SCUOLA DI SCIENZE

Dipartimento di Chimica Industriale “Toso Montanari”

Corso di Laurea Magistrale in

Chimica Industriale

Classe LM-71 - Scienze e Tecnologie della Chimica Industriale

Organocatalytic stereodivergent synthesis of β,β-disubstituted-α-aminoacids

Tesi di laurea sperimentale

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Anno Accademico 2016-2017

ABSTRACT

In this work we present an organocatalytic stereodivergent synthesis of β,β-disubstituted-α-aminoacids using arylidene azlactones as starting materials. The developed two step synthesis involves a sequential catalysis approach, in which two different catalysts act sequentially to control the absolute configuration of two different stereocenters. With an accurate selection of the catalysts absolute configuration it is possible to obtain all the stereoisomers of the product. The first synthetic step is a catalytic asymmetric transfer hydrogenation of the azlactone C=C double bond. A Jacobsen type thiourea and a Hantzsch ester were chosen as chiral catalyst and hydride donor, respectively. Different azlactones, Hantzsch esters and thioureas were synthetized and tested in the asymmetric transfer hydrogenation to achieve the best stereoselectivity. The second step involves a dynamic kinetic resolution on the reduced azlactone, through a nucleophilic addition to the carbonyl moiety promoted by a bifunctional chiral catalyst. A wide range of nucleophiles and organocatalysts were tested; the best results were reached with alcohols as nucleophiles and squaramide-based cinchona alkaloids as a chiral catalysts. With the optimized conditions two stereodivergent syntheses were then performed, enabling the selective obtainment of both diastereoisomeric product with high enantioselectivities.

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1. INTRODUCTION

1.1. Stereodivergent synthesis [1]

In the last 20 years, notable improvements have been achieved in the field of asymmetric catalysis. Despite of this, complete control of the absolute and relative configurations in molecules bearing multiple stereocenters still remains a challenge. Usually, during the development of a synthetic methodology, high selectivity can be achieved just in one diastereoisomer; while performing the same route, the access to other possible diastereoisomeric products is not feasible.

It is noteworthy that different biological properties could be displayed by different stereoisomers of a drug candidate. Indeed, during a lead optimization process of a drug candidate, an evaluation of therapeutic and toxicological properties of all the product stereoisomers is required by regulatory agencies. Due to this consideration, the synthesis of all of the stereoisomers of a chiral molecule has become a standard procedure. Therefore, when multiple stereocenters are present in the target product, the development of a complete stereodivergent process has recently become an important goal. A stereodivergent process is one that let to obtain each stereoisomers of a target molecule from the same set of starting materials. With the development of a stereodivergent methodology, time and efforts required for the preparation of all the stereoisomers of a product are lowered. To highlight the benefit that stereodivergence in asymmetric catalysis could bring, an example of non stereodivergent procedure is shown below.

Lariam is the trade name of a racemic mixture of *erythro*-mefloquine; both enantiomers are active against the malaria parasite. In order to investigate the antimalarian activity, all of the four stereoisomers had to be synthetized and analyzed. To this purpose, a non stereodivergent synthesis of the four stereoisomers was developed by Ding and Hall in 2013[2] (Figure 1).

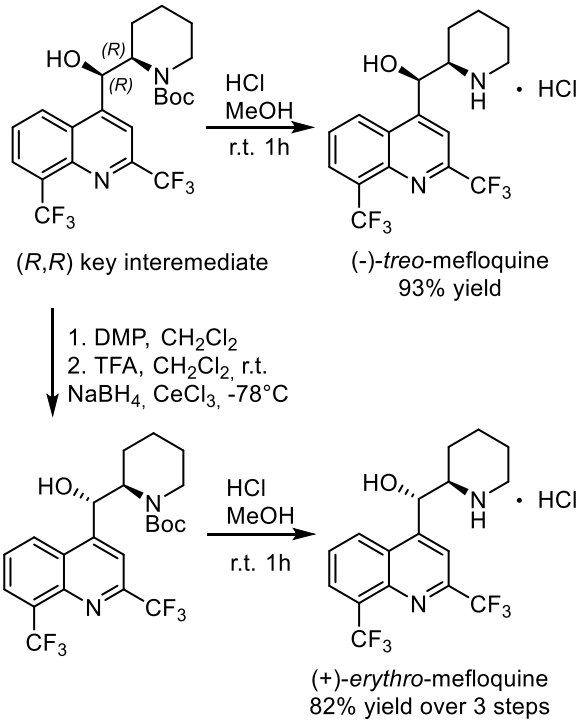


Figure 1: synthesis of both diastereoisomers of mefloquinine

The reported methodology involves a tandem process using chiral palladium catalysis to obtain in an enantioenriched form the (*R*,*R*) key intermediate, used for the synthesis of both diastereoisomers of mefloquinine. If it is reacted with concentrated HCl and methanol to cleave the *tert*-butyloxycarbonyl (Boc) protecting group, (-)-*threo*-mefloquine is obtained in one step. Instead, to synthesize the (+)-*erythro*-mefloquine from the key intermediate three synthetic step are required. So, additional labour and time were invested in order to achieve both diastereoisomers. It is clear that a stereodivergent method could let the access to both the diastereoisomers with the development of one methodology, saving time and efforts. The enantiomeric products (+)-*threo*-mefloquine and (-)-*erythro*-mefloquine) can be obtained using the enantiomers of the palladium catalyst employed in the first step.

Stereodivergent synthesis can be developed following different strategies: changing solvent, catalyst or starting material in a stereoselective synthesis has been reported to enable the reverse of the stereoselectivity in some cases. In order to highlight the distinction from non-stereodivergent synthesis and to well explain the stereodivergent methodology, a few key examples of the different approaches to stereodivergent synthesis are reported in this section.

Changing the starting material structure with the purpose of reversing the diastereoselectivity of a reaction, could be considered a *pseudo*-diastereodivergent approach, since the strict definition of stereodivergence entails the employing of the same starting material. Nevertheless, when enolate or alkene are involved in the reaction, control of the geometry of the double bond (*E* or *Z*) is often used to reverse the diastereoselectivity. A clear example of this approach is the phosphoramide-catalyzed addition of trichlorosilyl enolates to aldehydes studied and reported by Denmark[3] (Figure 2).

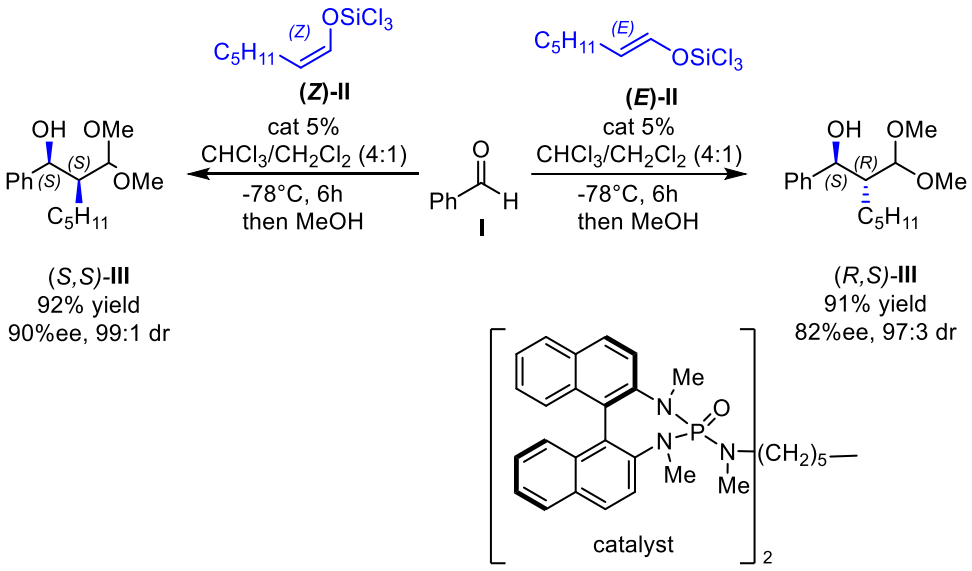


Figure 2: phosphoramide-catalyzed addition of trichlorosilyl enolates to aldehydes

The reported synthesis shows that reacting benzaldehyde **I** with the (*Z*)-**II** silyl enolate, product (*S,S*)-**III** is obtained as major stereoisomers. Conversely, treating under the same conditions benzaldehyde **I** with the (*E*)-**II** silyl enolate, the stereoselectivity is reversed and (*R,S*)-**III** is produced as the major stereoisomer. Although *pseudo*-stereodivergent strategy is efficient and often performed in reaction involving enolates or alkenes as starting material, it needs both of the stereoisomers of the starting material to be synthesized. Therefore, more time and efforts are needed compared to the other truly stereodivergent approaches.

An alternative strategy could be modifying catalyst structure in order to reverse the diastereoselectivity. Reacting the same starting material with two different catalysts, can let to obtain selectively one of the two different diastereoisomers of the same product. An example of this approach is the stereodivergent conjugate addition of α-cyanoketones to

α-chloroacrylonitriles, reported by Deng and co-workers[4] (Figure 3). In this synthesis, performing the reactions with the *pseudo*-enantiomeric phenanthryl-protected alkaloids **VII** and *ent*-**VII**, the enantiomers (*R,S)* and (*S,R*) of product **VI** are selectively obtained. On the other hand, through the use of 9-thiourea substituted chincona alkaloids **VIII** and *ent*-**VIII** the two complementary stereoisomers (*S,S*) and (*R,R*) are selectively synthesized.

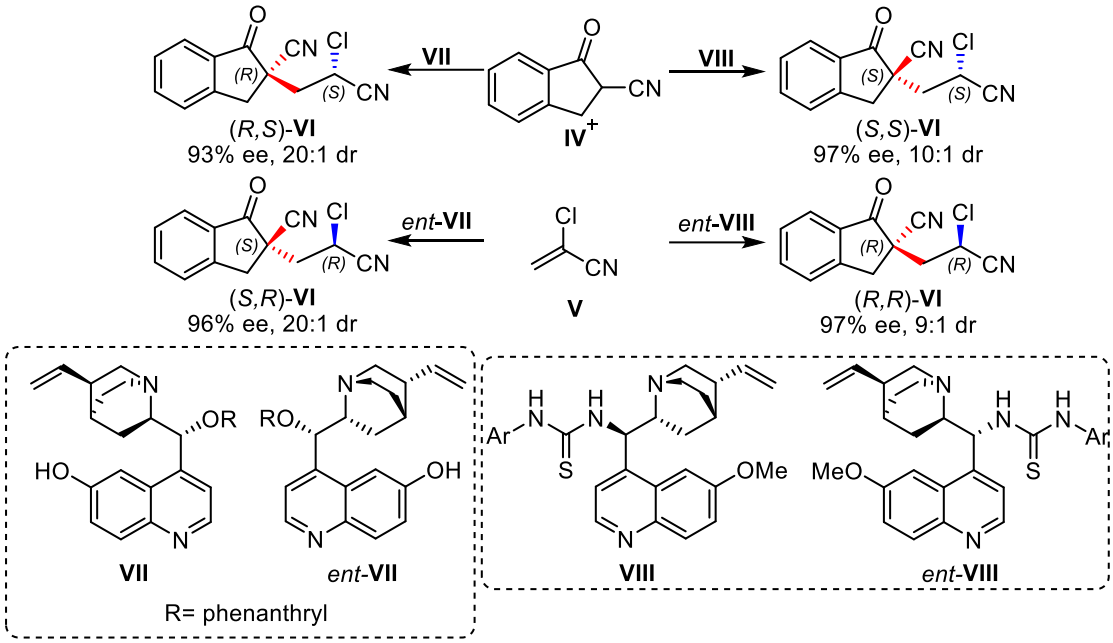


Figure 3: Stereodivergent conjugate addition of α-cyanoketones to α-chloroacrylonitriles

Another possibility to reverse the diastereoselectivity of a reaction is given by the change in the nature of the solvent and other reaction conditions. For example, Melchiorre and co-workers demonstrated that using a single chiral catalyst is possible to achieve complete control on the stereoselectivity of the asymmetric conjugate addition of alkyl thiols to α,β-disostituited unsaturated ketones[5] (Figure 4). Changing solvent and co-catalyst, but using the very same catalyst **X** and starting materials, the two diastereoisomers can be selectively obtained. In more detail, if the coniugate addition is performed with acetone as a solvent and phosphoric acid **XI** as acidic co-catalyst at 40°C, the *anti* diastereoisomers of **IX** are obtained as major diastereoisomers. The enantioselectivity of the reaction depend on catalyst **X** *pseudo*-enantiomers, since if quinine derived catalyst **X** is used in the reaction, (*R,R*)-**IX** is obtained as major stereoisomer, while, if quinidine derived catalyst *ent*-**X** is applied as a catalyst, the complementary enantiomer (*S,S*)-**IX** is achieved as a major stereoisomer. To produce diastereoselectively the *syn* diastereoisomers, chloroform ($CHCl_3$) is used as a solvent

and 2-fluorobenzoic acid as the acidic co-catalyst, at 25°C. The syntheses of both diastereoisomers are performed with the same catalysts and with the same staring material, the stereodivergence is achieved just changing some reaction conditions. Mechanistic investigations are still being performed in order to fully understand the causes of the diastereodivergency; a hypothesis is that different reaction conditions lead to diverse geometries in the intermediates, promoting different stereochemical outcomes.

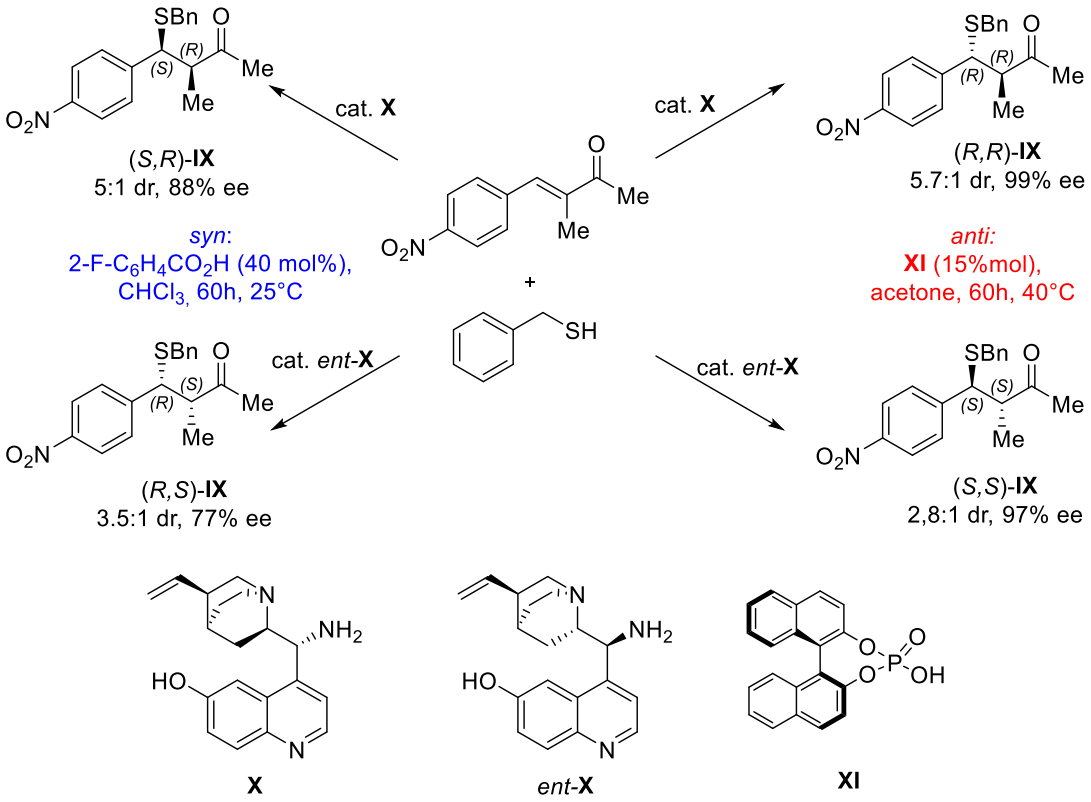


Figure 4: asymmetric conjugate addition of alkyl thiols to α,β-disubstituted unsaturated ketones

1.1.1. Sequential stereodivergent catalysis

The last example of stereodivergent approach presented in this work is based on sequential catalysis, which involves different catalysts acting sequentially to control the absolute configuration of (two) different stereocenters. Each one of the catalysts controls the absolute configuration of one stereocenter, without influencing the other one. With an accurate selection of the catalysts absolute configuration (*R* or *S*) it is possible to obtain each one of the stereoisomers of the product. The general principle of two step sequential stereodivergent synthesis is shown in Figure 5.

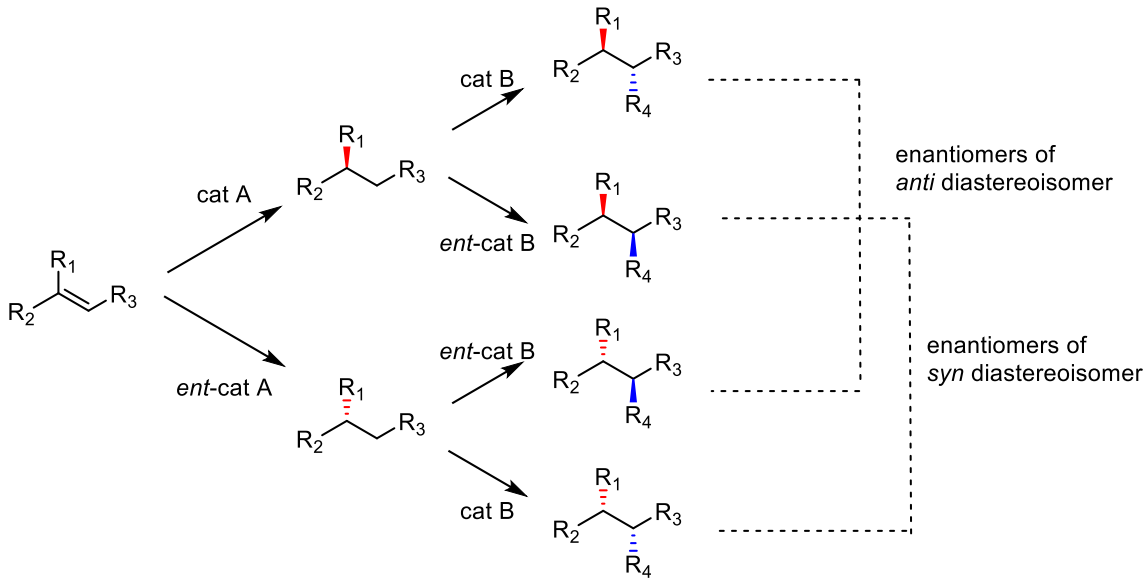


Figure 5: sequential stereodivergent synthesis

For example, in 2005, MacMillan and co-workers reported a sequential diasterodivergent approach for the formal hydrofluorination of enals with a cycle specific amine catalysis[6] (Figure 6). They showed that reacting the enal **XII** with the hydride donor Hantzsch ester and the amine catalyst (*R*)-**XIII**, intermediate (*S*)-**XIV** is formed with an almost complete stereocontrol of the newly formed β-carbon chiral center. Subsequently, (*S*)-**XIV** is treated with the fluorinating agent NFSI and with the amine catalyst (*S*)-**XV** in order to achieve diasteroselectively the (*R*,*S*)-**XVI** stereoisomer (*syn* diastereoisomer) as major product. On the contrary, reacting (*S*)-**XIV** with the amine catalyst (*R*)-**XV** under the same conditions, (*R*,*R*)-**XVI** stereoisomer (*anti* diastereoisomer) is obtained as the major product. The remaining two stereoisomers ((*S*,*R*)-**XVI** and (*S*,*S*)-**XVI**) could easily be accessed reacting enal **XII** with the enantiomeric amine (*S*)-**XIII** catalyst in the first reduction step. It is noteworthy that in the second step the absolute configuration of the β-carbon chiral center is not modified and it does not influence the stereoselectivity on the α-carbon chiral center. Therefore, involving a different enantiomers of the amine catalyst **XV** different **XVI** diastereoisomers are obtained.

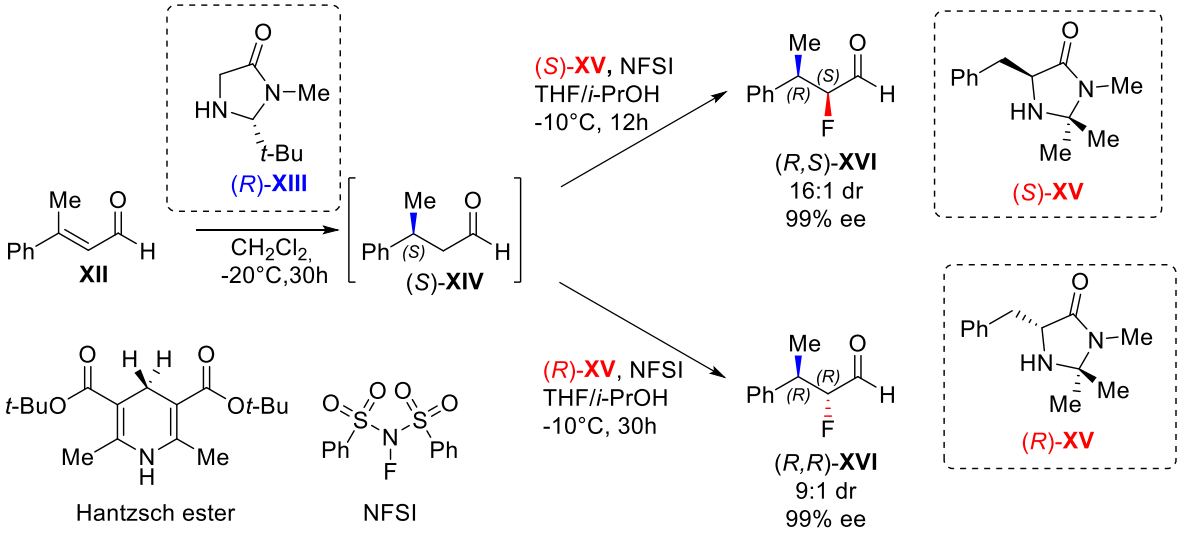


Figure 6: hydrofluorination of enals with a cycle specific amine catalysis

Contrary to the other approaches previously described, based on serendipitous and un-rationalized discoveries of stereodivergency with specific substrates/catalysts/conditions, this one appears more founded on rational planning, and seems more predictable and generalizable. Last, a noteworthy benefit of this stereodivergent approach is an enrichment on the enantiomeric excess during the second step of the synthesis. The mathematical principle behind the enantiomeric enrichment is described in the next section.

1.1.2. Horeau principle

The Horeau principle is the mathematical principle behind the enantiomeric enrichment in a sequential stereodivergent synthesis. An example of the application of the principle on a two step synthesis is shown in Figure 7. In a hypothetic synthesis, the starting material is treated with the enantiomerically pure chiral catalyst **A** and the first-step product is achieved with 80% enantiomeric excess, which means 90:10 enantiomeric ratio. The second step is performed using the enantiomerically pure chiral catalyst **B**, in order to control the absolute stereochemistry of the second newly formed chiral center and to obtain the *anti* diastereoisomer as major product. Supposing that this latter catalyst is able to give 70% (85:15) stereoinduction in the second chiral center, and assuming to reach complete conversion on both synthetic step, it is possible to mathematically prove the final values of enantiomeric excess calculating the final percentage amount of each stereoisomer:

$$\text{major enantiomer of } anti \text{ diastereoisomer} = 100 * 0.90 * 0.85 = 76.5\%$$

$$\text{minor enantiomer of } anti \text{ diastereoisomer} = 100 * 0.10 * 0.15 = 1.5\%$$

$$\text{major enantiomer of } syn \text{ diastereoisomer} = 100 * 0.90 * 0.15 = 13.5\%$$

$$\text{minor enantiomer of } syn \text{ diastereoisomer} = 100 * 0.10 * 0.85 = 8.5\%$$

Therefore, the enantiomeric excesses of both the diastereoisomers are calculated with the classical method involving the value of the final percentual amount of the enantiomers, for example, for the favorite stereoisomer obtained:

$$\text{ee} = \frac{\text{maj. ent. } anti - \text{min. ent. } anti}{\text{maj. ent. } anti + \text{min. ent. } anti} = \frac{76.5 - 1.5}{76.5 + 1.5} = 96\%$$

Figure 7 shows that with the second step the enantiomeric excess of the major diastereoisomer is increased, while the enantiomeric excess of the minor is lowered. A high selectivity on a different stereoisomer could be smoothly obtained changing the enantiomers of the catalysts involved in the reactions.

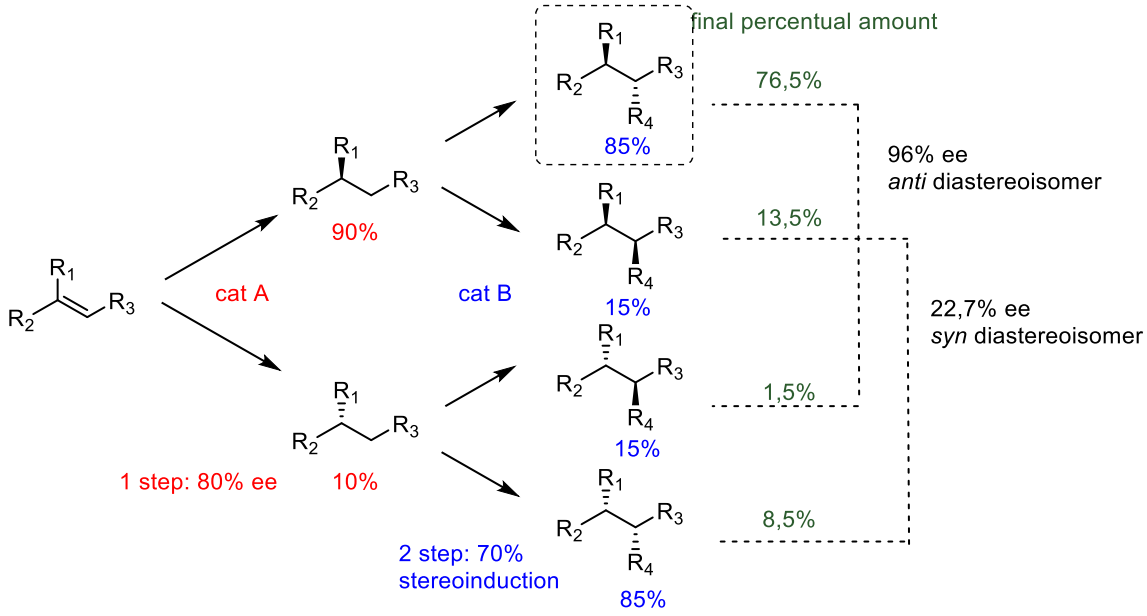
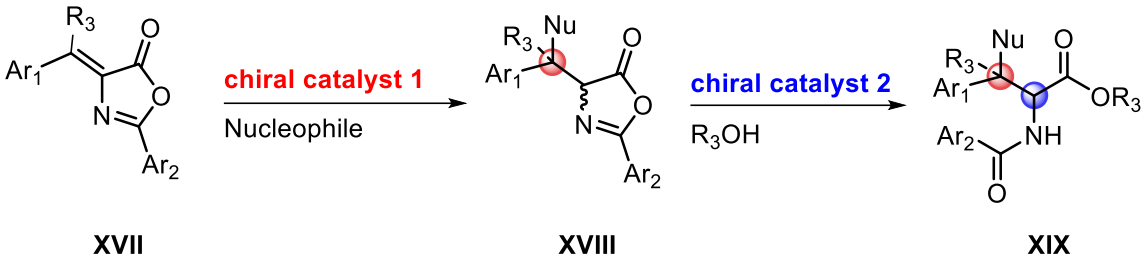


Figure 7: Horeau principle

This is an important point considering that usually the separation of diastereoisomers is considered to be easier than the separation of the enantiomers, since diastereoisomers display different physicochemical properties. It must however be noted that even if it is sufficient to have one out of two steps highly enantioselective to produce a highly enantioenriched product, it is mandatory to have good selectivity in both steps to achieve both high enantio- and diastereo-selectivity in the reaction.

1.2. Diasterodivergent synthesis of β,β-disubstituted-α-aminoacids

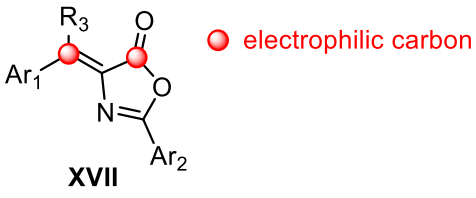


XVII **XVIII** **XIX**

Figure 8: catalytic asymmetric synthesis of β,β-disubstituted α-amminoacids

Enantiomerically pure natural and non natural α-amino acids are important building blocks for the obtainment of chiral drugs, peptides, chiral ligands and other chiral target molecules. However, the stereodivergent synthesis of β,β-disubstituted-α-amino acid derivatives has not received so much attention. This project took into consideration their stereodivergent synthesis from arylidene azlactones **XVII** exploiting a sequential two step route (Figure 8). The planned sequence involves first a Michael addition catalyzed by catalyst 1 and controlling the configuration at the β-carbonylic stereogenic centre (highlighted in red), and then the enantioselective ring opening of the azlactone moiety, occurring under dynamic kinetic resolution conditions under the action of catalyst 2 and controlling the configuration of the α-carbonylic chiral centre (highlighted in blue).

However, in literature there are no example of methodologies capable of isolating the Michael non opened product (**XVIII**). This is probably due to the double eletrophilic nature of arilydene azlactones[7] (Figure 9), since nucleophilic addition smoothly occurs on both the carbonylic carbon and the β-carbonylic carbon.



XVII

Figure 9: arylidene azlatones

Performing the above mentioned synthesis in one step it does not lead to the obtainment of both the diastereoisomers of the β,β-disubstituted-α-amino acid derivatives **XIX**, since the two stereocenters are controlled in the same synthetic step (i.e. with the same catalyst). The project, instead, aimed at the isolation of the Michael adduct **XVIII**,

enabling the obtainment of both α-amino acid diastereoisomers through a sequential diastereodivergent synthesis. After several attempts with different nucleophilic species and azlactones, it was found to be possible to isolate the Michael adduct for the diastereodivergent synthesis using the addition of a hydride in the first step (i.e. reduction of the olefin).

1.2.1. Catalytic enantioselective transfer hydrogenation

The first reaction of the synthesis is an asymmetric transfer hydrogenation of the exocyclic carbon double bond located on C5 of the azlactone ring, involving an Hantzsch ester as hydride donor and a Jacobsen-type thiourea as catalyst (Figure 10).

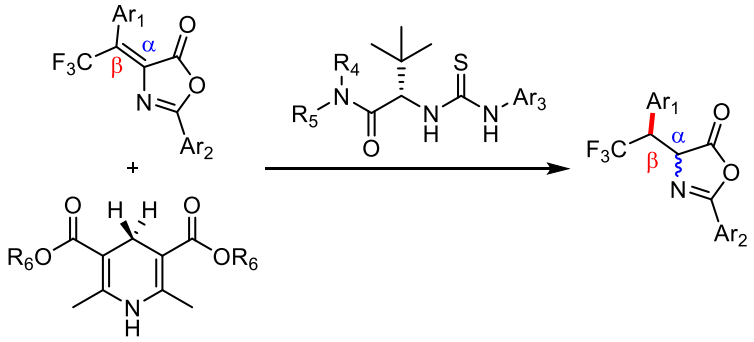


Figure 10: catalytic enantioselective transfer hydrogenation

The Hantzsch ester is a reducing agent very often used in the reduction of electrophilic double bonds;[8,6] the driving force of the hydride donation is the aromatization of the ring that occurs after the hydride donation (Figure 11).

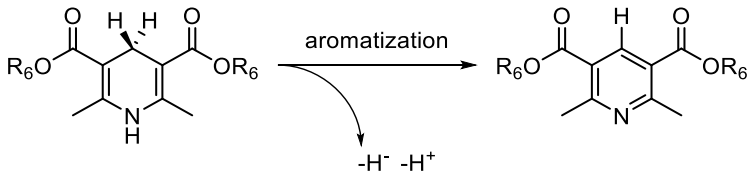


Figure 11: Hantzsch ester aromatization

The Jacobsen-type thiourea catalyst is a hydrogen bond donor and acceptor catalyst (Figure 12), it induces the selective formation of the stereocenter on the β-carbonylic carbon in one of the two possible absolute configurations.

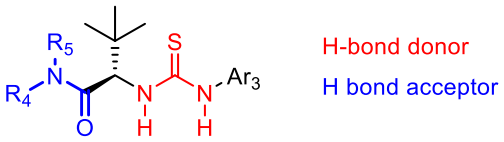


Figure 12: Jacobsen type thiourea

Thanks to both the hydrogen bonding acceptor and donor moieties of the catalyst,[8] the reaction transition state is formed through hydrogen bonds between the catalyst and both the arylidene azlactone and the Hantzsch ester. In the transition state, the hydride donor and the azlactone are fixed in a spatial conformation, where only one of the two pro-chiral faces of the azlactone is available for the hydride addition (see Results and Discussion). In this manner, the β-carbonylic chiral centre is selectively formed in a specific absolute configuration. It is noteworthy that the reduction of the C-C double bond creates two stereocenters, leading to the production of four different stereoisomers. However, due to the acidity of the α-carbonylic proton[9], the configuration of the α-carbonylic newly formed chiral centre cannot be controlled in this first step (Figure 10). Two diastereoisomers are thus formed.

1.2.2. Dynamic kinetic resolutions of azlactones[9]

A dynamic kinetic resolution is a methodology that leads to an enantioenriched product from a racemic substrate. An asymmetric transformation involving selectively one of the two enantiomers is performed on the racemic starting material. Meanwhile, racemization occurs. In order to achieve a high value of enrichment, the racemization has to be faster in rate than the asymmetric transformation, as exemplified in Figure 13 for the dynamic kinetic resolution of azlactones through an alcoholysis reaction, that is exploited in the second step of the sequential approach described in this work.

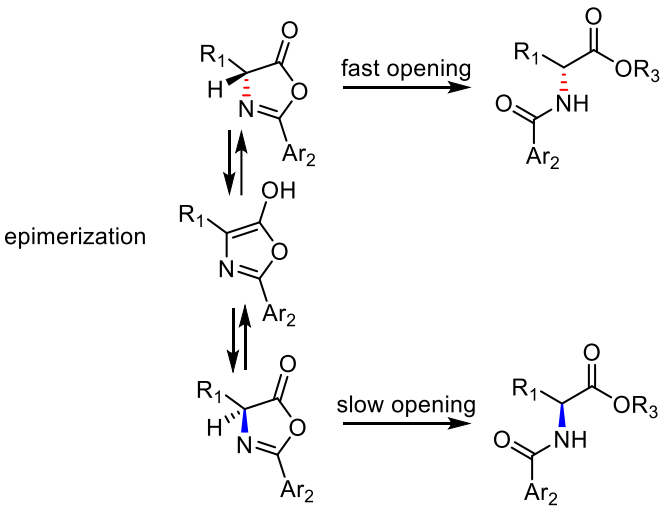


Figure 13: dynamic kinetic resolution of azlactones by alcoholysis

Dynamic kinetic resolution of azlactones has been deeply investigated in the last ten years, since it is a well established route for the synthesis of natural and non natural optically active α-aminoacids[10]. This process is performed through a nucleophilic addition to the carbonyl moiety, in presence of a bifunctional catalyst. The hydrogen bond donor group of the catalyst is needed in order to coordinate the azlactone, while the basic moiety is required to both activate the nucleophile and to promote the epimerization of the α-carbonylic chiral centre. Due to the bifunctionality of the catalyst, the transition state is formed through hydrogen bonds between the chiral catalyst and both the nucleophile and the azlactone, leading preferentially to the opening of the cycle with a defined absolute configuration on the α-carbonylic chiral centre. In the meantime, the substrate is subjected to a fast epimerization.

In this work, the dynamic kinetic resolution is performed on the enantioenriched β,β-disubstituted azlactones derived from the asymmetric reduction previously described (Figure 14). Due to the presence of the already defined β-carbon chiral center, the ring opening process can lead to the formation of four stereoisomers; according to the catalysts selection, one of them is produced as major stereoisomer. From Figure 14 it is deduced that the stereoinduction of dynamic kinetic resolution on the α-carbon chiral center can be detected by the diastereomeric ratio, since β-carbon absolute configuration does not change in this reaction.

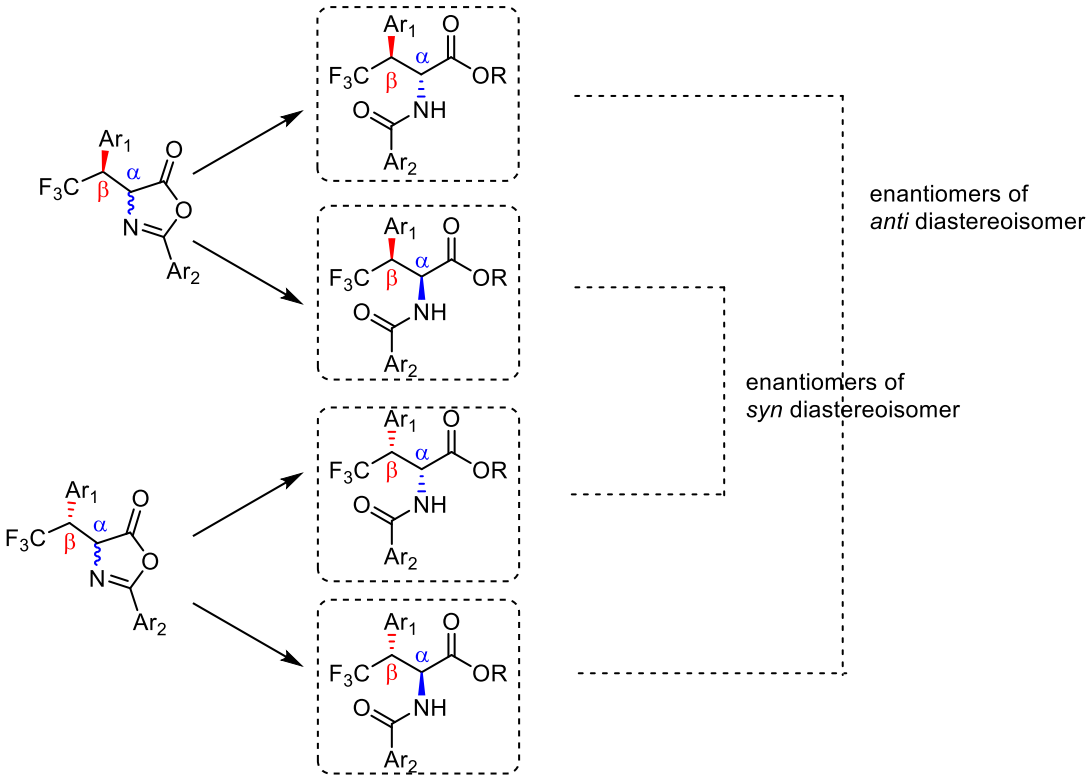


Figure 14: dynamic kinetic resolution to β-β-disubstituted-α-aminoacids

According to the previously reported literature[10c], squaramide-based chincona alkaloids are the most stereoselective catalysts in dynamic kinetic resolution of azlactones by alcoholysis (Figure 15).

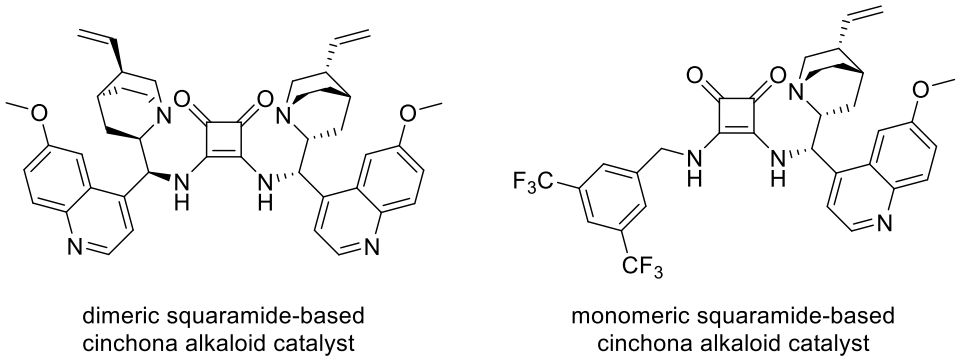


Figure 15: squaramide-based cinchona alkaloids catalyst

Cinchona alkaloids are a class of natural products isolated from a plant called Cinchona[11]. The most common available structures are two couples of *pseudo*-enantiomers: quinine (**QN**)-quinidine (**QD**) and cinchonidine (**CD**)-cinchonine (**CN**) (Figure 16). Properly, they are not enantiomers, since only two out of the five stereocenters present reverse configurations; however, they behave chemically like

enantiomers. Cinchona alkaloids are used as bifunctional catalysts, since they bear both an acidic and a basic group. In addition, they can be derivatized in order to obtain different structures, like squaramide-based catalysts.

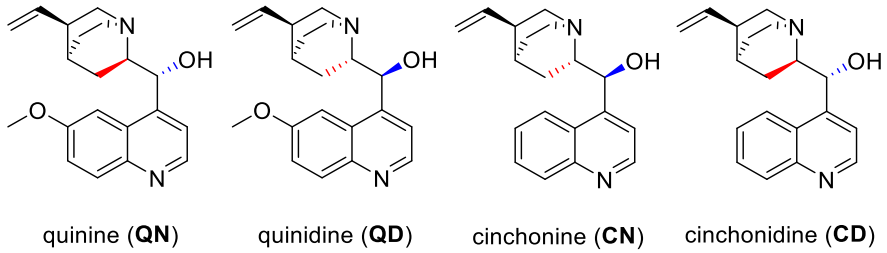


Figure 16: cinchona alkaloids

In squaramide-based cinchona alkaloids catalysts, the basic group is represented by the quinuclidine ring, which nitrogen presents a lone electron pair available for hydrogen bonding and proton abstraction (Figure 17). The acidic moiety, instead, is represented by the squaramidic group, which thanks to the electronic delocalization of the ring, acts as an efficient hydrogen bond donor.

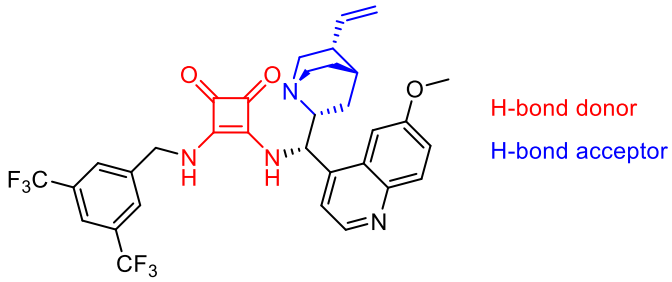


Figure 17: squaramide-based catalyst moieties

2. AIM OF THE PROJECT

When I began my internship, the project had already started (Figure 18). Some screening had already been performed to achieved stereoselectivity in the asymmetric transfer hydrogenation reaction. Jacobsen type thioureas were selected as catalysts and Hantzsch esters as a hydride donors. Performing the asymmetric reduction on the azlactone **1a**, with the Hantzsch ester **2a** and thiourea **4a** as a catalyst, 70% enantiomeric excess were achieved in both the diastereoisomers of the reduced azlactone **3a**. In addition, two tests were done in order to verify the feasibility of the diastereodivergent process. Employing dimeric squaramide-based quinidine as a catalyst (*ent*-**12a**) and allylic alcohol as nucleophile, product **5a** was obtained in 5.6:1 diastereomeric ratio and 90% enantiomeric excess. On the contrary, performing the reaction under the same condition and using dimeric squaramide-based quinine **12a** as a catalyst, an inversion on diastereoselectivity occurred. Product **5a** was obtained in 1:1.5 diastereomeric ratio and 95% enantiomeric excess. In both the reactions, complete conversions were reached. According to this results, the stereodivergent synthesis seemed to be achievable. However, higher values of selectivity were desirable both in the first and in the second step.

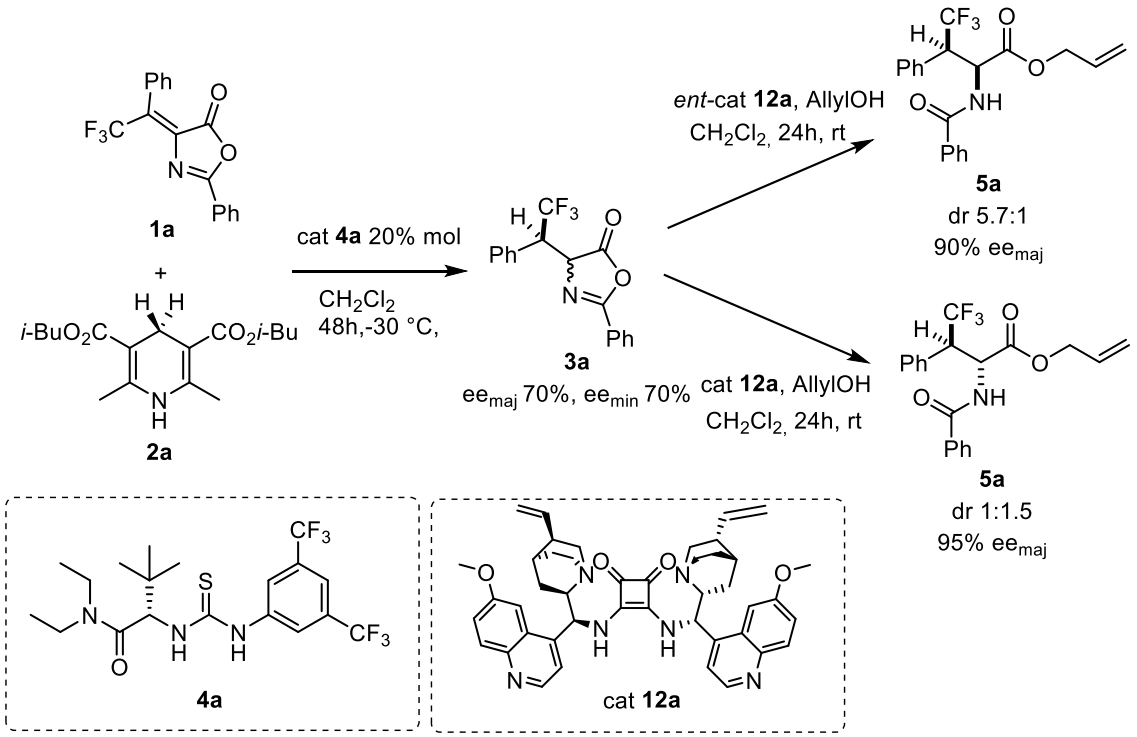


Figure 18: initial conditions

Based on these preliminary results, the aim of my work has been:

- To optimize the reaction conditions of the asymmetric transfer hydrogenation reaction, investigating the influence of different arylidene azlactones, Hantszch esters, Jacobsen type thiourea and other catalytic structures on the stereoselectivity.
- To analyze and optimize the dynamic kinetic resolution in order to prove the feasibility of the steredivergent process and to achieve high values of diastereomeric ratios for both diastereoisomers.

3. RESULTS AND DISCUSSION

3.1. Optimization of the first step

Initially, the first step was optimized with the aim of maximizing the enantiomeric excess. It involves the enantioselective reduction of the exocyclic double bond located at the C5 of the azlactone ring using the Hantzsch ester **2a** as hydride donor, and chiral hydrogen bond donors **4** acting as chiral catalysts to obtain enantioenriched product **3a** (Figure 19). However, due to the acidic proton on C5, this product **3a** is rather unstable and cannot be purified by means of column chromatography. Furthermore, the stereoisomers of **3a** (obtained as a diastereomeric mixture) proved to be inseparable by chiral stationary phase HPLC. Therefore, in order to determine its enantiomeric excess, it was converted into more stable ring-opened products **5a** or **6a**. At first, the azlactone **3a** was opened using triethylamine as a basic catalyst and allylic alcohol as a nucleophile, delivering amino acid **5a** as a mixture of diastereoisomers. Even if these stereoisomers could be separated by CSP HPLC, their low adsorption coefficient was not optimal for HPLC analysis. Therefore, diverse nucleophiles were tested in order to increase the UV-absorption of the final product. Between the different nucleophiles tested, 4-methoxyaniline appeared to be the best choice, even if in some cases the HPLC chromatograms of the corresponding amides **6a** were not fully reliable due to the presence of impurities overlapping the peaks of interest. Therefore, the two approaches were alternatively used during the first catalyst screening.

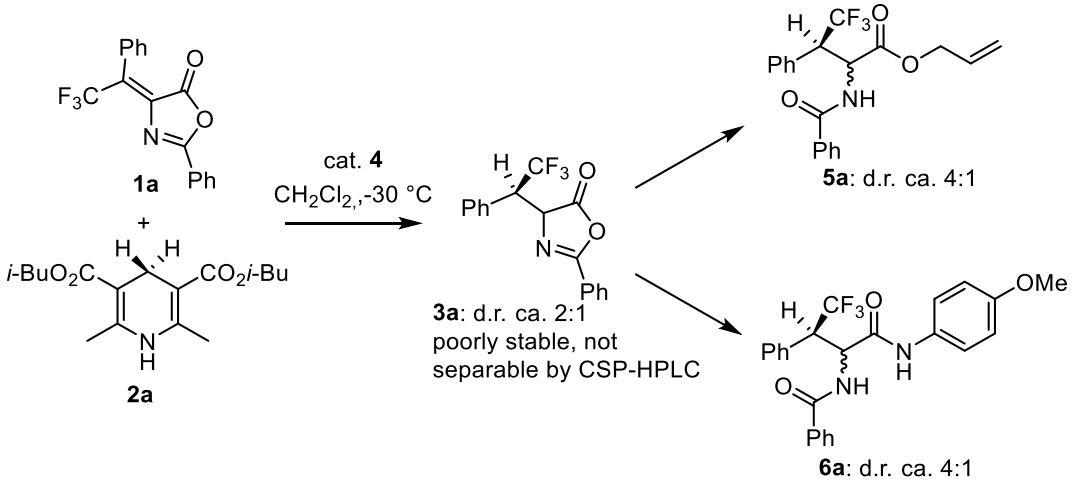


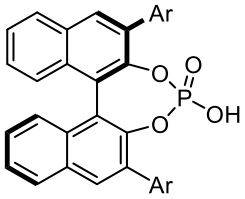
Figure 19: catalytic reduction and opening to generate stable products

Even if these products were obtained as diastereomeric mixtures, it can be assumed that their enantiomeric excesses reflected the enantioselectivity obtained at the benzylic carbon during the first asymmetric reduction process. Indeed, the enantiomeric excesses determined in the two diastereoisomers displayed comparable values (see next section), substantiating this assumption. The aim of this part of the project was to control the stereochemistry of the benzylic stereocentre, without considering the α-amino stereocentre which should be established during the second step.

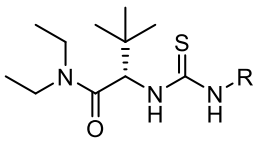
3.1.1. First screening of catalysts

My work started with a catalyst screening process. Every test conducted is showed in **Table1**. A complete conversion was achieved with all catalysts tested, even if accompanied by different enantioselectivities. Before studying in detail thiourea catalysts **4**, two hydrogen bond donors belonging to a different catalyst class were tested: chiral phosphoric acids **CPA-1** and **CPA-2**, which however did not seem to be able to control the stereoselectivity. A racemic mixture of both diastereoisomers was obtained in the reaction with these catalysts (entries 1 and 2). Moving back to Jacobsen-type thioureas **4**, catalysts bearing different groups on the amidic or thioureidic moieties were then tested, in order to analyze the influence of steric and electronic effects on the enantiomeric excess. Compared to the standard **4a**, which gave ca. 70% ee (see Aim of the Project) catalysts **4g** and **4h** with different amide groups did not show significant changes in stereoselectivity (entries 3,4): **4h** seemed to slightly decrease the enantiomeric excess value, perhaps due to its steric bulk, while **4g** gave the same results as **4a**. Consequently, different substituents on the thioureidic nitrogen were tested: catalysts with an aryl group seemed to function better than the ones with an alkyl chain (entries 5-9). As shown in Table1, thioureas **4c** and **4d** lowered the enantioselectivity to 55% and 60% respectively for the major diasteoisomer and 50% for the minor one. Between the four different aromatic groups employed, the 4-trifluoromethylphenyl (**4b**) appeared to be the best one, even when compared to the standard 3,5-bistrifluoromethylphenyl substituted catalyst **4a**. At the end, a reaction with 40% mol of catalyst was conducted, demonstrating that increasing in the catalyst loading did not seem to improve the enantioselectivity (entry 10Table1).

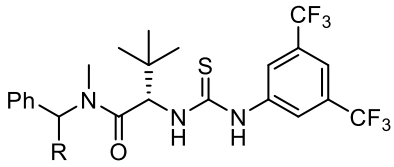
Table1: first screening of catalyst



CPA-1: Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$
CPA-2: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$



4a: R = 3,5-(CF$_3$)$_2$C$_6$H$_3$
4b: R = 4-CF$_3$C$_6$H$_4$
4c: R = 3,5-(CF$_3$)$_2$C$_6$H$_3$CH$_2$-
4d: R = CF$_3$CH$_2$-
4e: R = 4-FC$_6$H$_4$
4f: R = 4-NO$_2$C$_6$H$_4$



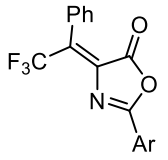
4g: R = H
4h: R = Ph

ENTRY	Cat.	Mol%cat.	t (h)	ee-5a[c]maj	ee-5a[c]min	ee-6a[c]maj	ee-6a[c]min
1[a]	**CPA-1**	10	66	Rac	rac	-	-
2[a]	**CPA-2**	10	42	Nd	rac	-	-
3[a]	**4g**	20	60	70	70	-	-
4[a]	**4h**	20	60	65	60	-	-
5[a]	**4c**	20	60	55	50	-	-
6[a]	**4d**	20	60	60	50	-	-
7[b]	**4b**	20	60	-	-	78	74
8[b]	**4e**	20	60	-	-	64	60
9[b]	**4f**	20	60	-	-	72	71
10[b]	**4a**	40	60	-	-	Nd	72

[a] **1a** 0,05 mmol, **2a** 0,075 mmol, catalyst (20 mol%), CH_2Cl_2 200 µL, -30 °C, then 4-methoxyaniline 0,05 mmol, rt; [b]**1a** 0,05 mmol, **2a** 0,075 mmol, catalyst (20 mol%), CH_2Cl_2 200 µL, -30 °C, then allylic alcohol 0,1 mmol, Et_3N 0,05 mmol, rt;[c] Determined by chiral HPLC analysis.

3.1.2. Synthesis of azlactones 1

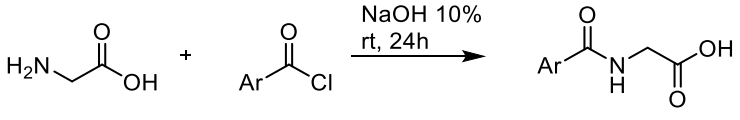
After the first screening of catalysts, three azlactones **1b-d** with different aryl groups on the C3 were synthesized, in order to investigate the influence of diverse chemical structures on the catalytic reaction (Figure 20). Synthesis of these type of azlactones had not been reported in literature yet.



1b: Ar= 4-$CH_3OC_6H_4$
1c: Ar= 1-naphtyl
1d: Ar= 4-BrC_6H_4

Figure 20: azlactones

The first step is the acylation of glycine **7** with the benzoyl chlorides **8,** to obtain the corresponding N-benzoylglycines **9** (Figure 21). Initially, this step was conducted following the procedure reported by Shinde et al in 2012[12], but after 24 hours we observed the presence of both product **9** and a benzoic acid by-product, derived from the hydrolysis of benzoyl chloride **8**. Some modifications were undertaken, in order to reduce the presence of this by-product. Lowering the equivalents of **8** used in the reaction and its portionwise addition led to more pure crude sample, but small amounts of benzoic acid were still present. This low chemoselectivity was a problem, since we were not able to separate the product from the contaminant. Nevertheless, the second step was not influenced by the presence of the benzoic acid, therefore the crude first-step mixture was directly used in the next step.



7 **8b-d** **9b-d**

Figure 21: first step of azlactones synthesis

The second reaction involves the condensation of *N*-benzoylglycines **9** and 2,2,2-trifluoroacetophenone **10** (Figure 22); sodium acetate is used as a base and acetic anhydride as solvent and activator. The process starts with an intramolecular cyclization of glycines **9**, in which acetic anhydride activates the oxygen of the acidic moiety (mixed anhydride). Then, addition of the nucleophilic oxygen of the carbonyl of the amide

moiety occurs on the activated mixed anhydride. Intermediate **9'** is thus obtained, and it is subsequently deprotonated by sodium acetate to give the relative enolate. Finally, an aldol condensation between this enolate and 2,2,2,-trifluoroacetophenone **10** produces azlactones **1**. Both the diastereoisomers (*E* and *Z* isomers of the newly formed double bond) were observed in the crude, with a variable prevalence in the Z-isomers; therefore, purification methods were needed to obtain pure product **1**, since the presence of a minor diastereoisomer would likely influence the final value of enantiomeric excess.

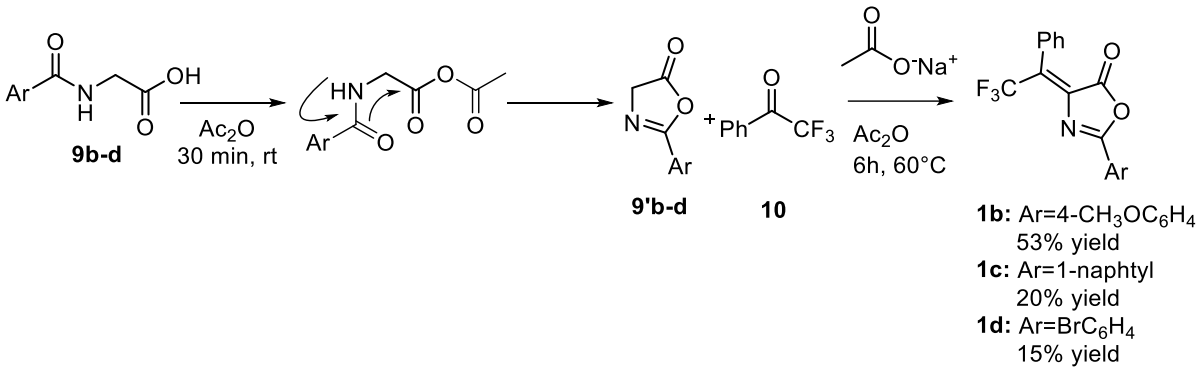


Figure 22: second step of the azlactones synthesis

Despite of the little difference in the chemical structure of the synthetizedazlactones **1**, very different physical properties were observed. Consequently, each one needed a different purification protocol. Azlactone **1b** was crystallized from a mixture of dichloromethane and *n*-hexane, and it was obtained pure as *Z*-isomer in 53% yield over the two steps; on the contrary **1c** appeared to have higher solubility in the previous dichlorometane-*n*-hexane mixture, since no precipitate was observed after the crystallization attempt. Consequently, column chromatography was performed on the crude, but **1c** resulted to be unstable over silica. Ultimately, crystallization from ether was performed, causing the minor diastereoisomers to crystallize, leaving the major one in the mother liquor, along with 2,2,2-trifluoroacetophenone **10**. After washings with cold *n*-hexane, product **1c** (as *Z*-isomer) was obtained with a 1% impurity and a yield of 20% over the two steps. It is noteworthy that **1c** has a high solubility in *n*-hexane, thus probably some of it was lost during the washings. To purify **1d**, a column chromatography was performed first, in order to remove some impurities present in the crude; after that, the diastereomeric mixture obtained was subjected to crystallization from *n*-hexane at -18°C, from which the major Z-diastereoisomers crystallized out. In order to confirm the hypothesized *Z* configuration of the azlactone carbon double bond,

X-ray analysis was performed on an azlactone **1b** crystal (Figure 23). Probably, the *Z* configured isomer is more stable than the *E* one for steric reasons. However, it cannot be excluded that the *Z* configuration is more stable due to the electric dipole minimization since the highly electronegative oxygen and fluorine atoms are placed in opposite positions.

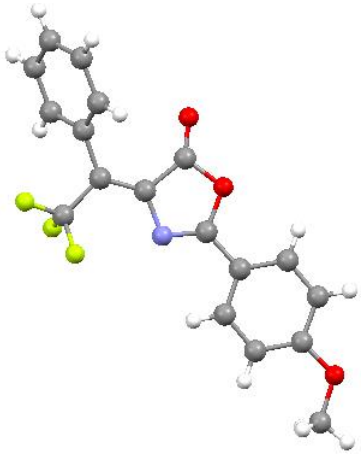
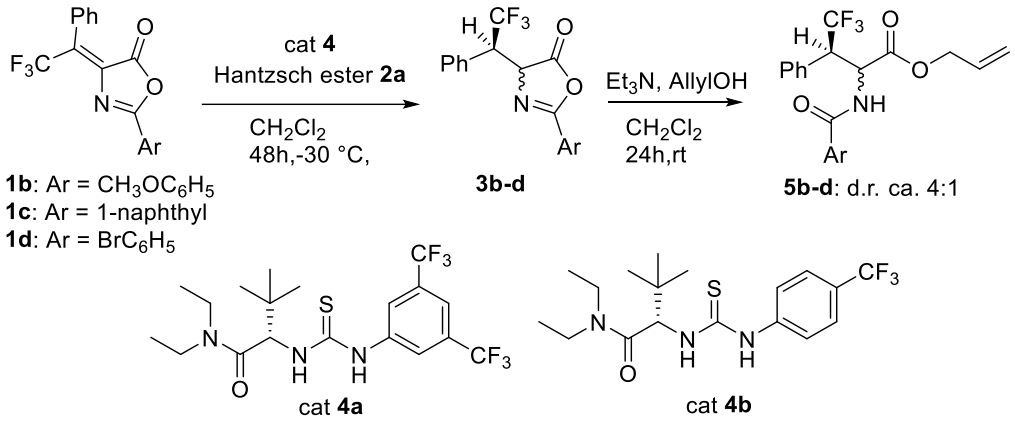


Figure 23: X-ray structure of azlactone **1b**

3.1.3. Screening of azlactones 1b-d

The azlactones **1b-d** previously synthetizedwere tested in the enantioselective reduction, to analyze the effect of the different structures on the enantiomeric excess (Table 2). Fortunately, the products **5b-d** obtained after ring-opening with allylic alcohol were much more UV-active than the previous **5a**, thus facilitating the HPLC analysis. Each substrate was reacted in the presence of both catalysts **4a** and **4b** with the purpose of demonstrating the effective superiority of **4b** compared to **4a**. Indeed, each azlactone tested confirmed the hypothesis: all enantiomeric excesses obtained with **4b** were higher than the respective values obtained with **4a**. Substrate **1c** led to 72% and 63% of enantiomeric excess (entries 3,4). Comparing these results with the other substrates **1a-b** and **1d**, it can be deduced that phenyl-like substituents on C3 are better than naphthyl ones. Azlactone **1d** bearing an electron withdrawing *para* substituent on the aryl ring led to lower enantioselectivity compared to **1b** substituted with an electron rich aryl group (compare entries 5,6 with 1,2). An enantiomeric excess of 75% for the major diastereoisomer and 73% for the minor was obtained with substrate **1d**. While, pleasingly, an enantiomeric excess of 83% and 84% was obtained on the major and the minor diastereoisomer of **1b**, respectively. For this reason any subsequent screening will be conducted with **1b** as the substrate.

Table 2: screening of azlactones



ENTRY[a]	1	T	Cat.	Conv%[b]	Ee-5[c]maj	Ee-5[c]min
1	**1b**	60h	**4a**	>95	70	72
2	**1b**	80h	**4b**	92	83	84
3	**1c**	60h	**4a**	>95	65	51
4	**1c**	60h	**4b**	>95	72	63
5	**1d**	60h	**4a**	>95	63	67
6	**1d**	60h	**4b**	>95	75	73

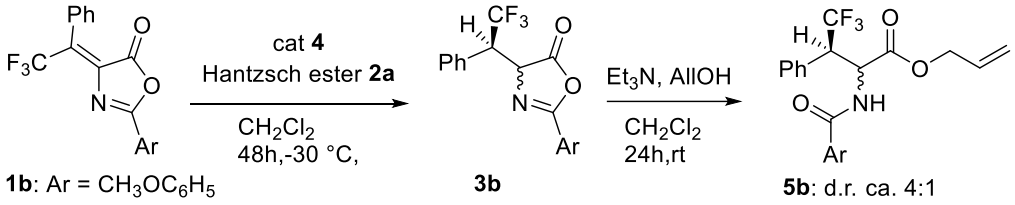
[a] General method: **1** 0,05 mmol, **2a** 0,075 mmol, catalyst **4** 0,02 mmol,CH_2Cl_2 200 μL, -30°C, then allylic alcohol 0,1 mmol, Et_3N 0,05 mmol, rt; [b] Determined on crude by ^{19} F-NMR analysis; [c] Determined by chiral HPLC analysis after chromatographic column.

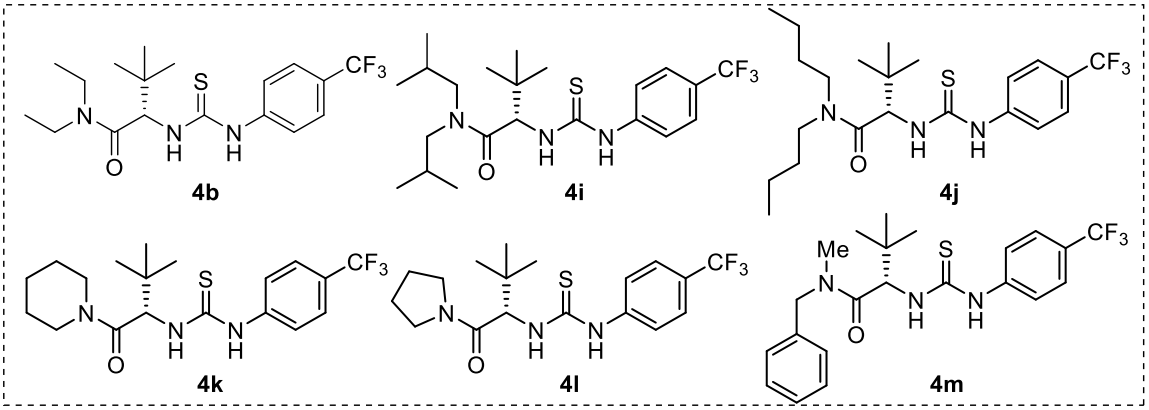
3.1.4. Second screening of catalysts

After the promising results obtained with catalyst **4b** and substrate **1b**, a new screening of catalysts was conducted: five new Jacobsen-type thioureas **4i-m** bearing the optimal 4-trifluoromethylphenyl group on thioureidic nitrogen but different amides were synthetized and tested in the enantioselective reduction of **1b**.

Catalyst **4i** proved to be worse compared to the other catalysts tested (Table 3, entry 1). This could be due to its higher steric bulk, impairing the achievement of a proper coordination with both azlactone **1b** and Hantzsch ester **2a**. Also **4j** and **4k** were less performing than **4b**, achieving an enantiomeric excess of 78% and 76%, respectively. As expected, isosterically hindered **4l** and **4b** led to almost the same value of enantiomeric excess (entries 5 and 1). Finally, thiourea **4m** proved to be the best in terms of enantioselection, leading to a satisfactory enantiomeric excess of 85% for both diastereoisomers. This catalyst was thus selected for the following screenings.

Table 3: second screening of catalyst





ENTRY[a]	Cat	ee_{mag} %[b]	ee_{min} %[b]	X_a %[c]
1	**4b**	83	84	> 95
2	**4i**	70	70	> 95
3	**4j**	78	78	> 95
4	**4k**	75	76	> 95
5	**4l**	78	80	> 95
6	**4m**	85	85	> 95

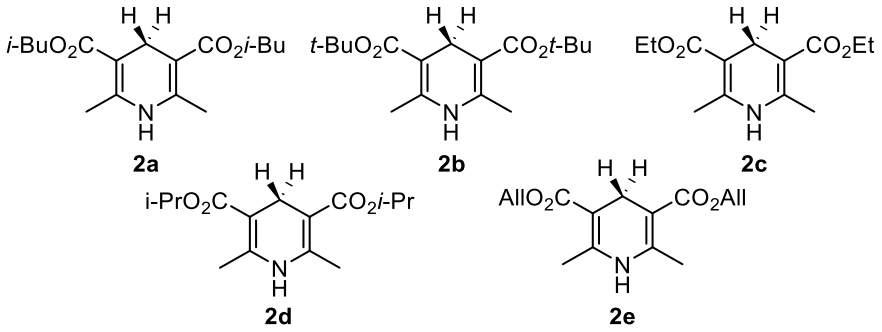
[a] General method: 1b 0,05 mmol, 2a 0,075 mmol, catalyst 4 0,02 mmol,CH_2Cl_2 200 µL, 48h, -30°C, then allylic alcohol 0,1 mmol, Et_3N 0,05 mmol, 18h, rt. [b] enantiomeric excess determined by chiral HPLC analysis after chromatographic column.[c] Conversion determined by ^{19}F NMR spectroscopy on the crude.

3.1.5. Screening of Hantzsch esters

To complete the optimization of the first step, a screening of different Hantzsch esters was performed (Table 4). Reactions with **2c**, **2d** and **2e** proceeded slower than the one with the standard hydride donor **2a**: after 48 hours conversions were still low. One equivalent of Hantzsch ester was then added in each of them, in order to increase the kinetics of the reductions. Moreover, the reactions were brought to room temperature and run at this temperature for 24 hours. However, conversions were not still complete: reaching values of 66%, 83%, and 50% for **2c**, **2d** and **2e** respectively (entries 3,4 and 5). Unfortunately, the enantiomeric excess values obtained were not improved. More in detail, Hantzsch ester **2e** proved to be the worst giving 69% of enantiomeric excess for both diastereoisomers. For the hydride donor **2d**, 80% of enantiomeric excess was reached; this value could possibly be improved carrying the reaction at -30°C for the

entire time, but the really slow kinetics would not allow the reaction to reach an acceptable value of conversion. For the these reasons, no further test was run and the Hantzsch ester **2a** was kept as the optimal hydride donor (entry 1).

Table 4: screening of Hantzsch ester



Prova[1]	**Hantzsch ester 2**	**ee$_{mag}$ %**[2]	**ee$_{min}$ %**[2]	**X$_a$%**[3]
1	**2a**	85	85	> 95
2	**2b**	70	70	> 95
3[4]	**2c**	70	73	66
4[4]	**2d**	80	80	83
5[4]	**2e**	69	69	50

[a]General method: **1b** 0,05 mmol, **2** 0,075 mmol, catalyst **4m** 0,02 mmol,CH_2Cl_2 200 μL, 48h, -30°C,then allylic alcohol 0,1 mmol, Et_3N 0,05 mmol, 18h, RT.; [2] Enantiomeric excess determined by chiral HPLC analysis after chromatographic column; [3] Conversion determined by ^{19}F-NMR analysis on the crude; [4] After 48h reaction was carried at room temperature and it was run at that temperature for 24h.

Summarizing, under the optimized conditions, we were able to obtain a mixture of diastereoisomers **3b** with 85% of enantiomeric excess, determined on the more stable products **5b**, as shown in Figure 24.

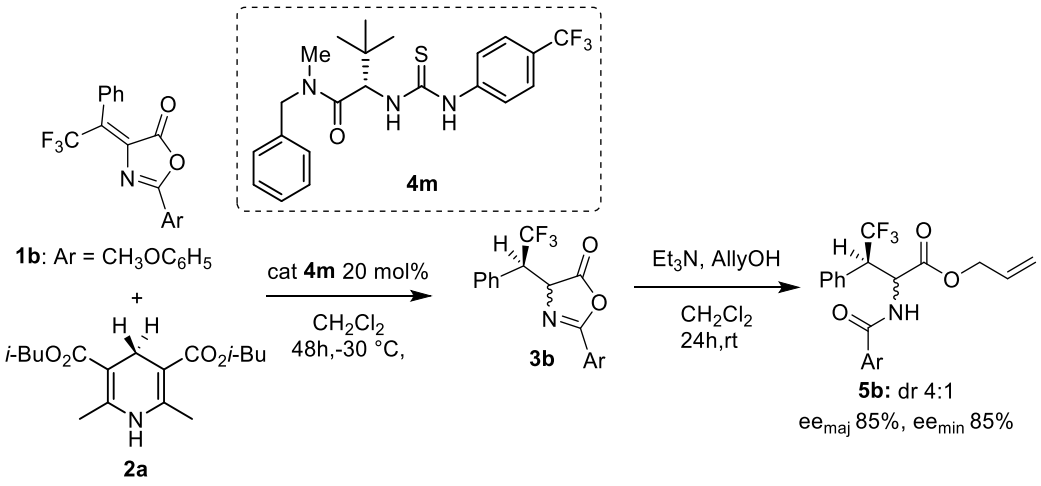


Figure 24: optimized conditions for the first step

Building upon previous determined conformations and mode of action of Jacobsen-type thioureas[8], it is possible to propose a transition state model involving the coordination of catalyst **4m** to both the azlactone **3b** and Hantzsch ester **2a** (Figure 25). In this ordered transition state, the thiourea moiety coordinates the carbonyl oxygen, stabilizing the negative charge at the azlactone group, while the amide oxygen of the catalyst coordinates the N-H of the Hantzsch ester, stabilizing its positive charge.

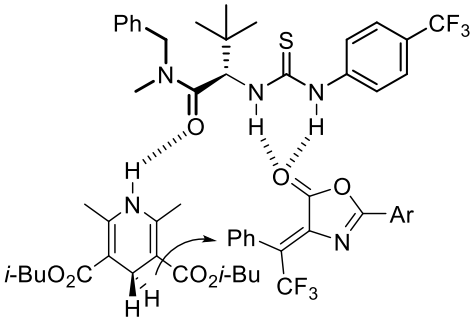


Figure 25: transition state model

Based on this model it could be tentatively hypothesized the absolute configuration of the newly formed benzylic stereocentre (β) in the major enantiomers of **3b** (Figure 26). This model assumes that the hydride was added selectively to the prochiral *(Si)* face of azlactone **1b**, leading to the *(R)* absolute configuration of the benzylic stereocentre. On the contrary, the absolute configuration of the newly formed α-amido stereocentre (α) was not controlled in this reaction.

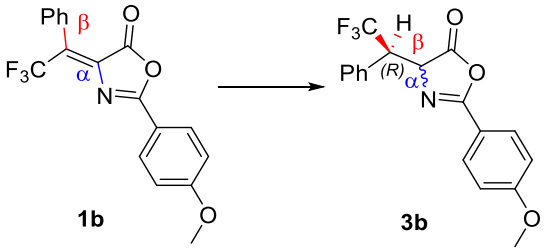


Figure 26: stereochemistry of newly formed chiral centre

3.2. Optimization of the second step

In the second period of my thesis I worked on the optimization of the second step, in order to produce selectively the *syn* or the *anti* diastereoisomer of the β,β-disubstituted N,O-diprotected α-aminoacid **5b**. The selected route involves a dynamic kinetic resolution of azlactone **3b**, in which a nucleophile is added to the carbonylic moiety of the ring. In the last decade, dynamic kinetic resolution on azlactones has been the subject of a lot of researches; according to these best results were obtained employing squaramide-based dimeric alkaloids as catalysts and alcohols as nucleophiles[10]. From a preliminary test involving squaramide-based dimeric quinidine *ent*-**12** as a catalyst, **5b** was obtained with a 5.6:1 diastereomeric ratio, favouring the same diastereoisomer obtained as major one when an achiral promoter is used in the ring-opening reaction. Meanwhile, using squaramide-based dimeric quinine **12** as a catalyst, the opposite diastereoisomer of **5b** was obtained with a 1.5:1 diastereomeric ratio. Based on literature precedents on dynamic kinetic resolution of azlactones[10c)], the preliminary results described above, and previous deduction concerning the absolute configuration of major enantiomer derived from the first synthetic step, it could be deduced that the (*R*,*S*) *syn* diastereoisomer is the one obtained as major isomer with quinidine derived catalysts, while quinine derivatives tend to give the opposite (*R*,*R*) *anti*-isomer of **5b**. The difference in the results obtained with the two catalysts was ascribed to the tendency of substrate **5b** to give the *syn* product upon opening (substrate control). Therefore, more selectively reaction conditions were needed in order to improve the diastereodivergent synthesis. Any subsequent screenings were then be developed in order to reach acceptable value of selectivity in the *anti* diastereoisomer synthesis.

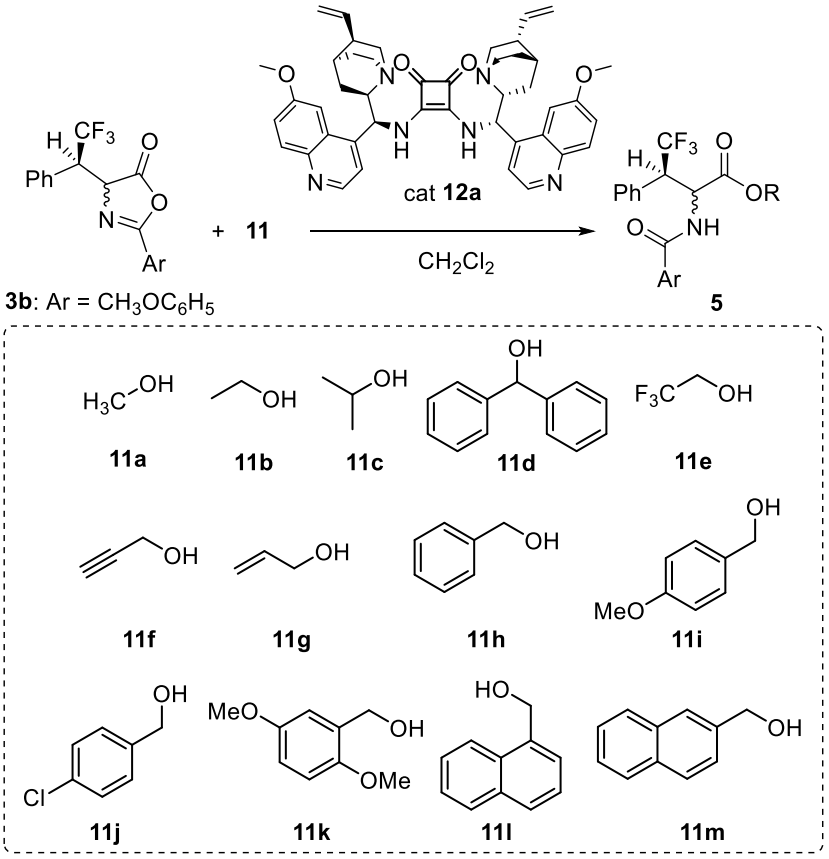
3.2.1. Screening of alcohols

Initially, a screening of some different alcohols was performed in order to verify the influence of different chemical structures on the diastereomeric ratio. The reactions were performed using enantioenriched **3b** with catalyst **12a** (Table 5). At first, methanol **11a** and ethanol **11b** were employed as nucleophiles but low diastereomeric ratios were reached with both of them (entries 1 and 2). No reaction occurred with isopropyl alcohol **11c**, this may be due to its high steric hindrance which did not let the nucleophilic addition to the carbonylic moiety of **3b** (entry 3). Even benzydrol **11d**, 2,2,2-

trifluoroethan-1-ol **11e**, and propargylic alcohol **11f** appeared to be ineffective, since after 24-30 hours of running, conversion was only 10-25% (entries 4-6).

The most promising results were achieved with the previously employed allyl alcohol **11g** and benzyl alcohol **11h** (entries 7 and 8). After 30 hours, allyl alcohol **11g** led to a 2.3:1 diastereomeric ratio with 66% conversion, while with benzyl alcohol **11h** as a nucleophile, 2.0:1 diastereomeric ratio and 91% conversion were detected after 18 hours. Allyl alcohol **11g** seemed thus to be slightly more selective than its benzyl counterpart **11h**, but with slower kinetics. Due to these results, screening of some substituted benzyl alcohol was conducted. Unfortunately, both electron rich and electron poor *para*-substituted benzyl alcohol **11i** and **11j** seemed to lower the diastereomeric ratio compared to **11h** (entries 9 and 10). On the contrary, 2-4-dimethoxybenzyl alcohol **11k** seemed to slightly improve the stereoselectivity compared to benzyl alcohol **11h,** 2.1:1 diastereomeric ratio was achieved employing **11k** as a nucleophile (entry 11). In addition, naphthyl alcohols **11l** and **11m** proved to be inefficient in stereochemistry control, leading to a 1.1:1 and a 1.5:1 diastereomeric ratio, respectively (entries 12 and 13). For the these reasons, no further alcohols were tested, and benzyl alcohol **1h** was used as a nucleophile in the subsequent screening.

Table 5: screening of alcohols



ENTRY[a]	11	T(°C)	T	X%[b]	*anti:syn*[c]
1	**11a**	0	30h	56	1.4:1
2	**11b**	0	30h	46	1.6:1
3[d]	**11c**	rt	30h	-	-
4[d]	**11d**	rt	30h	25	-
5	**11e**	0	24h	nd	Nd
6	**11f**	0	24h	19	1.2:1
7	**11g**	0	30h	66,4	2.3:1
8	**11h**	0	18h	91	2.0:1
9	**11i**	0	66h	79	1.8:1
10	**11j**	0	18h	>99	1.1:1
11	**11k**	0	18h	96	2.1:1
12	**11l**	0	18h	>99	1.5:1
13	**11m**	0	18h	>95	1.1:1

[a] General method: azlactone **3b** 0,04 mmol, alcohol 0,08 mmol, catalyst **12a** 0,004 mmol, CH_2Cl_2 160 μL; [b] Determined by ^{19}F-NMR on the crude; [c] Determined by ^{19}F-NMR after plug on silica;[d] After 18h reaction is carried out at room temperature and run at that temperature for 12h.

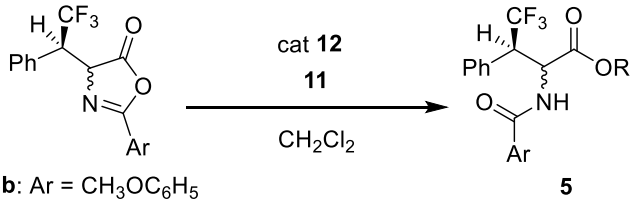
3.2.2. Screening of catalysts

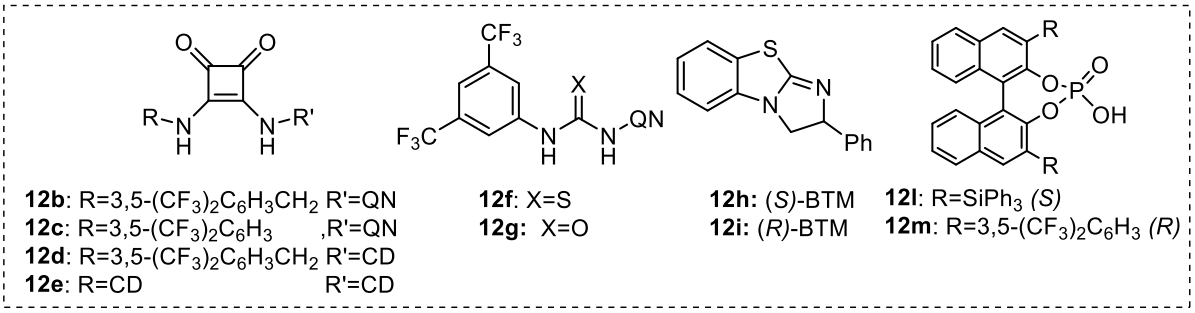
Different types of bifunctional catalysts were then tested in order to improve the diasteroselectivity of the reaction. According to previous studies, squaramide-based chincona alkaloids catalysts appeared to be the more efficient in stereochemistry control. Therefore, some of them were at first tested in the screening (**Errore. L'autoriferimento non è valido per un segnalibro.**). Employing the N-aryl substituted **12c** no inversion of stereoselectivity occurred (entry 2). On the contrary, using N-benzyl substituted **12b** and **12d** as a catalysts 2.4:1 diastereomeric ratio was reached, showing that the same result could be obtained using quinine (QN) or cinchonidine (CD) derived catalysts (entries 1 and 3). At last, squaramide-based dimeric cinchonidine (CD) **12e** was tested as a catalyst. Unfortunately, no improvement in stereoselectivity was obtained, since 1.71:1 diastereomeric ratio was detected (entry 4). Then, the stereoselectivity of thiourea-based **12f** and urea-based **12g** catalysts was investigated, but they did not appear to induce high stereoselectivity, since 1:1 and 1.3:1 diastereomeric ratios were obtained, respectively (entries 5 and 6).

In order to verify if some better results could be achieved, some completely different bifunctional catalysts, that have proved sometimes useful for the dynamic kinetic resolution of azlactones, were screened. Unfortunately, in all cases no good results were obtained. More in detail, both the enantiomers of tetramisole were tested, since it was not known which of them can promote the stereoselectivity in favour of the *anti* diastereoisomer. Unfortunately, after 18 hours of reaction conversions resulted below

20% (entries 7 and 8). Moreover, neither (*S*)-tetramisole **12h** nor (*R*)-tetramisole **12i** appeared to be efficient on the diastereoselectivity. (*R*)-tetramisole **12i** produced only the *syn* diastereoisomer of **5**, while 1:2.8 diastereomeric ratio were reached in the reaction involving *(S)*-tetramisole **12h.** According to these latter results, it could be deduced that *(S)* enantiomer could promote the *anti* diastereoisomer. Since Birman et al. in 2009[13] reported an efficient dynamic kinetics resolution of azlactones employing tetramisole **12h** as a catalyst and benzhydrol **11d** as a nucleophile, one reaction was performed under these conditions. Unfortunately, a 5% conversion was detected after 24 hours (entry 9). For this reasons, no further experiments were developed employing tetramisoles as catalysts.

Table 6: screening of catalysts





ENTRY[a]	Cat 12	11	T(°C)	T	Cat%	X%[b]	*anti:syn*[c]
1	**12b**	**11h**	0	18h	10	>99	2.4:1
2	**12c**	**11h**	0	18h	10	>95	1:2.0
3	**12d**	**11h**	0	18h	10	91	2.4:1
4	**12e**	**11h**	0	24h	10	>99	1.8:1
5	**12f**	**11h**	0	18h	10	>95	1:1
6	**12g**	**11h**	0	24h	10	>95	1.3:1
7	**12h**	**11h**	Rt	18h	10	22	1:2.8
8	**12i**	**11h**	Rt	18h	10	16,9	Only*syn*
9	**12h**	**11d**	Rt	24h	10	<5	--
10	**12l**	**11f**	Rt	24h	5	40	1:6.0
11	**12m**	**11f**	Rt	24h	5	>99	1:4.7

[a] General method: azlactone **3b** 0,04 mmol, alcohol **11** 0,08 mmol, CH_2Cl_2 160 µL; [b] Determined by ^{19}F-NMR on the crude; [c] Determined by ^{19}F-NMR after plug on silica.

To complete the screening the catalytic activity and stereoselectivity of chiral phosphoric acids were investigated. In line with literature[14], the (*S*) enantiomer of this type of catalyst could be the right one to obtain selectively the *anti*-diastereoisomer. Therefore, at first the selectivity of catalyst **12l** was analyzed. After 24 hours 40% conversion and 1:6 diastereomeric ratio in favour of *syn* diastereoisomers were detected by ^{19}F-NMR analysis on the crude sample (entry 10). The (*R*) chiral phosphoric acid **12m** gave similar results, since 1:4.7 diastereomeric ratio has been obtained with it (entry 11). Anyway, due to these unpromising results, no further experiments were run with chiral phosphoric acids as catalysts and alcohols as nucleophiles. Ultimately, squaramide-based monomeric chincona alkaloid catalysts **12b** and **12e** were selected for subsequent screening employing alcohols as nucleophiles.

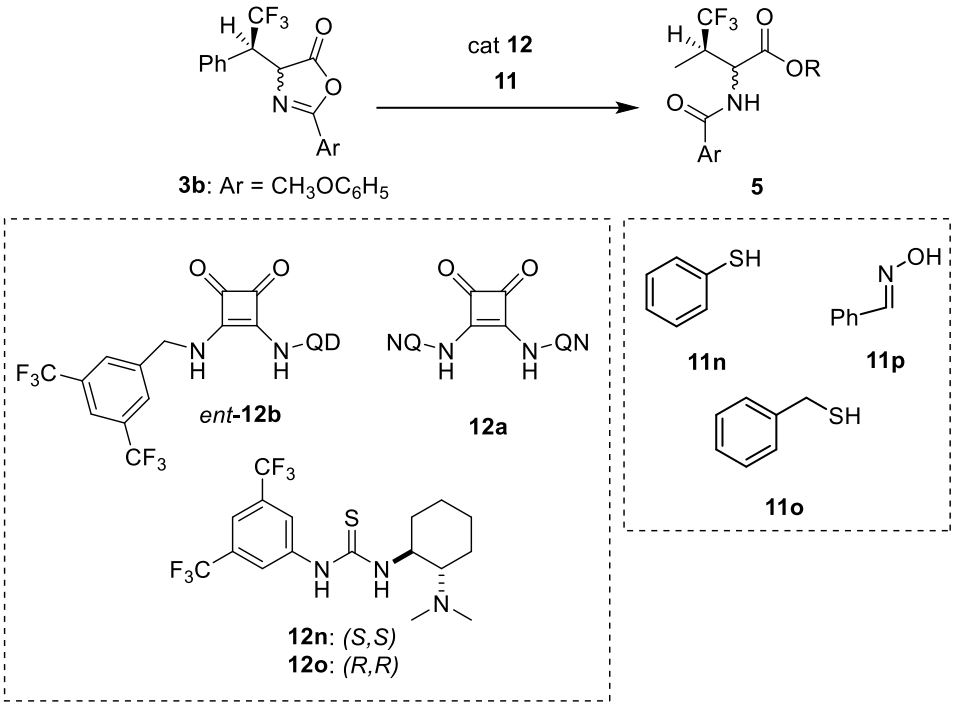
3.2.3. Screening of different nucleophiles

Recently, it has been proved that the use of thiols[15] and oximes[16] as nucleophile could be used in the dynamic kinetic resolution reactions of a range of azlactones using the proper catalyst. Even if the catalysts that were reported as optimal for these reactions were not available, we decided to preliminary test thiophenol **11n,** benzylthiol **11o** and *(E)*-benzaldehyde oxime **11p** as nucleophiles in our reaction with available catalyst structures (Table 7). Initially, reactions with an achiral promoter (Et_3N) were run in order to determine which diastereoisomer was favored by the substrate itself. As expected, even with these nucleophiles, formation of the *syn* diastereoisomer appeared favored compared to its *anti* counterpart. Reactions involving thiophenol **11n** and benzylthiol **11o** produced the diastereomeric mixture with 1:2.0 and 1:1.8 diastereomeric ratio, respectively (entries 1 and 2). Instead, with (*E*)-benzaldehyde oxime **11p** as nucleophile, 1:2.2 diastereomeric ratio was obtained (entry 3).

Asymmetric conditions were then applied with these nucleophiles using an enantioenriched sample of substrate **3b**. With thiols as nucleophiles, squaramide-based catalysts **12a** and *ent*-**12b** appeared not to control stereoselectivity, since the resulted diastereomeric ratio were similar to the ones achieved employing Et_3N as basic promoter (entry 4,5 and 7). Instead, the same catalyst with oxime **11p** seemed to improve the selectivity in favor of the *syn*-diastereoisomer, since 1:3.0 diastereomeric ratio was detected on the crude sample (entry 6). Based on this, a reaction using squaramide-based quinidine *ent*-**12b** as catalyst was conducted. Unfortunately, even with this catalyst no inversion on stereoselectivity occurred (entry 8). Finally, two more reactions employing

thiophenol **11n** as nucleophile and Takemoto thioureas **12n** and *ent*-**12n** as catalysts were performed, but even under this conditions an inversion of diasteroselectivity was not achieved (entry 9 and 10). No more experiments were run with thiols or oximes as a nucleophiles, and the attention was set back to alcohols.

Table 7: screening of some different conditions



ENTRY[a]	Cat	11	Solvente	T(°C)	T	*anti:syn*[b]
1	Et_3N	**11n**	CH_2Cl_2	rt	18h	1:2.0
2	Et_3N	**11o**	CH_2Cl_2	rt	18h	1:1.8
3	Et_3N	**11p**	CH_2Cl_2	rt	18h	1:2.2
4	**12a**	**11o**	CH_2Cl_2	rt	60h	1:1.9
5	**12a**	**11n**	CH_2Cl_2	0	60h	1:2.3
6	**12a**	**11p**	CH_2Cl_2	0	24h	1:3.0
7	***ent*-12b**	**11n**	CH_2Cl_2	rt	18h	1:2.0
8	***ent*-12b**	**11p**	CH_2Cl_2	rt	18h	1:2.7
9	**12n**	**11n**	Toluene	0	18h	1:2.0
10	***ent*-12n**	**11n**	Toluene	0	18h	1.3:1

[a] General method: azlactone **3b** 0,04 mmol, nucleophile **11** 0,08 mmol, catalyst **12** 0,004 mmol, solvent 160 μL; [b] Determined by ^{19}F-NMR after plug on silica.

3.2.4. Fine tuning of the reaction conditions

In order to established the optimized conditions for dynamic kinetic resolution of azlactone **3b** delivering selectively the *anti*-product **5b**, a final optimization has been performed (Table 8). According to previous screening, the maximum level of stereoselectivity could be achieved employing squaramide-based chincona alkaloid

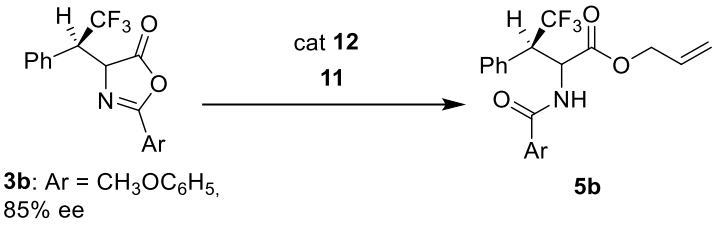
(quinine or cinchonidine) as catalysts and allylic alcohol **11g** as a nucleophile. Anyway, since some promising results were obtained even with benzyl alcohol **11h**, some experiments were performed also with this nucleophile.

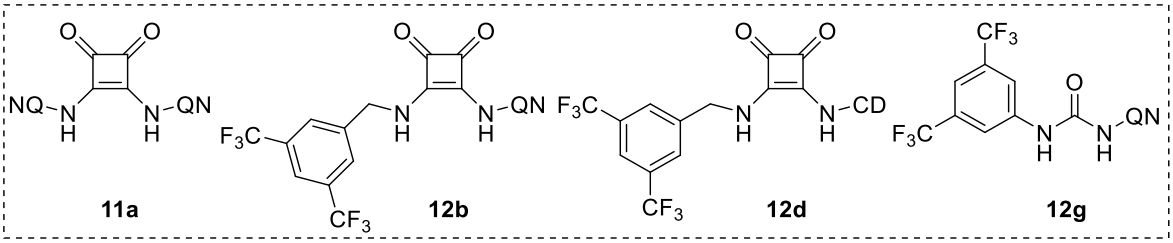
At first, toluene (instead of CH_2Cl_2) was tested as a solvent with both allylic alcohol **11g** and benzyl alcohol **11h**. In case of allylic alcohol, stereoselectivity was lowered, since 1.4:1 diastereomeric excess was detected (entry 1,Table 8). Reaction involving benzyl alcohol **11h** as a nucleophile did not led to diastereomeric ratio in favour of *anti* diastereoisomer (entry 2). Therefore, dichloromethane was kept as solvent and it was used any subsequent experiments.

The effect of temperature was then studied. The stereoselectivity could not be improved performing the reaction at -30 °C, since 1.4:1 and 1.5:1 diastereomeric ratio were obtained with benzyl alcohol **11h** and allylic alcohol **11g** , respectively (entries 3 and 4). Moreover, at that temperature catalyst **12a** showed low catalytic activity. In contrast, a 2.4:1 diastereomeric ratio was achieved performing the reaction at room temperature with allylic alchol as nucleophile and squaramide based quinine **12b** as a catalyst (entry 5). Since stereoselectivity appeared to improve increasing temperature, subsequent tests were performed at room temperature.

Finally, squaramide based chinconidine catalyst **12d** proved to be the most selective catalyst tested until now, achieving 2.7:1 diastereomeric ratio with allylic alcohol **11g** as nucleophile (entry 6). Unfortunately, reaction kinetics resulted very slow, since after 18 hours conversion was only 56%. The same catalyst **12d** used with benzyl alcohol **11h** as nucleophile reached 2.4:1 of diastereomeric ratio (entry 7). The urea derivative **12g** was also tested, but did not even revert the tendency of the substrate to give the *syn*-isomer (entry 8). Based on the obtained results, allylic alcohol **11g** and catalyst **12b** (entry 5) were considered as the optimal nucleophile-catalyst combination for the reaction.

Table 8:final screening





ENTRY[a]	Cat 12	11	Solvente	T(°C)	T	Cat%	X%[b]	*Anti:syn*[c]
1	**12b**	**11g**	Toluene	rt	18h	10	95	1.4:1
2	**12a**	**11h**	Toluene	0	24h	10	23	1:1.5
3	**12a**	**11g**	CH_2Cl_2	-30	30h	20	25	1.45:1
4	**12a**	**11h**	CH_2Cl_2	-30	30h	20	41	1.4:1
5	**12b**	**11g**	CH_2Cl_2	rt	18h	10	>99	2.4:1
6	**12d**	**11g**	CH_2Cl_2	rt	18h	10	56	2.7:1
7	**12d**	**11h**	CH_2Cl_2	rt	24h	10	>99	2.4:1
8	**12g**	**11g**	CH_2Cl_2	rt	18h	10	>99	1:6.0

[a] General method: azlactone **3b** 0,04 mmol, alcohol **11** 0,08 mmol, solvent 160 µL; [b] Determined by ^{19}F-NMR on the crude; [c] Determined by ^{19}F-NMR after plug on silica.

Finally, building upon the mode of action typically displayed by the most common hydrogen-bond-donor catalysts present in literature[17], a transition state for the dynamic kinetic resolution of the azlactone **3b** object of this work, was hypotized (Figure 27). Based on this, both squaramidic N-H bonds coordinate the carbonyl oxygen, stabilizing the negative charge on the azlactone group, meanwhile the quinuclidinic nitrogen activates the allylic alcohol.

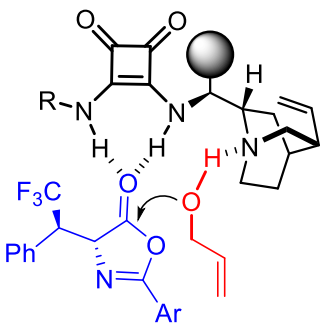


Figure 27: squaramide-based cinchona alkaloid catalysis in dynamic kinetic resolution of alzactones

This ring-opening reaction occurs preferentially on the anti-isomer of azlactone **3b**, thus leading to the preferential formation of the *anti*-isomer of **5b**.

3.3. Diastereodivergent synthesis: final results

Both *syn-anti*-relative routes were conducted under the optimized conditions on a larger scale, to isolate and characterize the products **5b** and obtain final values of diastereomeric ratio, enantiomeric excess and yield (Figure 28). First step was performed under the same conditions for both diastereoisomers: it involved azlactone **1b** as a starting material, thiourea **4m** as a catalyst, Hantzsch ester **2a** as a hydride donor and dichloromethane as a solvent. The diastereomeric mixture of azlactone **3b** was isolated by a short filtration on silica gel, and then used for the dynamic kinetic resolution. One of the two diasteromeric mixtures of **3b** was reacted with allylic alcohol in the presence of squaramide- based monomeric quinine **12b** to obtain as major product the (*R*,*R*)-stereoisomer (*anti* diastereoisomer) of **5b** in a 2.5:1 diastereomeric ratio and 93% enantiomeric excess. The second one was treated under the same conditions except that squaramide- based monomeric quinidine *ent*-**12b** was used as a catalyst. The (*R*,*S*) stereoisomer (*syn* diastereoisomer) of **5b** was obtained as major product with 6.6:1 diastereomeric ratio and 99% enantiomeric excess.

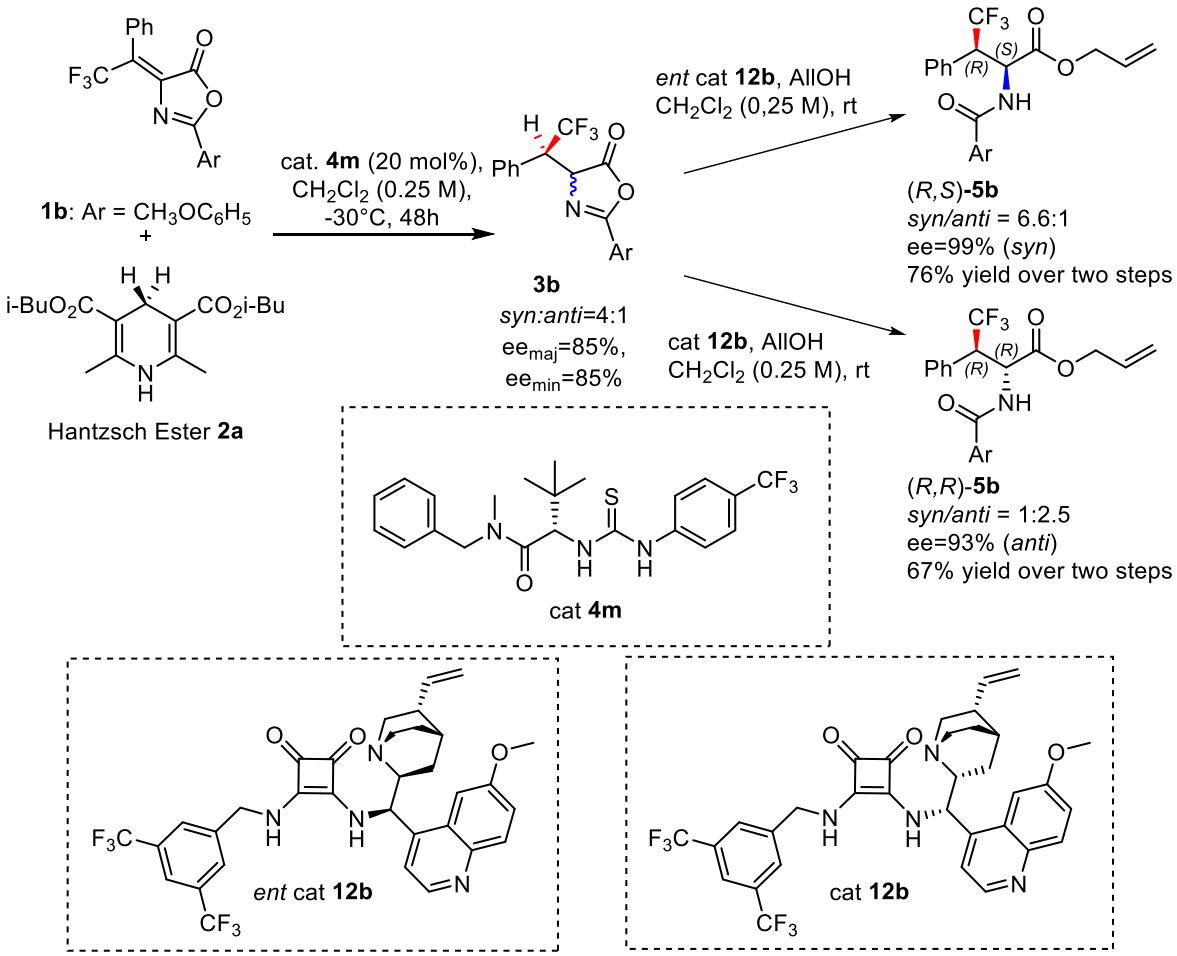


Figure 28: final optimized conditions

Two one pot synthesis were conducted to investigate the feasibility of the process. In this reaction, the dynamic kinetic resolution was developed on the reaction solution resulting from the asymmetric reduction without any treatment, by just adding the allylic alcohol **11g** and the catalyst **12b** to the mixture. After 60 hours several by-products were detected by ^{19}F-NMR spectroscopy. Therefore, unfortunately, the one pot synthesis of **5b** appears not to be feasible; further experiments should be performed in order to investigate the feasibility of the one pot process.

4. CONCLUSION AND PERSPECTIVES

At first, the asymmetric transfer hydrogenation reaction conditions (first step) were optimized in order to achieve high value of stereoselectivity. Some different arilydene azlactones **1** and thiourea catalysts **4** were synthetizedand tested in the reaction. After some screenings, arylidene azlactone **1b**, bearing 4-methoxyphenyl on the C3 of the azlactone ring, was selected as starting material. Jacobsen type thiourea **4m,** bearing 4-trifluoromethylphenyl on one of the two nitrogen of the thioureidic moiety and presenting methyl and benzyl group on the nitrogen of the amidic moiety, was chosen as most selective catalyst. After a screening of some different Hantzsch ester, **2a** was kept as hydride donor for the optimized conditions. Thus, a good control in the β-carbonylic carbon formation was achieved, since performing the reaction in dichloromethane at -30 °C for 48 hours, 85% enantiomeric excess was reached on both the diastereoisomers of **3b** (Figure 28). Then, the dynamic kinetic resolution on the azlactone **3b** was investigated in order to achieve high control on the α-carbonylic carbon stereocentre. Some different nucleophiles and catalyst were screened, then alcohols and squaramide-based cinchona alkaloids catalysts were chosen as the best nucleophile and catalyst type, respectively. Allylic alcohol **11g** was selected as best nucleophile and squaramide-based quinine **12b** and quinidine *ent*-**12b** as catalysts for the synthesis of the *syn*-diastereoisomer and the *anti*-diastereoisomer of **5b**, respectively. To summarize, employing allylic alcohol as a nucleophile and squaramide-based quinine **12b** as a catalysts, the (*R*,*S*)-**5b** product (*anti*-diastereoisomer) was achieved with 2.5:1 diastereomeric ratio and 93% enantiomeric excess. On the contrary, performing the reaction under the same conditions and involving squaramide-based quinidine *ent*-**12b** as a catalysts, the (*R*,*R*)-**5b** product (*syn*-diastereoisomer) was achieved with 6.6:1 diastereomeric ratio and 99% enantiomeric excess. The obtained diastereomeric ratio proved the stereodivergent process to be feasible with the performed route. However, diastereomeric ratios reached could be higher with more stereoselective route for the α-carbon stereocenter stabilization. Fortunately, in both the diasteroselective syntheses, complete conversion and high yield and enantiomeric excess were achieved. In the next future, different reactions for the second step will be investigate in order to improve the stereocontrol on the α-carbonylic stereocenter and to reach higher diastereomeric ratio in

both the diasteroselective synthesis. Then, arylidene azlactone with different arylic substituent on the β-carbonylic carbon will be tested for the scope of the developed synthesis.

5. MATERIAL AND METHODS

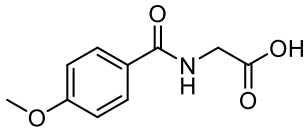
5.1. General methods and materials

^{1}H-NMR, ^{19}F-NMR and ^{13}C-NMR spectra were measured by means of Varian AS 300 and 400 spectrometers. ^{13}C-NMR specters were record using broadband decoupling. Chemical shifts were reported on ppm scale and calibrated from residual signals of deuterates solvents. (for $CDCl_3$, ^{1}H-NMR: 7.26 ppm, ^{13}C-NMR: 77.0 ppm; for DMSO-d_6, ^{1}H-NMR: 2,50 ppm). Product enantiomeric excess (ee) were detected by means of chiral stationary phase HPLC, using an UV detector operative at 254 nm. Solvents and commercially available reagents were used as received, unless otherwise stated. Chromatographic purifications were performed by means of 70-230 mesh silica. Racemic samples for the double bond reduction (first step) were performed employing 1.5 eq of Hantzsch ester in 200 μL of dicholomethane at room temperature with no catalyst.

5.2. General procedure for the synthesis of N-benzoyl glycine 9

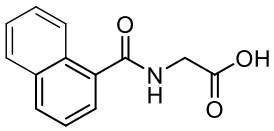
In a round bottom flask equipped with magnetic stirring bar, glycine (20 mmol, 1,597 g) is dissolved in 15 mL of 10% sodium hydroxide at room temperature. To this solution benzoyl chloride (14 mmol, 2,120 mL) is added in four portions. After 18h the solution is transferred to a conical flask with a few crush ice, then concentrated HCl is added with stirring until the mixture is acidic. The white precipitate is filtered and washed with cold water and dichlorometane. N-benzoyl glicine **9** is obtained containing amount of benzoic acid and directly used in the next step.

Synthesis of (4-methoxybenzoyl)glycine 9b



Following the above described procedure, the product was obtained with a 10% of impurities. After a water stripping by means of acetonitrile, it is used in subsequentially step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (t, J = 5.9 Hz, 1H), 7.88 – 7.82 (m, 2H), 7.09 – 6.93 (m, 2H), 3.91 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H).

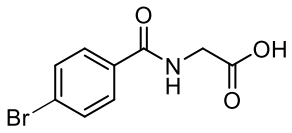
Synthesis of (1-naphthoyl) glycine 9c



Following the above described procedure, the product was obtained with a 1% of impurities. After a water stripping with acetonitrile, it is used in subsequentially step without further

purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.84 (t, J = 5.8 Hz, 1H), 8.37 – 8.23 (m, 1H), 8.18 – 7.91 (m, 2H), 7.74 – 7.40 (m, 4H), 3.98 (d, J = 6.0 Hz, 2H).

Synthesis of (4-bromobenzoyl)glycine 9d

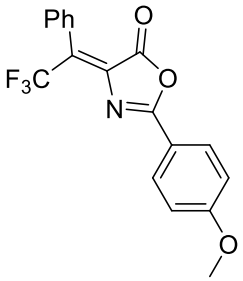


Following the above described procedure, the product was obtained with a 1% of impurities. After a water stripping by means of acetonitrile, it is used in subsequentially step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.93 (t, J = 5.9 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.76 – 7.63 (m, 2H), 3.92 (d, J = 5.9 Hz, 2H).

5.3. General procedure for the synthesis of azlactone 1

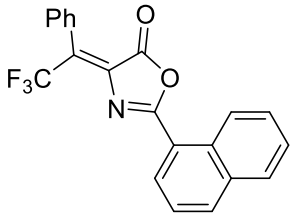
In a round bottom flask equipped with magnetic stirring bar, N-benzoyl glycine **9** (5 mmol, 1,046 g) and sodium acetate (5 mmol, 410,2 mg) are dissolved in 3 mL of acetic anidride at room temperature with stirring. After 30 minutes 2,2,2-trifluoroacetophenone (5 mmol, 0,702 mL) is added. The reaction is carried out at 60°C for 6 hours and then at room temperature for 18 hours. The solution is diluted with water and dichlorometane, the organic phase is washed four times with sat. $NaHCO_3$ and at the end with sat. NaCl. Then organic phase is dried with $MgSO_4$, filtered and evaporated in vacuum.

Synthesis of *(Z)*-2-(4-methoxyphenyl)-4-(2,2,2-trifluoro-1-phenylethylidene)oxazol-5(4H)-one 1b



Following the above described procedure, diastereomeric mixture of **1b** is obtained. Then, product **1b** is crystallized from a mixture of *n*-hexane and dichlorometane and it is obtained pure in 53% yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.22 – 8.06 (m, 2H), 7.64 – 7.41 (m, 3H), 7.41 – 7.30 (m, 2H), 7.09 – 6.93 (m, 2H), 3.92 (s, 3H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -59.38(s).

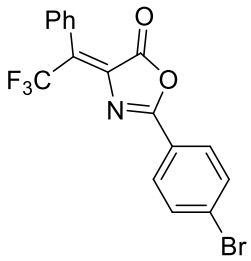
Synthesis of (Z)-2-(naphthalen-1-yl)-4-(2,2,2-trifluoro-1-phenylethylidene)oxazol-5(4H)-one 1c



Following the above described procedure, diastereomeric mixture of **1c** is obtained. Then, the crude is dissolved in a minimum amount of Et_2O. The precipitate is filtered and discarded; the organic phase is evaporate in vacuum and the

yellow solid is washed with a few amount of cold hexane. Product **1c** is obtained pure in 20% yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.55 (dd, *J* = 8.7, 0.9 Hz, 1H), 8.39 (dd, *J* = 7.5, 1.3 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.77 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.70 – 7.34 (m, 7H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -59.57(s).

Synthesis of (Z)-2-(4-bromophenyl)-4-(2,2,2-trifluoro-1-phenylethylidene)oxazol-5(4H)-one 1d



Following the above described procedure, diastereomeric mixture of **1c** is obtained. After chromatographic column (petroleum ether: *n*-hexane 5:1) the orange solid is dissolved in the minimum amount of *n*-hexane and stored up in freezer. The yellow precipitate is filtered and washed with cold hexane. Procuct **1c** is isolated in 15% yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.08 – 7.99 (m, 2H), 7.74 – 7.65 (m, 2H), 7.54 – 7.44 (m, 3H), 7.40 – 7.33 (m, 2H). ^{19}F NMR (300 MHz, Chloroform-*d*) δ -59.44 (s).

5.4. Generale procedure for catalytic asymmetric reduction of azlactone 1 to produce product 5.

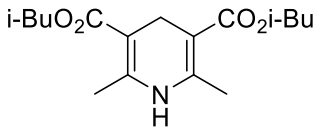
In a tube equipped with magnetic stirring bar, azlactone **1** (0,05 mmol) and catalyst **4** (0,01 mmol) are dissolved in 200 CH_2Cl_2 (200 μL). Then the mixture is carry at -30°C. Five minutes later, Hantzsch ester (0,075 mmol) is added in the tube. The reaction is run for 48h at -30°C and the conversion is controlled by means of ^{19}F-NMR. Then the mixture is carry at room temperature and Et_3N (0,05 mmol) and allylic alcohol (0,10 mmol) are added. After 18h, a column chromatography (dichlorometane) is performed on the crude. A diastereomeric mixture of **5** is isolated. Enantiomeric excess of both the diastereoisomers are detected by means of chiral stationary phase HPLC.

5.5. General procedure for dynamic kinetic resolution on azlactone 3b

In a tube equipped with magnetic stirring bar, azlactone **3b** (0,04 mmol), catalyst **12** and CH_2Cl_2 (160 μL) are added. Then, the mixture is carry at the reaction temperature and nucleophile **11** (0,08 mmol)is added in the tube. The reaction is run until complete

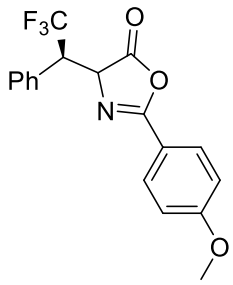
conversion is detected by ^{19}F-NMR. After that, a plug on silica is perfomed on the crude, then diastereomeric ratios are determined by means of ^{19}F-NMR.

Synthesis of diisobutyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 2a



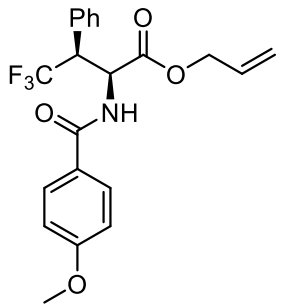
In an-oven dried round bottom flask equipped with magnetic stirring bar, isobutyl 3-oxobutanoate (60 mmol, 9,685 mg) paraformaldehyde (30 mmol, 900 mg) and $AcO^{-}NH_4^{+}$ are added sequentially. The reaction is carried out at 70°C under nitrogen atmosphere. After 30 minutes the crude is washed with ice cold water and filtered, then is recrystallized from MeOH to obtain product **2a** in 41% yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.17 (s, 1H), 3.88 (d, *J* = 6.4 Hz, 4H), 3.31 (s, 2H), 2.19 (s, 6H), 1.96 (dq, *J* = 13.3, 6.6 Hz, 2H), 0.95 (d, *J* = 6.7 Hz, 12H).

Synthesis of 2-(4-methoxyphenyl)-4-((*R*)-2,2,2-trifluoro-1-phenylethyl)oxazol-5(4H)-one 3b



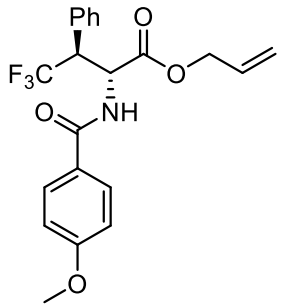
In a test tube equipped with magnetic stirring bar, ***(Z)***-2-(4-methoxyphenyl)-4-((*R*)-2,2,2-trifluoro-1-phenylethylidene)oxazol-5(4H)-one **1b** (0,05 mmol) is dissolved in 200 μL of CH_2Cl_2 . Then catalyst **4b** (0,01 mmol) is added to the solution and the mixture is placed at -30°C. Five minutes later Hantzsch esther **2a** (0,075 mmol) is added and the mixture is carry out under stirring at -30°C. After 48 hours, plug on silica is done on the crude and solvent evaporate on vacuum. Product **3b** is obtained as mixture of diastereoisomers with 85% enantiomeric excess, 4:1 diastereomeric ratio (detected after opening with allylic alcohol and Et3N) and 80% of yield. Major diastereoisomers: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.94 – 7.83 (m, 2H), 7.37 – 7.29 (m, 2H), 7.29 – 7.22 (m, 3H), 6.97 – 6.87 (m, 2H), 5.02 (d, *J* = 2.9 Hz, 1H), 4.06 (ddd, *J* = 20.4, 9.5, 2.7 Hz, 1H), 3.87 (s, 3H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -67.02 (d, *J* = 9.8 Hz). Minor diastereoisomers: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05 – 7.97 (m, 2H), 7.74 – 7.67 (m, 2H), 7.47 – 7.38 (m, 3H), 7.04 – 6.97 (m, 2H), 4.75 (d, *J* = 2.7 Hz, 1H), 4.06 (ddd, *J* = 20.4, 9.5, 2.7 Hz, 1H), 3.89 (s, 3H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -65.88 (d, *J* = 9.1 Hz).

Synthesis of (*R*,*S*)-allyl 4,4,4-trifluoro-2-(4-methoxybenzamido)-3-phenylbutanoate 5b



In a test tube equipped with magnetic stirring bar, 2-(4-methoxyphenyl)-4-(2,2,2-trifluoro-1-phenylethyl)oxazol-5(4H)-one **3b** (0,05 mmol) is dissolved in 200 μL of CH_2Cl_2 . Then catalyst *ent*-**12b** (0,005 mmol) and AllOH (0,1 mmol) are added to the solution. The reaction is carry out at room temperature for 24 hours. After chromatografic column (CH_2Cl_2) the (*R*,*S*) stereoisomer of product **5b** is obtained with 95% of yield, 6,6:1 diastereomeric ratio and 99% enantiomeric excess. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.58 (m, 2H), 7.44 – 7.30 (m, 5H), 6.94 – 6.87 (m, 2H), 6.26 (d, *J* = 9.3 Hz, 1H), 5.97 – 5.82 (m, 1H), 5.67 (q, *J* = 9.3 Hz, 1H), 5.37 – 5.26 (m, 2H), 4.64 (dq, *J* = 6.1, 1.3 Hz, 2H), 4.19 – 4.09 (m, 1H), 3.84 (s, 3H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -66.28 (d, *J* = 9.4 Hz). ^{13}C NMR (400 MHz, Chloroform-*d*) δ 169.6, 166.2, 162.6, 130.9, 130.4, 129.3, 129.1, 129.0, 128.9, 125.6 (q, *J*=280 Hz), 66.9, 55.4, 52.9, 51.5 (m) HPLC: (AD-H, n-esano/*i*-PrOH 80:20, 0,75 mL/min, λ = 254 nm) *syn*-isomer: t_{maj}^1 = 11'; t_{min}^2 = 21'; *anti*-isomer t_{anti}^1 = 14 min, t_{anti}^2 = 24 min.

Synthesis of (*R*,*R*)-allyl 4,4,4-trifluoro-2-(4-methoxybenzamido)-3-phenylbutanoate 5b



In a test tube equipped with magnetic stirring bar, 2-(4-methoxyphenyl)-4-(2,2,2-trifluoro-1-phenylethyl)oxazol-5(4H)-one **3b** (0,05 mmol) is dissolved in 200 μL of CH_2Cl_2 . Then catalyst **12** (0,005 mmol) and AllOH (0,1 mmol) are added to the solution. The reaction is carry out at room temperature for 24 hours. After chromatografic column (CH_2Cl_2) the (*R*,*R*) stereoisomer of product **5b** is obtained with 95% of yield, 2.5:1 diastereomeric ratio and 93% enantiomeric excess. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 – 7.69 (m, 2H), 7.40 – 7.29 (m, 5H), 6.94 – 6.89 (m, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 5.72 – 5.58 (m, 1H), 5.44 (dd, *J* = 9.1, 7.3 Hz, 1H), 5.22 – 5.11 (m, 2H), 4.52 – 4.39 (m, 2H),4.08 – 3.99 (m, 1H) 3.83 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.66 (d, *J* = 9.4 Hz). ^{13}C NMR (400 MHz, Chloroform-*d*) δ 169.7, 166.5, 162.6, 131.1, 130.8, 129.3, 129.0, 128.9, 128.8, 125,8 (q, *J*=281 Hz), 66.6, 64.3, 55.4, 52.9, 51.5 (m). HPLC: (AD-H, n-esano/*i*-

PrOH 80:20, 0,75 mL/min, λ = 254 nm, t_{syn}^{1} = 11'; t_{syn}^{2} = 21' t_{anti}^{1} = 14 min, t_{anti}^{2} = 24 min).

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