at the same rate, and the

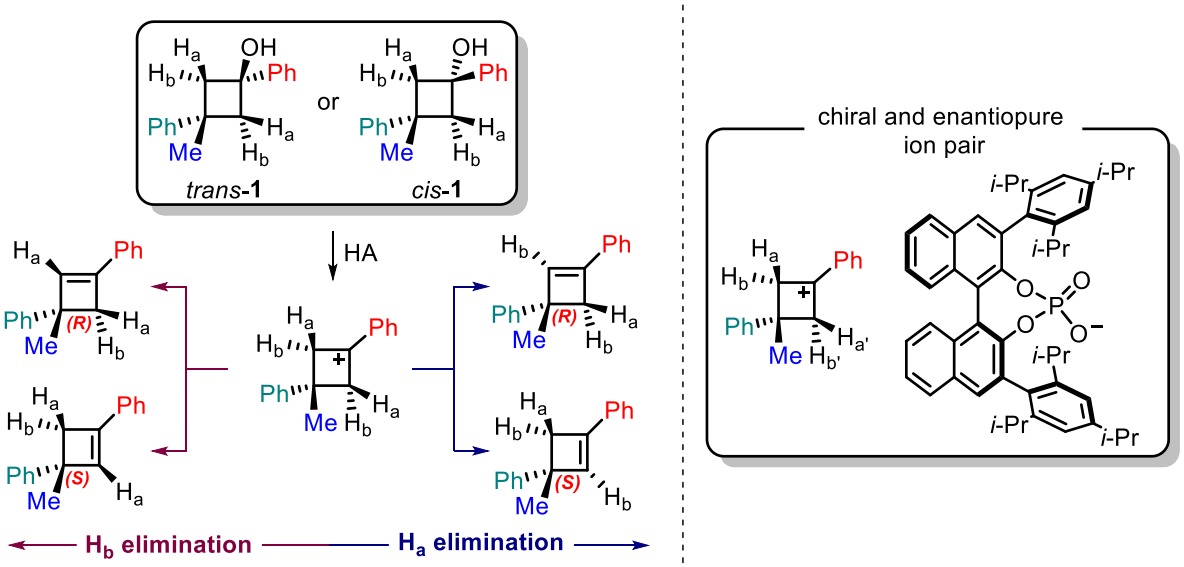
same will happen for the two enantiotopic $H_b$'s, resulting in an equimolar amount of the two enantiomers (racemic mixture). (

*Scheme 9.12*)

Regarding the asymmetric dehydration reaction, the simple chiral phosphoric acid TRIP as catalyst will be taken into consideration. Once a water molecule is released, a chiral and enantiopure ion pair (

*Scheme 9.12*), is formed. At this point, due to the coordination of the carbocation and the conjugated base, the two hydrogen atoms previously named $H_a$ or $H_b$ are not anymore equivalent ($H_a \neq H_{a'}$ and $H_b \neq H_{b'}$). Therefore, if the conjugated base can fully discriminate within the two couples of hydrogen atoms, that is between $H_a$ and $H_{a'}$and between $H_b$ and $H_{b'}$located on opposite sides of the symmetry plane, a complete enantioselection is verified. While, if the conjugated base is not able to discriminate between the hydrogen atoms, a racemic mixture will be obtained. These are the two borderline cases, for intermediate levels of discrimination, different enantiomeric excess values will be obtained. Furthermore, if the catalyst is capable of discriminate efficiently between Ha and Ha', that is favouring for example Ha, but has a different topicity for the diasteromeric couple of enantiotopic hydrogens, that is favours Hb' over Hb, the enantioselectivity of the reaction will be poor, unless the catalyst favours the abstraction of one of the two couples over the other.

Thus, to obtain the product with high enantioselectivity via an E1 reaction pathway, the catalyst must be able to not only discriminate between one of the two enantiotopic hydrogens $H_a$, but also to have the same topicity in the remaining couple. Alternatively, if the abstraction proceeds much faster on one of the couples compared to the other one, it will be sufficient for the catalyst to give selectivity on the fast reacting couple.

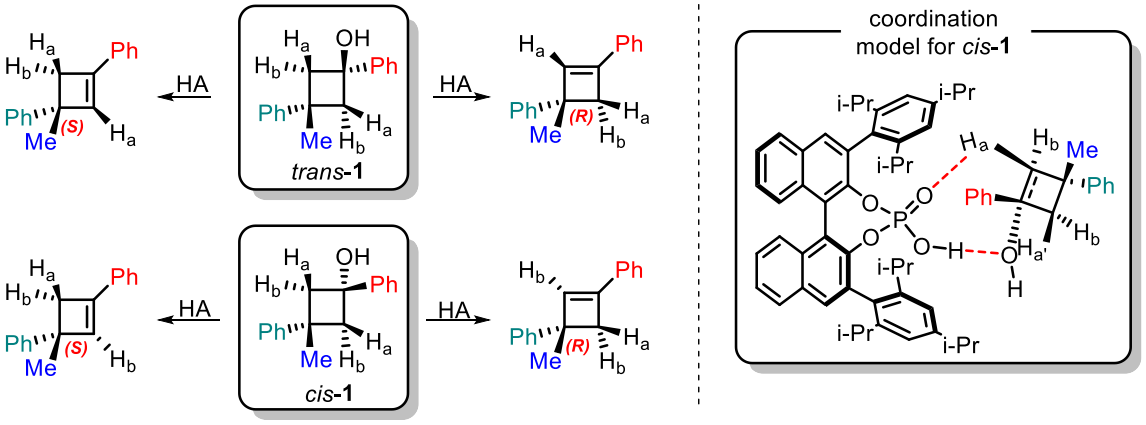



*Scheme 9.12. E1 elimination reaction*

2. Bimolecular elimination reaction (E2): the second possible limiting mechanism is represented by the E2 elimination reaction model. This model based on a concerted mechanism is namely bimolecular because, during the rate determining step, two molecules, the substrate and the catalyst, are involved. In particular, the acidic proton of the catalyst coordinates the oxygen atom of the hydroxylic group and, at the same time, the conjugated base ($A^-$) coordinates the hydrogen atomsatom in the α position of the quaternary carbon substituted by the hydroxylic group and in a periplanar position to the leaving group. This interaction between the substrate and the catalyst causes a weakening of the bonds between the interested atoms (O or H) and the corresponding carbon atom, facilitating the formation of the new π-bond and at the same time the release of the water molecule. In the E2 model, during the rate-determining step, the two diastereoisomers have a completely different behavior because the hydrogen atom which will be removed by the catalyst must be in an anti-periplanar arrangement to the leaving group. So, regarding diastereoisomer *trans*-**1** the hydrogen atoms removed will be $H_b$, while for diastereoisomer *cis*-**1** the hydrogen atoms removed will be $H_a$. Eliminating with the same rate the two $H_b$ for the *trans*-**1** isomer or the two $H_a$ for the *cis*-**1** isomer**,** a racemic mixture of the product will be obtained. (*Scheme 9.13*)

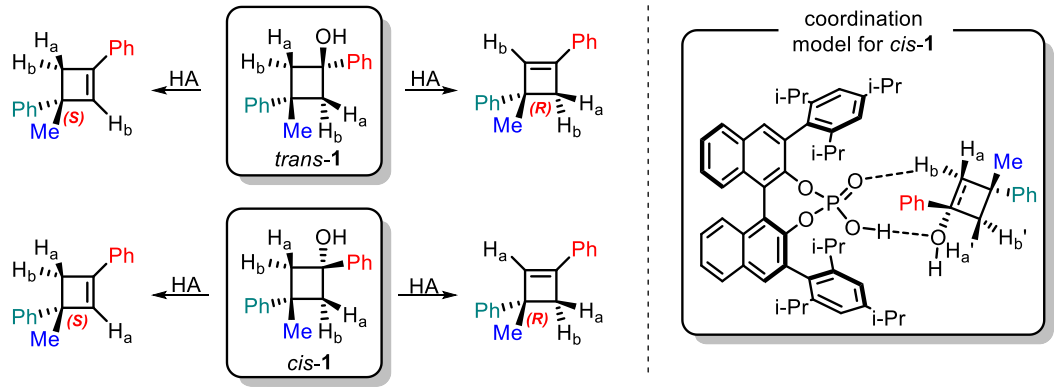
Regarding the asymmetric dehydration reaction (possible coordination model for *cis*-**1** isomer reported in *Scheme 9.13*) the coordination between the catalyst and the substrate make the enantiotopic hydrogen atoms $H_a$ and $H_{a'}$ no longer

equivalents. If the basic moiety of the catalyst fully discriminates between $H_a$ and $H_{a'}$ a complete enantioselection will be obtained. If the catalyst is not able to discriminate between the two hydrogen atoms, a racemic mixture of the product will be obtained. Also in this case the described cases are the two borderline cases, for intermediate levels of discrimination, different enantiomeric excess values will be obtained.




*Scheme 9.13. E2 elimination reaction*

3. Syn elimination reaction (Ei): another possible reaction pathway could be represented by the syn elimination reaction model. (*Scheme 9.14*) This model is based on a cyclic transition state, due to the double coordination by the catalyst. The two vicinal substituents of the cyclobutene with *syn* disposition leave simultaneously the substrate allowing the formation of the π-bond. In this model the two diastereoisomer have a completely different reactivity, indeed the stability of the hydrogen bonds between the catalyst and the substrates depends by the disposition of the substituents on the substrate. In particular, for *trans*-**1** isomer, the catalyst coordinates the hydroxylic group and one of the $H_a$ hydrogen atoms, while for the cis-**1** isomer the catalyst coordinates the OH group and one of the $H_b$ hydrogen atoms. Regarding the racemic reaction, the catalyst coordinating with the same rate the two $H_a$ for *trans*-**1** isomer and the two $H_b$ for *cis*-**1** isomer, the product is obtained as racemic mixture. Regarding the enantioselective version of the reaction, the two $H_a$ are not anymore equivalent ($H_a \neq H_{a'}$ and $H_b \neq H_{b'}$). The catalyst is able to discriminate between $H_a$ and $H_a$' allowing only one enantiomer as the product of the reaction. Also in this case the described cases are the two borderline cases, for intermediate levels of discrimination, different enantiomeric excess values will be obtained.




*Scheme 9.14. Ei elimination reaction*

## 9.3 Conclusions

In conclusion, a preliminary study of a desymmetrization reaction exploiting an asymmetric elimination reaction under acidic conditions was carried out. Particular attention was focused on screening acids, solvents, and synthesis of new substrates to improve both the yield and the enantioselectivity of the reaction. Different substrates were synthesized modulating the electronic properties to encourage a E1 or a E2 mechanism or modulating the conformation of the molecule to be better accommodated in the chiral task of the catalyst.

Taking into consideration the obtained results, it may be possible to speculate that an E1 elimination model, promoted by the substates with an electron-rich aromatic ring as substituent of the carbocation carbon, has good reactivity, but the reaction proceeds in a racemic version. While, performing the reaction with electron neutral or electron-poor aromatic rings as substituents of the carbocation carbon, so trying to promote an E2 elimination reaction, the reactivity is characterized by poor reactivity but cheering enantioselectivity.

Moreover, it was also ascertained that the presence of a phenyl ring in $C_3$ position to the hydroxylic ring is crucial for both reactivity and enantioselectivity of the reaction. Also the steric hindrance of the other substituent must be specific to have promising results in terms of reactivity and enantioselectivity.

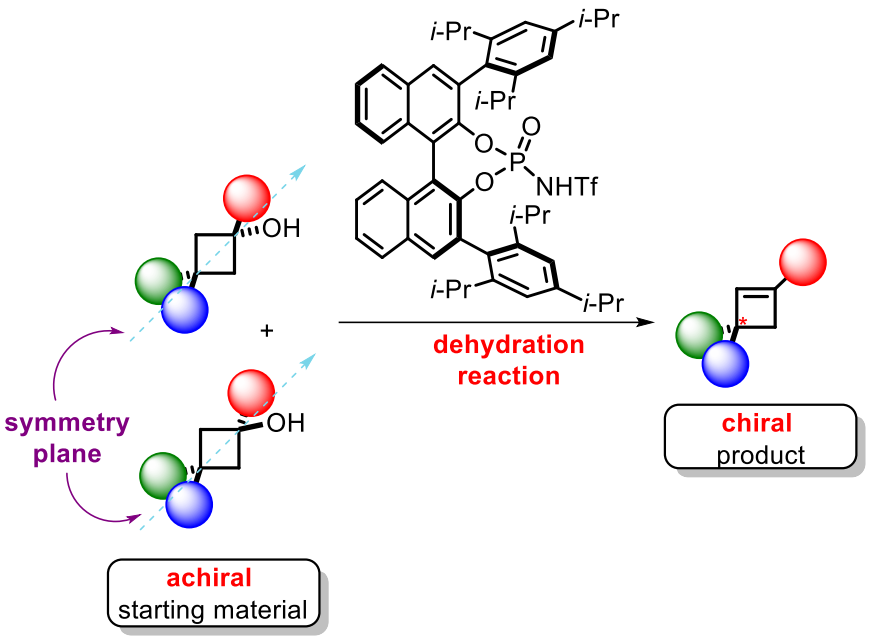



*Figure 9.7. Summary of the project*

## 9.4 Experimental section

**General methods and materials**

**NMR**: Monodimensional nuclear magnetic resonance proton and carbon spectra ($^{1}$H NMR and $^{13}$C NMR) were acquired at 25 ºC on a Bruker AC-300 spectrometer (300 MHz for $^{1}$H and 75.5 MHz for $^{13}$C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for $^{1}$H NMR, $CHCl_3$, 77.16 ppm for $^{13}$C NMR) and coupling constants (J) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. $^{13}$C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distorsionless Enhancement by Polarization Transfer) for assigning different types of carbon environment.

**IR**: Infrared spectra (IR) were measured in a Jasco FT/IR 4100 in the interval between 4000 and 400 $cm^{-1}$ with a 4 $cm^{-1}$ resolution. Only characteristic bands are given in each case.

**HRMS**: High-resolution mass spectra on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization ($ESI^+$ or $ESI^-$ ) or on a Micromass GCT spectrometer using chemical ionization (CI).

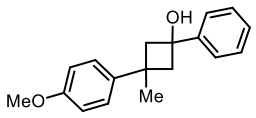
**Optical rotations $[\alpha]_D^{20}$**: were measured at 20 ºC on a Jasco P-2000 polarimeter with sodium lamp at 589 nm and a path of length of 1 dm. Solvent and concentration are specified in each case.

**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.[128] 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 use in an oven at 140 ºC, and allowed to cool under a dehumidified atmosphere.[129] Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kiesegel 60 F254). For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[130] For the removal of the solvents under reduced pressure Büchi R-2 series rotatory evaporators were used.

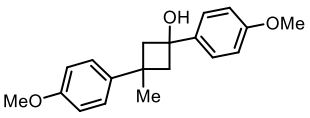
128 (a) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals, 7th* ed.; Elsevier: Oxford, 2012. (b) Williams, D. B. G.; Lawton, M. *J. Org. Chem*. **2010**, *75*, 8351.
129 Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*, John Wiley & Sons, New York, 1975
130 Still, W. C.; Kahn, H.; Mitra, A. J. *J. Org. Chem*. **1978**, 43, 2923

**General procedure for the synthesis of alcohols**

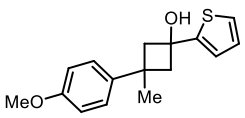
Alcohols **1a-n** were synthesized according to literature procedure. [131]



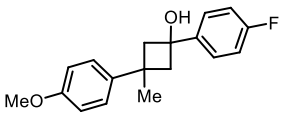

**1a**



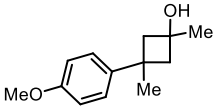

**1b**



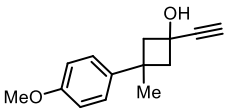

**1c**



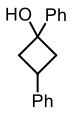

**1d**



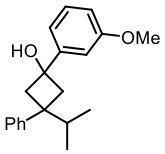

**1e**



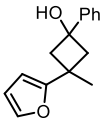

**1f**



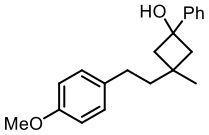

**1g**



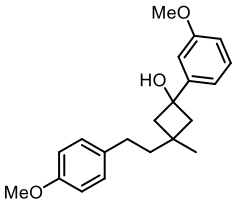

**1h**



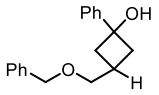

**1i**




**1l**

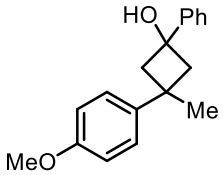



**1m**




**1n**

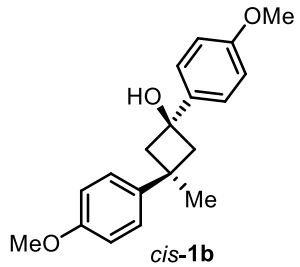
**3-(4-methoxyphenyl)-3-methyl-1-phenylcyclobutan-1-ol 1a: 1.7:1 mixture of diastereoisomers**




**1a**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1a** was obtained in 78% yield (209 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ = 7.62 – 7.52 (m, 3H), 7.50 – 7.39 (m, 3H), 7.39 – 7.18 (m, 9H), 7.18 – 7.06 (m, 2H), 6.96 – 6.80 (m, 7H), 3.83 (s, 5H), 3.80 (s, 3H), 3.04 – 2.82 (m, 11H), 2.67 – 2.55 (m, 2H), 1.73 (s, 3H), 1.29 (s, 5H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.4, 157.3, 147.5, 146.5, 143.8, 143.8, 128.6, 128.4, 127.4, 127.0, 126.4, 126.2, 125.7, 124.7, 113.8, 113.6, 72.8, 72.5, 55.35, 55.31, 49.1, 48.7, 35.3, 33.8, 32.8, 31.5. **IR** (ATR): 3324 (OH st), 2934 (CH st) 1512 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{18}H_{20}O_2$ + $Na^+$]: 291.1356; found 291.1360.

**1,3-bis(4-methoxyphenyl)-3-methylcyclobutan-1-ol** ***cis*****-1b**

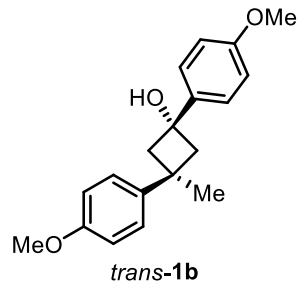



***cis*****-1b**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1b'** as single diastereoisomer was obtained in 53% yield (158 mg) after flash chromatographic purification (PE:EtOAc = 9:1). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ = 7.33 – 7.23 (m, 2H), 7.18 – 7.08 (m, 2H), 6.90 – 6.80 (m, 4H), 3.83 (s, 3H), 3.80 (s, 3H), 3.07 – 2.87 (m, 2H), 2.71 – 2.48 (m, 2H), 1.72 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 158.6, 157.3, 143.8, 139.9, 126.2, 126.0, 113.7, 113.6, 72.5, 55.3, 55.3, 48.7, 35.1, 32.8. **IR** (ATR): 3392 (OH st), 2932 (CH st), 1509 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{19}H_{22}O_3$ + $H^+$]: 298.3820; found 298.3540.

131 (a) B. D. W. Allen, M. D. Hareram, A. C. Seastram, T. McBride, T. Wirth, D. L. Browne, L. C. Morrill, *Org. Lett.*, **2019**, *21*, 9241 − 9246. (b) Y. Gan N. Zhang, S. Huang, Y. Liu, *Chin. J. Chem.*, **2020**, *38*, 1686 – 1690.

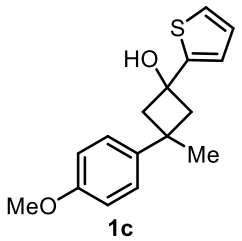
**1,3-bis(4-methoxyphenyl)-3-methylcyclobutan-1-ol** *trans*-**1b**



*trans*-**1b**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1b''** as single diastereoisomer was obtained in 33% yield (98 mg) after flash chromatographic purification (PE:EtOAc =9:1). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.56 – 7.41 (m, 2H), 7.33 – 7.18 m, 2H), 7.03 – 6.84 (m, 4H), 3.85 (s, 3H), 3.83 (s, 3H), 2.98 – 2.89 (m, 2H), 2.85 (d, *J* = 12.5 Hz, 2H**)**, 1.27 (s, 3H)**. $^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 158.9, 157.4, 143.9, 138.8, 127.0, 126.3, 113.9, 113.7, 72.1, 55.3, 55.3, 49.1, 33.6, 31.3. **IR** (ATR): 3392 (OH st), 2960 (CH st), 1508 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{19}H_{22}O_3 + H^+$]: 298.3820; found 298.3724.

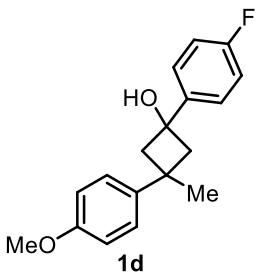
**3-(4-methoxyphenyl)-3-methyl-1-(thiophen-2-yl)cyclobutan-1-ol 1c: 1:1 inseparable mixture of diastereoisomers**



**1c**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1c** was obtained in 83% yield (227 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.31 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.19 – 7.08 (m, 4H), 7.02 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.97 – 6.74 (m, 6H), 3.83 (s, 3H), 3.81 (s, 3H), 3.07 – 2.96 (m, 2H), 2.97 – 2.92 (m, 4H), 2.75 – 2.57 (m, 2H), 1.67 (s, 3H), 1.37 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.5, 157.4, 153.3, 152.6, 143.7, 143.3, 126.8, 126.8, 126.3, 126.3, 125.2, 124.4, 123.8, 122.5, 113.8, 113.7, 70.8, 69.7, 55.3, 55.3, 50.9, 50.6, 35.0, 33.5, 32.8, 31.4. **IR** (ATR): 3394 (OH st), 2953 (CH st), 1511 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{16}H_{18}O_2S + Na^+$]: 297.0920; found 297.0925.

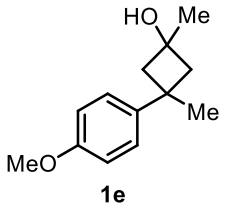
**1-(4-fluorophenyl)-3-(4-methoxyphenyl)-3-methylcyclobutan-1-ol 1d: 1:1 inseparable mixture of diastereoisomers**



**1d**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1d** was obtained in 80% yield (229 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.59 – 7.47 (m, 2H), 7.35 – 7.22 (m, 4H), 7.17 – 7.05 (m, 4H), 7.03 – 6.82 (m, 6H), 3.83 (s, 3H), 3.80 (s, 3H), 3.01 – 2.81 (m, 6H), 2.69 – 2.50 (m, 2H), 1.65 (s, 3H), 1.34 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.5, 143.5, 127.6, 127.5, 126.6, 126.5, 126.4, 126.2, 115.5, 115.2, 114.9, 113.8, 113.6, 72.4, 72.1, 55.35, 55.33, 49.3, 48.9, 35.2, 33.8, 32.9, 31.6. **IR** (ATR): 3393 (OH st), 2932 (CH st) 1509 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{18}H_{19}FO_2 – H_2O + H^+$]: 269.1336; found 269.1333.

**3-(4-methoxyphenyl)-1,3-dimethylcyclobutan-1-ol 1e: 1:1 inseparable mixture of diastereoisomers 1e**

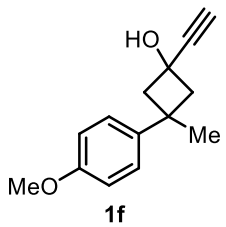


**1e**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1e** was obtained in 40% yield (83 mg) after flash chromatographic purification (PE:EtOAc =8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.08 (dd, *J* = 8.8, 2.5 Hz, 4H), 6.84 – 6.72 (m, 4H), 3.72 (s, 6H), 2.48 (dd, *J* = 12.8, 10.0 Hz, 4H), 2.33 – 2.25 (m, 1H), 2.25 – 2.14 (m, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.10 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.3, 157.3, 144.7, 142.7, 126.7, 126.3, 113.7, 113.6, 68.7, 68.5, 55.3, 55.3, 50.4, 49.6, 34.5, 33.7, 32.2, 31.9, 29.8, 29.4.

**IR** (ATR): 3362 (OH st), 2959 (CH st), 1509 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{13}H_{18}O_2 – H_2O + H^+$]: 189.1274; found 189.1276.

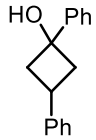
**1-ethynyl-3-(4-methoxyphenyl)-3-methylcyclobutan-1-ol 1f: 1:1 inseparable mixture of diastereoisomers**



**1f**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1f** was obtained in 47% yield (101 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.12 – 6.96 (m, 4H), 6.84 – 6.72 (m, 4H), 3.72 (s, 6H), 2.91 – 2.78 (m, 2H), 2.71 – 2.50 (m, 4H), 2.48 – 2.33 (m, 3H), 2.35 – 2.22 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.5, 143.7, 142.6, 126.3, 125.9, 113.7, 113.6, 88.5, 87.5, 72.3, 72.2, 63.3, 62.8, 55.3, 55.3, 50.5, 50.1, 35.6, 33.3, 32.7, 30.9. IR (ATR) 3393 (OH st), 3286 (≡CH st), 2934 (CH st), 1512 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{14}H_{15}O – H_2O + H^+$]: 199.1117; found 199.1122.

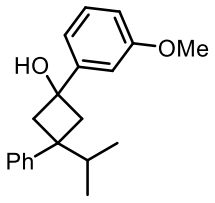
**1,3-diphenylcyclobutan-1-ol 1g: 1:1 inseparable mixture of diastereoisomers**



**1g**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1g** was obtained in 56% yield (125 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^1$H NMR** and **$^{13}$C NMR** are in accordance with literature.[132]

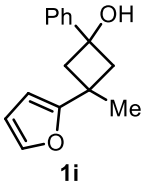
**3-isopropyl-1-(3-methoxyphenyl)-3-phenylcyclobutan-1-ol 1h: 1:1 inseparable mixture of diastereoisomers**



**1h**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1h** was obtained in 42% yield (125 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.44 – 6.78 (m, $8H_{maj}$+$9H_{min}$), 6.73 (ddd, *J* = 8.1, 2.6, 1.0 Hz, $1H_{maj}$), 3.87 (s, $3H_{maj}$), 3.66 (s, $2H_{min}$), 3.07 – 2.82 (m, $3H_{maj}$+$4H_{min}$), 2.82 – 2.73 (m, $1H_{maj}$), 2.54 – 2.41 (p, *J* = 6.8 Hz, $1H_{min}$), 1.90 – 1.76 (p, *J* = 6.8 Hz, $1H_{maj}$), 0.81 (d, *J* = 6.8 Hz, $6H_{min}$), 0.71 (d, *J* = 6.8 Hz, $6H_{maj}$). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 159.8, 159.5, 149.5, 148.4, 145.0, 144.7, 129.6, 129.3, 128.3, 128.2, 128.1, 127.4, 127.1, 125.6, 125.4, 117.6, 116.9, 112.6, 112.5, 111.3, 110.3, 72.7, 72.2, 55.3, 55.0, 48.3, 48.2, 43.2, 42.5, 38.1, 17.2, 16.9. **IR** (ATR): 3334 (OH st), 2958 (CH st) $cm^{-1}$. **HRMS** calculated for [$C_{21}H_{27}O_2 + Na^+$]: 349.1774; found 349.1783.

**3-(furan-2-yl)-3-methyl-1-phenylcyclobutan-1-ol 1i: 2:1 inseparable mixture of diastereoisomers 1i: 1:1 inseparable mixture of diastereoisomers**



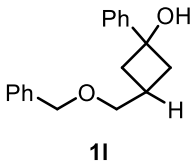
**1i**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1i** was obtained in 65% yield (148 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.63 – 7.47 (m, 6H), 7.47 – 7.29 (m, 12H), 6.36 (dd, *J* = 3.2, 1.9 Hz, 2H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.13 (dd, *J* = 3.2, 0.9 Hz, 2H), 6.00 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.14 – 3.02 (m, 2H), 2.90 (d, *J* = 12.7 Hz, 4H), 2.85 – 2.72 (m, 4H), 2.54 – 2.36 (m, 2H), 1.58 (s, 6H), 1.43 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 162.2, 162.1, 147.3, 146.3, 141.3, 141.1, 129.6, 128.5, 128.5, 128.4, 127.4, 127.1, 125.5, 124.9, 120.4, 115.4,

132 (a) B. D. W. Allen, M. D. Hareram, A. C. Seastram, T. McBride, T. Wirth, D. L. Browne, L. C. Morrill, *Org. Lett.*, **2019**, *21*, 9241 − 9246. (b) Y. Gan N. Zhang, S. Huang, Y. Liu, *Chin. J. Chem*., **2020**, *38*, 1686 – 1690.

110.2, 110.0, 103.3, 103.3, 72.9, 72.1, 48.9, 48.0, 31.2, 30.2, 26.6, 25.9. **IR** (ATR): 3334 (OH st), 2985 (CH st) $cm^{-1}$. **HRMS** calculated for [$C_{15}H_{15}O - H_2O + H^+$]: 211.1117; found 211.1120.

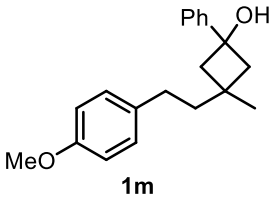
**3-((benzyloxy)methyl)-1-phenylcyclobutan-1-ol 1l**



**1l**

Following the literature procedure and performing the reaction on 0.5 mmol scale, alcohol **1l** was obtained in 75% yield (100 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.60 – 7.50 (m, 2H), 7.45 – 7.23 (m, 8H), 4.64 (s, 2H), 3.63 (d, *J* = 4.6 Hz, 2H), 3.38 (s, 1H), 2.96 – 2.67 (m, 2H), 2.61 – 2.16 (m, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 146.1, 138.1, 128.5, 128.3, 127.8, 127.8, 127.1, 125.0, 73.8, 73.7, 73.4, 40.4, 26.3. **IR** (ATR): 3393 (OH st), 3059 (CH st), 3028 (CH st), 2974 (CH st), 2929 (CH st), 2853 (CH st) $cm^{-1}$. **HRMS** calculated for [$C_{18}H_{20}O_2 + Na^+$]: 291.1356; found 291.1364.

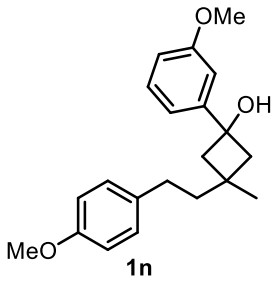
**3-(4-methoxyphenethyl)-3-methyl-1-phenylcyclobutan-1-ol 1m: 1:1 inseparable mixture of diastereoisomers**



**1m**

Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1m** was obtained in 67% yield (198 mg) after flash chromatographic purification (PE:EtOAc = 8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.53 – 7.24 (m, 10H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.10 – 6.99 (m, 2H), 6.90 – 6.77 (m, 4H), 3.82 (s, 3H), 3.79 (s, 3H), 2.66 – 2.41 (m, 8H), 2.32 (d, *J* = 12.8 Hz, 2H), 2.27 – 2.15 (m, 2H), 2.02 – 1.90 (m, 2H), 1.73 – 1.60 (m, 2H), 1.45 (s, 3H), 1.09 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.7, 157.6, 147.6, 147.4, 135.0, 134.8, 129.2, 129.1, 128.5, 128.5, 127.2, 127.2, 125.3, 125.0, 113.8, 113.8, 72.7, 72.4, 55.3, 55.3, 47.7, 47.6, 45.6, 45.1, 30.7, 30.2, 30.2, 29.9, 26.9, 26.2. **IR** (ATR): 3393 (OH st), 2953 (CH st), 2924 (CH st), 1509 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{20}H_{24}O_2 + Na^+$]: 319.1669; found 319.1673.

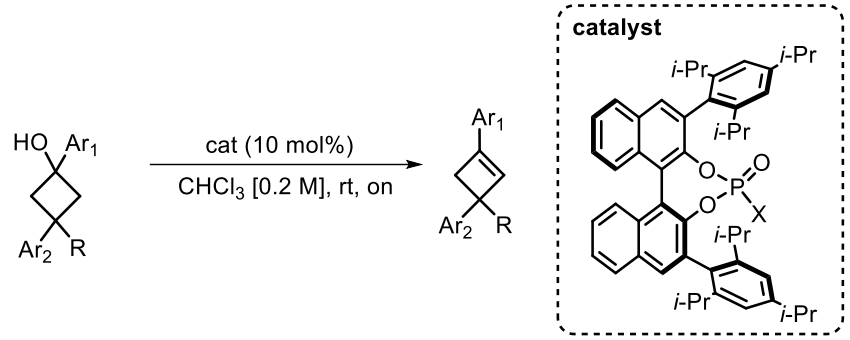
**3-(4-methoxyphenethyl)-1-(3-methoxyphenyl)-3-methylcyclobutan-1-ol 1n**



**1n**

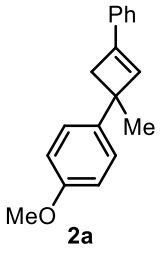
Following the literature procedure and performing the reaction on 1 mmol scale, alcohol **1n** was obtained in 72% yield (235 mg) after flash chromatographic purification (PE:EtOAc =8:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.38 – 7.24 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.11 – 6.94 (m, 4H), 6.92 – 6.73 (m, 5H), 3.85 (s, 2H), 3.84 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 2.63 – 2.53 (m, 1H), 2.49 (dd, *J* = 13.2, 4.0 Hz, 4H), 2.30 (d, *J* = 13.0 Hz, 1H), 2.26 – 2.15 (m, 2H), 2.01 – 1.85 (m, 2H), 1.72 – 1.61 (m, 2H), 1.44 (s, 3H), 1.10 (s, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 159.8, 157.6, 149.3, 149.2, 135.1, 134.9, 130.1, 129.6, 129.3, 129.2, 117.7, 117.4, 113.8, 113.8, 112.5, 112.4, 111.4, 111.1, 107.9, 106.1, 101.6, 72.7, 72.4, 55.3, 55.3, 55.3, 55.2, 47.7, 47.6, 45.6, 45.1, 30.7, 30.2, 30.2, 29.9, 26.9, 26.2. **IR** (ATR): 3420 (OH st), 2993 (CH st), 2953 (CH st), 2925 (CH st), 2833(CH st), 1509 (CH arom) $cm^{-1}$. **HRMS** calculated for [$C_{21}H_{25}O_2 + H^+$]: 309.1849; found 309.1855.

**General procedure for the synthesis of products 2**




Into a 4mL vial alcohol 1 (0.05 mmol) and S-TRIP superacid catalyst (10 mol%, 4.4 mg) were dissolved in 250 µL of $CHCl_3$ and stirred overnight. The crude mixture was then analyzed with $^1H$ NMR analysis and subsequently purified through flash column chromatography PE: EtOAc = 50:1 to obtain products **2** as colorless oils.

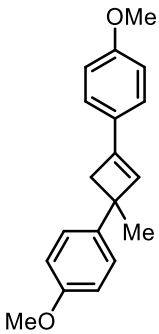
**1-methoxy-4-(1-methyl-3-phenylcyclobut-2-en-1-yl)benzene 2a**



**2a**

Following the general procedure, olefin **2a** was obtained as colorless oil in 17% yield (2.2 mg) and 40% ee. **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.39 (td, *J* = 6.2, 5.6, 3.1 Hz, 3H), 7.34 (dd, *J* = 8.3, 2.0 Hz, 4H), 6.94 – 6.84 (m, 2H), 6.71 (s, 1H), 3.82 (s, 3H), 2.92 (d, *J* = 2.9 Hz, 2H), 1.63 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.6, 143.7, 139.9, 134.8, 134.1, 128.3, 127.8, 126.9, 124.6, 113.5, 55.3, 45.3, 44.4, 27.5. **IR** (ATR): 2952 (CH st), 2917 (CH st) $cm^{-1}$. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 1 mL/ min, $t_1$ = 10.9, $t_2$ = 14.4. $[\alpha]_D^{20}$ = -3.2 (c = 0.2 $CHCl_3$). **HRMS** calculated for [$C_{18}H_{18}O + H^+$]: 251.1430; found 251.1437.

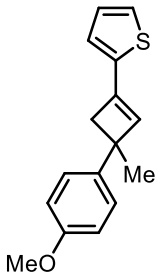
**4,4'-(3-methylcyclobut-1-ene-1,3-diyl)bis(methoxybenzene) 2b**



**2b**

Following the general procedure, olefin **2b** was obtained as colorless oil in 65% yield (29.1 mg) and in a racemic form .**$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.28 – 7.19 (m, 4H), 6.85 – 6.72 (m, 4H), 6.47 (s, 1H), 3.72 (d, *J* = 6.0 Hz, 6H), 2.79 (d, *J* = 2.6 Hz, 2H), 1.52 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 159.4, 157.6, 143.2, 140.2, 131.5, 128.0, 126.9, 126.0, 113.7, 113.5, 55.3, 55.3, 45.1, 44.5, 27.6. **IR** (ATR): 3032 (CH st), 2998 (CH st), 2959 (CH st), 2916 (CH st), 2838 (CH st) $cm^{-1}$. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 1 mL/ min, $t_1$ = 25.6, $t_2$ = 32.9. **HRMS** calculated for [$C_{19}H_{20}O_2 + H^+$]: 281.1536; found 281.1540.

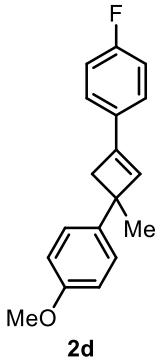
**2-(3-(4-methoxyphenyl)-3-methylcyclobut-1-en-1-yl)thiophene 2c**



**2c**

Following the general procedure, olefin **2c** was obtained as colorless oil in 17% yield (8.2 mg) and in a racemic form. **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.37 – 7.26 (m, 3H), 7.26 – 7.12 (m, 2H), 7.03 – 6.93 (m, 2H), 6.93 – 6.82 (m, 2H), 6.48 (s, 1H), 3.82 (s, 3H), 2.93 (d, *J* = 2.7 Hz, 2H), 1.57 (d, *J* = 1.3 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.7, 139.7, 139.2, 137.6, 132.7, 127.3, 126.8, 125.1, 124.0, 113.5, 55.3, 46.6, 45.7, 27.5. **IR** (ATR): 2952 (CH st), 2916 (CH st), 2832 (CH st) $cm^{-1}$. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 1 mL/ min, $t_1$ = 9.9, $t_2$ =11.6. **HRMS** calculated for [$C_{16}H_{16}OS + H^+$]: 257.0995; found 257.0993.

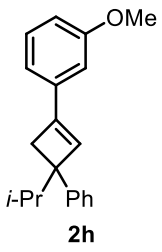
**1-fluoro-4-(3-(4-methoxyphenyl)-3-methylcyclobut-1-en-1-yl)benzene 2d**



**2d**

Following the general procedure, olefin **2d** was obtained as colorless oil in 20% yield (2.7 mg) and 40% ee. **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.46 – 7.24 (m, 6H), 6.94 – 6.81 (m, 2H), 6.65 (s, 1H), 3.82 (s, 3H), 2.90 (d, *J* = 3.3 Hz, 2H), 1.63 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.7, 142.6, 139.8, 133.5, 133.4, 126.8, 126.4, 126.3, 115.4, 115.1, 113.5, 55.3, 45.3, 44.4, 27.6. **IR** (ATR): 2952 (CH st), 2914 (CH st), 2833 (CH st) cm$^{-1}$. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 1 mL/ min, $t_1$ = 16.4, $t_2$ = 27.5. $[\alpha]_D^{20}$ = -14.2 (c = 0.2 $CHCl_3$). **HRMS** calculated for [$C_{18}H_{18}FO + H^+$]: 269.1336; found 269.1332.

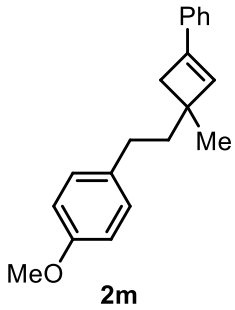
**1-(3-isopropyl-3-phenylcyclobut-1-en-1-yl)-3-methoxybenzene 2h**



**2h**

Following the general procedure, olefin **2h** was obtained as colorless oil in 23% yield (3.2 mg) and 8% ee. **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.41 – 7.11 (m, 6H), 7.00 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.96 – 6.90 (m, 1H), 6.87 (s, 1H), 6.82 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 3.84 (s, 3H), 3.04 (d, *J* = 12.6 Hz, 1H), 2.92 (d, *J* = 12.6 Hz, 1H), 2.07 (h, *J* = 6.8 Hz, 1H), 0.94 – 0.90 (m, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 159.7, 144.6, 144.4, 136.1, 131.8, 129.3, 128.1, 127.3, 125.4, 117.2, 113.6, 109.7, 55.2, 54.1, 40.3, 36.8, 19.0, 18.2. **IR** (ATR): 2956 (CH st), 2925 (CH st), 2869 (CH st) cm$^{-1}$. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 1 mL/ min, $t_1$ = 5.8, $t_2$ = 6.1. $[\alpha]_D^{20}$ = -3.6 (c = 0.2 $CHCl_3$). **HRMS** calculated for [$C_{20}H_{22}O + H^+$]: 279,1749; found 279,1669.

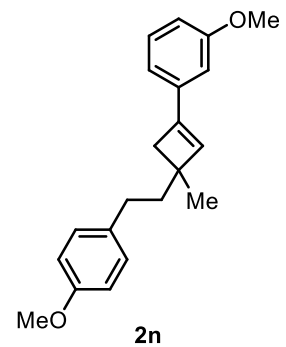
**1-methoxy-4-(2-(1-methyl-3-phenylcyclobut-2-en-1-yl)ethyl)benzene 2m**



**2m**

Following the general procedure, but using diphenyl ((trifluoromethyl)sulfonyl)phosphonate as catalyst olefin **2m** was obtained as colorless oil in 56% yield (7.8 mg). The racemic product was not separable in the chiral column present in lab. **$^1$H NMR** (300 MHz, $CDCl_3$) δ = 7.47 – 7.21 (m, 5H), 7.19 – 7.07 (m, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.43 (s, 1H), 3.81 (s, 3H), 2.71 – 2.54 (m, 3H), 2.49 (d, *J* = 12.6 Hz, 1H), 1.92 – 1.77 (m, 2H), 1.33 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 157.6, 142.6, 135.4, 135.2, 135.0, 129.2, 128.3, 127.5, 124.4, 113.7, 55.3, 42.8, 42.3, 40.9, 31.5, 24.1. **IR** (ATR): 2959 (CH st), 2918 (CH st) cm$^{-1}$.

**1-methoxy-3-(3-(4-methoxyphenethyl)-3-methylcyclobut-1-en-1-yl)benzene 2n**



**2n**

Following the general procedure, olefin **2n** was obtained as colorless oil in 12% yield (1.9 mg) and 8% ee. **$^1$H NMR** (300 MHz $CDCl_3$) δ = 7.25 (d, *J* = 7.9 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.97 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.89 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.88 – 6.77 (m, 3H), 6.43 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.70 – 2.53 (m, 3H), 2.47 (d, *J* = 12.6 Hz, 1H), 1.93 – 1.75 (m, 2H), 1.58 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 159.7, 157.7, 142.5, 136.5, 135.9, 135.1, 129.4, 129.2, 129.1, 117.1, 113.8, 113.7, 113.4, 109.7, 55.3, 55.2, 42.8, 42.3, 41.0, 31.5, 24.1. **IR** (ATR): 3027 (CH st), 2995 (CH st), 2949 (CH st), 2932 (CH st), 2910 (CH st), 2857 (CH st), 2831(CH st) cm$^{-1}$. **HPLC**: OJ-H (*n*-hexane/*i*-PrOH 90:10, 1 mL/ min, $t_1$ = 13.2, $t_2$ =15.1. $[\alpha]_D^{20}$ = -14.2 (c = 0.2 $CHCl_3$). **HRMS** calculated for [$C_{21}H_{25}O_2 + H^+$]: 309.1849; found 309.1855.

# 10 Conclusions

In summary, my Ph.D. work was based on the development of three main topics: i) sulfoxonium ylides;[133] ii) donor-acceptor cyclopropanes;[134] iii) desymmetrization reactions.

First of all, the reactivity of sulfoxonium ylides was analyzed, paying particular attention to the literature background (*Figure **10.1***). From this study, a short review based on the typical reactivity of sulfoxonium ylides, the comparison with their sulfonium counterparts, and the differences with diazocompounds was compiled. Moreover, the review included several reactions performed under asymmetric catalytic conditions.

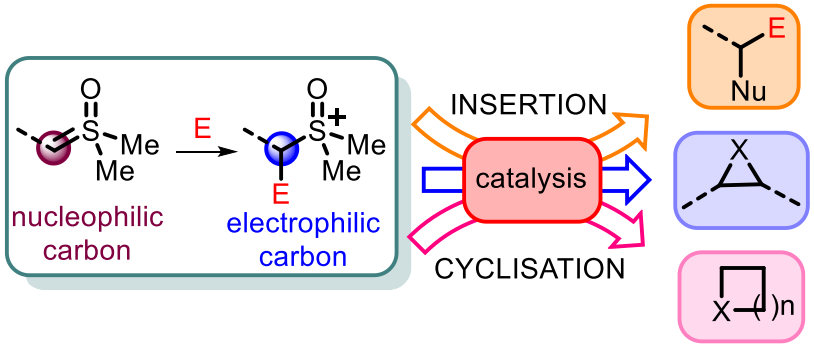



*Figure 10.1. Summary of sulfoxonium ylides review*

Subsequently, the unconventional reactivity of sulfoxonium ylides and salicylaldehyde was discovered and developed, focusing our attention on the mechanism of the reaction (*Figure **10.2***). The peculiarity of this reaction is not only the stoichiometry of the reaction but also the observed chemodivergency. Regarding the divergency, performing the reaction in the absence of a catalyst and with electron-poor salicylaldehydes, dihydrobenzofurans were the main products of the reaction. On the contrary, performing the reaction in the presence of an acidic catalyst and with electron-neutral salicylaldehydes is possible to diverge the route of the reaction obtaining 2*H*-chromenes as main products. In both cases, the stoichiometry of the reactions is appealing, indeed, in both cases, unconventional double participation of the sulfoxonium ylides was observed. Particular attention was paid to the mechanism of the reaction trying to understand both the double participation of the sulfoxonium ylides and the divergency of the reaction.

133 a) G. D. Bisag, S. Ruggieri, M. Fochi, L. Bernardi, *Org. Biomol. Chem.*, **2020**, *18*, 8793. b) G. D. Bisag, S. Ruggieri, F. Fochi, L. Bernardi, *Adv. Synth. Catal.*, **2021**, *363*, 3053. c) G. D. Bisag, P. Pecchini, M. Mancinelli, M. Fochi, L. Bernardi, *Org. Lett.*, **2022**, *24*, 5468.

134 G. D. Bisag, L. Bernardi, M. Fochi: *Maniscript in preparation*

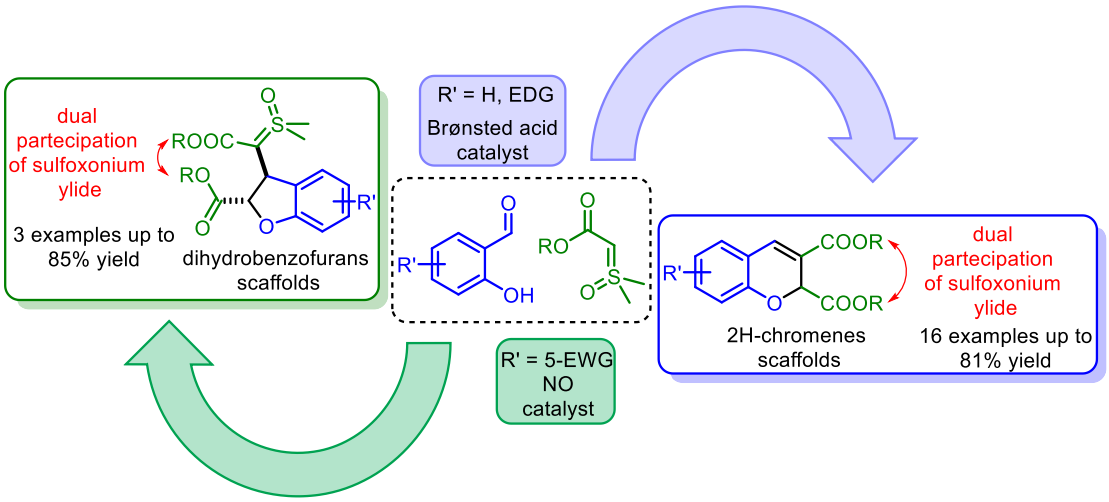



*Figure 10.2. Graphical abstract: Sulfoxonium ylides and salicilaldehydes*

On the basis of the previously developed reaction with salicylaldehydes, we move to better understand the reactivity between sulfoxonium ylides and a related α,β-unsaturated aldehyde, 2'-hydroxycinnamaldehyde, in this case under asymmetric aminocatalysis. The main product of this reaction, embedding an enantioenriched cyclopropa[*c*]chromene framework, is not sufficiently stable to be analyzed by HPLC. To give stability to the obtained product, a Wittig reaction was performed to determine its enantiomeric excess. Herein, due to the importance of the cyclopropa[*c*]chromene framework four different synthetic elaborations were carried out taking advantage of the synthetic versatility of the hemiacetal group.

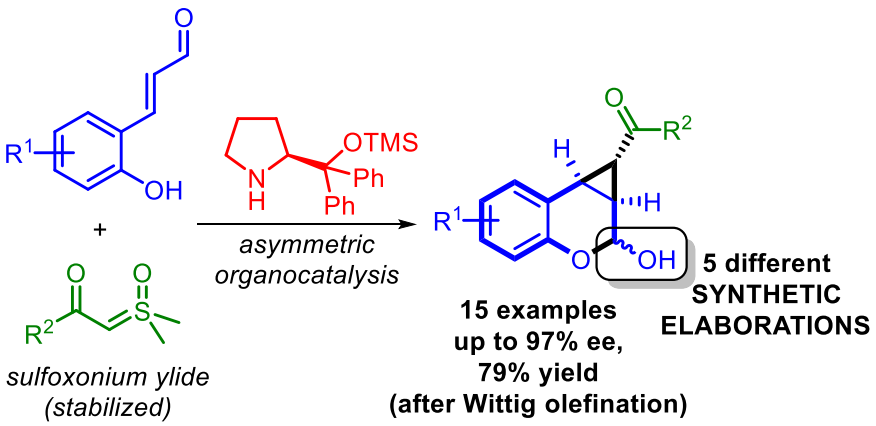



*Figure 10.3. Graphical abstract: Sulfoxonium ylides and 2'-hydroxycinnamaldehydes*

Then, we moved our attention to the study of the reactivity between donor-acceptor cyclopropanes and different nucleophilic species. After numerous attempts, we found that the reaction between a particular donor-acceptor cyclopropane (characterized by two cyano moiety as electron withdrawing groups) and thioacetic acid, under basic phase-

transfer catalysis leads to the formation of two completely different products in function of the reaction conditions. In particular, modulating the reaction conditions is possible to obtain an open-chain product derived from the typical reactivity of the donor-acceptor cyclopropane, and another donor-acceptor cyclopropane derived from an unconventional non-reductive decyanation reaction followed by an acylation.

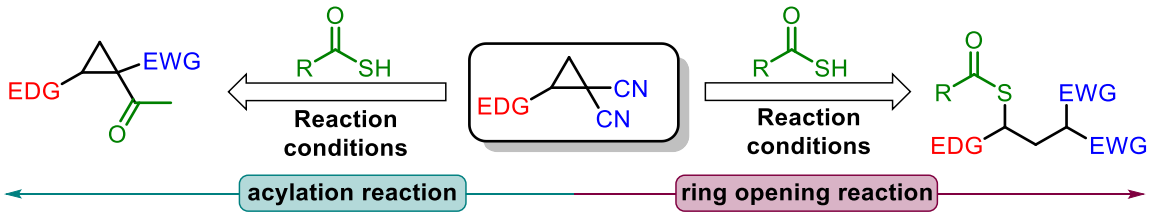



*Figure 10.4. Graphical abstract: chemodivergent reactions between donor-acceptor cyclopropanes and thioacetic acid*

Finally, during the period spent abroad, under the supervision of Prof. J. H. Vicario I focused my attention on the development of a desymmetrization reaction. A preliminary investigation on the enantioselective desymmetrization reaction of cyclobutanols trying to exploit an asymmetric elimination reaction was carried out. Particular attention was given to the substrate research, but also numerous solvents and catalyst screening were carried out leading to promising preliminary results which will be the subject of future investigations.

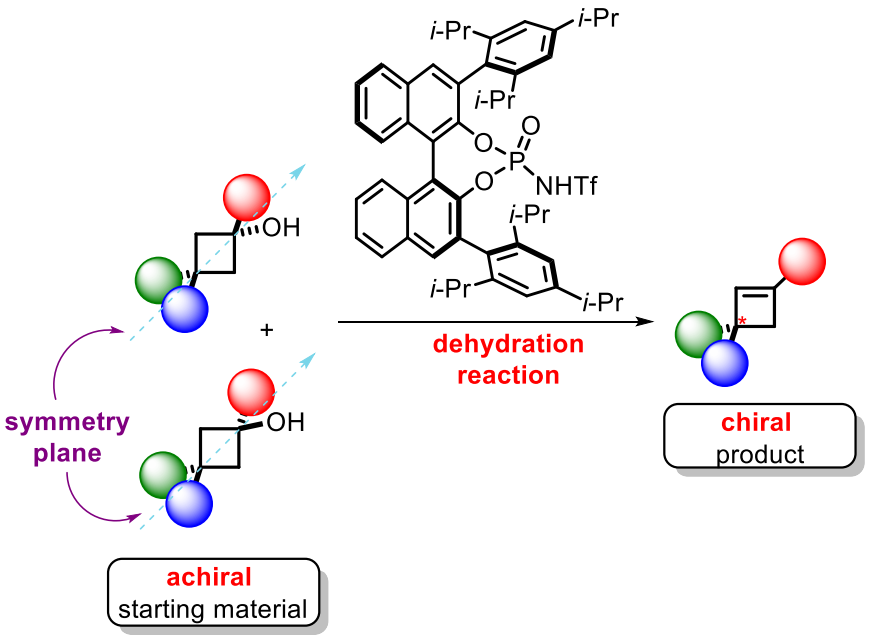



*Figure 10.5. Graphical abstract: asymmetric desymmetrization reactions of cyclobutanols*