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Treball Final de Grau

Synthesis of *N*-acyl thioimides. New direct, catalytic and asymmetric reactions of construction of C-C bonds

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B:KC Barcelona Knowledge Campus
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Puedo asegurarles a ustedes que haré todo lo que pueda y un poco más de lo que pueda si es que eso es posible y haré todo lo posible e incluso lo imposible si también lo imposible es posible.

M. Rajoy

Primer de tot agrair a en Fèlix per supervisar tot el projecte, guiar-me, aconsellar-me i fer-me créixer com a futura química.

A en Miquel, per ser el millor DJ i cantant del laboratori però, sobre tot, per ajudar-me i fer-me costat en tot aquest projecte.

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Y a mis abuelos, os tengo presentes siempre.

REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (SDG)

L'economia és la paraula clau per entendre l'evolució de la química sintètica en les darreres dècades. Aquest concepte en química apunta a la necessitat de disposar de mètodes selectius i sostenibles que facilitin l'obtenció de qualsevol estructura amb el màxim rendiment i eficiència possible. Per això, el control de la selectivitat i el desenvolupament de processos catalítics i/o verds juguen un paper fonamental i estimulen la recerca de solucions més sostenibles.

Com serà explicat en aquest treball, el que s'està investigant actualment en el grup de recerca en el que he portat a terme aquest projecte implica la utilització de catalitzadors asimètrics metàl·lics, útils per la preparació de productes naturals biològicament actius, com ara els antibiòtics, per tal de fer la síntesi més econòmica i mediambientalment sostenible

Aquest concepte encaixa en els objectius de desenvolupament sostenible 12.4 i 12.5, que poden actuar com a activadors de la recuperació econòmica y de la reorientació de la economia cap a un creixement més intel·ligent i sostenible.

L'ODS 12.4 apunta cap a la gestió ecològicament racional dels productes químics i de tots els residus generats al voltant del seu cicle de vida, així com la reducció significativa del seu alliberament a l'atmosfera, l'aigua i la terra per tal de minimitzar els seus efectes adversos. A més a més, l'ODS 12.5 pretén reduir la generació de residus mitjançant activitats de prevenció, reducció, reciclatge i reutilització, sent aquests els objectiu principals de la catàlisi metàl·lica asimètrica.

CONTENTS

1. SUMMARY

A key step in the synthesis of natural and biologically active products is the stereoselective construction of carbon-carbon bonds. Hence, the reactions involving metal enolates occupy a preeminent position in organic synthesis.

Metal enolates can react with a large variety of electrophiles to generate new C-C bonds and, in the last decades, stereoselective methodologies have been developed. In the beginning, stereochemical control was based on the use of substrate control or chiral auxiliaries. Despite the great synthetic capacities, stoichiometric amounts of the chiral auxiliary and the metal complex were needed. Also, in the synthetic path, two extra steps were needed to add and eliminate the chiral auxiliary. Given the need to develop more sustainable methodologies, direct and catalytic approaches have been studied.

In recent years, our group has developed a new methodology based on the use of chiral Ni(II) complexes to catalyze direct and enantioselective alkylation of *N*-acyl-1,3-thiazinane-2-thiones with electrophiles. Initially, the formation of a single stereocenter was studied using electrophiles that were activated with TESOTf, generating oxocarbenium cations and stable carbocations. The asymmetric formation of two stereocenters is currently being studied by direct and catalytic reactions with acetals and aldehydes activated with silyl triflates in presence of chiral Ni(II) complexes.

In this context, the aim of this project is to obtain large quantities of 1,3-thiazinane-2-thione and 1,3-oxazinane-2-thione to carry out acylation reactions with the mentioned scaffolds. The obtained *N*-acyl thioimides may be used in the previously mentioned studies. Finally, a first assay of a direct, catalytic and asymmetric alkylation reaction will be performed using a chiral nickel(II) catalyst and a commercially available acetal activated with TESOTf as an electrophile.

Keywords: direct enantioselective reactions, enolates, asymmetric catalysis, nickel catalyst.

2. RESUM

L'etapa clau en la síntesis de productes naturals biològicament actius és la construcció estèreoselectiva d'enllaços carboni-carboni. Per això, les reaccions que involucren enolats metàl·lics ocupen una posició molt destacada en la síntesis orgànica. De fet, els enolats metàl·lics poden reaccionar amb una gran quantitat d'electròfils, generant nous enllaços C-C i per això, a les últimes dècades, s'han desenvolupat noves metodologies estereoselectives. En les primeres etapes, el control de l'estereoquímica implicava la utilització del control per substrat o d'auxiliars quirals. Tot i la gran capacitat sintètica d'aquestes metodologies, en ambdós casos calia emprar quantitats estequiomètriques de l'auxiliar quiral i del complex metàl·lic i afegir dues etapes extra (la introducció de l'auxiliar quiral i la seva eliminació). La necessitat de metodologies sintètiques més sostenibles ha obert el camí a l'estudi de les reaccions directes i catalítiques.

En els darrers anys, el nostre grup ha desenvolupat una nova metodologia basada en la utilització de complexos quirals de Ni(II) per catalitzar reaccions d'alquilació directes i enantioselectives de *N*-acil-1,3-tiazinan-2-tiones amb electròfils. Inicialment, es va estudiar la formació d'un únic estereocentre, utilitzant com electròfils precursors de cations oxocarbeni activats amb TESOTf i carbocations estables. Actualment, s'està estudiant la formació de dos estereocentres, mitjançant reaccions directes i asimètriques amb acetals i aldehids activats amb triflats de silici en presencia de complexos quirals de Ni(II).

En aquest context, en aquest projecte es pretén obtenir la 1,3-tiazinan-2-tiona i la 1,3-oxazinan-2-tiona a gran escala i portar a terme les corresponent reaccions d'acilació. Les *N*-acil tiomides obtingudes podran ser utilitzades per seguir amb els estudis mencionats anteriorment. Finalment, es realitzarà un primer assaig d'una reacció d'alquilació directa i catalítica, utilitzant un catalitzador quiral de níquel(II) i un acetal disponible comercialment que generarà l'electròfil en ser activat amb TESOTf.

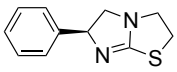
Paraules clau: reaccions enantioselectives directes, enolats, catàlisis asimètrica, catalitzador de níquel.

3. INTRODUCTION

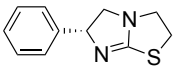
Lately, stereoselectivity has been one of the most studied fields in organic chemistry. Since it is well known that the spatial arrangement of atoms can determine many physicochemical properties of a molecule, it is important to obtain enantiomerically pure compounds.

Many commercially available drugs are chiral and, for the most part, a racemic mixture. Talking about biologic or pharmacologic uses, each enantiomer may have its own activities or effects in our organism, so having a racemic mixture can be a problem. That's why, in some cases, it is necessary to have a single enantiomer rather than a mixture of both.[1]

An example of the importance of obtaining enantioselective products is the case of tetramisole **(Figure 1)**. This drug was first used in a racemic mixture, but it was found that the dextrorotatory isomer, the (*R*)-(+)-enantiomer, cause side-effects such as headache, vomiting or abdominal pain. So, the levorotatory isomer, the (*S*)-(-)-enantiomer, also called levamisole, was the one with interesting medicine uses.[2]



(*S*)-(-)-Tetramisole



(*R*)-(+)-Tetramisole

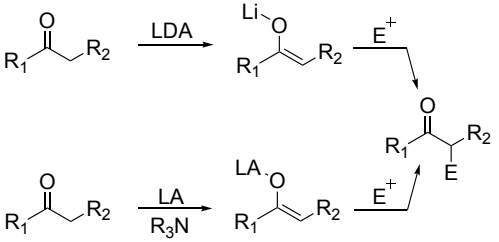
Figure 1. Tetramisole structure

To face problems like that, chiral compounds should be synthesized in their enantiomerically pure form. Therefore, asymmetric synthesis methods are being improved constantly. In this context, the stereoselective construction of carbon-carbon bonds has become one of the key challenges for modern organic synthesis.[3]

3.1. CLASSICAL ENOLATE REACTIONS

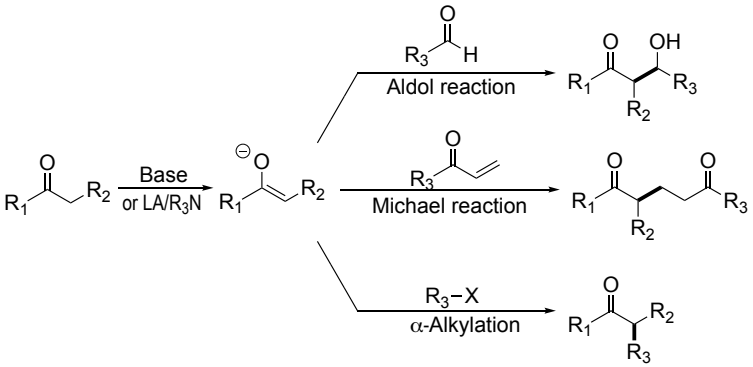
One of the most common strategies to create carbon-carbon bonds is based on the reaction between an enolate and an electrophilic specie. Classically, this methodology was based on a two-step reaction: i) the stoichiometric preformation of the enolate by using a strong base, such

as LDA or NaHMDS, or the combination of a Lewis acid, such as Bu_2BOTf or $TiCl_4$, and a tertiary amine as a base in the well-known soft enolization procedure, and ii) the addition of the electrophile (**Scheme 1**),



Scheme 1. Classical two-step reactions

Depending on the nature of the electrophile employed, three main categories are described (**Scheme 2**). The aldol reaction, using aldehydes as the electrophiles, leads to β-hydroxy carbonyl compounds, also called aldols adducts. The Michael addition allows the construction of a new carbon-carbon bond in the β carbonyl position using α,β-unsaturated carbonyl compounds as the electrophile. The last reaction, the α-alkylation, is performed using alkyl halides as electrophiles in a S_N2 reaction, where the α-hydrogen is replaced with an alkyl group and a new C-C bond is formed.[4]



Scheme 2. Types of enolate reactions regarding electrophile nature

3.2. STEREOCHEMICAL CONTROL IN THE C-C BOND FORMATION REACTION WITH ENOLATES

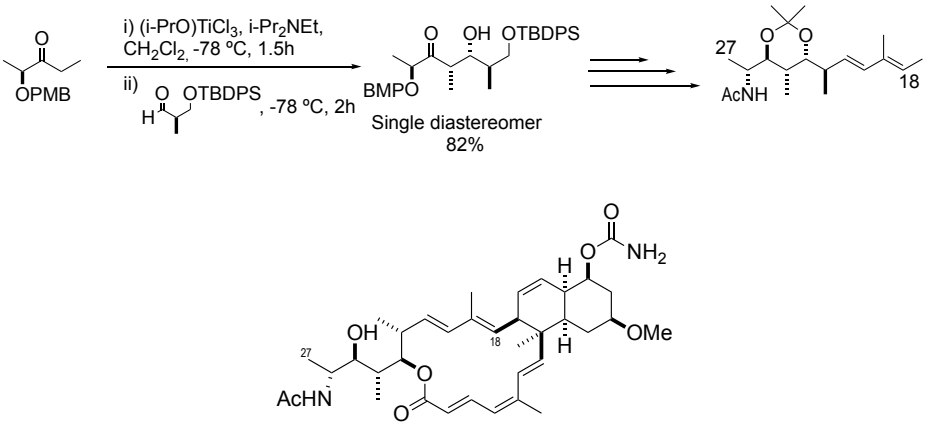
Classically, there are two ways to control the stereoselectivity in the formation of carbon-carbon bonds: the substrate-controlled synthesis and the diastereoselective induction using chiral auxiliaries.[5]

3.2.1. Substrate control

Substrate-controlled reactions are based on the use of reactants that have chiral elements their structure with a specific configuration which guide the reaction to achieve a certain product. The configuration of this product can usually be predicted by models such as Felkin-Anh or Cram when there is chelation between the Lewis acid and the reactant. Therefore, the chirality of the obtained product is determined by the original reactant.

This type of reactions presents, in some cases, an extraordinary diastereofacial preference, forcing the nucleophile to approach on a certain way. Therefore, knowing the configuration of the reactant, the stereoselectivity of the reaction can be controlled.[6]

An example of a substrate-controlled reaction is the synthesis of C18-C27 fragment of superstolide A taking a specific ketone and aldehyde as the only source of chirality yielding a single diastereomer as a product (**Scheme 3**).[7]



Scheme 3. Substrate-controlled synthesis of the C18-C27 fragment of superstolide A

3.2.2. Chiral auxiliaries control

Chiral auxiliaries are enantiopure scaffolds that are temporally and covalently attached to the reactant. A diastereoselective reaction takes place and the configuration of the chiral auxiliary is the responsible of the stereo-controlled formation of the new stereocenters. Once the reaction is finished, the auxiliary is easily removed from the isolated major diastereomer and recycled without affecting the enantiomeric purity of the product and avoiding undesired epimerization. Some examples of this chiral auxiliaries are chiral 1,3-oxazolidine-2-ones, introduced by Evans in the early 1980's and the ones described by Fujita-Nagao or Crimmins by changing the scaffold heteroatoms (**Figure 2**).[8-11]

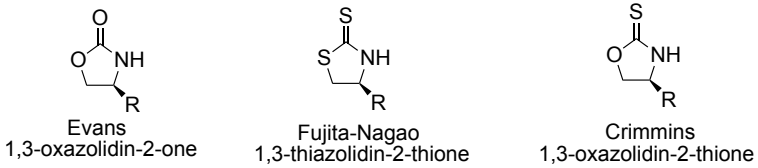
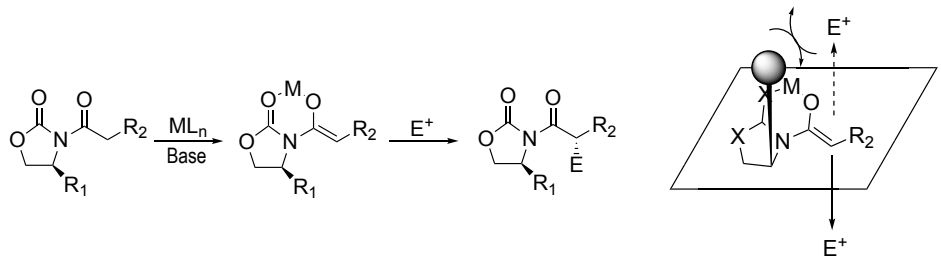


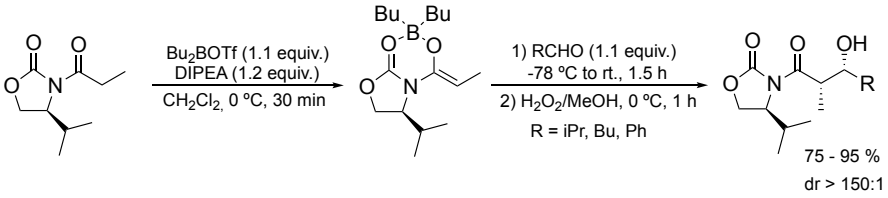
Figure 2. Chiral auxiliaries

The fact that the chiral auxiliary must be bonded and then removed from the reactant, implies two extra steps in the reaction. Once the enolate is formed, a chelate is formed between the metal of the enolate and the carboxyl group of the chiral auxiliary. The chiral center of the auxiliary blocks one of the faces of the enolate thanks to the planar structure formed by chelation. Therefore, the electrophile is forced to approach from the opposite side, allowing the stereoselective control (**Scheme 4**).[11-12]



Scheme 4. Stereocontrol approach of chelated enolates from Evans auxiliary

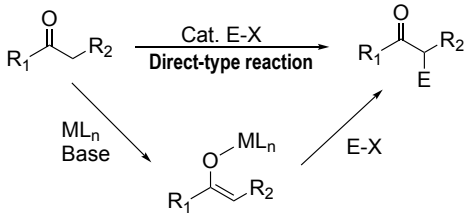
An example of this kind of methodology is the classical aldol reaction described by Evans, using a boron enolate and a chiral auxiliary to get high yields and stereoselectivities (**Scheme 5**).[13]



Scheme 5. Stereoselective aldol reaction using a chiral auxiliary

3.3. DIRECT AND CATALYZED REACTIONS

Asymmetric catalytic reactions have been developing over the past years, leaving aside traditional two-steps reactions above mentioned. This leads to the possibility of performing one-step reactions, which are considered direct reactions, in which the enolate can be generated catalytically and the electrophilic specie is added in the same step. These types of procedures include the use of species in sub-stoichiometric quantities for the enolate generation (**Scheme 6**).[14] One of the advantages is that these methodologies follow the terms of the atom economy. By adding catalytic quantitates of reagent, higher yields of the desired product have been obtained, making this method more economically sustainable.[3]



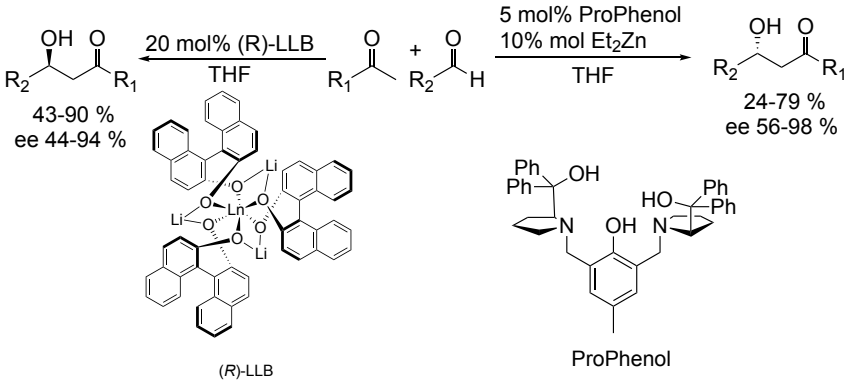
Scheme 6. Comparison of the classical two-step reaction and the direct method

3.3.1. Metal enolates

Over the past few years, methodologies that use metal complexes with the aim of catalyzing direct and asymmetric aldol reaction, are currently being studied. In these types of approaches,

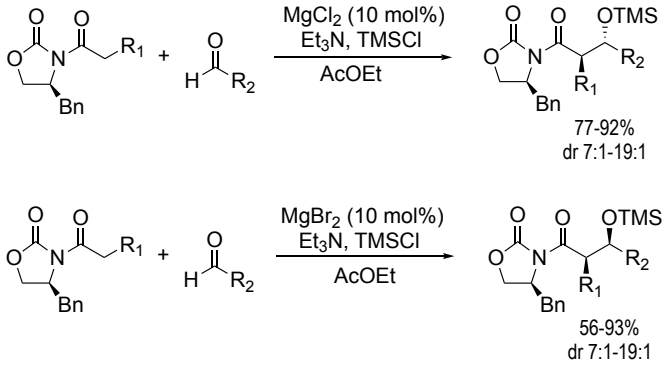
the metal complex is coordinated to the carbonyl group of the starting material, increasing the acidity of the α-proton, and generating the enolate (by deprotonation of the α-proton) which will later react with the electrophile.

Trost and Shibasaki described the first direct, catalytic, and enantioselective acetate aldol reactions from methyl ketones and branched aldehydes, both bimetallic catalysts function by dual activation since they contain a Lewis acid and a Brönsted base centers. Therefore, both nucleophilic ketone and electrophilic aldehyde are simultaneously linked. In Trost's methodology a ProPhenol catalyst, which is a binuclear zinc complex, was used to achieve low and moderate yields but high enantioselectivities. On the other hand, in Shibasaki's methodology, large quantities of catalysis (20 mol%) with BINOL structures and aldehydes were used and moderate to high yields and enantioselectivities were obtained (**Scheme 7**).[14-16]



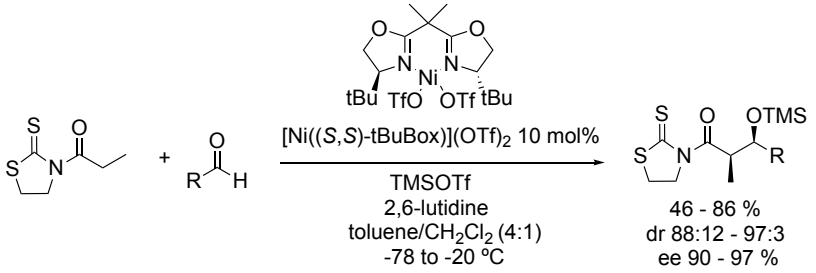
Scheme 7. Shibasaki and Trost approach to direct, catalytic and asymmetric aldol reactions

Later on, Evans studied the stereochemical control of a catalytic aldol reaction using their classical Evans chiral auxiliaries. Magnesium halides were used as catalysts in presence of trimethylsilyl chloride and triethylamine in stoichiometric amounts to obtain the two *anti*-aldol adducts in good yields and high stereoselectivity (**Scheme 8**).[17,18]



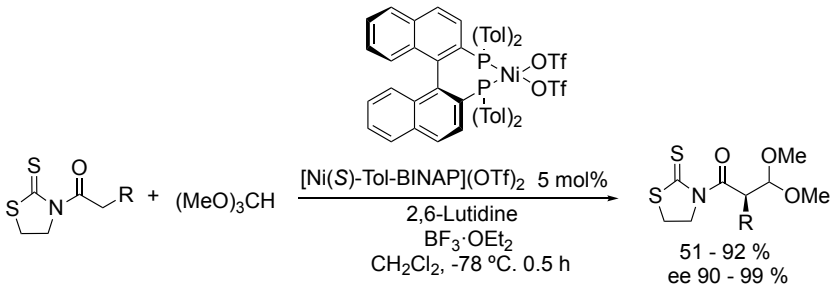
Scheme 8. Catalytic aldol reaction based on chiral auxiliaries

Furthermore, Evans also reported the use of achiral starting materials, in this cases *N*-acyl thiazolidintiones, and a chiral Ni(II) complexes to perform direct aldol reactions. The reaction was carried, again, under silylating conditions.[14] This methodology has been performed using different aldehydes, including aromatic and aliphatic aldehydes, to obtain the *syn* aldol product in good yields and stereoselectivity (**Scheme 9**).



Scheme 9. Ni(II) catalyzed direct asymmetric aldol reaction

Evans also explored the asymmetric alkylation reaction using a similar procedure but changing the structure of the Ni(II) chiral catalyst and trimethyl orthoformate as electrophile, in presence of BF_3-OEt_2, to obtain the oxocarbenium ion that reacts with the Z enolate affording the adduct in high yields and enantioselectivities (**Scheme 10**).[19]

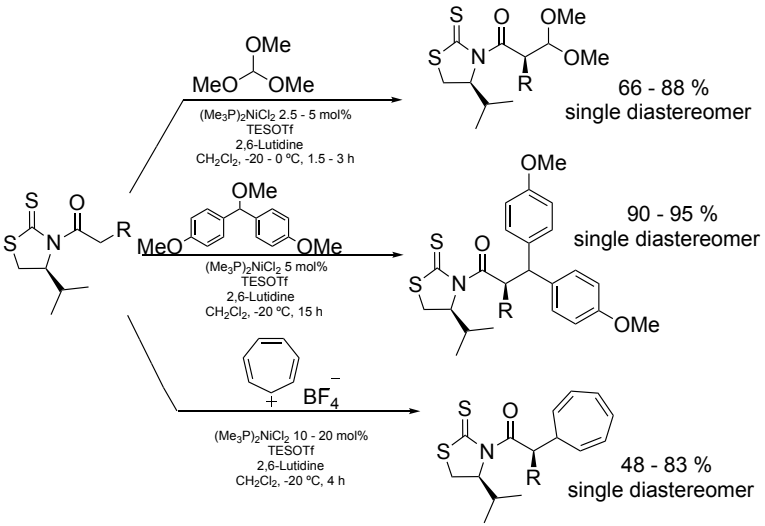


Scheme 10. Ni(II) catalyzed direct asymmetric alkylation reaction

3.4. ALKYLATION REACTIONS BASED ON NI(II) CATALYSTS IN OUR GROUP

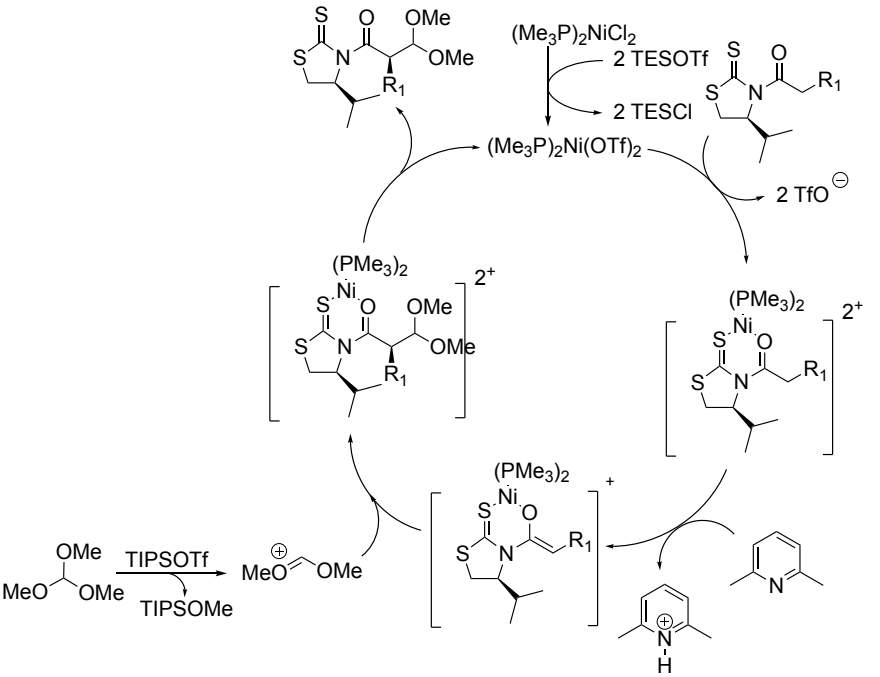
3.4.1. Achiral Ni(II) complexes

Inspired by previously described Evans' work, our group has developed direct, diastereoselective and catalytic alkylation reactions of chiral *N*-acyl-1,3-thiazolidine-2-thiones using a commercially available Ni(II) achiral complex. In this methodology the stereochemistry is controlled by the chiral auxiliary, which is a L-valine derivative. These *N*-acyl tioimdes react with different electrophiles such as trimethyl orthoformate, diarylmethyl methyl ethers and stable carbocationic salts in presence of an achiral Ni(II) complex, TESOTf as a Lewis acid and 2,6-lutidine as a base to give high yields and excellent diastereoselective products (**Scheme 11**).[20-22]



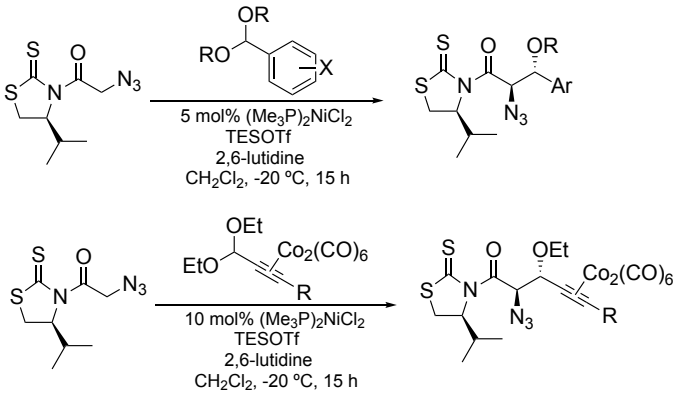
Scheme 11. Diastereoselective alkylation of chiral *N*-acyl-1,3-thiazolidine-2-thiones with electrophiles

In this type of reactions, the Lewis acid is essential. The electrophiles, oxonium and carbenium ions, are generated in the reaction mixture when the electrophilic species react with the Lewis acid (TESOTf). At the same time, the Lewis acid itself is involved in the generation of the true catalyst, the $(Me_3P)_2Ni(OTf)_2$, by activating the pre-catalyst. The Ni(II) in the catalyst complex creates a chelate in the *N*-acyl thioamide via coordination of the soft Ni(II) metal. Due to the enhanced acidity of the proton in the α-carbon to the carboxyl, the chelate system is deprotonated by the 2,6-lutidine to form the Z-enolate. One of the faces of the Z-enolate can't react because of the steric hindrance given by the isopropyl group of the chiral auxiliary. The alkylation undergoes an S_N1 mechanism, favoring the antiperiplanar approach in the transition state to minimize interactions and steric hindrances (**Scheme 12**).[23]



Scheme 12. Catalytic cycle of the alkylation reaction

The previously mentioned reactions afforded the creation of one stereocenter in high yield and diastereoselectivity. The simultaneous introduction of two stereocenters has also been described employing acetals as electrophiles. The alkylation reaction of chiral *N*-azidoacetyl-1,3-thiazolidine-2-thione with aromatic and cobalted propargylic acetals afforded excellent stereoselectivities and high yields (**Scheme 13**).[24]

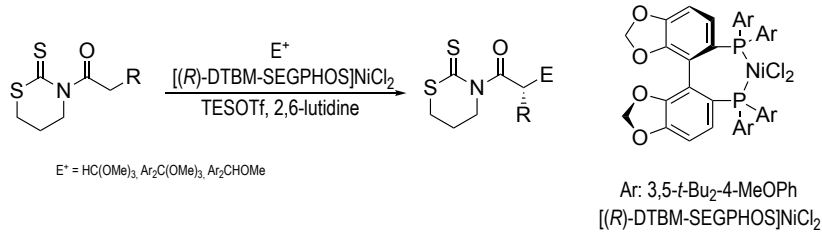


Scheme 13. Direct and catalytic alkylation of chiral *N*-azidoacetyl-1,3-thiazolidine-2-thione

Even though the approach in this methodology is well described, it needs a chiral auxiliary and the addition of two steps to the process to incorporate and eliminate this auxiliary. Looking for alternatives, our group studied a new methodology where the stereochemistry is controlled with a chiral Ni(II) catalyst.

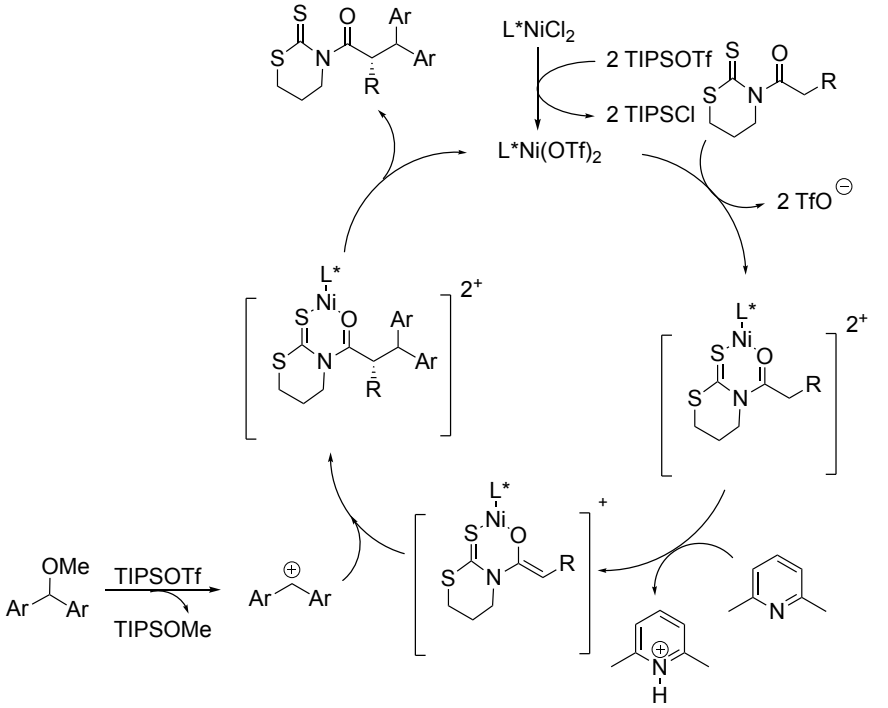
3.4.2. Chiral Ni(II) complexes

Instead of using chiral auxiliaries, chiral catalysts can also be used to perform direct, catalytic, and enantioselective reactions where the stereochemical outcome depends on the configuration on the complex ligand. Therefore, the scaffold may be achiral and 1,3-thiazinone-2-thiones have been employed. Then, *N*-acyl thiazinanethiones undergone a direct reaction which leads to enantiomerically pure compounds in high yields wising chiral complex as [(*R*)-DTBM-SEGPHOS]$NiCl_2$ (**Scheme 14**).[25]



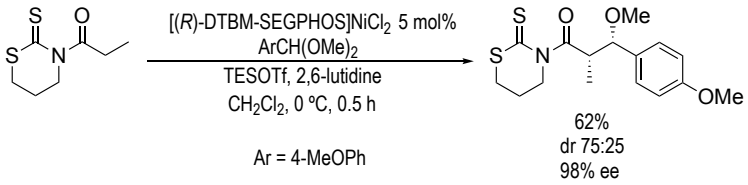
Scheme 14. Asymmetric and direct α-alkylation with chiral Ni(II) complex

The propped mechanism is analogous to Scheme 12. Nonetheless, in these cases the stereocontrol hinges upon the catalyst ligands. Indeed, the electrophiles approach is limited only to the most accessible π-face of the enolate due to steric hindrance created by the ligands (**Scheme 15**).[25]



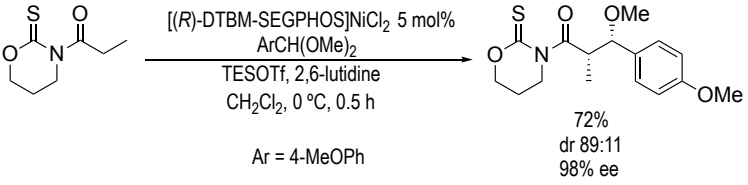
Scheme 15. Catalytic cycle of the reaction

Remarkably, the use of dimethyl acetals as the electrophiles afforded the desired product in moderate diastereomeric ratio but with an excellent enantiomeric excess (**Scheme 16**). Thus. this provides a platform for the development of new promising methodology where two stereocenters can be simultaneously created in a highly selective manner. [25]



Scheme 16. Stereoselective formation of two stereocenters catalyzed with chiral Ni(II) complex

Up to know, the optimization of this reaction has been carried out. After evaluating variables such as the scaffold, the catalyst and the Lewis acid, the ideal conditions for the simultaneous formation of two stereocenters have been established and summarized in the following Scheme. However, the full scope of the methodology is still currently unknown (**Scheme 17**).



Scheme 17. Simultaneous formation of two stereocenters catalyzed by a Ni(II) complex

4.OBJECTIVES

The first objective of this project is to prepare large quantities of the two heterocycles that are used as scaffolds for the direct, catalyzed, and enantioselective reactions that are being studied in the group. Following the experimental procedures already tested by the research group, the aim is to obtain similar yields to demonstrate that the synthetic protocol is reproductible for a not fully trained chemist.

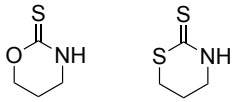


Figure 3. Heterocyclic scaffolds

The second objective is to acylate the scaffolds with propanoyl chloride in order to obtain the corresponding *N*-propanoyl thioimides. Then, different scaffolds were acylated both with carboxylic acids and acyl chlorides, following different synthetic methodologies. The acylated products will be used as starting materials to carry out different types of direct reactions, such as aldol or alkylation reactions.

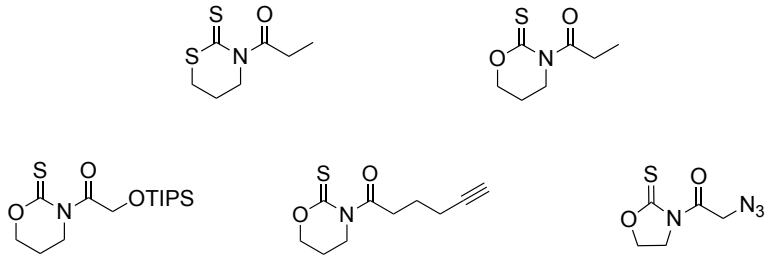


Figure 4. Acylated scaffolds

The next objective is to prepare the *o*-anisaldehyde dimethyl acetal which should be used to study the direct alkylation reaction using a chiral catalyst.

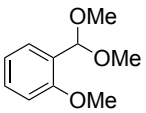
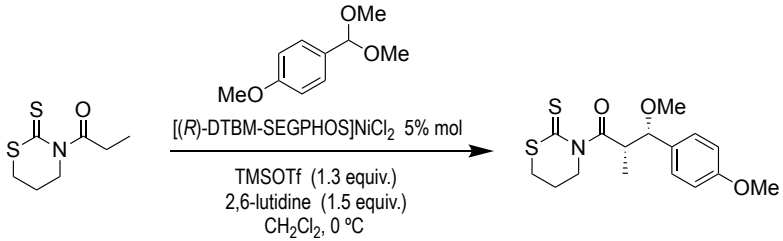


Figure 5. *o*-Anisaldehyde dimethyl acetal

The last objective is to perform a direct alkylation reaction of the previously prepared *N*-propanyol-1,3-thiazinane-2-thione using a chiral Ni(II) catalysts and *p*-anisaldehyde dimethyl acetal activated with TMSOTf to obtain the alkylated product.



Scheme 18. Direct catalyzed alkylation reaction

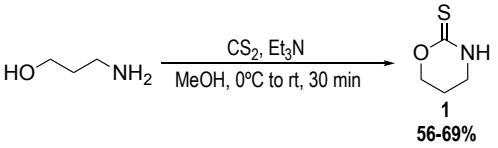
5. RESULTS AND DISCUSSION

5.1. SYNTHESIS OF THE SCAFFOLDS

As mentioned before, the first objective was to prepare both 1,3-oxazinane-2-thione (**1**) and 1,3-thiazinane-2-thione (**2**), scaffolds that have been used by the research group to accomplish their projects. Following an already described procedure, large quantities were prepared to demonstrate the reproducibility by looking at the yields and purity of the obtained products.

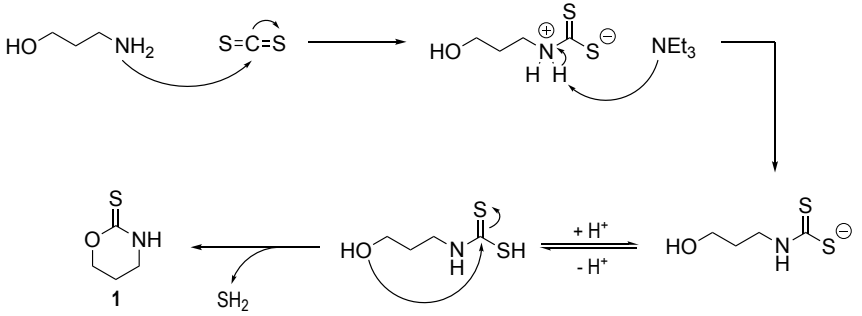
5.1.1. Synthesis of 1,3-oxazinane-2-thione (1)

A one step reaction (**Scheme 19**), with an aminoalcohol as starting material, is performed to synthetize 1,3-oxazinane-2-thione (**1**). Indeed, 3-amino-1-propanol reacts with carbon disulphide in presence of Et_3N, at 0 ºC in absolute MeOH. This procedure was performed at 5 mmol scale, obtaining the desired scaffold in good yield (69%), and at 50 mmol scale giving a quite good yield (56%). In both cases, the obtained yields were similar to the one reported by the group (52%).



Scheme 19. Synthesis of 1,3-oxazinane-2-thione (**1**)

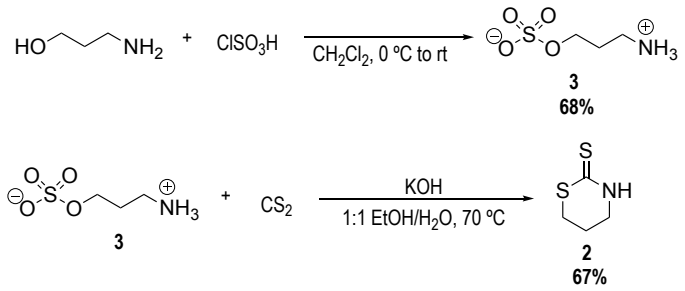
Carbon disulphide reacts with the amino group of the aminoalcohol and, under basic conditions, a dithiocarbamate is formed. Then, the hydroxyl group undergoes an intramolecular nucleophilic attack to give the desired scaffold (**Scheme 20**).



Scheme 20. Mechanism of the synthesis of 1,3-oxazinane-2-thione (**1**)

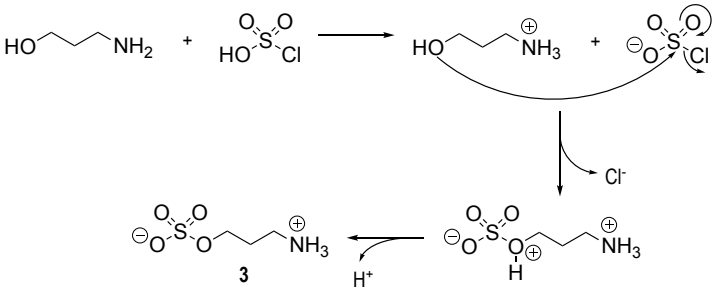
5.1.2. Synthesis of 1,3-thiazinane-2-thione (2)

To synthetize 1,3-thiazinane-2-thione (**2**) a two-step process must be carried out (**Scheme 21**). In the first step, the formation of 3-amminopropylsulfate (**3**) is achieved by mixing 3-amino-1-propanol with chlorosulfonic acid in anhydrous CH_2Cl_2 at 0ºC and stirring a 0ºC to rt. This reaction was performed obtaining the sulfate **3** in good yield (68%), but lower than the one described (89%) in the synthetic protocol of our group. The second step involves the reaction of the sulfate **3** with carbon disulfide, under basic conditions, and in 1:1 ethanol/water. This leads to the formation of the desired 1,3-thiazinane-2-thione (**2**) in good yield (67%) and similar to the one reported by the group (63%).[26]



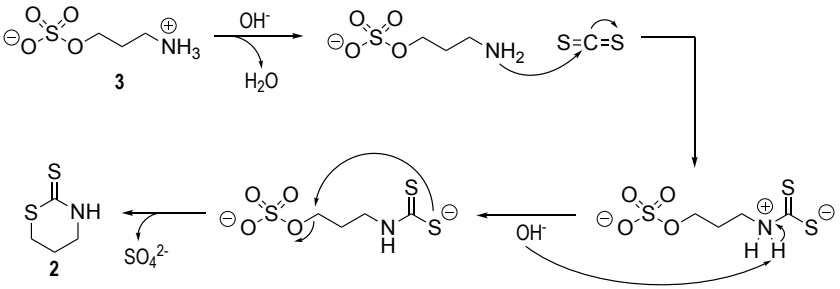
Scheme 21. Synthesis of 1,3-thiazinane-2-thione (**2**)

The mechanism of the first step reaction in the synthesis of 1,3-thizianae-2-thione (**2**) involves an acid-base reaction and a nucleophilic attack. First, chlorosulfonic acid, which is a strong acid, protonates the most basic group of the aminoalcohol, the amino group. Then, having an ammonia salt which is less nucleophilic than the alcohol, it is the hydroxyl that undergoes a nucleophilic attack to the chlorosulfonate to afford the 3-amminopropylsulfate (**3**) (**Scheme 22**).



Scheme 22. Mechanism of the 3-amminipropylsulfate (**3**) synthesis

For the second step of the reaction, the mechanism starts with an acid-base reaction between the amine group and the KOH. Then, the amine reacts with carbon disulfide to form a thiocarbamate, which undergoes an intramolecular nucleophilic attack to form the desired 1,3-thiazinane-2-thione (**2**) as it is summarized in the **Scheme 23**.



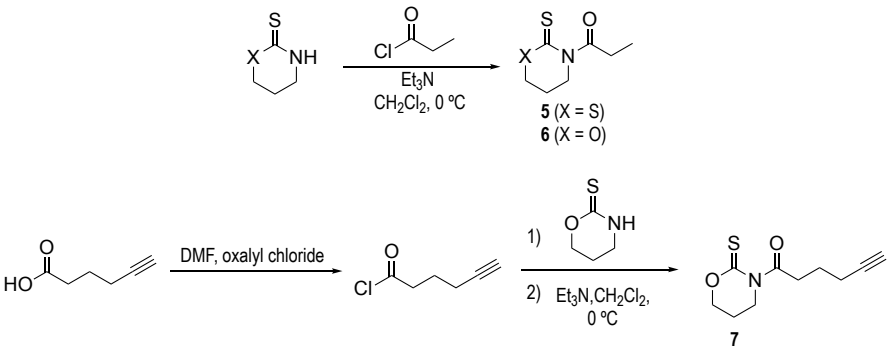
Scheme 23. Mechanism of the synthesis of 1,3-thiazinane-2-thione (**2**)

5.2. ACYLATION OF THE SCAFFOLDS

The second objective of this work was to acylate the heterocyclic scaffolds following two types of methodologies, one using carboxylic acids and the other with acyl chlorides. Different chains were used to acylate the previously prepared scaffolds and the commercially available 1,3-oxazolidin-2-thione (**4**).

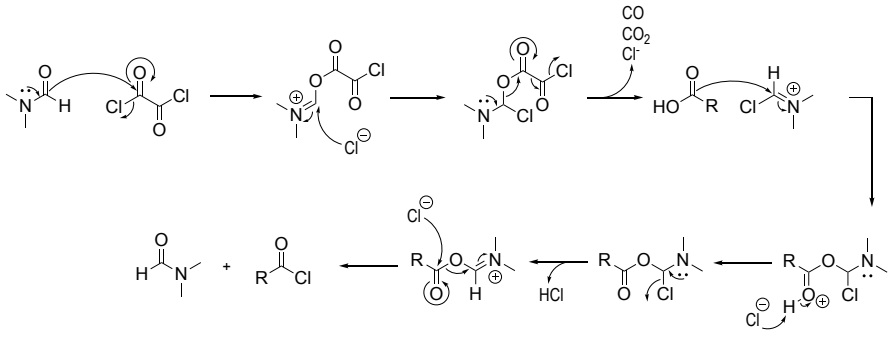
5.2.1. Acylation with acyl chlorides

To perform this synthetic route an acyl chloride is needed to react with the scaffold. This acyl chloride can be commercially available or synthetized from a carboxylic acid. If the acyl chloride has to be synthetized an extra step is necessary, making the synthesis into a two-step reaction instead of one. So, two different paths can be described (**Scheme 24**), the first one is used to synthetize *N*-propanoyl-1,3-thiazinane-2-thione (**5**) and *N*-propanoyl-1,3-oxazinane-2-thione (**6**) and the second one for *N*-(5-hexenoyl)-1,3-oxazinane-.2-thione (**7**).



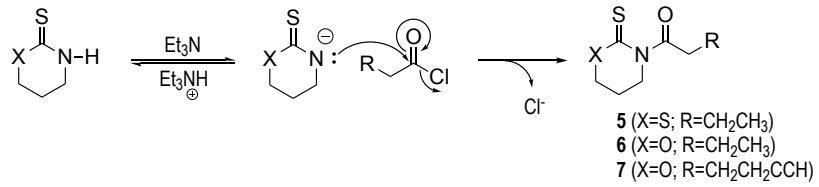
Scheme 24. Acylation with acyl chlorides

The mechanism of the preparation of the acyl chloride from the carboxylic acid involves a catalyst, DMF, which reacts with oxalyl chloride to give a more nucleophilic specie. This specie will attack the carboxylic acid to afford the acyl chloride as described in **Scheme 25**.



Scheme 25. Mechanism of the acyl chloride formation

For the reaction of the scaffold with the acyl chloride, the first step of the mechanism is the deprotonation of the scaffold with Et_3N, which allows the addition-elimination to form the *N*-acyl derivative (**Scheme 26**).



Scheme 26. Mechanism of the *N*-acyl derivative formation with acyl chloride

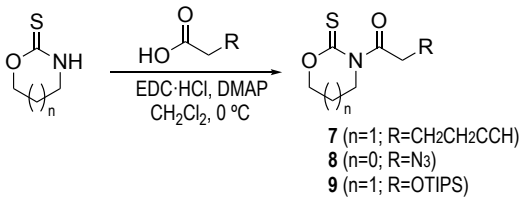
The obtained yields for the acylated products are shown in Table 1.

Scaffold	Product	Yield (%)
2	**5**	61
1	**6**	44
1	**7**	66

Table 1. Synthesis of *N*-acyl derivatives with acyl chlorides

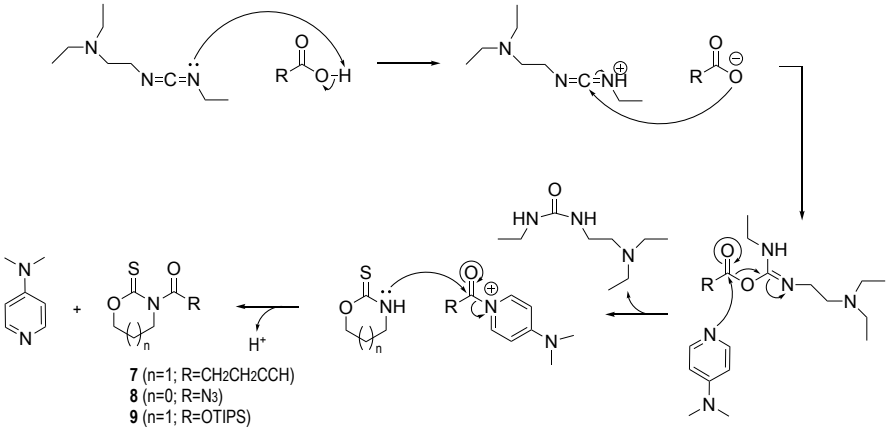
5.2.2. Acylation with carboxylic acids

To perform this synthetic route, the reaction has to be done in presence of a catalyst, 4-DMAP, and a coupling reagent, EDC·HCl (**Scheme 27**). The *N*-(5-*h*exynoyl)-1,3-oxazinane-2-thione (**7**), *N*-(2-azidoacetyl)-1,3-oxazolidine-2-thione (**8**) and *N*-(2-triisopropylsilyloxyacetyl)-1,3-oxazinane-2-thione (**9**) were acylated using this methodology.



Scheme 27. Acylation with carboxylic acid

The mechanism starts with the reaction of the carboxylic acid with the coupling reagent to form an activated ester which, in presence of the catalyst, the DMAP, forms a N-acylpyridinium salt, a more electrophilic species and, therefore, a more reactive species able to being attacked by the scaffold to give de *N*-acyl derivative (**Scheme 28**).



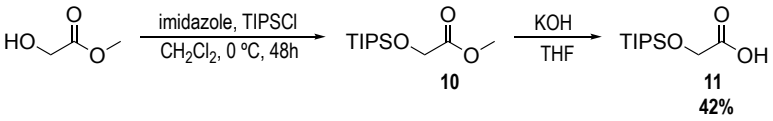
Scheme 28. Mechanism of the *N*-acyl derivative formation with carboxylic acid and DMAP

The obtained yields in the reaction for the acylated products are shown in Table 2.

Scaffold	Product	Yield (%)
1	**7**	21
4	**8**	38
1	**9**	22

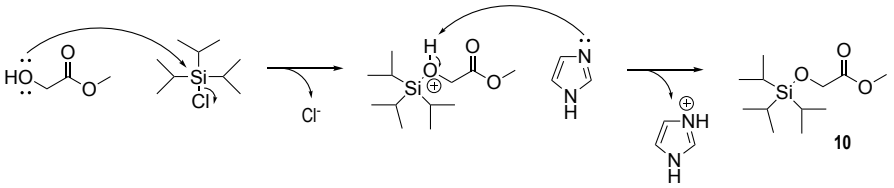
Table 2. Synthesis of *N*-acyl derivatives with carboxylic acid

It should be noted that in order synthetize the acylate product **9,** the hydroxyl group of the methyl glycolate should be protected. To achieve this protection, methyl glycolate had to react with TIPSCl and imidazole to give the corresponding silylated methyl ester **10**, which was further hydrolyzed in basic medium to give the desired carboxylic acid **11** (**Scheme 29**).



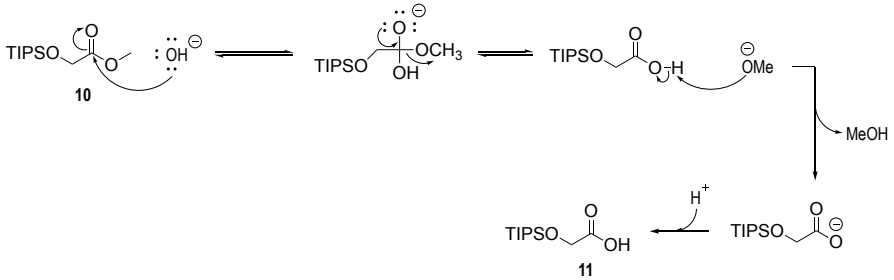
Scheme 29. Synthesis of silylated carboxylic acid **11**

The first step of this synthetic sequence is a nucleophilic substitution between the alcohol and the TIPSCl, followed by a deprotonation with imidazole to give the silylated methyl ester **10** (**Scheme 30**).



Scheme 30. Mechanism of the alcohol protection with TIPSCl

The second step is the basic hydrolysis of the ester, also called saponification. First, hydroxy attacks the carboxyl to afford the tetrahedral intermediate. After the addition, the elimination of the methoxy afford the carboxylic acid, which is deprotonated in an irreversible reaction. After an acidic quenching, the reaction affords the desired protected glycolic acid **11** (**Scheme 31**).



Scheme 31. Mechanism of the ester hydrolysis

5.2.3. Comparison of both methodologies

By looking at the yields summarized at Tables 1 and 2, it is observed that for the first methodology higher yields are obtained. This could mean that acylating with acyl chlorides is more effective than with carboxylic acids but, since different chains and scaffolds were used, a direct comparison cannot be made.

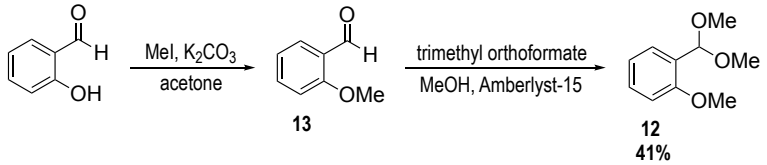
To be able to make a direct comparison, *N*-(5-*h*exynoyl)-1,3-oxazinane-2-thione (**7**) (entry 3 in Table 1 and entry 1 in Table 2) were synthetized using the two methodologies. *N*-(5-

*H*exynoyl)-1,3-oxazinane-2-thione (**7**) synthetized using an acyl chloride was obtained with a higher yield (66%) than the obtained using the carboxylic acid and the coupling agent (21%).

Also, by looking at Table 2, in entry 2 a five-membered ring scaffold was used and, in entries 1 and 3, six-membered ring scaffolds were used. The scaffolds were not acylated with the same side chains, but the results made us think that the acylation with carboxylic acid works better with five-membered ring scaffolds. To confirm this assumption, both scaffolds should be acylated with the same carboxylic acid.

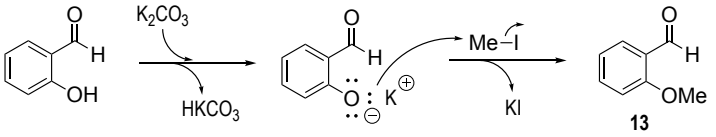
5.3. ACETAL SYNTHESIS

Having the *N*-acylated scaffolds, the next objective was the synthesis of an acetal, compounds which are used in the group to the study of the direct, catalyzed, and asymmetric alkylation reactions. To synthetize the *o*-anisaldehyde dimethyl acetal (**12**) two-reactions were performed. Using 2-hydroxybenzaldehyde as starting material, first 2-methoxybenzaldehyde (**13**) was synthetize by reacting with MeI and K2CO3. The obtained crude mixture was mixed with trimethyl orthoformate alongside Amberlyst-15 resin, giving the desired acetal 11 in good overall yield (Scheme 32). It is important to notice that in the flash column chromatography to purify acetal **12**, it is important to add a base such as Et_3N. As it is well known, the acetal synthesis is an equilibrium, and the acidic conditions of the silica gel would move the equilibrium in favor to the aldehyde formation.



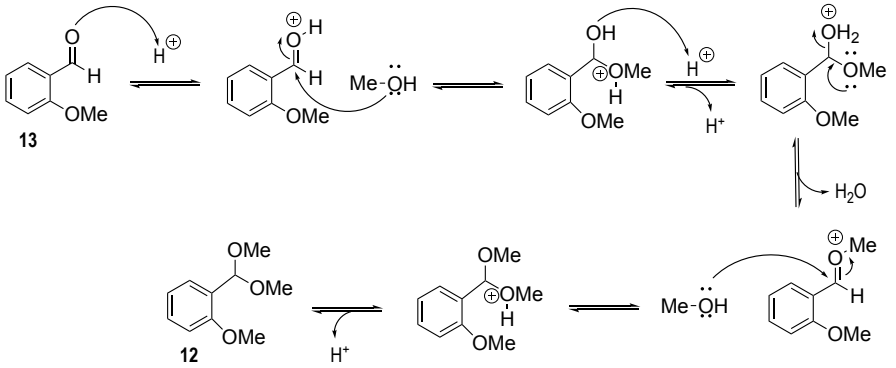
Scheme 32. Synthesis of *o*-anisaldehyde dimethyl acetal (**12**)

In the first step of this synthesis the deprotonation of the phenol takes place with K_2CO_3 to form an alkoxide salt which is a much better nucleophile and undergoes a fast S_N2 reaction with MeI to form the corresponding methyl ether **13**. This kind of reactions are known as Williamson ether synthesis (**Scheme 33**).



Scheme 33. Mechanism of the Williamson ether synthesis

In the second step, trimethyl orthoformate is needed to react with the water formed in the acetal synthesis (see **Scheme 34**) affording methyl formate and methanol and displacing the equilibrium in the formation of the dimethyl acetal. The mechanism of the acetal formation with acid catalysis is described in **Scheme 34**.

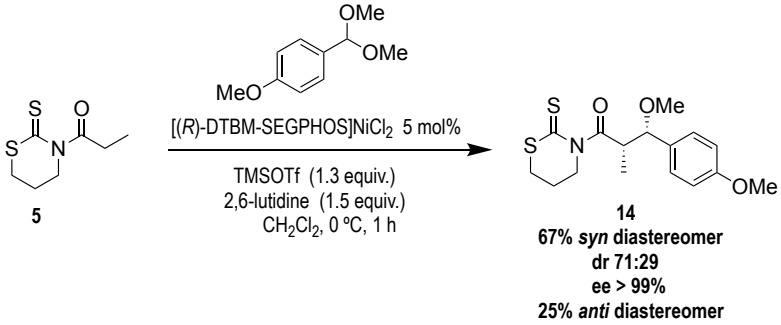


Scheme 34. Mechanism of the acetal synthesis

5.4. FIRST ATTEMPT OF A DIRECT AND CATALYZED ALKYLATION REACTION

The already prepared *N*-propanoyl-1,3-thiazinane-2-thione (**5**) was used as starting material for the direct, catalyzed, and asymmetric alkylation reaction with *p*-methoxybenzaldehyde dimethyl acetal as a proof of concept of the asymmetric alkylation reaction developed in the group. The methodology has been optimized and involves, as it has been commented on the introduction, a catalytic cycle where a simple, cheap and chiral Ni(II) catalyst, the [(*R*)-DTBM-SEGPHOS]$NiCl_2$, promotes the direct, catalytic, and asymmetric reaction between the *N*-acyl thioimide and an aromatic acetal activated with TMSOTf.

The reaction takes place with a very low quantity of catalyst (5 mol%) in presence of the Lewis acid, TMSOTf, and using 2,6-lutidine as the base (**Scheme 35**).



Scheme 35. Direct, catalyzed, and asymmetric alkylation reaction

The reaction affords very overall high yield (92%) of a syn/anti mixture showing good diastereoselectivity (dr 71:29) in favor of the *syn* adduct by NMR, demonstrating the reproducibility of the alkylation reaction described by the research group. Also, from the NMR of the purified mixture, we could determine the yields of the major diastereomer (67%) and the minor one (25%). The obtained results are similar to the ones reported by the group in both diastereoselectivity (dr 75:25) and yield (83%).

Analyzing by HPLC this purified mixture, we could determine the enantioselectivities for both major *syn* adduct (ee > 99%) and minor anti adduct (ee 80%) diastereomers. It should be noted the excellent yield of the alkylation adducts and the almost perfect enantioselectivity afforded for the major *syn* adduct, which it suggests that this direct, asymmetric, and catalytic reaction of alkylation with acetals is very robust and reproducible. Also, by comparing the obtained HPLC with a reference one (both run with the same column and conditions) where an achiral nickel catalyst was used (see Appendix 1), we can see that, while in the performed chiral reaction *syn* adduct is the major diastereomer, in the achiral reaction it is the minor.

With this excellent result, the next step should have been to carry out the reaction with the *o*-anisaldehyde dimethyl acetal previously prepared in this work. Unfortunately, there has not been enough time to test this reaction in this TFG and now it is currently being studied in the research group.

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND METHODS

The described reactions were all carried out in oven-dried glassware and under nitrogen atmosphere with anhydrous solvents. When necessary, other solvents were dried and purified following standard procedures. Otherwise, all commercially available reagents were used.

Column chromatography was performed using low pressure (flash) and SDS silica gel 60 (35-75 μm particle size. The eluents used are indicated in each experimental procedure and the R_f are approximated. Analytical thin layer chromatography (TLC) were realized on Merk silica gel 60 F_{254} plates and analyzed by UV light (254 nm). If the products could not be seen under UV light, they were revealed.

High-Performance Liquid chromatography (HPLC) analyses were conducted on Shimadzu LC-20 HPLC system, under isocratic conditions with a 1 mL/min flow at room temperature ad detected at 254 nm by ab UV-Vis spectrophotometer. The column, mobile phase and retention times are indicated in each case.

Melting points (Mp) were determined with a Stuart SMP10 apparatus and are uncorrected.

^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded at room temperature on Varian Mercury 400 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ 0.00) for ^{1}H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR. Data for ^{1}H NMR are reported as follow: chemical shift (signal multiplicity, Integration, coupling constant, assignment) and the signal multiplicity according to these abbreviations: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. The coupling constants (*J*) are quoted in Hz.

IR (ATR, Attenuated Total Reflectance) spectra were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer and the most representative frequencies (ν) are quoted in cm^{-1}.

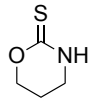
6.2. PREPARATION OF SCAFFOLDS

6.2.1. Synthesis of 1,3-oxazinane-2-thione (1)

An oven dried single-necked 25 mL round-bottomed flask was equipped with a 2.5 cm magnetic stir bar and charged with 3-amino-1-propanol (0.4 mL, 5 mmol, 1 equiv.). The aminoalcohol was dissolved in absolute methanol (5 mL) and the system was purged with N_2. While stirring, anhydrous Et_3N (0.7 mL, 5 mmol, 1 equiv.) was added to the flask. The flask was placed in an ice/water bath and CS_2 (0.5 mL, 7.5 mmol, 1.5 equiv.) was added, dropwise, to the reaction mixture. This mixture was left stirring at 0 ºC for 30 mins and then was left to warm to room temperature for 30 min while still stirring. The reaction was slowly quenched with H_2O_2 (30 % v/v in water, 0.8 mL) giving a cloudy yellow solution.

A number 3 glass filter funnel with a Büchner setup was used to filter the solid, which was washed with MeOH (10 mL). The organic extract was concentrated under reduced pressure. A yellow solid was obtained, which was dissolved with NaOH (2 M, 2.5 mL). The solution was acidified until pH 1 with HCl (2 M, 5 mL) and then extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. 1,3-Oxazinane-2-thione (**1**) was obtained as a white solid (0.405 g, 3.5 mmol, 69% yield).

The reaction was repeated following the same procedure but in a 10 times larger scale. So 3-amino-1-propanol (3.8 mL, 50 mmol, 1 equiv.), absolute methanol (50 mL), anhydrous Et_3N (7 mL, 50 mmol, 1 equiv.), CS_2 (4.5 mL, 75 mmol, 1.5 equiv.), H_2O_2 (30 % v/v in water, 8 mL), NaOH (2 M, 25 mL) and HCl (2 M, 50 mL) were used in order to obtain 1,3-oxazinane-2-thione (**1**) (3.295 g, 28.1 mmol, 56% yield).

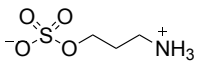


White solid. Mp 126-127 ºC. **Rf** 0.3 (hexanes/EtAcO 1:9)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (s, 1H, NH), 4.42-4.35 (m, 2H, OCH_2), 3.40-3.38 (m, 2H, $NHCH_2$), 2.16-2.05 (m, 2H, OCH_2CH_2).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 186.7 (C), 68.0 (CH_2), 40.3 (CH_2), 19.6 (CH_2).
IR (ATR): 3162, 2976, 2946, 1567, 1462, 1311, 1227, 1151 cm^{-1}.

6.2.2 Synthesis of 3-ammoniopropylsulfate (3)

An oven dried single-necked 100 mL round-bottomed flask, equipped with a 2.5 cm Teflon-coated magnetic stir-bar, was changed with 3-amino-1-propanol (11.5 mL, 150 mmol, 1 equiv.) and anhydrous dichloromethane (35 mL). A 50 mL pressure relieving addition funnel was attached to the round-bottomed flask and was charged with chlorosulfonic acid (10.5 mL, 159 mmol, 1.06 equiv.) using a 20 mL glass test tube. The flask was immersed in an ice/water bath and the solution was stirred for 5 min. The chlorosulfonic acid was added dropwise for over 30 min., allowing the fumes to scape. A white foam was formed during the addition. Once the addition was complete, the reaction mixture was stirred at 0 ºC for 20 min. Then, it was left to warm slowly to room temperature for over 30 min. Once at room temperature, the reaction mixture was stirred for 1 h.

The resulting mixture was filtered through a 70 mm diameter number 3 glass filter funnel with a Büchner setup and a bent spatula and methanol (25 mL) were used to remove the remaining product. The mixture in the filter funnel was triturated with methanol (2x20 mL), using a spatula to break up the lumps each time. The resulting white solid was broken up into a powder and transferred to a 100 mL round-bottomed flask. The flask was placed on a rotatory evaporator (40 ºC, 12 mmHg) for 1 h to obtain the pure 3-amminopropylsulfate (**3**) as a white powder (15.879 g, 102.45 mmol, 68% yield).



White powder. Mp 205-207 ºC
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (s, 3H, NH_3), 3.82 (t, J = 6.1 Hz, 2H, NH_3CH_2), 2.88-2.83 (m, 2H, SO_4CH_2), 1-84-1.77 (m, 2H, $NH_3CH_2CH_2$).
^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 63.4 (CH_2), 36.9 (CH_2), 27.3 (CH_2).
IR (ATR): 3123, 3066, 2974, 1622, 1572, 1192, 1166, 1030 cm^{-1}.

6.2.3 Synthesis of 1,3-thiazinane-2-thione (2)

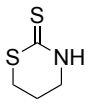
First, KOH beads (12.736 g, 225.25 mmol, 2.2 equiv.) are weighed in a 250 mL conical flask equipped with a 4 cm Teflon-coated magnetic stir bar and dissolved in 1:1 ethanol/water (100 mL) solution, which will be used later.

An oven dried single-necked 250 mL round-bottomed flask, equipped with a 4 cm Teflon-coated magnetic stir-bar, was charged with 3-amminopropylsulfate (**2**) (15,848 g, 102,85 mmol, 1 equiv.) and absolute ethanol (15 mL) at room temperature. The resulting solution was stirred at room temperature for a couple of minutes and neat carbon disulfide (8.2 mL, 136 mmol, 1.3 equiv.) was quickly added using a 10 mL syringe. A 250 mL pressure relieved addition funnel was attached to the round-bottomed flask, charged with the KOH solution, sealed with a rubber septum, and purged with N_2. The KOH solution was added dropwise for over 30 min, giving a yellow solution. Once the addition was complete, the addition funnel was replaced by a reflux condenser sealed with a rubber septum, where a N_2-filled balloon was attached. The mixture was heated to reflux (70 ºC) in an aluminum heating block for 1 h. Then, it was slowly cooled to room temperature to give a fluffy white precipitate, which was cooled to 0 ºC with an ice/water bath for 15 min.

The precipitate was filtered using a 70 mm diameter number 3 glass filter funnel with a Büchner setup. The flask was rinsed with cold deionized water and the washings were added to the filter funnel. The solid was dried in vacuo for 15 min and then washed with dichloromethane (3x35 mL), breaking up the solid with a spatula each time. The combined organic extracts were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to give the pure white powder of 1,3-thiazinane-2-thione (**2**) (4.07 g, 30.56 mmol, 30% yield).

The remaining solid from in the filter funnel was transferred to a 250 mL round-bottomed flask, equipped with a 4 cm Teflon-coated magnetic stir bar, which was charged with dichloromethane (150 mL) and attached to a rubber septum sealed reflux condenser. The system was purged with N_2, and a N_2-filled balloon was left attached. The mixture was heated to reflux (70 ºC) and stirred for 1h. Then whilst warm, it was filtered through a number 3 glass filter funnel with a Büchner setup. The solid is washed with dichloromethane (2x50 mL) and breaking up the solid with a spatula each time. The combined filtrates were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to give the pure 1,3-thiazinane-2-thione (**2**) (5.119 g, 38.44 mmol, 37% yield).

Overall, 9.189 g of 1,3-thiazinane-2-thione (**2**) were obtained (67% yield).



White powder. Mp 138-140 ºC**. R_f** 0.3 (hexanes/EtAcO 6.4)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (s, 1H, NH), 3.50-3.46 (m, 2H, $NHCH_2$), 3.01-2.98 (m, 2H, SCH_2), 2.21-216 (m, 2H, SCH_2CH_2).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 194.6 (C), 44.3 (CH_2), 30.0 (CH_2), 20.5 (CH_2).
IR (ATR): 3164, 3088, 2946, 1565, 1461, 1309, 1226, 1154 cm^{-1}.

6.3. SCAFFOLDS ACYLATION

6.3.1. Acylation with acyl chlorides. General procedure.

An oven-dried single-necked round-bottomed flask, equipped with a 4 cm Teflon-coated stir-bar, was charged with the corresponding scaffold (1 equiv.). The flask was sealed with a rubber septum and the system was purged with N_2, leaving a N_2 filled balloon attached. The flask was charged with anhydrous dichloromethane and immersed in an ice/water bath. The solution was stirred for 2 min and freshly distilled triethylamine (1.3 equiv.) was added dropwise. The solution was stirred for 2 min and the acyl chloride (1.2 equiv.) was added dropwise. The ice/water bath was removed, and the reaction mixture was left stirring overnight.

The resulting mixture was cooled with and ice/water bath and quenched with an ammonium chloride saturated solution and left stirring for 5 min. The mixture was transferred to a separating funnel. The aqueous phase was rinsed with and water and extracted with dichloromethane. The combined organic extracts were washed with NaOH (2 M), dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The resulting crude was characterized using ^{1}H NMR and purified by flash chromatography column on silica gel, obtaining the pure acylated product.

6.3.2. Acylation with carboxylic acids. General procedure.

An oven-dried single-necked round-bottomed flask, equipped with a 4 cm Teflon-coated stir-bar, was charged with the corresponding scaffold (1 equiv.), EDC·HCl (1.2 equiv.), DMAP (0.05 equiv.) and dissolved in dichloromethane. The flask was sealed with a rubber septum and the system was purged with N_2, leaving a N_2 filled balloon attached. The solution was stirred at 0 ºC. A solution of the carboxylic acid (1.1 equiv.) in dichloromethane was prepared

under N_2 atmosphere and was added to the previous solution. The mixture was left stirring at 0 ºC for 15 min. Once the time was over, it was left stirring overnight at room temperature.

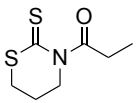
Dichloromethane was added and the organic phase was extracted with H_2O. The aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure.

The resulting crude was characterized using ^{1}H NMR and purified by flash chromatography column on silica gel, obtaining the pure acylated product.

6.3.3 Synthesis of *N*-propanoyl-1,3-thiazinane-2-thione (5)

Following the general procedure 6.3.1, a 25 mL round-bottomed flask was charged with 1,3-thiazinane-2-thione (0.671 g, 5 mmol, 1 equiv.) and dissolved in anhydrous dichloromethane (5 mL). Later, anhydrous triethylamine (0.9 mL, 6 .6 mmol, 1.3 equiv.) was added, followed by propionyl chloride (0.5 mL, 6 mmol, 1.2 equiv.) to obtain a yellow solution. The reaction was quenched with an ammonium chloride saturated solution (2 mL) and transferred to a 100 mL separating funnel. The aqueous phase was rinsed with water (15 mL) and extracted with dichloromethane (4 x 5 mL). The combined organic extracts were washed with NaOH (2 M, 15 mL) dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude was purified by flash chromatography column on silica gel (90:10 hexanes/ethyl acetate), obtaining the pure *N*-propanyol-1,3-thiazinane-2-thione (**5**) as a yellow oil (0.415 g, 2.19 mmol, 44% yield).The non-pure fractions were columned again (90:10 hexanes/ethyl acetate), obtaining the pure *N*-propanyol-1,3-thiazinane-2-thione (**5**) as a yellow oil (0.161 g, 0.85 mmol, 17% yield).Combining both products, 0.576 g of pure *N*-propanyol-1,3-thiazinane-2-thione (**5**) were obtained as a yellow oil (61% overall yield).

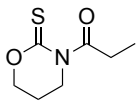


Yellow oil. R_f 0.3 (90:10 hexanes/EtOAc)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.97-3.90 (m, 2H, NCH_2), 3.09 (q, *J* = 7.3, Hz, 2H, $COCH_2$), 3.03 (t, *J* = 6.8 Hz, 2H, SCH_2), 2.31-2.19 (m, 2H, SCH_2CH_2), 1.22 (t, *J* = 7.3 Hz, 3H, OCH_2CH_3).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 202.8 (C), 178.9 (C), 46.4 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 22.8 (CH_2), 10.0 (CH_3).
IR (ATR): 2974, 2933, 2873, 1698, 1470, 1347, 1302, 1189, 1125, 1020 cm^{-1}.

6.3.4 Synthesis of *N*-propanoyl-1,3-oxazinane-2-thione (6)

Following the general procedure 6.3.1, a 25 mL round-bottomed flask was charged with 1,3-oxazinane-2-thione (0.590 g, 5 mmol, 1 equiv.) and dissolved in anhydrous dichloromethane (5 mL). Later, anhydrous triethylamine (0.91 mL, 6 .6 mmol, 1.3 equiv.) was added, followed by propionyl chloride (0.52 mL, 6 mmol, 1.2 equiv.) to obtain a brown solution. The reaction was quenched with an ammonium chloride saturated solution (2 mL) and transferred to a 100 mL separating funnel. The aqueous phase was rinsed with water (15 mL) and extracted with dichloromethane (4 x 5 mL). The combined organic extracts were washed with NaOH (2 M, 15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude was purified by flash chromatography column (80:20 hexanes/ethyl acetate), obtaining the pure *N*-propanyol-1,3-oxazinane-2-thione (**6**) as a white solid (0.380 g, 2.19 mmol, 44% yield).



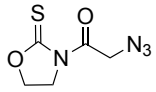
White solid. Mp 59-61 ºC. $\mathbf{R_f}$ 0.3 (80:20 hexanes/EtOAc)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.34 (t, *J* = 7.1 Hz, 2H, OCH_2), 3.75 (t, *J* = 7.1 Hz, 2H, NCH_2), 3.16 (q, *J* = 7.3 Hz, 2H, $N(CO)CH_2$), 2.23-2.20 (m, 2H, OCH_2CH_2), 1.25 (t, *J* = 7.3 Hz, 3H, OCH_2CH_3).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 190.1 (C); 179.2 (C); 68.3 (CH_2); 43.9 (CH_2); 32.2 (CH_2); 22.3 (CH_2); 10.2 (CH_3).
IR (ATR): 2977, 2873, 1712, 1471, 1300, 1250, 1038 cm^{-1}.

6.3.5 Synthesis of *N*-(2-azidoacetyl)-1,3-oxazolidine-2-thione (8)

Following the general procedure 6.3.2, a 25 mL round-bottomed flask was charged with 1,3-oxazolidine-2-thione (1.219 g, 11.8 mmol, 1 equiv.), EDC·HCl (2.700 g, 14.08 mmol, 1.2 equiv.), DMAP (0.076 g, 0.62 mmol, 0.05 equiv.) and dissolved in dichloromethane (11 mL). After stirring, a solution of azidoacetic acid (1.298 g, 12.84 mmol, 1.1 equiv.) in dichloromethane (6 mL) was added to the flask to obtain a yellow solution.

After stirring overnight, an orange-red solution was obtained. Dichloromethane (25 mL) was added, and the organic phase was extracted with H_2O. The aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure.

The crude was purified by flash chromatography column (85:15 hexanes/ethyl acetate), obtaining the pure *N*-(2-azidoacetyl)-1,3-oxazolidine-2-thione (**8**) as a white solid (0.837 g, 4.50 mmol, 38% yield).



White solid. R_f 0.3 (85:15 hexanes/EtOAc)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.91 (s, 2H, $COC\underline{H_2}$), 4.65 (t, *J* = 8.5 Hz, 2H, $C\underline{H_2}O$), 4.29 (t, *J* = 8.5 Hz, 2H, $C\underline{H_2}N$).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 184.9 (C); 169.0 (C); 67.5 (CH_2); 54.5 (CH_2); 46.9 (CH_2).
IR (ATR): 2917, 2100, 1697, 1364, 1320, 1212, 1168, 1017 cm^{-1}.

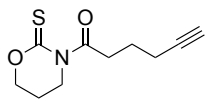
6.3.6 Synthesis of *N*-(5-hexynoyl)-1,3-oxazinane-2-thione (7)

6.3.6.1 From 5-hexynoic acid and a coupling agent

Following the general procedure 6.3.2, a 25 mL round-bottomed flask was charged with 1,3-oxazinane-2-thione (0.588 g, 5 mmol, 1 equiv.), EDC·HCl (1.135 g, 5.5 mmol, 1.2 equiv.), DMAP (0.031 g, 0.25 mmol, 0.05 equiv.) and dissolved in dichloromethane (5 mL). After stirring, a solution of 5-hexynoic acid (0.6 mL, 5.5 mmol, 1.1 equiv.) in dichloromethane (3 mL) was added to the flask to obtain an orange solution.

After stirring overnight, a dark red solution was obtained. Dichloromethane (12 mL) was added, and the organic phase was extracted with H_2O. The aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure.

The crude was purified by flash chromatography column (60:40 hexanes/ethyl acetate), obtaining the pure *N*-(5-hexynoyl)-1,3-oxazolidine-2-thione (**7**) as a yellow oil (0.226 g, 1.07 mmol, 21% yield).



Yellow oil. R_f 0.3 (80:20 hexanes/EtOAc)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.37-4.32 (m, 2H, $OC\underline{H_2}$), 3.75 (t, *J* = 7.1 Hz, 2H, $NC\underline{H_2}$), 3.33-3.24 (m, 2H, $OCH_2\underline{CH_2}$), 2.63 (t, 2H, *J* = 7.3 Hz, $COCH_2CH_2\underline{CH_2}$), 2.33-2.21 (m, 2H, $COC\underline{H_2}$), 2.00-1.87 (m, 3H, $COCH_2C\underline{H_2}$, $C\underline{H}$).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 190.1 (C); 177.7 (C); 69.6 (C); 69.3 (CH); 68.3 (CH_2); 43.8 (CH_2); 37.4 (CH_2); 24.7 (CH_2); 22.4 (CH_2); 17.7 (CH_2).
IR (ATR): 3303, 2943, 1704, 1637, 1515, 1204, 1154, 1041, 644 cm^{-1}.

6.3.6.2 From 5-hexynoil chloride

Recently distilled oxalyl chloride (0.62 mL, 7.2 mmol, 1.2 equiv.) was added dropwise to a solution of 5-hexynoic acid (0.66 mL, 6 mmol, 1 equiv.) in dichloromethane (20 mL) under N_2 atmosphere at 0 ºC. A few drops of *N,N*-dimethylformamide (0.05 mL, 0.6 mmol, 0.1 equiv.) were added and the resultant solution was warmed to room temperature and stirred for 5 h. The solution was concentrated under vacuo to obtain 5-hexynoyl chloride.

Following the general procedure 6.3.1, a 25 mL round-bottomed flask was charged with 1,3-oxazinane-2-thione (0.588 g, 5 mmol, 1 equiv.) and dissolved in anhydrous dichloromethane (5 mL). Later, anhydrous triethylamine (0.7 mL, 6.5 mmol, 1.3 equiv.) was added, followed by the 5-hexynil chloride prepared before (6 mmol, 1.2 equiv.) to obtain a brown solution. The reaction mixture was stirred 24 h at room temperature. The reaction was quenched with an ammonium chloride saturated solution (2 mL) and transferred to a 100 mL separating funnel. The aqueous phase was rinsed with water (15 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude was purified by flash chromatography column on silica gel (70:30 hexanes/ethyl acetate), obtaining the pure *N*-(5-hexynoyl)-1,3-oxazolidine-2-thione (**7**) as a dark yellow solid (0.698 g, 3.31 mmol, 66% yield).

6.3.7 Synthesis of *N*-(2-triisopropylsilyloxyacetyl)-1,3-oxazinane-2-thione (9)

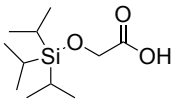
6.3.7.1 Synthesis of 2-(trisisopropylsilyloxy)acetic acid (11)

A 50 mL round-bottomed flask was charged with methyl glycolate (0.78 mL, 8.4 mmol, 1 equiv.), imidazole (1.354 g, 20 mmol, 2.38 equiv.) and dissolved in dichloromethane (10 mL). Then, TIPSCl (2.2 mL, 10.3 mmol, 1.23 equiv.) was added and the reaction mixture was left stirring for 48 h.

The mixture was diluted in diethyl ether (50 mL) and washed with water (2 x 30 mL), HCl (2 M, 2 x 30 mL) and brine (30 mL). The organic layer is dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to obtain the crude mixture.

A solution of KOH (1 M in water/MeOH 2:1, 10 mL) was added to over a solution of the previous crude in THF (16 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 72 h.

Then, the reaction mixture was diluted in diethyl ether (70 mL) and washed with water (2 x 50 mL). The aqueous layer was acidified with HCl (2 M) until pH 1. Then, it was extracted with diethyl ether (2 x 80 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to obtain 2-(trisisopropylsilyloxy)acetic acid (**11**) as a colorless oil (0.81 g, 3.55 mmol, 42% yield).



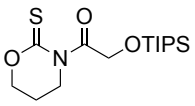
Colorless oil.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.28 (s, 2H, $SiOC\underline{H}_2$), 1.23 (m, 3H, $(CH_3)C\underline{H}$), 1.05 (d, J = 6.6 Hz, 18H, $(C\underline{H}_3)CH$).

6.3.7.2 Synthesis of *N*-(2-triisopropylsilyloxyacetyl)-1,3-oxazinane-2-thione (9)

Following the general procedure 6.3.2, a 25 mL round-bottomed flask was charged with 1,3-oxazinane-2-thione (0.350 g, 3 mmol, 1 equiv.), EDC·HCl (0.690 g, 3.6 mmol, 1.2 equiv.), DMAP (0.020 g, 0.15 mmol, 0.05 equiv.) and dissolved in dichloromethane (5 mL). After stirring, a solution of 2-(trisisopropylsilyloxy)acetic acid (**11**) (0.77g, 3.3mmol, 1.1equiv.) in dichloromethane (3 mL) was added to the flask.

After stirring overnight, dichloromethane (12 mL) was added, and the organic phase was extracted with H_2O. The aqueous phase was extracted with dichloromethane and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude mixture was purified by flash chromatography column on silica gel (90:10 hexanes/ethyl acetate), obtaining the pure *N*-(2-triisopropylsilyloxyacetyl)-1,3-oxazinane-2-thione (**8**) as a yellow oil (0.205 g, 0.65 mmol, 22 % yield).



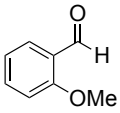
Yellow oil. R_f 0.3 (90:10 hexanes/EtOAc)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.12 (s, 2H, SiOC$\underline{H_2}$), 4.34 (m, 2H, OC$\underline{H_2}$), 3.80 (t, *J* = 7.0 Hz, 2H, NC$\underline{H_2}$), 2.23 (m, 2H, OCH$_2$C$\underline{H_2}$), 1.20 (m, 3H, (CH$_3$)C$\underline{H}$), 1.09 (d, *J* = 6.1 Hz, 18H, (C$\underline{H_3}$)CH).

6.4. Synthesis of o-anisaldehyde dimethyl acetal (12)

6.4.1 Synthesis of 2-methoxybenzaldehyde (13)

2-Hydroxybenzaldehyde (1.6 mL, 15 mmol, 1 equiv.) and K_2CO_3 (4.177 g, 30 mmol, 1 equiv.) were added to a 250 mL round-bottomed flask. The mixture was purged with N_2. Pure acetone (75 mL) and MeI (1.4 mL, 23 mmol, 1.5 equiv.) were added to the previous mixture, giving a yellow solution. The mixture was left stirring at room temperature overnight.

The reaction was quenched with distilled water (75 mL) and extracted with ethyl acetate (3 x 40 mL) and brine (80 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain the unpurified 2-methoxybenzaldehyde (**13**) (2.214 g, 16.28 mmol, 109 % yield), which was used in the next step without purification.



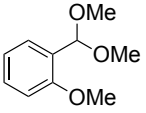
Yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.48 (s, 1H, CO$\underline{H}$), 7.85-7.80 (m. 1H, Ar$\underline{H}$), 7.56-7.50 (1H, m, Ar$\underline{H}$), 7.03-6.98 (2H, m, Ar$\underline{H}$), 3.94 (s, 3H, OC$\underline{H_3}$).

6.4.2 Synthesis of o-anisaldehyde dimethyl acetal (12)

Trimethyl orthoformate (7 mL, 64 mmol, 4 equiv.) was added to the unpurified 2-methoxybenzaldehyde (**13**) and dissolved with anhydrous dichloromethane (6.5 mL) alongside with Amberlyst-15. The solution was left stirring at room temperature for 72 h to give a dark red solution.

The mixture was filtered to remove the resin, washed with methanol, and concentrated under vacuum. The dark pink oil was purified by flash chromatography column on silica gel

(98:2 hexanes/diethyl ester + 3 % Et_3N), obtaining the pure *o*-anisaldehyde dimethyl acetal (**12**) as a colorless oil (1.201 g, 6.59 mmol, 41 % yield).



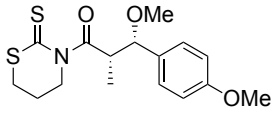
Colorless oil. R_f 0.1 (98:2 hexanes/Et_2O)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (1H, dd, *J* = 7.5, 1.8 Hz, Ar-H), 7.30 (1H, ddd, *J* = 8.3, 7.5, 1.8 Hz, Ar-H), 6.97 (1H, dd, J = 7.5, 1.1 Hz, Ar-H)6.90 (1H, dd, *J* = 8.3, 1.1 Hz, Ar-H), 5.58 (s, 1H, C<u>H</u>C(OCH_3)$_2$, 3.85 (s, 3H, ArO<u>C</u>H_3), 3.36 (s, 3H, CH(O<u>C</u>H_3)$_2$.

6.5. FIRST ATTEMPT OF A DIRECT, CATALYZED AND ASYMMETRIC ALKYLATION REACTION

6.5.1 (2*S*,3*S*)-N-[3-Methoxy-3-(4-methoxyphenyl)-2-methylpropanoyl]-1,3-thiazinane-2-one (14)

Neat TMSOTf (120 μL, 0.65 mmol, 1,3 equiv.) were added dropwise to a stirred solution of <u>N</u>-propanoyl-1,3-thiazinane-2-thione (**5**) (0.096 g, 0.5 mmol, 1.0 equiv.), *p*-anisaldehyde dimethyl acetal (95 μL, 0.55 mmol, 1.1 equiv.) and the chiral Ni(II) catalyst, [(*R*)-DTBM-SEGPHOS]$NiCl_2$ (0.0328 g, 0.025 mmol, 0.05 equiv.) in anhydrous CH_2Cl_2 (2 mL) are added into a 10 mL oven dried round-bottomed flask. Then, the system is purged with N_2, stirred at 0 ºC in an ice/water bath. Then, 2,6-lutidine (90 μL, 0.75 mmol, 1.5 equiv.) are added to the mixture and the reaction is left stirring at 0 ºC for 1 h.

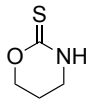
The reaction mixture is quenched, at 0 ºC, with a NH_4Cl saturated solution (2 mL) and left stirring at room temperature for 5 min. The reaction mixture is transferred to a separating funnel and the flask is rinsed with water (3x10 mL). The aqueous layer is extracted with CH_2Cl_2 (3x10 mL) and the organic layer is dried over $MgSO_4$, filtrated, and concentrated under reduced pressure, obtaining the adducts as a dark yellow oil which was analyzed by 1H NMR to determine *syn/anti* diastereoselectivity and conversion of the reaction (93% conversion, dr 71:29). Finally, the crude was purified via flash column chromatography (80:20 hexane/EtOAc) giving both major *syn* diastereomer (67% yield, 115 mg, 0.34 mmol, ee > 99%) and the corresponding minor anti diastereomer (25% yield, 43.7 mg, 0.13 mmol, ee 80%) were isolated as yellow oils.



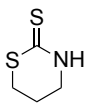
Major (2*S*,3*S*) enantiomer. Yellow oil. R_f 0.44 (80:20 CH_2Cl_2/hexanes) **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.21-7.19 (m, 2H, ArH), 6.89-6.86 (m, 2H, ArH, 2H), 4.11-4.06 (m, 2H, $COC\underline{H}CH_3$), 3.82 (s, 3H, $ArOCH_3$), 3.67 (dt,1H, J = 13.2, 5.4 Hz, NCH_aH_b), 3.15 (s, 3H, $C\underline{H}OCH_3$), 3.09-3.04 (m, 1H, $NC\underline{H}_aH_b$), 2.66 (dt, J = 12.5, 6.8 Hz, $CSC\underline{H}_aH_b$), 2.38-2.33 (m, 1H, $CSCH_a\underline{H}_b$), 1.90-1.85 (m, 1H, $NCH_2C\underline{H}_aH_b$), 1.49 (d, J = 6.1Hz, $COCHC\underline{H}_3$),1.31-1.27 (m,1H, $NCH_2\underline{C}H_a\underline{H}_b$).

7. CONCLUSIONS

The first objective of this project was to prepare large quantities of the heterocycles that are used as scaffolds, which were obtained in similar yields compared with the ones described by the group.

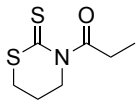


69%



67%

The second objective was to acylate the scaffolds both with carboxylic acids and acyl chlorides, following different synthetic methodologies. Since different methodologies were used, different yields have been obtained.



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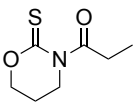

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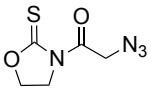

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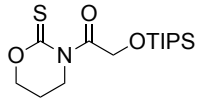
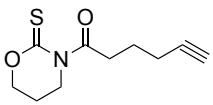
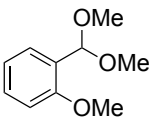


22%



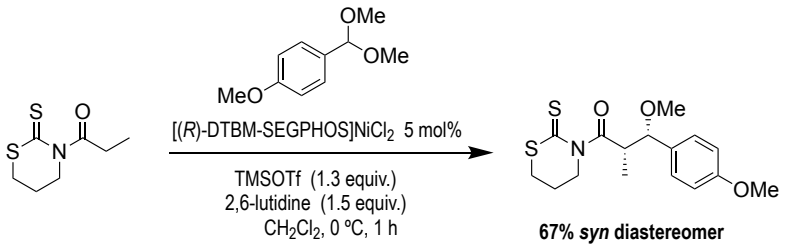
21-66%

o-Anisaldehyde dimethyl acetal was obtained in moderated yield and will be used by the group to study the direct alkylation reaction using a chiral catalyst.



41%

The last objective was to perform a direct, catalyzed and asymmetric alkylation reaction of the previously prepared *N*-propanyol-1,3-thiazinane-2-thione using a chiral Ni(II) catalysts and *p*-anisaldehyde dimethyl acetal activated with TMSOTf to obtain the alkylated product in high yields, good diastereoselectivity and excellent enantioselectivity.



67% *syn* diastereomer
dr 71:29
ee > 99%
25% *anti* diastereomer

8. REFERENCES AND NOTES

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9. ACRONYMS

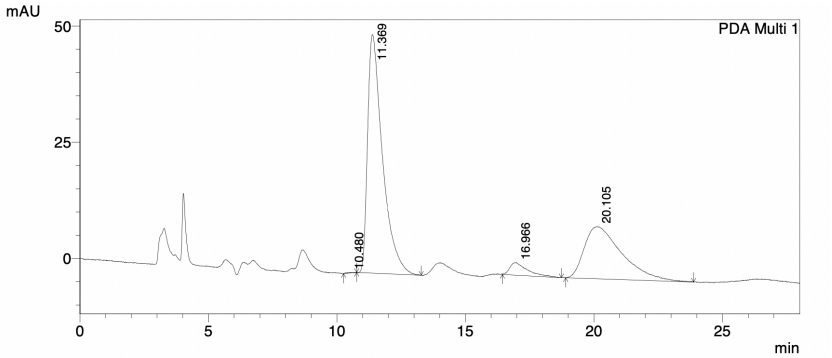
Ar	Aromatic
ATR	Attenuated Total Reflectance
δ	Chemical shift
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
E^+	Electrophile
EDC	1-Ehyl-3-(3-dimethylanimopropyl)carbodiimide
equiv.	Equivalent(s)
Et	Ethyl
Et_3N	Triethylamine
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
HPLC	High performance liquid chromatography
IR	Infrared spectroscopy
LA	Lewis acid
LDA	Lithium diisopropylamide
Me	Methyl
MeI	Iodomethane
MeOH	Methanol
NMR	Nuclear Magnetic Resonance
Ph	Phenyl

R_f	Retention factor
rt	Room temperature
TESOTf	Trimethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TIPSCl	Triisopropylsilyl chloride
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

APPENDICES

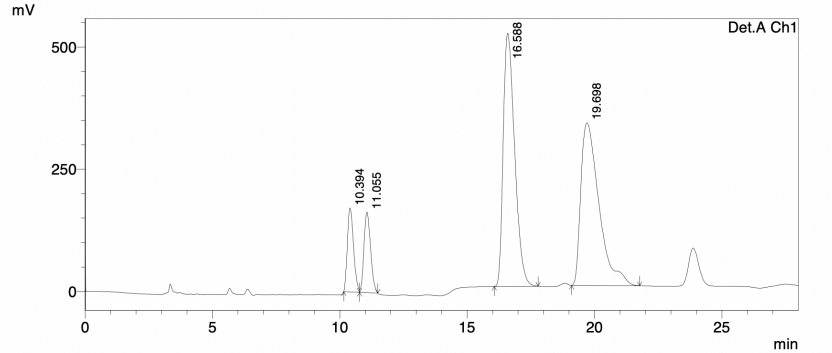
APPENDIX 1: HPLC COMPARISON IN CHIRAL AND ACHIRAL CATALYST REACTIONS

→ Chiral catalyst



Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.480	1851	188	0.055	0.287
2	11.369	2071675	51328	61.988	78.367
3	16.966	127961	2732	3.829	4.171
4	20.105	1140591	11249	34.128	17.175
Total		3342078	65497	100.000	100.000

→ Achiral catalyst



Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.394	2887967	171754	7.497	14.475
2	11.055	2977409	164743	7.729	13.884
3	16.588	16141663	517393	41.904	43.603
4	19.698	16513695	332698	42.870	28.038
Total		38520734	1186588	100.000	100.000