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# Stereodivergent synthesis of β-trifluoromethyl-α-amino acids by sequential catalytic processes

Tesi di laurea sperimentale

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ABSTRACT

In this work is presented a sequential organocatalytic process for the stereodivergent synthesis of β-trifluoromethyl-α-amino acids using Erlenmeyer azlactones as starting material. The strategy developed consist of a sequential catalytic approach, employing two catalysts that act independently to control the absolute configuration of two different stereocenters. The first step is a catalytic asymmetric hydrogen transfer of the activated double bond of the azlactone promoted by a Jacobsen type thiourea and Hantzsch ester as hydride donor. The second step involves a nucleophilic addition of an alcohol to the carbonyl moiety controlled by a chiral bifunctional catalyst typically used in the dynamic kinetic resolution of azlactones. The catalyst structure for the second synthetic step was thoroughly investigated in order to maximize the selectivity. Both product were achieved with a good diastereoselectivity and high enantioselectivity. Taking into account the obtained result was possible to set up an initial study for the feasibility of straightforward one-pot procedure. In conclusion, with this works was possible to set up a synthetic strategy for the synthesis of all four diastereoisomers starting from the set of starting material.

## SUMMARY

# 1. INTRODUCTION

## 1.1. Stereodivergence in asymmetric catalysis

In the few past decades research in asymmetric catalysis saw a remarkable development. In the case of a molecule with two or more stereogenic centers the complete control of both absolute and relative configuration become challenging. However, several systems have proven to be able to give excellent absolute and relative stereocontrol. For example, proline catalyst in direct cross-aldol reaction of aldehydes is able to control efficiently the stereochemistry approach of the reacting species, both in an absolute and relative sense (Figure 1).

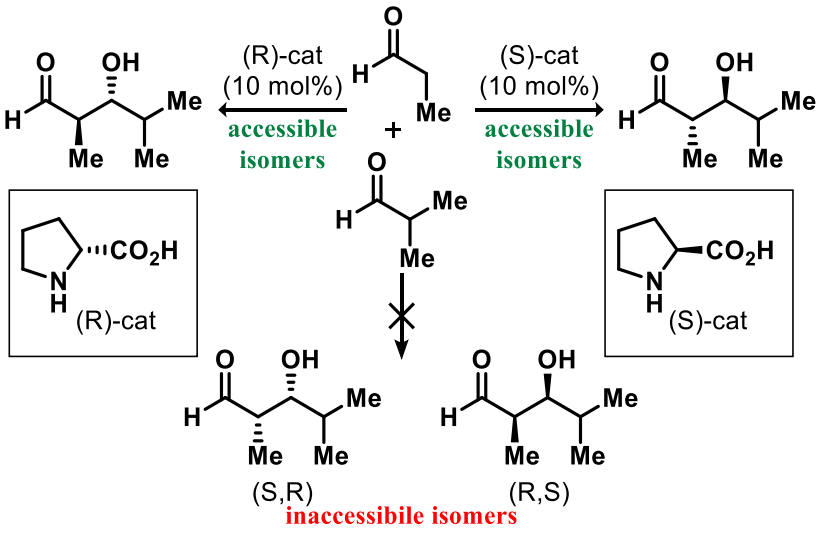



**Figure 1:Proline catalyzed direct cross-aldol reaction aldehydes**

However, as a consequence, we can be obtain only two of the four possible stereoisomers (the two enantiomers of one diastereoisomer) of a molecule with two stereogenic centers. Such limitation is not only correlated to proline-based catalysts but is rather general in stereoselctive catalysis. It is worth to note the example reported by Asaf Alimardanov et al.[1] who tried to obtain a 3-aryl-3-trifluoromethyl-2-amminopropanol-**I** planning to use an asymmetric hydrogenation of a tetrasubstituted olefin as a short and efficient synthetic pathway (Figure 2). Due to the stereospecificity of this reaction, in order to obtain the product whit required relative syn-stereochemistry is mandatory starting with the right olefin (the E-isomer **II**), which however proved not to be possible.

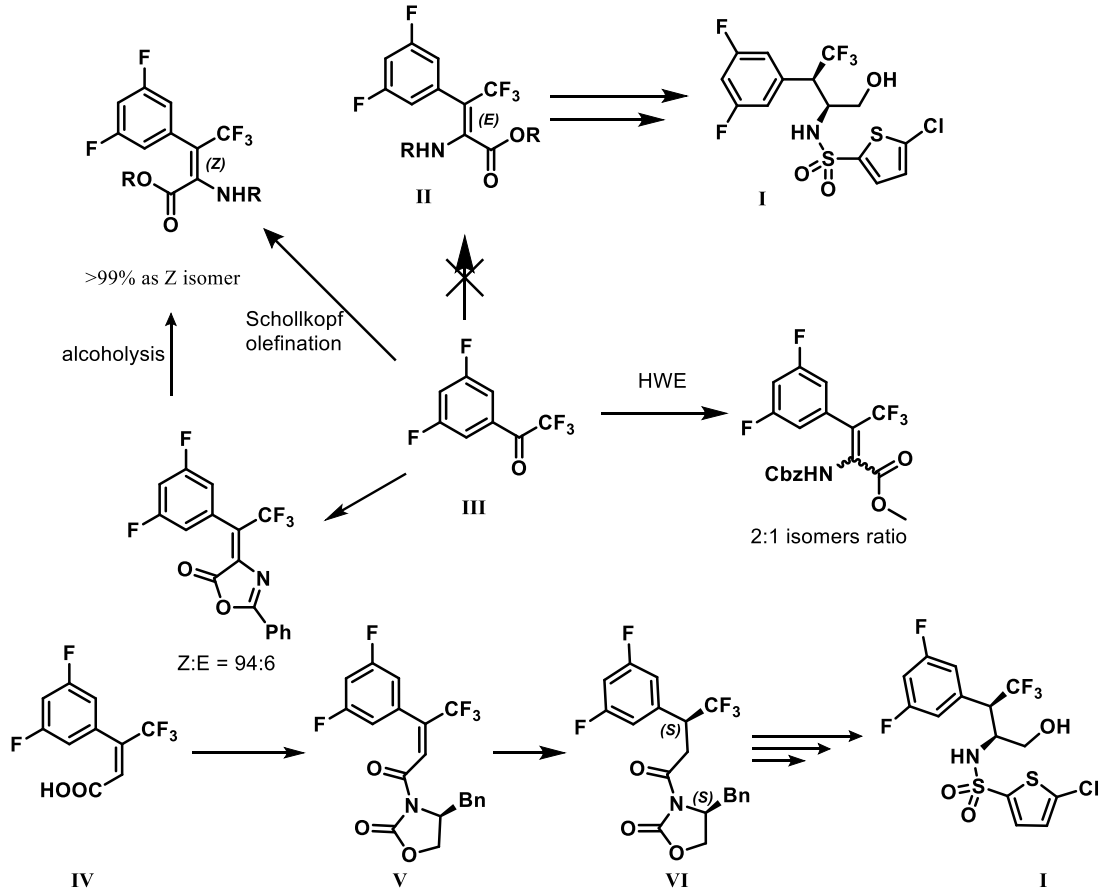



**Figure 2**

In more detail, the Schöllkopf olefination afforded only the Z-isomer (>99%) of this olefin; same results were obtained using another olefination reaction such as Horner–Wadsworth–Emmons olefination with a glycine derivative. They tried to convert the starting ketone into an Erlenmeyer azlactone that also produced the Z-isomer as major in Z:E = 96/6. Due to the stereoselectivity problem in the formation of the olefin, the authors were thus forced to operate in a different way throughout a multistep synthesis. The starting ketone **III** was converted to an ester using triethyl phosphonoacetate in a Horner-Wadsworth-Emmons olefination followed by acidic hydrolysis achieving the acidic species **IV**. This species was then converted to an oxazolidinone derivative **V**. Finally, the intermediate **VI** was obtained diastereoselectively by hydrogenation in presence of a Lewis acid ($MgBr_2$). The L.A. forced the molecule in the right conformation achieving **VI** (S,S) predominantly (95:5). At this point, the nitrogen functionality was introduced via an electrophilic amination reaction.

Problem correlated to the stereospecifity of a reaction could be frustrating and force the synthesis in more long and complex way as seen above. An approach that goes around this problem is to set up a stereodivergent synthesis. This method allows the chemist to achieve all

the possible stereoisomers for a given molecule with multiple stereogenic centers. Ideally, such process use the same set of reagents, catalysts and reaction conditions to produce all the diastereoisomers. Stereodivergence is the result of ad hoc tuning of the catalyst structure and reaction conditions. Be able to synthetize all the stereoisomers of a given molecule become a powerful instrument, for example in the preparation of a drug candidate. Nowadays, it is well known that certain drugs can interact with more than one biological target and this can lead to side effects. For that reason, is important to be in a position to modulate the structure of a drug candidate, not only for safety aspects but also for develop more effective API's (active pharmaceutical ingredients). For this kind of application the evaluation of therapeutic and toxicological properties are necessary for all the stereoisomers and is required by regulatory agencies. In order to achieve a stereodivergent strategy, there are many parameters that can be changed such as: reaction conditions, ligands and metal cations, as summarized by Carreira in his perspective[2]. An appealing and predictable route involves cascade (sequential) catalysis (Figure 3). It is carried out with the use of two or more catalysts where they act independently in control of the absolute configuration without influencing each other.

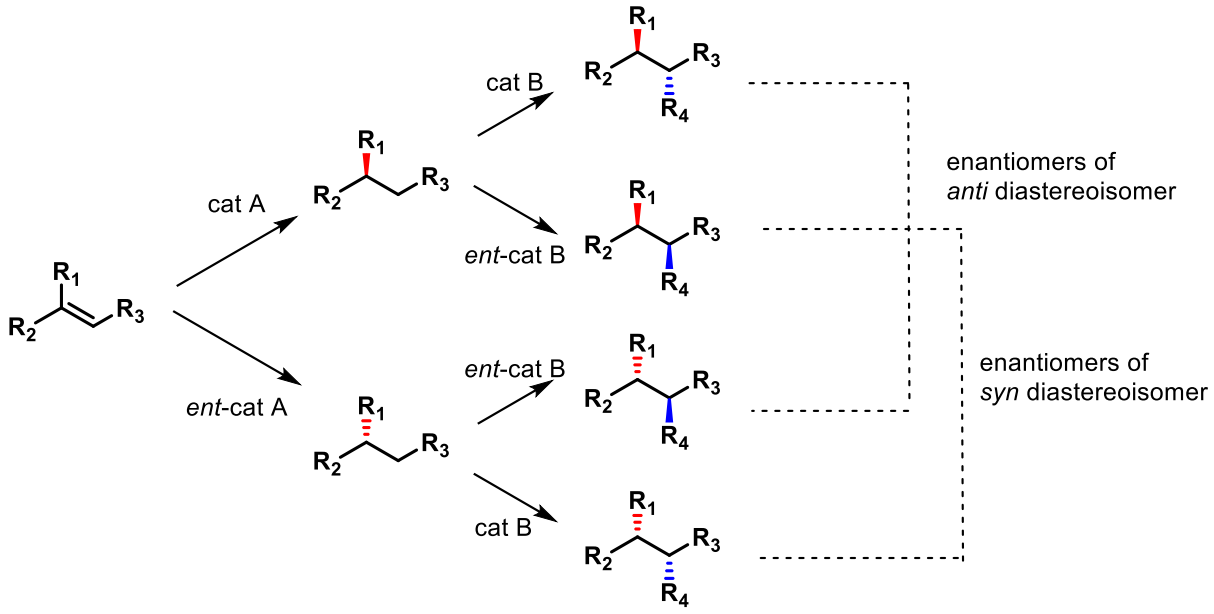



**Figure 3:Sequential stereodivergent catalysis**

A remarkable example of diasterodivergence was reported by Buchwald and co-workers[3] for the synthesis of a 1,3-amino alcohol. This example, which is based on the combination of stereodivergency based on substrate and sequential catalysis, is stunning since they achieved the creation of three contiguous stereocenters using copper/biphosphine catalyst systems (Figure 4).

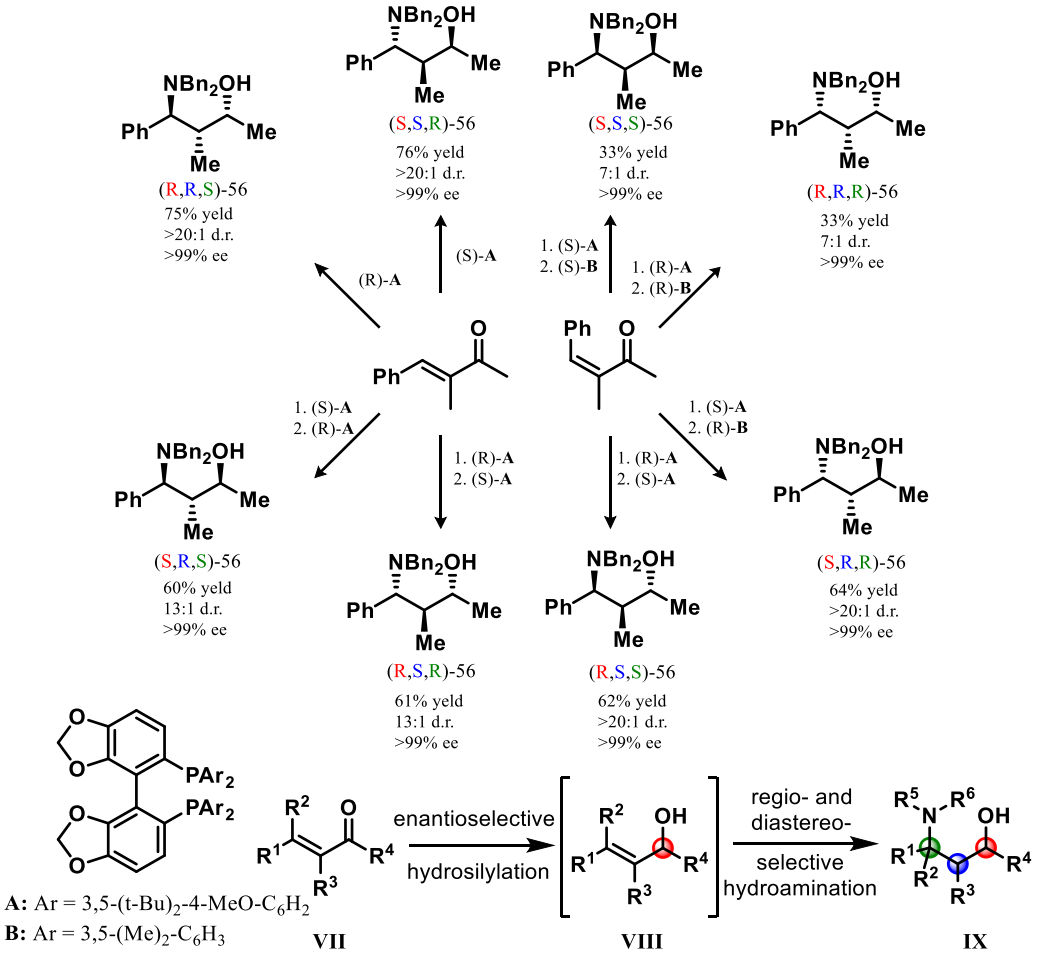



**Figure 4: Buchwald and co-workers stereodivergent synthesis**

The synthesis consists in a first step of copper-catalyzed enantioselective hydrosilylation of an α,β-unsatured carbonyl compound, with formation of an allylic alcohol **VIII** bearing the first chiral center. Once the allylic alcohol has formed, it can be isolated and used for the following hydroamination step, also performed with copper/bisphosphine catalyst system. Essentially, the two step process using copper as central active metal is guided by choice of the ligand. More in detail, changing the aryl group on phosphinic ligand and its chirality, together with the olefin geometry, allowed Buchwald et al. to completely control the three contiguous stereocenters in **IX**.

## 1.2. Erlenmeyer azlactone as precursor of β,β-disubstituted-α-amino acid derivatives

The development of a practical method for the synthesis of enantiomerically pure natural and non-natural α-amino acids is a challenge. Amino acids are widely used in synthesis of chiral ligand, catalysts, API's, peptides and many other valuable target molecules. β,β-Disubstituted-α-amino acids with two different β substituents are molecules bearing 2 chiral centers at α and β position. In order to achieve all the four possible stereoisomers we plan a stereodivergent synthesis involving a prochiral molecule. Regarding the different stereodivergent approaches, a sequential (cascade) approach could be a suitable route from arylidene azlactones (Figure 5). The first step involves a Michael addition under the stereochemical control of catalyst 1, able to control the stereochemical outcome in β position. The Michael product is then brought to the second step that involves a ring opening through alcoholysis reaction under DKR (dynamic kinetic resolution) exploiting the activity of catalyst 2 (see below).

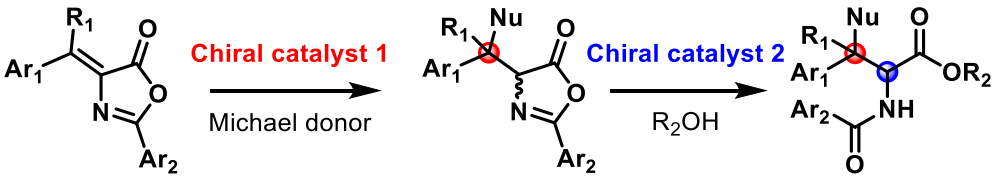



**Figure 5: streodivergent synthesis of β,β-disubstituted α-aminoacids**

The first step of the synthesis is accomplished with an asymmetric hydrogen transfer onto the double bond. The reduction can be achieved with Hantzsch ester as donor under the stereochemical control of a Jacobsen-type thiourea as chiral catalyst. Hantzsch-type esters are often use as reduction agent for electrophilic double bonds;[4,5] such activity is driven by ring aromatization after the hydride donation (Figure 6b). The approach of the Hantzsch ester on the right prochiral face of the azlactone is guided from the catalyst. The transition state is formed through hydrogen bonds between catalyst, arylidene azlactone and the Hantzsch ester where the acidic moiety of catalyst interact with the carbonyl compound and the basic with the N-H of the Hantzsch ester. This system forces the molecules in a fixed spatial conformation where only one of the two prochiral faces of the azlactone is able to undergo hydride addition (Figure 6a). Now the β-carbon is fixed in a specific configuration while the α-position cannot be controlled in this step due to the epimerization equilibria; as a consequence, two diastereoisomers are formed.

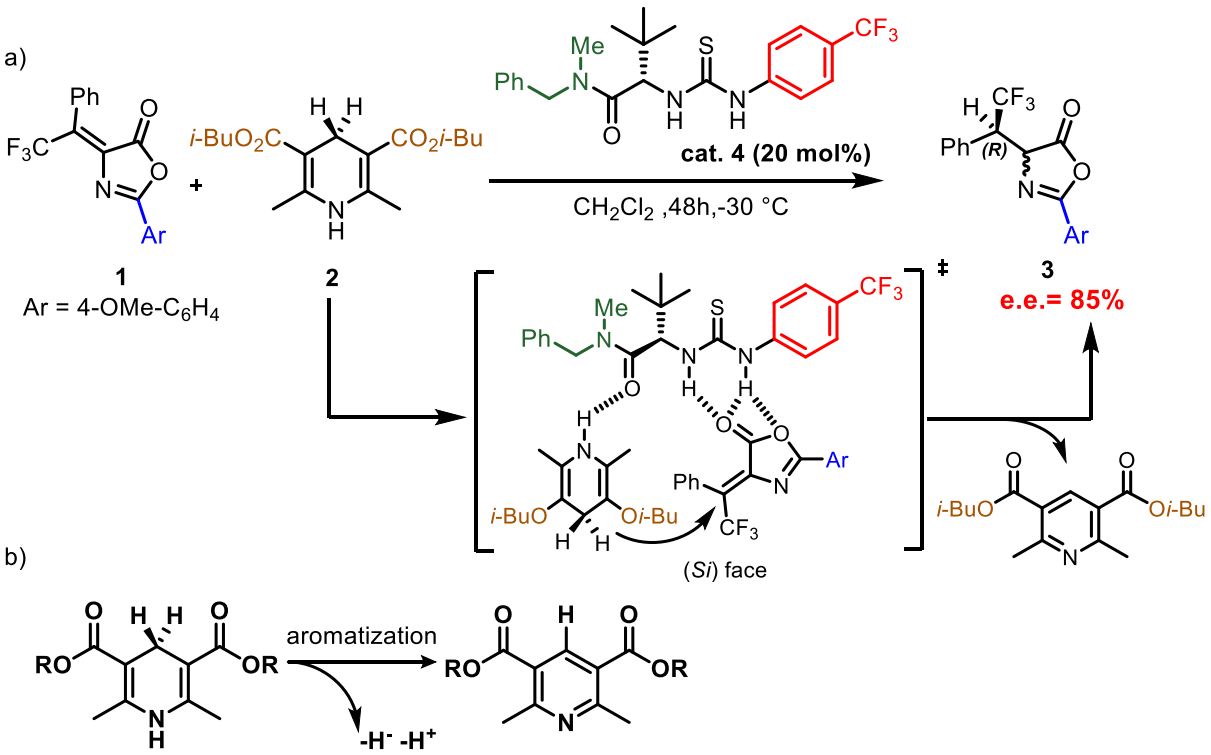



**Figure 6: a) transition state in the reaction mechanism between arylidene azlactone and Hantzsch ester; b) Hantzsch ester aromatization reaction**

As mentioned above, the second step concerns an asymmetric transformation under DKR conditions, where one of the two stereoisomers (in equilibrium) reacts faster than the other. Due to the presence of defined β-carbon chiral center, that was previously fixed, the ring opening can lead to the formation of two stereoisomers. The right selection of catalyst allow to obtain one of them as major diastereoisomer.

Azlactone can easily undergo under dynamic kinetic resolution, due to the acidity of the α-carbonyl proton ($pK_a$ 9) which is caused by the aromatic character of the corresponding tautomer as shown in the Figure 7a. Thanks to this easy racemization, DKR of azlactone is well known in literature. For example, Berkessel and co-worker showed the preparation of amino acids from the alcoholysis reaction of azlactone under DKR condition using a bifunctional organocatalyst[6].

In order to achieve a high value of enrichment the epimerization equilibrium has to be faster than the rate of the asymmetric transformation ($k_{rac} > k_1$, $k_2$; Figure 7b). In this way, it is feasible to convert the racemic mixture in the desired diastereoisomer, virtually in 100% yield. The reaction occurs with a nucleophilic addition of an alcohol to the carbonyl moiety, in the presence of a bifunctional catalyst. The catalysis in this step works in same way as the first, the hydrogen bond donor of the catalyst coordinates the carbonyl group activating the

azlactone, while the basic moiety activates the nucleophile. Besides, the basic catalyst can promote the racemization at the α-carbonyl center.

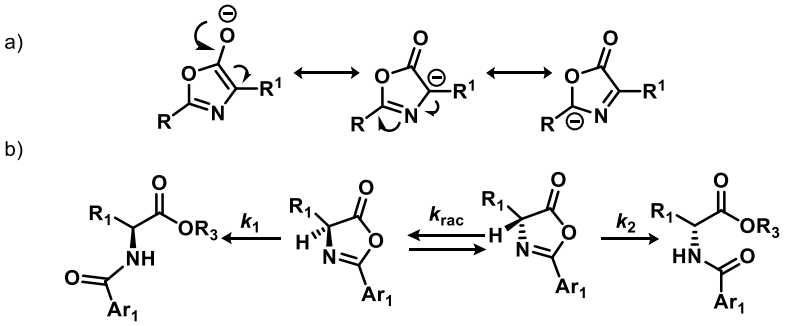



**Figure 7: a) aromatic tautomer of azlactone; b) Dynamic kinetic resolution of azlactone**

Song and co-workers[7] reported squaramide-based cinchona alkaloids as the most selective catalysts in dynamic kinetic resolution of azlactone in alcoholysis reaction; they found that dimeric catalysts were slightly better than more common benzyl substituted ones for this application (Figure 8a).

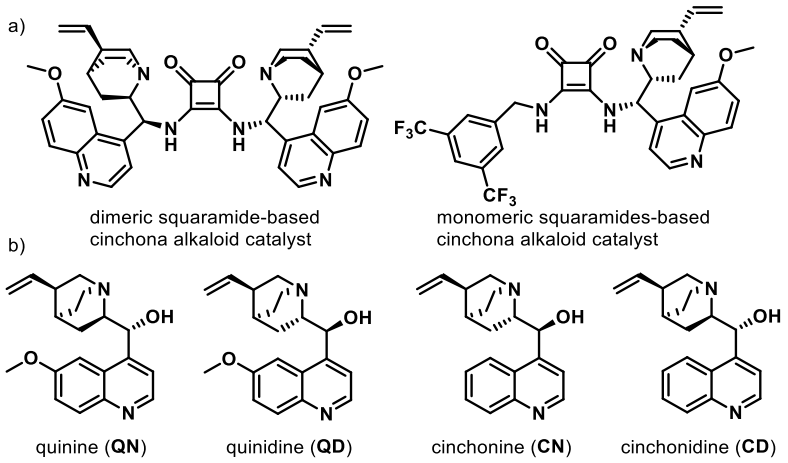



**Figure 8: a) squaramides-based cinchona alkaloids catalyst; b) Cinchona alkaloids**

Cinchona alkaloids are a class of natural compounds obtained from a plant called Cinchona. These compounds exist in two couples of *pseudo*-enantiomers (Figure 8b): quinine (**QN**)-quinidine (**QD**) and cinchonidine (**CD**)-cinchonine (**CN**). These natural product are not fully enantiomers since only two out of five chiral centers have an opposite configuration; nevertheless, they behave as enantiomers. Cinchona alkaloids are bifunctional organocatalysts and they can be transformed in different structures such as squaramide catalysts. In this type of catalysts the basic moiety is located on the quinuclidine (tertiary amine). The acidic part is represented by squaramide that acts as an efficient hydrogen bond donor.

## 2. AIM AND OBJECTIVES

At the beginning of my internship, the project was already under investigation (Figure 9). The best conditions for the first step were found to involve a Jacobsen type thiourea (20 mol%) as chiral catalyst, the Hantzsch Ester **HE** with *iso*butoxy substituents (1.5 equiv.) as hydride donor, at a temperature of -30° C in $CH_2Cl_2$ as solvent. The azlactone with *p*-metoxyphenyl group at the 2-position seemed to be the best starting material to work with. Under these reaction conditions, this protocol afforded the reduced product with 85% enantiomeric excess in both diastereoisomers, measured upon ring-opening reaction (in an achiral fashion employing triethylamine as base) since it was not possible to isolate the intermediate due to its instability.

Starting from these results regarding the first step, in order prepare two stereoisomers of the target compounds **5** from **3**, the use of dynamic kinetic resolution (DKR) was planned. In literature, several examples of enantioselective alcoholysis reactions under DKR for azlactones involving bifunctional catalysts are reported. A remarkable result was achieved from Song and co-workers using dimeric squaramide-based cinchona alkaloids. Bis-HQD-SQA catalyst was able to guide the resolution toward the R-isomer with 91 % ee, while the corresponding S-isomer was selectively obtained in 96 % ee employing Bis-HQN-SQA. Taking into account the results obtained for the intermediate **3**, and these catalysts as suitable candidates for the dynamic kinetic resolution, it seemed to be possible to setting up a stereodivergent synthesis.

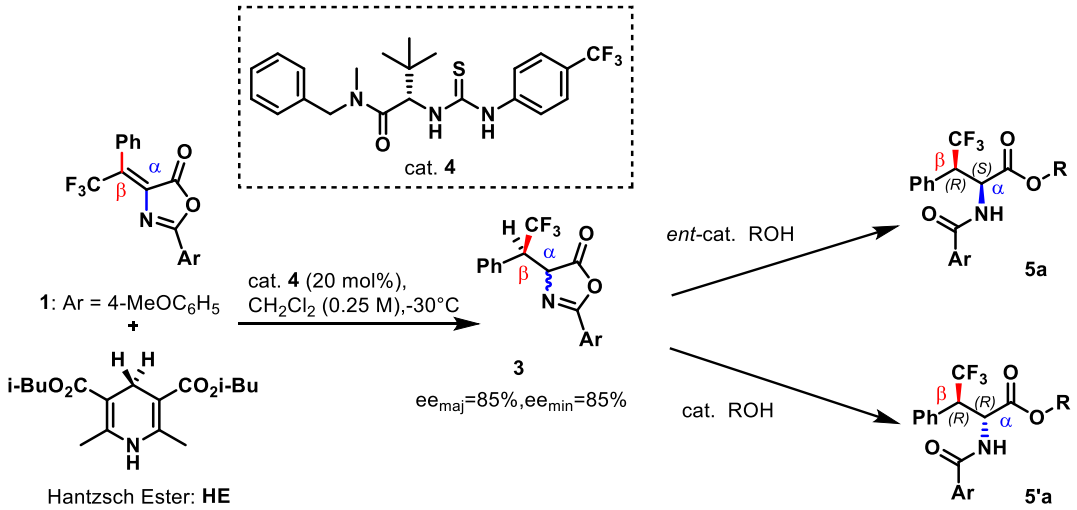



**Figure 9**

Setting the aforementioned results as starting point, objectives of the present work are:

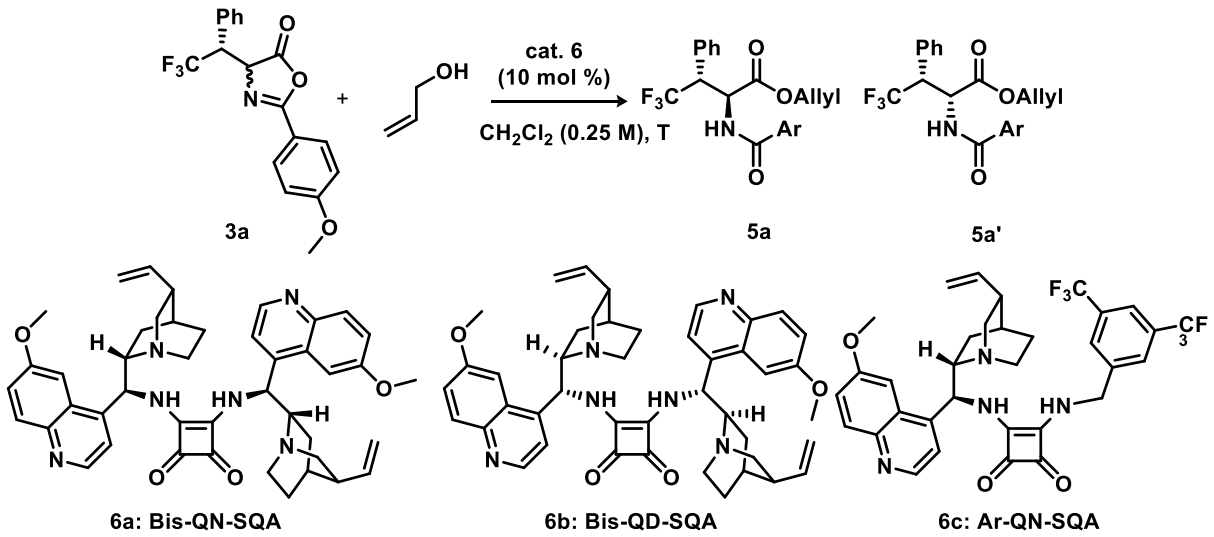
- A thorough optimization of the reaction conditions for the dynamic kinetic resolution, with a particular focus on the catalyst design, in order to obtain higher value of selectivity;
- A preliminary study of the influence of different aryl groups at the β-position of substrate **1** during the alcoholysis step;
- The development of a straightforward one-pot procedure thus skipping the troublesome purification and isolation of intermediate **3**.

## 3. RESULTS AND DISCUSSION

### 3 Optimization of the second synthetic step

During this decade, dynamic kinetic resolution of azlactones has been widely studied. For this reason, since the first period of my internship I have tried to increase the diastereoselectivity based on precedent results and literature data. Setting as starting point the results obtained by Song and co-workers, I have studied the influence of squaramide-based dimeric cinchona alkaloid in DKR with allyl alcohol as nucleophile on my own azlactone in order to investigate the diastereoselectivity. Taking into account the natural bias of the substrate in the ring-opening reaction (5.7:1 dr towards the syn diastereoisomer **5'a**), a lot of effort was expected to be required in order to maximize the selectivity.

**Table 1: First screening of catalyst**




| ENTRY | Cat. | T (° C) | t (h) | X % [e] | *anti:syn*[d] | *ee %* |
|---|---|---|---|---|---|---|
| 1 | 6a | 0 | 30 | 66,4 | 2.3:1 | > 95 |
| 2 | 6b | 0 | 24 | 70 | 1:10 | 90 |
| 3 | 6c | 0 | 18 | > 99 | 2.4:1 | 93 |

[a]General method: azlactone **3a** 0,04 mmol, allyl alcohol alcohol 0,08 mmol, solvent: 160 µL; [d] Determined by $^{19}$F NMR analysis on the crude mixture; [e] Determined by $^{19}$F NMR after a short silica plug.

As shown in the

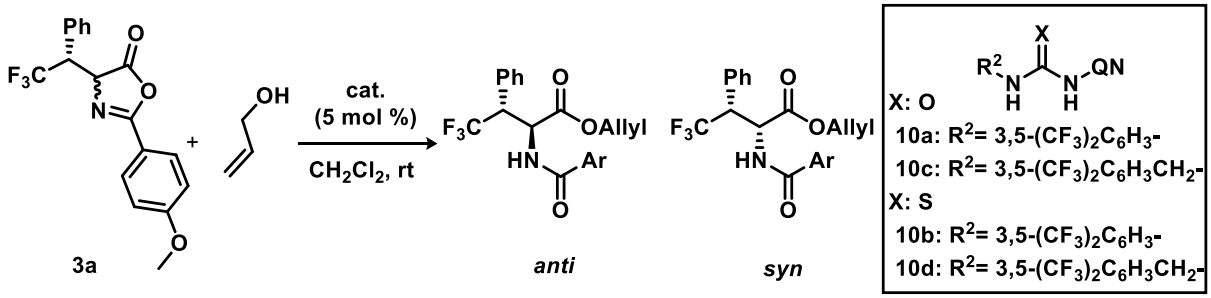
Table 1, the use of these catalysts seemed to be promising: we were able to control the absolute configuration in the newly formed stereocenter and also to obtain the major diastereoisomer with high enantiomeric excess. Paying more attention to this latter data, the enantiomeric excess increased during the transformation, going from 85 to 90 % and more. This trend is in accord with the Horeau principle; in a multistep process that involves the

formation of two (or more) chiral centers on the same molecule, each step increases the enantiomeric excess of the major diastereoisomer. From these preliminary results, it could be deduced that when a squaramide-based quinidine as catalyst is employed the reaction afforded 10:1 diastereoisomeric ratio (entry 2), therefore this catalyst promotes the alcoholysis reaction toward the same diastereoisomers (syn-**5'a**) of an achiral promoter such as triethylamine (matched case). On the other hand, the use of squaramide-based quinine **6a** is able to switch the stereoselectvity in favor of the *anti*-diastereoisomer **5a** with a 2.3:1 diastereomeric ratio (mismatched case). The lower selectivity of the *anti* diastereoisomer can be attributed to the tendency of the substrate to give the *syn* product in the ring opening reaction (substrate control). For these reasons, we focused our efforts on the synthesis of *anti* diastereoisomer **5a** aiming for better values of diastereoselectivity. From the results reported in entry 3 with catalyst **6c**, it seemed a better option to work with monomeric squaramide-based cinchona alkaloid.

### 3.1. Screening of urea/thiourea-based cataslysts

Even if the best catalyst to work with has turned out to be the monomeric squaramide-based cinchona alkaloid **6c**, in the literature there are also reported a series of urea and thiourea-based catalysts[8]. Therefore, such catalysts were tested in order to fully understand the acidic center property and confirming the literature's data. In Table 2 are reported the results, all the catalysts performed almost in same way, except for catalyst **10b** (entry 2) that shown to be the most active but with lower selectivity. After these results no more urea/thiourea catalyst have been further investigated.

**Table 2: Urea and thiourea screening**



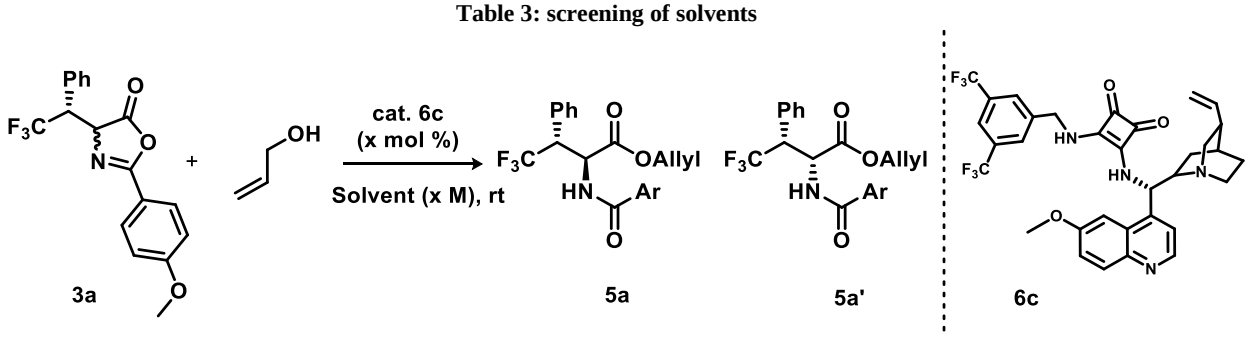

| ENTRY | Cat. | t (h) | X (%) | *anti:syn* |
|---|---|---|---|---|
| **1** | **10a** | 68 | 90 | 1.8:1 |
| **2** | **10b** | 68 | > 99 | 1.1:1 |
| **3** | **10c** | 96 | 94 | 1.5:1 |
| **4** | **10d** | 96 | > 99 | 1.6:1 |

[a]General method: azlactone **3a** 0,05 mmol, alcohol **2** 0,1 mmol, 800µL; [b] Determined by $^{19}$F NMR analysis on the crude mixture; [e] Determined by $^{19}$F NMR after a short silica plug.

### 3.1.1. Reaction conditions: screening of solvents, concentration and catalyst loading

In order to optimize the selectivity of the dynamic kinetic resolution the effect of solvent was investigated (Table 3). The best results were previously achieved with 10 mol% catalyst loading, allylic alcohol as nucleophile, $CH_2Cl_2$ as solvent and 0.25 M substrate concentration at room temperature. In these conditions the reaction performed full conversion in 16 h and 2.5:1 diastereoisomeric ratio. As you can see in Table 3 (entry 2-9), many solvents were tested, however no improvements in selectivity were observed. Even though the dicloroethane (**DCE**) showed to be a possible candidate for future experiments, dichloromethane (**DCM)** had better performances and an easier availability.

**Table 3: screening of solvents**




| ENTRY[a] | Cat. (mol%) | Solvent (M) | t (h) | X % | *anti:syn* |
|---|---|---|---|---|---|
| **1** | (10%) | $CH_2Cl_2$ (0,25) | 16 | >99 | 2.5:1 |
| **2** | (10%) | Toluene (0,25) | 16 | >99 | 1.3:1 |
| **3** | (10%) | THF (0,25) | 16 | 74 | 1.4:1 |
| **4** | (10%) | $CH_3CN$ (0,25) | 16 | 80 | 1.1:1 |
| **5** | (10%) | $ClCH_2CH_2Cl$ (0,25) | 16 | >99 | 2.0:1 |
| **6** | (10%) | Ph-$CF_3$ (0,25) | 16 | >99 | 1.14:1 |
| **7** | (10%) | EtOAc (0,25) | 16 | >99 | 1.4:1 |
| **8** | (10%) | $CH_3Cl$ (0,25) | 16 | >99 | 1.7:1 |
| **9**[b] | (10%) | $CH_2Cl_2$ (0,125) | 16 | >99 | 2.5:1 |
| **10** | (10%) | $CH_2Cl_2$ (0,06) | 16 | >99 | 2.9:1 |
| **11**[c] | (10%) | $CH_2Cl_2$ (0,5) | 16 | >99 | 2.2:1 |
| **12** | (10%) | $CCl_4$ | 24 | 50 | 1.5:1 |
| **13**[c] | (5%) | $CH_2Cl_2$ (0,06) | 17 | >99 | 2.8:1 |
| **14**[c] | (2,5%) | $CH_2Cl_2$ (0,06) | 24 | 73 | 2.1:1 |

[a]General method: azlactone **3a** 0.05 mmol, alcohol **2** 0.1 mmol, solvent: 200 µL, [b]400 µL, [c]800 µL; [d] Determined by $^{19}F$ NMR analysis on the crude mixture; [e] Determined by $^{19}F$ NMR after a short silica plug.

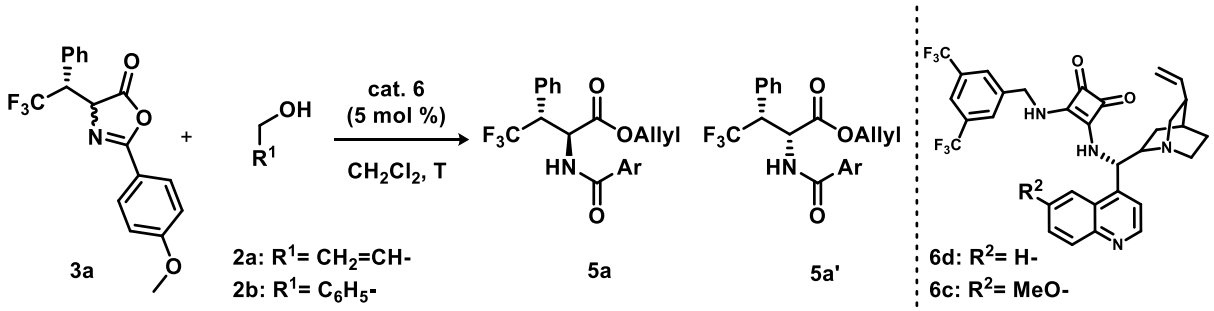
Thanks to the work of Song and co-workers, it is known that the aggregation of these catalysts is possible. Speculating on this, we diluted the catalyst in order to overcome the self-

aggregation. In Table 3 are reported the data from these observations, entry 9 shows that reducing the concentration from 0.25 M to 0.125 M with a 10 mol% as catalyst loading no improvements in selectivity were observed. Decreasing further the concentration, 0.06 M, the diastereoisomeric ratio goes from 2.5:1 to 2.9:1. In accordance with these results, a reaction in more concentrated conditions was performed (0.5 M, entry 10) affording 2.2:1 as d.r. demonstrating the beneficial effect of the dilution. As final setting for the reaction condition the catalyst loading was lowered achieving a similar performance when a 10 mol% is used (entry 13). A further reduction to 2.5 mol%, resulted in a worse selectivity (entry 14).

### 3.1.2. Reaction conditions: temperature, co-catalyst and drying agents

In this phase of the project, other several attempts were done for the purpose of increasing the diastereoselctivity towards the *anti*-stereoisomer. Even though in this part of the project the catalyst was not fully investigated, two types of catalyst **6** were used, **6c** quinine-based and catalyst **6d** based on cinchonidine, since they showed similar diastereoselectivities.

**Table 4: temeperature, cocatalyst and drying agent**




| ENTRY[a] | Alcohol | Cat. (5 mol%) | T (°C) | t (h) | X (%) [e] | *anti:syn* [d] |
|---|---|---|---|---|---|---|
| **1** | **2a** | 6d | r.t. | 16 | 73 | 3.1:1 |
| **2** | **2a** | 6d | 0 | 24 | 60 | 3.2:1 |
| **3** | **2a** | 6d | 35 | 24 | > 99 | 2.3:1 |
| **4** | **2b** | 6d | r.t. | 24 | > 99 | 2.7:1 |
| **5** | **2b** | 6d | 0 | 24 | 54 | 2.9:1 |
| **6**[c] | **2a** | 6d | r.t. | 24 | 90 | 3.0:1 |
| **7** | **2b** | 6c | 0 | 24 | 95 | 3.1:1 |
| **8** | **2b** | 6c | -30 | 140 | 52 | 2.8:1 |
| **9**[d] | **2a** | 6c | r.t. | 24 | 99 | 3.2:1 |
| **10**[e] | **2a** | 6c | r.t. | 24 | 73 | 3.0:1 |

[a]General method: azlactone **3a** 0.05 mmol, alcohol **2** 0.1 mmol, 800µL; [b] Determined by $^{19}$F NMR analysis on the crude mixture; [e] Determined by $^{19}$F NMR after a short silica plug. [c] 10 mg of $MgSO_4$. [d] 0.05 mmol of $NaHCO_3$. [e] 5 mol% of benzoic acid.

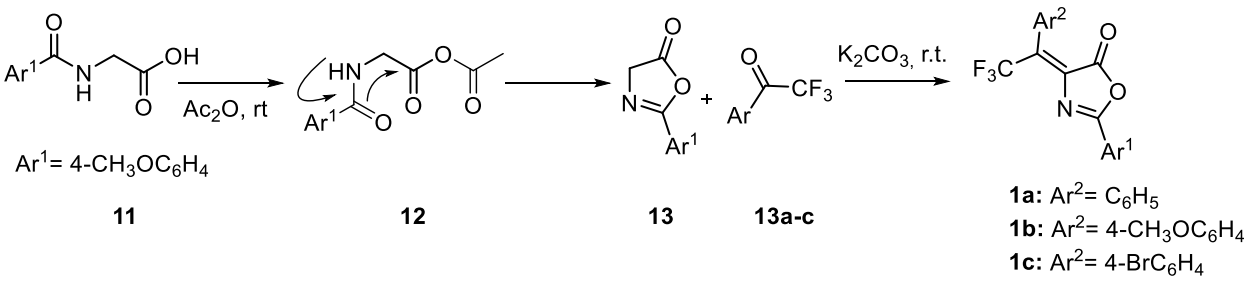
The results are shown in Table 4; employing catalyst **6d** (entry 1) the selectivity was a little bit higher with slower kinetics, probably due to the lower solubility of **6d**. Starting from this

point, we lowered the temperature to 0° C (entry 2). As result the kinetic slowed down, as expected and the selectivity remained almost the same at r.t. Working on these results we increased the temperature until 35° C; although the rate of reaction increased, the selectivity worsened (entry 3). In order to improve the selectivity and the rate of reaction, a different nucleophile such as benzyl alcohol was tested affording 2.7:1 as diastereoisomeric ratio and full conversion in 24 h (entry 4). Speculating on the negative effect of water on the hydrogen network we used 10 mg of $MgSO_4$; as result we were able to achieve a faster kinetic (entry 6), almost the same when catalyst **6c** was employed. Unfortunately, any satisfactory enhancement in selectivity were observed. Taking into account the conditions for a faster rate of reaction, **6c** as catalyst and benzyl alcohol like nucleophile, we thought to work at 0° C in order to improve the selectivity (entry 7). Comparing the two reactions at 0° C (entry 5-7), the use of the catalyst **6c** and benzyl alcohol speed up the reaction rate (X= 95% in 24 h) with a slight improvement in selectivity. Because of that, we further reduced the temperature to -30° C but the reaction rate was too low and the diastereoselectivity did not improved (entry 8). Sometimes, these type of bifunctional catalysts have been used in conjunction with co-catalyst like $NaHCO_3$ or benzoic acid. These species are employed to facilitate the catalyst regeneration and promoting an easier hydrogen transfer (entry 9-10). Employing this type of co-catalyst seemed to have a beneficial effect on the kinetics however without any improvement in selectivity.

## 3.2. Synthesis and screening of azlactones

After studying the reaction conditions to achieve a better diastereoselectivity, three azlactones were prepared with different aryl groups in beta position, in order to consider the electronic effects.

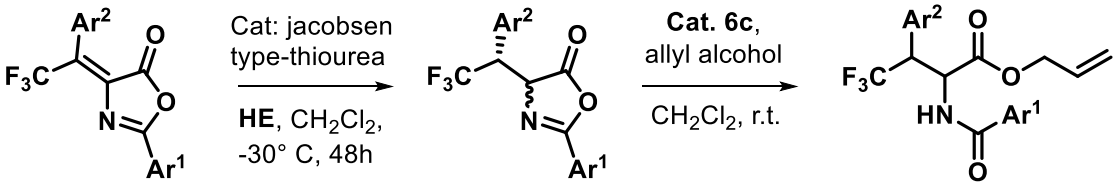
**Figure 10: General synthesis for azlactones**



The azlactones are synthesized in a two step process. In the first step N-benzoylglycine is prepared from glycine and 4-(methoxy)benzoyl chloride following a procedure reported by Asaf Alimardanof et al.[9]

The second reaction step involves the condensation of N-benzoylglycines with the appropriate 2,2,2-trifluoroacetophenone. The reaction was carried out neat with acetic anhydride as activator in presence of potassium carbonate as base. The reaction starts with an intramolecular cyclization of glycine promoted by acetic anhydride that activate the acid moiety (mixed anhydride), thus the nucleophilic addition of the carbonyl oxygen of the amide on the anhydride moiety. The cyclized intermediate is then deprotonated by the base (potassium carbonate) to give the corresponding enolate.

**Table 5: Screening on the influence of different β-aryl derivate azlactones**




$Ar^1$= 4-$CH_3OC_6H_4$
**1a:** $Ar^2$= $C_6H_5$
**1b:** $Ar^2$= 4-$CH_3OC_6H_4$
**1c:** $Ar^2$= 4-$BrC_6H_4$

| ENTRY | Substarte | t (h) First step[a] | X' (%)[b] | t (h) second step | X'' (%)[b] | *anti:syn*[c] |
|---|---|---|---|---|---|---|
| **1** | **1a** | o.w. | > 95 | 24 | > 95 | 2.9:1 |
| **2** | **1b** | o.w. | > 95 | 24 | 30 | 2.3:2 |
| **3** | **1c** | o.w. | > 95 | 24 | 45 | 2.85:1 |

[a]General method: **1** 0.1 mmol, **HE** 0.15 mmol, catalyst **4** 0.02 mmol, $CH_2Cl_2$ 400 µL, 48h, -30°C,then allylic alcohol 0.2 mmol, **6c** 0.05 mmol, o.n., RT.;[b] Conversion determined by $^{19}$F-NMR analysis on the crude, [c] Determined by $^{19}$F NMR after a short silica plug

Due the presence of 2,2,2-trifluoroacetophenone an aldol condensation occur leading to the final α,β-unsatured carbonyl compound, also known as Erlenmeyer azlactone. Analyzing the crude mixture both diastereoisomers are formed (Z and E isomers of newly formed double bond) with a prevalence of the Z isomer. It is important to purify the Z isomer from the E, since the presence of a minor diastereoisomer would affect the enantiomeric excess of the first step and overall the feasibility of the diastereodivergent synthesis. After work up, the reaction was quickly purified with column chromatography using $CH_2Cl_2$ as eluent to get rid of the impurities. The final pure Z-isomer is obtained after recrystallization from n-hexane.

The newly synthesized azlactones were then tested in the sequential stereodivergent synthesis, in order to understand the electronic effects in β-position. One substrate was prepared with electron rich aryl group, 4-$CH_3OC_6H_4$ (**1b**), and the second one with electron poor aryl group like 4-$BrC_6H_4$ (**1b**). In the reduction step with Hantzsch ester the substrate electronic diversity seems not to affect the reaction kinetics and selectivities as it can see in Table 5. In contrast, when these substrates are employed in the second reaction step they behave differently, **1c** showed higher selectivity than **1b**. Both electron rich and poor substrates gave the opened product in a less selective way compared to phenyl group, and also both substrates suffer from slower reaction rates.

### 3.3. Focussed screening of squaramides

Attempting to increase the selectivity for the *anti*-isomer, the role of for the squaramide substituent was investigated in more detail. The catalysts were synthesized following the Rawal procedure[10] as it shown in Figure 11**Errore. L'origine riferimento non è stata trovata.**. The final product is accessed from dimethyl squarate **X** via an addition-elimination reaction in presence of an amine (**XI**). In the second step the final coupling is realized among the intermediate **XII** and the alkaloids whit the formation of **XIII.** Rawal and Rambola proposed simple method for the synthesis of a variety of thiosquaramides from a common dithionated intermidiate[11] To understand the effect of this thiocarbonil compound a thiosquaramide-based catalyst **7** bearing the same substituents of **6c** we prepared. In the first two entries in Table 6 are reported the results achieved from catalyst **7**. Unfortunately thiosquaramide-based catalyst did not performed as expected, rendering a very poor selectivity with both alcohols.

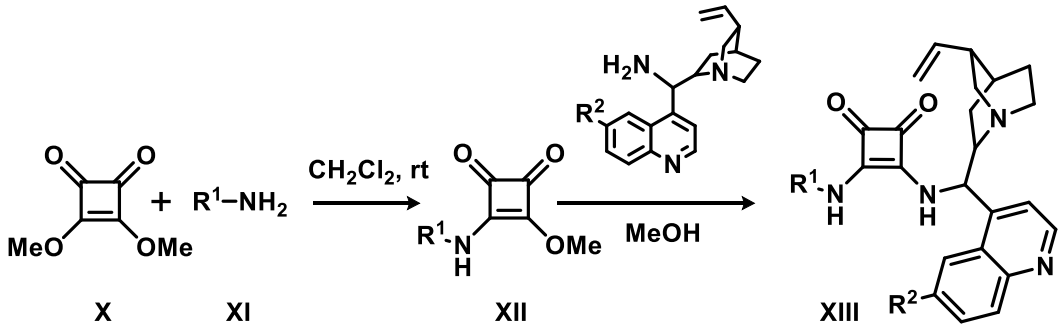
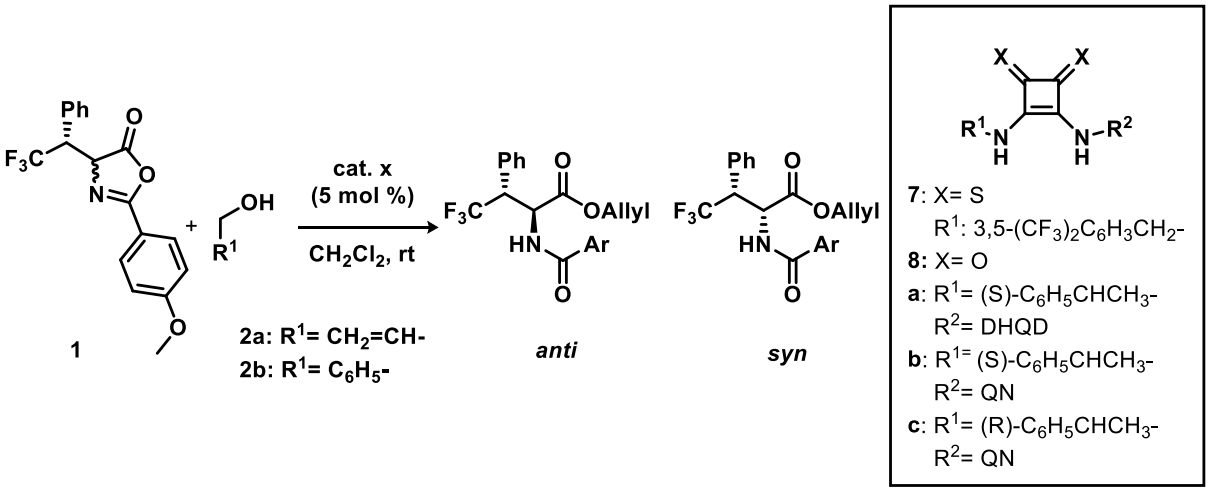



**Figure 11: Genela synthesis for squaramide-based cinchona alkaloids**

Due the availability in the laboratory of the dihydroquinidine catalyst **8a** bearing a chiral benzyl amine we tested it in the ring opening reaction, as reported in Table 6. In entries 3 and 4 is possible to see the results from these catalysts, with allylic and benzyl alcohol

respectively. Catalyst **8a** shown highest selectivity toward the *syn*-isomer **5a** also with a fast kinetics. This remarkable result can be referred to a "match case" where the catalyst and the substrate cooperate for the same product. Since quinidine moiety direct the ring-opening reaction for the *syn* product in a high selective fashion with the (S)-benzyl amine derivative, we prepared two more catalysts thinking in this way. In catalyst **8b** with quinine no improvement in selectivity was observed (entry 5). The second catalyst **8c** was prepared with the (R)-benzylamine and quinine (entry 6), that is the pseudoenantiomer of catalyst **8a**. Unfortunately, catalyst **8c** did not perform as good as expected.

**Table 6**



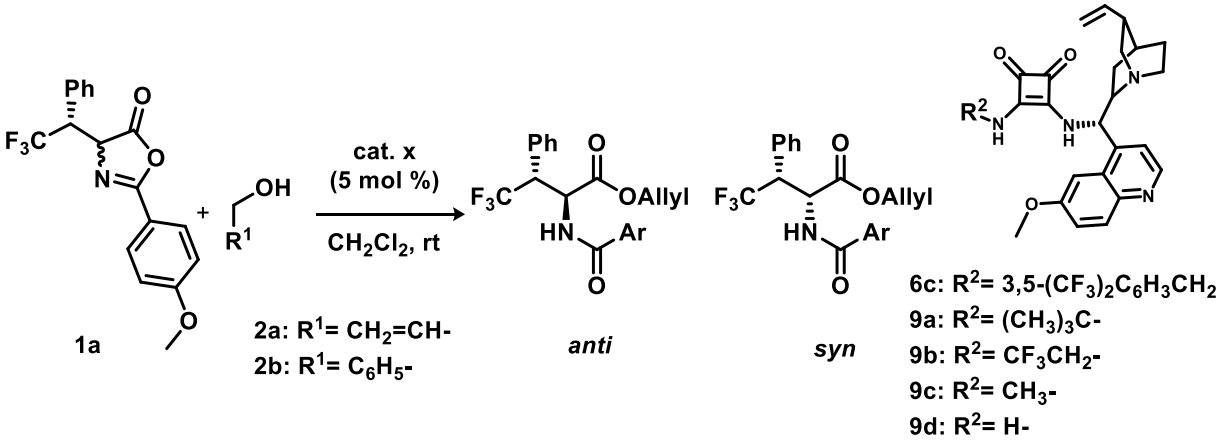

| ENTRY | Alcohol | Cat. (5 mol%) | t (h) | X (%) | *anti:syn* |
|---|---|---|---|---|---|
| **1** | **2a** | **7** | 19 | 63 | 0.78:1 |
| **2** | **2b** | **7** | 19 | 88 | 0.66:1 |
| **3** | **2a** | **8a** | 24 | > 99 | 1:14 |
| **4** | **2b** | **8a** | 24 | > 99 | 1:16 |
| **5** | **2a** | **8b** | 17 | 93 | 1.8:1 |
| **6** | **2a** | **8c** | 42 | > 95 | 2.4:1 |

[a]General method: azlactone **3a** 0.05 mmol, alcohol **2** 0.1 mmol, 800µL; [b] Determined by $^{19}$F NMR analysis on the crude mixture; [e] Determined by $^{19}$F NMR after a short silica plug.

Ever since the first attempts, we learnt the ring opening reaction controlled by these catalysts has the tendency for the *anti*-isomers when a quinine or cinchonidine alkaloid is employed, vice versa quinidine and cinchonine favors the *syn* isomers. So, in order to increase the diastereoselectivity for the mismatched case, we investigated on the influence of $\mathbf{R^2}$ catalyst moiety. The results are shown in Table 7 from four newly prepared catalysts whit different steric hindrance. In entry 1-2 are reported the standard condition using 3,5-$(CF_3)_2C_6H_3CH_2$ substituent with both alcohols, **2a** and **2b**. Catlyst **9a** bearing a *tert*-butyl substituent did not

performed so well achieving 1.98:1 and 1.8:1 diastereomeric ratio using alcohol **2a** and **2b** respectively (entry 3-4). Instead of using a bulky substituent as *tert*-butyl, a catalyst with less steric hindrance was studied (**9b**). In entry 5-6 are shown the selectivity values obtained under the control of a catalyst with a trifluoroethyl group derivative. In this case, the use of allyl alcohol seems to be better, giving almost the same performance as catalyst **6c**. In both entries 5 and 6, the catalyst suffers from slow kinetic (68 and 15 % in 42 h).

**Table 7: Catalysts screening**




| ENTRY[a] | Cat | Alcohol | t (h) | X (%)[e] | *Anti:syn*[d] |
|---|---|---|---|---|---|
| **1** | **6c** | **2a** | 42 | > 90 | 2.8:1 |
| **2** | **6c** | **2b** | 42 | > 90 | 2.6:1 |
| **3** | **9a** | **2a** | 42 | > 90 | 1.98:1 |
| **4** | **9a** | **2b** | 42 | > 90 | 1.8:1 |
| **5** | **9b** | **2a** | 42 | 68 | 2.7:1 |
| **6** | **9b** | **2b** | 42 | 15 | 1.1:1 |
| **7** | **9c** | **2a** | 42 | 80 | 3.2:1 |
| **8** | **9c** | **2b** | 42 | > 90 | 2.8:1 |
| **9** | **9d** | **2a** | 48 | 50 | 5.0:1 |
| **10** | **9d** | **2b** | 48 | 57 | 3.7:1 |

[a]General method: azlactone **3a** 0.05 mmol, alcohol **2** 0.1 mmol, 800µL; [b] Determined by $^{19}$F NMR analysis on the crude mixture; [e] Determined by $^{19}$F NMR after a short silica plug.

Since going from a bulky substituent to a $CF_3CH_2$- brought to a slight improvement in selectivity, we decided to test the methyl group and un unexpected result comes out. In entry 7-8 are reported the selectivity values, 3.2:1 when allylic alcohol is used and 2.8:1 for benzylic alcohol, one and the other with satisfactory kinetics. Speculating that the improvement in selectivity was linked with the lower steric hindrance of the latter catalyst, a squaramide-based catalyst with $NH_2$ free moiety was prepared. As it can see from entry 9 and 10 a remarkable value of selectivity was achieved in the case of allylic alcohol and a good

result even with benzyl alcohol. Despite the good value of selectivity the reaction rate is slow for both isomers. This problem could be correlated to the low catalyst solubility.

### 3.4. One-pot procedure

A one-pot procedure is an extremely attractive strategy to improve the efficiency of a reaction, especially where the isolation of the intermediate is problematic such as the present case. Thus, skipping the column chromatography after the first step, which was carried out in order to get rid of the first catalyst, pyridine co-product and excess HE, a straightforward procedure could be a suitable strategy to increase yield, and moreover, simplify a two step synthesis into just one step.

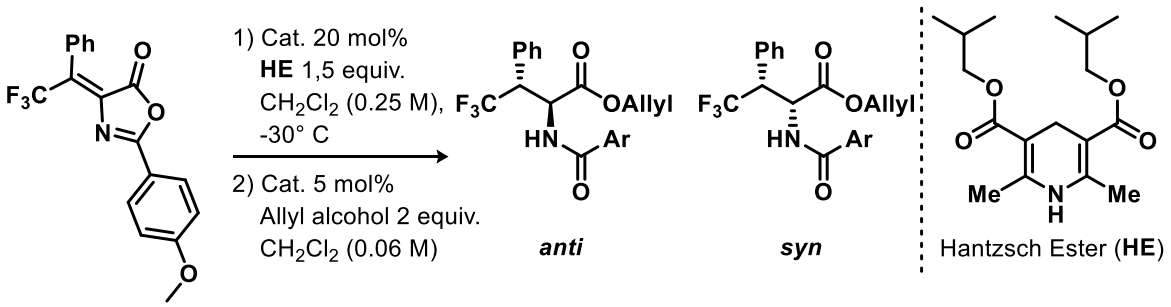
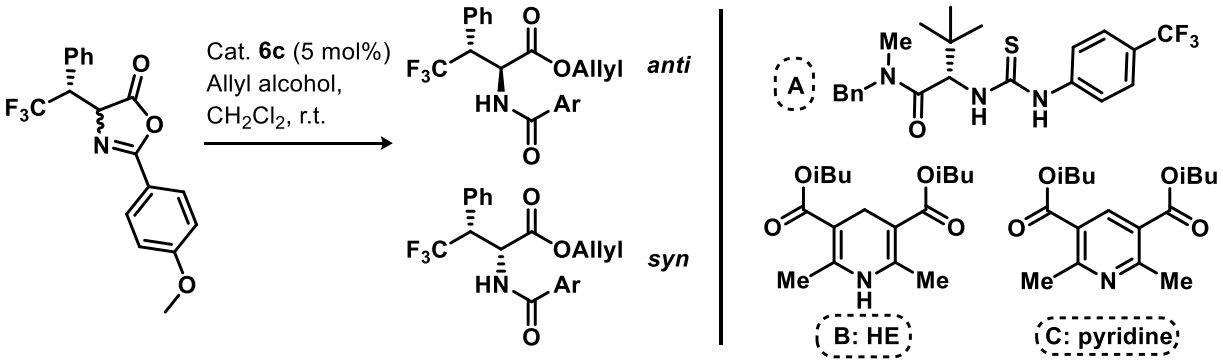



**Figure 12: One-pot reaction scheme**

For a successful telescoping it is mandatory that catalyst, non-reacted species and all the co-products that come from the previous step do not interfere in the following step. For this reason, the ring opening reaction was conducted in presence of these species things in order to understand the influence of their presence.

In Table 8 are reported three different reactions carried out in order to understand the effect of **A**, **B** and **C** species. The catalyst (**A**) involved in the first step seems to not interfere in the ring opening reaction. On the other hand, the presence of **B** (**HE**) affected negatively both kinetic and selectivity.

**Table 8: One-pot feasibility and reaction scheme**




| ENTRY[a] | Interferent | t (h) | X (%)[b] | *Anti:Syn*[c] |
|---|---|---|---|---|
| **1** | **A**[e] | 48 | > 99 | 3.0:1 |
| **2** | **B**[d] | 48 | 73 | 2.2:1 |
| **3** | **C**[f] | 48 | > 99 | 3.0:1 |

[a]General method: azlactone 1 0,05 mmol, alcohol 2 0,1 mmol, 800µL; [b] Determined by 19F NMR analysis on the crude mixture; [c] Determined by 19F NMR after a short silica plug. [d] 20 mol% of cat **4**, [e] 0.05 mmol of **HE**, [f] 0.05 mmol.

As it can see from entry 3, it seems that the presence of pyridine does not interfere in the second step. So, to overcome this problem the equivalents of **HE** were lowered from 1.5 to 1.1 and the enantiomeric excess measured to verify the feasibility. These experiments were perfomed with the quindine catalyst **8a** which affords the syn-isomer. The preliminary results are reported in Table 9.

**Table 9: one-pot feasibility**

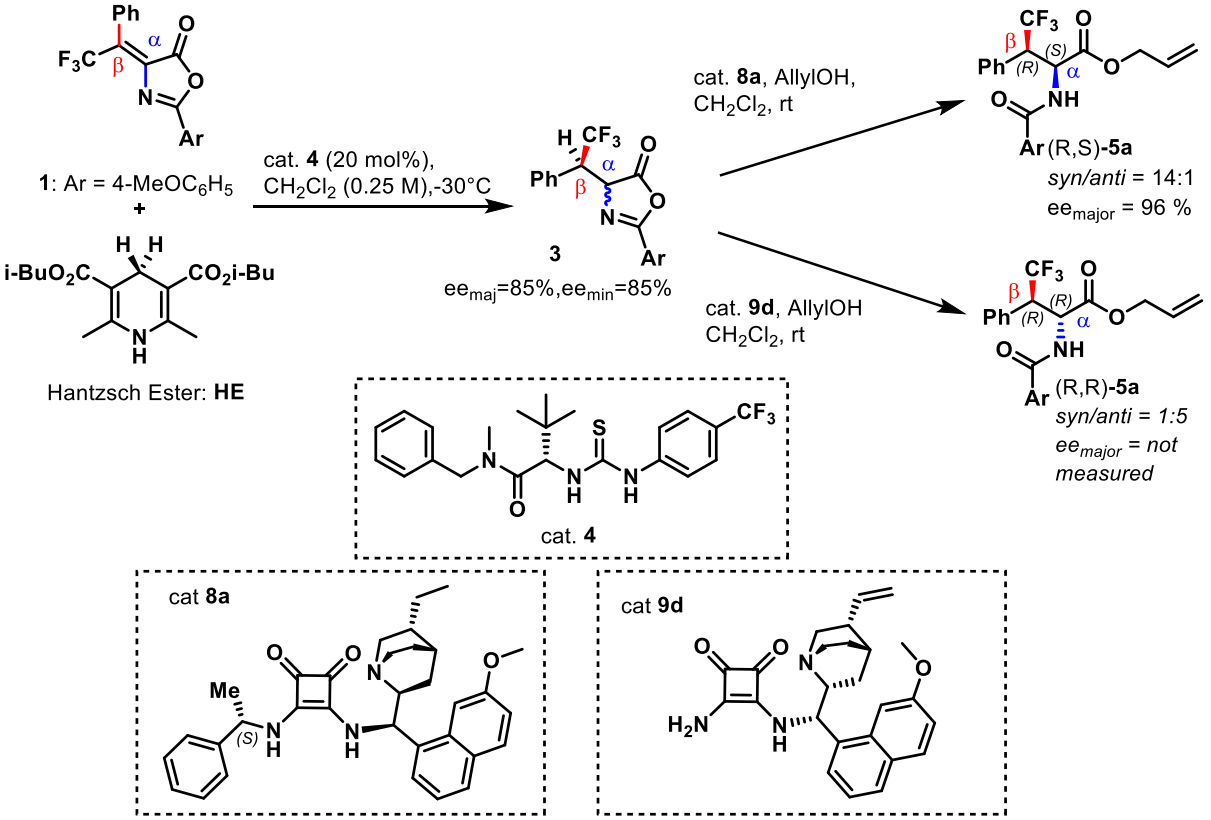
| ENTRY[a] | Alcohol | t (h) | X (%)[b] | *Syn:anti*[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | AllylOH | 24 | > 95 | 14:1 | 96 |
| 2 | BnOH | 24 | > 95 | 16:1 | / |
| 3 | BnOH | 24 | > 95 | 16:1 | / |

[a]General method: azlactone **1a** 0.05 mmol, **HE** 0.075 mmol, at -30° C for 48 h in 400 µL, then allyl alcohol 0,1 mmol, catalyst **8a** 0.0025mmol in 800µL; [b] Determined by $^{19}$F NMR analysis on the crude mixture; [c] Determined by $^{19}$F NMR after a short silica plug. [d] Determinated after short filtration on silica gel with HPLC on chiral stationary phase AD-H, 254 nm, *syn*-isomer: $t_{maj}^{1}$ = 11'; $t_{min}^{2}$ = 21'; *anti*-isomer $t_{anti}^{1}$ = 14 min, $t_{anti}^{2}$ = 24 min.

## Diastereodivergent synthesis concluding remarks

Thanks to results previously achieved in the first step involving azlactone **1a** as starting material, Jacobsen type thiourea as chiral catalyst and Hantzsch ester as hydride donor in dichlomethane as solvent, it was possible to plan and develop the second step to complete the stereodivergent synthesis. The ring opening reaction was carried out after short filtration on silica gel in order to remove non-reacted species, co-products and catalyst. The intermediate

as diastereomeric mixture in then used in dynamic kinetic resolution with allylic or benzyl alcohol under the control of chiral squaramide-based monomeric cinchona alkaloids. The *syn* product (R,S) is obtained as major stereoisomer when catalyst **7a** is employed in a 14:1 as diastereomeric ratio for allylic alcohol and 16:1 ratio for benzyl alcohol and 96% enantiomeric excess. The second stereoisomer (*anti*) was selectively synthesized with catalyst **4d** achieving up to 5.0:1 as diastereisomeric ratio. The one-pot synthesis was initially investigated in order to find possible interferences. The reaction was carried out with less equivalents of Hantzsch ester (1.1) since it seems to interfere in the ring opening reaction.




The crude reaction mixture is then brought to room temperature, thus alcohol and catalyst are added. The use of catalysts **6c** and **8a** were both tested whit positive result. Catalyst **8a** works very well also in this condition achieving 14:1 as d.r. and 96% e.e. for the *syn* product, while catalyst **6c** works slightly worse (2.6:1 as diastereoisomeric ration) compared to case where it is used with the purified intermediate. Catalyst **9d** was not tested for the one-pot reaction because improvements are needed due to its slow kinetic.

# 4. CONCLUSION AND FUTURE AIMS

Thanks to the promising results reached in the previous work for the first step, it was possible to plan and study the azlactones dynamic kinetic resolution feasibility to achieve the synthesis of β,β-disubstituted-α-aminoacids in a sequential stereodivergent fashion. To fully control the chirality in the α-carbonil stereocenter different catalyst and reaction conditions were screened. Squaramide-based cinchona alkaloids were confirmed to be the best catalyst to work with, and then a broad study on the catalyst substituents was done in order to maximize the selectivity. For the (R,R)-**5a** product (*syn*-diastereoisomer) the squaramide catalyst bearing dihydroquinidine and (*S*)-methylbenzilamine susbstituents achived 14:1 diastereoisomeric ratio and 96% enantiomeric excess when allyl alcohol was used as nucleophile, otherwise employing benzyl alcohol the selectivity rise to 16:1 ratio. Performing the ring opening reaction under the same condition with squaramide-based quinine bearing $NH_2$ moiety, lead to the (R,R)-**5a** product with 5.0:1 diastereomeric ratio when allylic alcol is used, and 3.7:1 ratio for the benzylic alcohol. A more straightforward simple one-pot procedure was initially investigated. The potential interferences that come from the previous step was studied. As outcome, the equivalents of Hantzsch ester need to be reduced as minimum as possible, since it seems to slow down the reaction also reducing the selectivity. In this optimized conditions, catalyst **8a** was tested due to its high selectivity and activity achieving the same results when a purified oxazolone is employed. For the mismatch case was not possible to study the one-pot procedure since the catalyst suffers from low activity. In the near future, the one-pot strategy will be in-depth studied and the catalyst activity of **9d** will be investigated in order to reach higher and consequently tested in one-pot synthesis.

# 5. MATERIAL AND METHODS

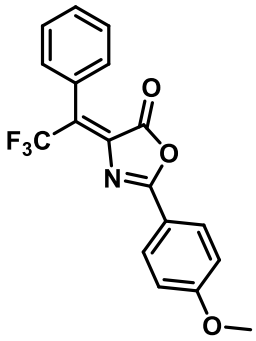
## 5.1. General methods and materials

$^{1}$H-NMR and $^{19}$F-NMR spectra were measured by means of Varian AS 300 and 400 spectrometers. 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 final opened product were measured upon the ring opening reaction employing 5 mol% of $Et_3N$ as an achiral in 800 μL of dicholomethane at room temperature.

## 5.2. General procedure for the synthesis of azlactone 1a-c

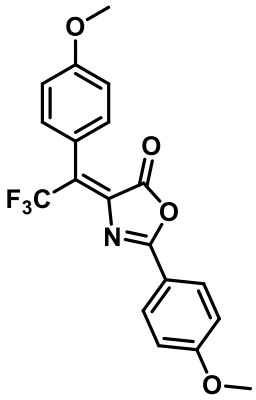
A suspension of N-(4-methoxybenzoyl) glycine, acetic anhydride and potassium carbonate has been added to a round bottom flask equipped with magnetic stirring bar at room temperature. After 30 minutes, 2,2,2-trifluoroacetophenone is added and stirred for 18 h. Subsequently, the suspension is poured in another round bottom flask with water and stirred for 18 h. The resulting suspension is then filtered and the filtrate washed with cold water. The solid is then purified with chromatographic column on silica gel using $CH_2Cl_2$ as eluent. The fraction containing the Z-E mixture is finally recrystallized from *n*-hexane achieving the pure Z isomer.

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



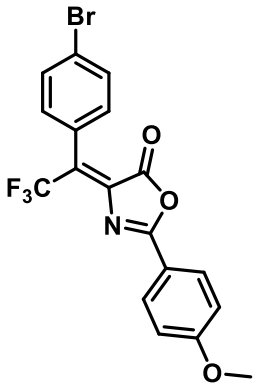

Following the procedure described above the product was obtained diastereoisomeric pure after recrystallization in 45% yield as yellow needle shape crystals. $^{1}$H NMR (300 MHz, Chloroform-*d*) δ 8.22 – 8.06 (m, 2H), 7.64 – 7.41 (m, 3H), 7.41 – 7.30 (m, 2H), 7.09 – 6.93 (m, 2H), 3.92 (s, 3H). $^{19}$F NMR (282 MHz, Chloroform-*d*) δ -59.38 (s).

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



Following the above described procedure the product **1b** was obtained in 27 % yield in orange needle shape crystals as pure diastereoisomer. $^{1}$H NMR (CDCl3 ,300 MHz ) δ 8,17-8,07 (m , 2H), 7,35-7,28 (m, 2H), 7,05-6,99 (m, 2H), 6,99-6,93 (m, 2H), 3,91 (s, 3H) , 3,86 (s, 3H). $^{19}$F NMR ( CDCl3 , 300 MHz ) δ -59,25 (s).

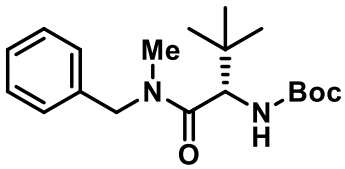
**1c) Synthesis of ((Z)-2-(4-methoxyphenyl)-4-(2,2,2-trifluoro-1-(4-Bromophenyl)ethylidene)oxazol-5(4H)-one**



Following the above described procedure the product **1b** was obtained in 48 % yield in yellow needle shape crystals as pure diastereoisomer. $^{1}$H NMR ($CDCl_3$,300 MHz) δ 8.18-8.08 (m, 2H), 7.64-7.54 (m ,2H), 7.64-7.54 (m 2H), 7.22 (d, J=12.2 Hz, 2H), 7.07-6.97 (m, 2H), 3.91 (s, 3H). $^{19}$F NMR ($CDCl_3$, 282 MHz) δ = -59.34 (s)

## 5.3. Procedure for the synthesis of Jacobsen type thiourea

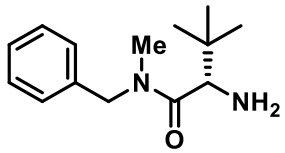
**tert-butyl (S)-(1-(benzyl(methyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate**



In a oven dried 100 mL round bottom flask under nitrogen atmosphere are added: *N-Boc-(S)-tert*-leucine (5 mmol, 1156.45 mg), HBTU (5,5 mmol, 2085.9 mg) $CH_2Cl_2$ (56 mL) previously treated on aluminum oxide activated basic and N-Benzylmethylamine (6 mmol, 727.08 mg). The reaction was then stirred for 24 h. The organic phase is washed with HCl 1M (2x85 mL), a satured solution of $NaHCO_3$ (2x65 mL) e finally with brine (2x65 mL). The resulting organic phase in anhydrified with $MgSO_4$, filtrated and the solvent was removed under low pressure. The yellow oil product is finally purified by means chromatographic column on silica gel and eluted with $CH_2Cl_2$: $Et_2O$ = 95:5 affording

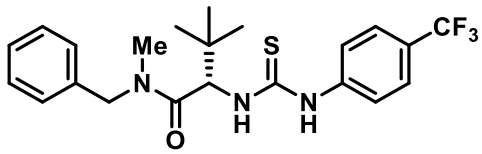
86 % yield. $^1$H NMR (300 MHz, $CDCl_3$): [From the spectra is possible to see the presence of 2 rotamers in 7:3 ratio] δ 7.35-7.19 (m, 5H), 5.41-5.31 (m, 1H), 5.00 (d, J=15.9 Hz, 0.28H), 4.71 (d, J=15.0 Hz, 0.72 H), 4.75-4.66 (m, 0.28H), 4.51 (d, J=14.6, 0.72H), 4.58-4.47 (m, 0.72H), 4.31 (d, J=16.1 Hz, 0.28H), 3.06 (s, 2.2H), 2.88 (s, 0.9H), 1.44 (s, 9H), 1.01 (s, 9H).

**(S)-2-amino-N-benzyl-N,3,3-trimethylbutanamide**



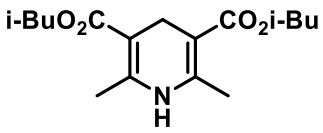

In a vial with tert-butyl (S)-(1-(benzyl(methyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (4.3 mmol, 1438.8 mg) were added $CH_2Cl_2$ (18 mL), trifluoroacetic acid (43 mmol, 3.3 mL) and stirred for 90 minutes. After this amount of time the reaction was cooled down to 0° C and a solution of NaOH (5.5 M) was added in order to obtain a basic solution (pH= 12). The organic layer was the separated from the acqueous one, washed whit brine and finally anhydrified with $MgSO_4$. After filtration and solvent evaporation a yellow oil was obtained as product that can be directly use in following step without purification (72% yield). $^1$H NMR (300 MHz, $CDCl_3$): [From the spectra is possible to see the presence of 2 rotamers in 65:35 ratio] δ 7.40-7.17 (m, 5H), 4.96 (d, J=16.6 Hz, 0.33H), 4.74 (d, J=14.5 Hz, 0.66H), 4.49 (d, J=14.5 Hz, 0.66H), 4.30 (d, J=16.6 Hz, 0.33H), 3.55 (s, 0.66H), 3.50 (s, 0.33H), 2.98 (s, 1.98H), 2.95 (s, 0.99H), 1.65 (s, 2H), 1.00 (s, 9H).

**(S)-N-benzyl-N,3,3-trimethyl-2-(3-(4-(trifluoromethyl)phenyl)thioureido)butanamide**



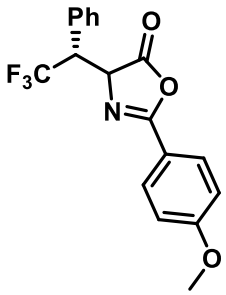

In a vial with (S)-2-amino-N-benzyl-N,3,3-trimethylbutanamide (3.13. mmol, 733.6 mg) were added $CH_2Cl_2$ (6.8 mL) and 1-isothiocyanato-4-(trifluoromethyl)benzene (3.13 mmol, 635.98 mg) and stirred for 24 h. After this amount of time the crude reaction mixture was purified by chromatographic column on silica gel using initially only $CH_2Cl_2$. The polarity was gradually increased with 10% of $Et_2O$ in order to elute the product achieving 32 % as overall yield of a white solid (1.59 mmol, 693.8 mg). $^1$H NMR (300 MHz, $CDCl_3$): [From the spectra is possible to see the presence of 2 rotamers in 8:2 ratio] δ 8.68 (s, 1H), 7.61-7.17 (m, 9H), 5.96 (d, J=9.5 Hz, 0.2H), 5.66 (d, J=9.4 Hz, 0.8H), 5.16 (d, J= 15.0 Hz, 0.2H), 4.82 (d, J=14.7 Hz, 0.8H), 4.40 (d, J=15.1 Hz, 0.2H), 4.33 (d, J=14.6 Hz, 0.8H), 3.20 (s, 2.4H), 2.80 (s, 0.6H), 1.80 (s, 1.8H), 1.07 (s, 7.2H).

### 5.4. Synthesis of diisobutyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate




In a heat gun dried round bottom flask equipped with magnetic strirring bar, isybutyl 3-oxobutanone (60 mmol, 9685 mg) paraformaldehyde (30 mmol, 900 mg) and $AcO^-NH_4^+$ (30 mmol, 2300 mg) 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 the title product in 43% yield after hot filtration. $^1$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).

### 5.5. General procedure for catalytic asymmetric reduction of azlactone 1

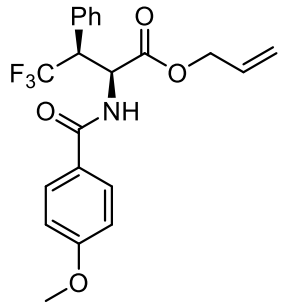



In a tube equipped with magnetic stirring bar, azlactone **1** (0,5 mmol) and catalyst **4** (20 mol %) are dissolved in $CH_2Cl_2$ (2 mL). The mixture is cooled down to -30° C and after five minutes the Hantzsch ester (0,75 mmol) is added to the tube. The reaction is run for 48 h at -30° C and the conversion checked by $^{19}$F NMR. Once reached full conversion, the reaction crude mixture is directly charged on a chromatographic column on silica gel e quickly eluted with $CH_2Cl_2$ for a fast filtration. The reduced product is obtained as yellowish sticky oil (0.32 mmol, 64% yield). $^1$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).

**General procedure for dynamic kinetic resolution on azlactone**

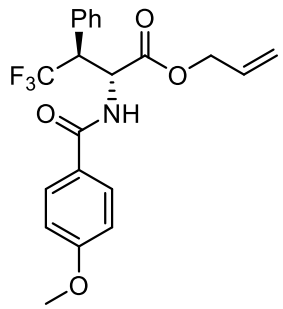
In a tube equipped with magnetic stirring bar, azlactone **3b** (0,05 mmol), catalyst **7a** and $CH_2Cl_2$ (800 μL) are added. Then, the mixture is taken to the reaction temperature and the appropriate alcohol (0,1 mmol) is added to the tube. The reaction is run until complete conversion as detected by TLC or $^{19}$F-NMR. After that, a plug on silica is performed on the crude, then diastereomeric ratios are determined by means of $^{19}$F-NMR.

**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 800 μL of $CH_2Cl_2$ . Then catalyst **7a** (0,005 mmol) and AllOH (0,1 mmol) are added to the solution. The reaction is carried out at room temperature for 24 hours. After chromatografic column ($CH_2Cl_2$: $Et_2O$ 40:1) 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*-hexane/*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**



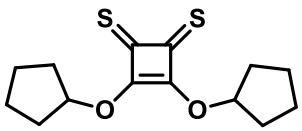

In a test tube equipped with magnetic stirring bar, 2-(4-methoxyphenyl)-4-(2,2,2-trifluoro-1-phenylethyl)oxazol-5(4H)-one **3b** (0,05 mmol) is dissolved in 800 μL of $CH_2Cl_2$ . Then catalyst **4d** (0,05 mmol) and AllOH (0,1 mmol) are added to the solution. The reaction is carried out at room temperature for 24 hours. After chromatografic column ($CH_2Cl_2$: $Et_2O$ 40:1 ) 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).

### 5.6. General procedure for the synthesis squaramide-based catalyst

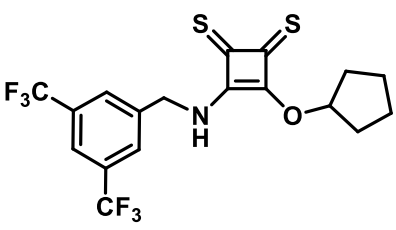
In a vial equipped with magnetic stirring bar, to a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (1 mmol, 142 mg) in $CH_2Cl_2$ (4 mL) the 3,5-bis(trifluoromethyl)-benzylamine (1.05 mmol, 255 mg) in $CH_2Cl_2$ (1 mL) is added. After 18 h, the reaction mixture was filtered, and the filtrate washed with acqueous HCl 1M (1 x 10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to afford 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione as a white solid (299 mg, 85% yield). The monosubstituted intermediate (127, 0.360 mmol) is dissolved in MeOH (4 mL) and a solution of *epi*-ammino-quinine, 0.300 mmol in 1mL of MeOH. After 24 h, the reaction mixture was filtered and the precipitate washed with cold MeOH (2 x 0.5 mL) to afford the final squaramide (132 mg, 72%) as white solid.

### 5.7. Procedure for the synthesis of 3,4-bis(cyclopentyloxy)cyclobut-3-ene-1,2-dithione




To a solution of Lawesson's reagent (3.70 g, 9.15 mmol) in dry $CH_2Cl_2$ (40 mL) was added 3,4-bis(cyclopentyloxy)cyclobut-3-ene-1,2-dione (2.29 g, 9.15 mmol). The reaction was stirred for 37 h, during which time dry $CH_2Cl_2$ was added as needed to maintain constant volume. The reaction mixture was then gravity filtered, concentrated to roughly half the original volume, and immediately loaded onto column. Quickly eluting with 1:1 hexanes: $CH_2Cl_2$ afforded the product (1,83 g, 6,48 mmol, 71%) as an amorphous orange solid. $^{1}$H NMR (300 MHz, $CDCl_3$): δ = 6.06 (m, 2H), 2.02 (m, 8H), 1.86 (m, 4H), 1.70 (m, 4H).

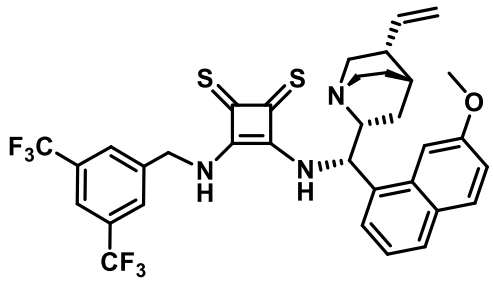
**3-((3,5-Bis(trifluoromethyl)benzyl)amino)-4-(cyclopentyloxy)cyclobut-3-ene-1,2-dithione (5a)**




To a solution of dithione (237 mg, 0.84 mmol, 1.2 equiv) in dry CH2Cl2 (2 mL) was added 3,5-$(CF_3)_2$-benzylamine (76 µL, 0.70 mmol, 1.0 equiv) at 0 °C and the resulting solution was stirred for 15 min at that temperature, then 15 min at

room temperature. The solution was then loaded directly onto column and quickly eluted with $CH_2Cl_2$ to afford **5a** (166 mg, 0.55 mmol, 79%) as an amorphous yellow solid. The compound exists as two rotamers in DMSO at room temperature in a ratio of 0.55:0.33. Major rotamer: $^1$H NMR (300 MHz, DMSO-d6): δ = 10.26 (t, J = 6.2 Hz, 1H), 7.35 (m, 5H), 6.37 (m, 1H), 4.56 (d, J = 6.5 Hz, 2H), 1.81- 2.08 (m, 4H), 1.53-1.81 (m, 4H). Minor rotamer: $^1$H NMR (500 MHz, DMSO-d6): δ = 10.15 (t, J = 6.3 Hz, 1H), 7.35 (m, 5H), 6.32 (m, 1H), 5.19 (d, J = 6.5 Hz, 1H), 1.81-2.08 (m, 4H), 1.53-1.81 (m, S6 4H).

**3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-(((S)-(7-methoxynaphthalen-1-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dithione**




To a solution of monosubstituted product (85 mg, 0.20 mmol, 1.0 equiv) in dry CH2Cl2 (1 mL) was added a solution of diamine QA in dry $CH_2Cl_2$ (0.5 M, 0.4 mL, 1.0 equiv) at 0 °C and the resulting solution was stirred for 0.5 h at that temperature, then 3 h at room temperature. About 4 mL hexanes was then added. The suspension was filtered and washed with ice-cold 4:1 hexanes:$CH_2Cl_2$ to afford 6g (93 mg, 0.14 mmol, 70%) as an amorphous yellow solid. NMR characterization for the final product was done after the salt formation 2HCl: $^1$H NMR (300 MHz, $CD_3CN$): δ = 12.36 (s, 1H), 11.72 (s, 1H), 9.82 (s, 1H), 9.03 (s, 1H), 8.61 (s, 1H), 8.55 (d, J = 8.8 Hz, 1H), 8.37 (s, 2H), 8.06 (s, 1H), 7.71 (m, 2H), 7.53 (s, 1H), 5.85 (m, 1H), 5.18 (d, J = 16.5 Hz, 1H), 5.12 (d, J = 10.0 Hz, 1H), 4.38 (s, 1H), 4.15 (s, 3H), 4.15 (buried, 1H), 3.70 (m, 1H), 3.34 (s, 2H), 2.81 (s, 1H), 1.54-2.09 (m, 5H), 1.14 (s, 1H).

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