Tutor/s

Dr. Pedro Romea García
Departament de Química Inorgànica i Orgànica.

Grau de Química

Treball Final de Grau

Enantioselective carbon-carbon bond forming reactions catalyzed by chiral nickel (II) complexes.

Reaccions enantioselectives de formació d'enllaços carboni-carboni catalitzades per complexos quirals de níquel (II).

Otman Lamrhari Elabiad

June 2023

Universitat de Barcelona

B:KC Barcelona Knowledge Campus
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- Who are you?

- You know. You all know exactly who I am. Say my name. I'm the cook.

Heisenberg "W.W".

En primer lugar, deseo expresar mi gratitud a Pedro, por su orientación experta y su paciencia a lo largo de todo el proceso. Sus conocimientos y comentarios críticos han sido invaluables para el desarrollo de este trabajo, y estoy sinceramente agradecido/a por su guía constante.

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Y, por último, a mi abuela, que desde Marruecos sigue preocupándose por mí. Tu amor y apoyo incondicional son un motor constante en mi vida.

REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (SDG)

Chemistry in general, but especially synthetic chemistry, has been heavily influenced and conditioned by the economic sphere in recent years. Therefore, one of the objectives of synthesis is the production of complex compounds, optimizing the methodology to reduce both costs and generated waste.

As explained in this project, our group is investigating a methodology for the synthesis of desired compounds using an asymmetric catalyst to control stereoselectivity and, consequently, make the synthesis more sustainable and economically viable.

Consequently, this project could align with the objectives of improving scientific research (9.5), sustainable development (12.4 and 12.5), and climate action (13).

The objective of SDG 9.5 is related to promoting scientific and technological research. This project, by involving the development and application of a catalyst for enantioselectivity control, could contribute to advancements in the chemical industry.

SDG 12.4 aims to achieve environmentally sound management of chemicals and all waste throughout their life cycle, following agreed international frameworks, and significantly reduce their emissions to air, water, and soil to minimize adverse impacts. SDG 12.5 aims to substantially reduce waste generation through prevention, reduction, recycling, and reuse. All of this can be achieved through the use of a metallic catalyst.

Although not directly related to synthesis, the objective of SDG 13, the use of efficient catalysts, can contribute to emissions reduction and resource efficiency, which can have a positive impact on environmental sustainability.

CONTENTS

1. SUMMARY

Over the past decades, the construction of new carbon-carbon bonds has been of great importance in the synthesis of organic products, such as in the pharmaceutical industry. The significance of this synthesis lies in the control of stereoisomerism, which has been made possible through the use of chiral auxiliaries, such as 1,3-oxazolidin-2-ones, also known as Evans auxiliaries. This methodology provides good yield and stereochemical control but requires stoichiometric amounts of the chiral auxiliary and involves multiple steps. The need for more efficient conditions has opened up the possibility of synthesizing direct reactions using catalysts.

A few years ago, our group developed a new method based on the reaction of chiral nickel(II) complexes as catalysts and *N*-acyl-1,3-thiazinane-2-thiones as platforms for nucleophilic enolates. Initially, this method involved the construction of a single stereocenter using electrophiles from an activated oxacarbenium cation generated in the reaction mixture. Currently, the group is working on the expansion of such a method for the simultaneous installation of two stereocenters using nickel(II) complexes and similar nucleophilic partners.

With all the aforementioned points, this project aims to synthesize the scaffolds 1,3-oxazinane-2-thione and 1,3-oxazolidine-2-thione on a large scale for their subsequent acylation with carboxylic acids and acyl chlorides. The products obtained from acylation will be used in direct aldol reactions, employing both chiral and achiral nickel(II) complexes to observe their potential effect on conversion and enantioselectivity.

Keywords: Asymmetric Synthesis, aldol reaction, Chiral nickel catalyst, thioimides, aldehydes.

2. RESUM

Durant les últimes dècades, la construcció de nous enllaços carboni-carboni ha estat d'una gran importància en la síntesi de productes orgànics, com ara en la indústria farmacèutica. La importància d'aquesta síntesi rau en el control de l'estereoisomeria, que s'ha fet possible mitjançant l'ús d'auxiliars quirals, com ara les 1,3-oxazolidin-2-ones, també conegudes com a auxiliars d'Evans. Aquesta metodologia proporciona bons rendiments i control estereoquímic, però requereix quantitats estequiomètriques de l'auxiliar quiral i implica múltiples etapes. La necessitat de condicions més eficients ha obert la possibilitat de sintetitzar reaccions directes utilitzant catalitzadors.

Fa uns anys, el nostre grup va desenvolupar un nou mètode basat en la reacció de complexos de níquel(II) quiral com a catalitzadors i N-acil-1,3-tiazinan-2-tiones com a plataformes per als enolats nucleòfils. Inicialment, aquest mètode implicava la construcció d'un sol estereocentre utilitzant electròfils a partir d'un catió oxacarbeni activat generat en la mescla de reacció. Actualment, el grup està treballant en l'ampliació d'aquest mètode per a la instal·lació simultània de dos estereocentres utilitzant complexos de níquel(II) i socis nucleòfils similars.

Amb tots els punts esmentats, aquest projecte té com a objectiu sintetitzar els scaffolds 1,3-oxazinan-2-tiona i 1,3-oxazolidina-2-tiona a gran escala per a la seva posterior acilació amb àcids carboxílics i clorurs d'acil. Els productes obtinguts de l'acilació s'utilitzaran en reaccions d'aldol directes, emprant tant complexos de níquel(II) quirals com aquirals per observar el seu efecte potencial en la conversió i l'enantioselectivitat.

Paraules clau: Síntesis asimètrica, reacció aldol, catalitzador quiral de níquel, tiomides, aldehids.

3. INTRODUCTION

Organic chemistry has been highly prevalent in the pharmaceutical industry, as it is responsible for synthesizing the organic compounds that give rise to medications. In recent decades, one of the topics that has generated significant interest is stereochemistry, which focuses on the study of three-dimensional arrangements and their influence on the properties and reactivity of molecules. Stereochemistry is essential in organic chemistry since many molecules have isomers that can possess very distinct properties due to a change in the spatial distribution of the functional groups involved in reacting processes. Therefore, controlling stereochemistry is paramount for the pharmaceutical industry because the enantiomer synthesized determines the properties one may be biologically active, while the other may be inactive or even toxic and detrimental. Hence, one of the objectives of pharmaceutical chemistry is to control and synthesize a single enantiomer, avoiding racemic mixtures that can yield a toxic compound.[1]

One example of the difference in effects between the two enantiomers is ibuprofen, an anti-inflammatory drug used to treat muscle and headache pain. In this case, both enantiomers have the same effect, with the difference being that *S*-ibuprofen is a more potent inhibitor than the *R*-ibuprofen enantiomer. The racemic mixture in this case is not detrimental since both isomers have the same function **(Figure 1)**. [2]

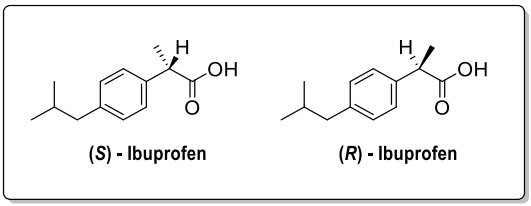


Figure 1. Ibuprofen structure

Another example is thalidomide, where the clear importance of stereochemistry is seen. This compound was first marketed as a racemic mixture in 1967 in Germany, to treat morning sickness in pregnant women. However, over time, women who took medication during their pregnancy

gave birth to babies with malformations and also had a very high mortality rate. In this racemic mixture, the *R* enantiomer was biologically active, while the *S* enantiomer was responsible for the malformations **(Figure 2)**. [3]

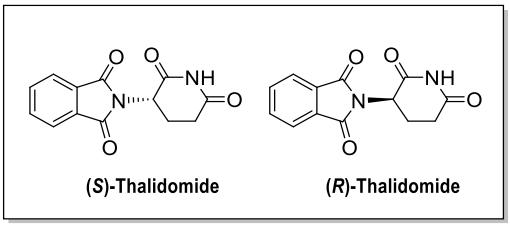
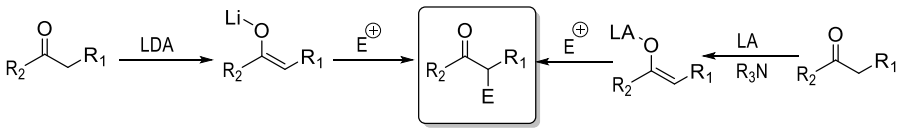


Figure 2. Thalidomide structure

This is the reason why many stereoselective methods aiming to control the configuration of the stereocenters embedded in chiral molecules have been recently developed. One of the most important avenues to achieve such a goal involves the use of metal enolates, as they participate in a variety of the most useful reactions in organic synthesis.

3.1. CLASSICAL ENOLATE REACTION

There are two main methods for generating a metal enolate: treatment with a strong and weakly nucleophilic base, such as lithium diisopropylamide (LDA), followed by the addition of the electrophile; or treatment with a Lewis acid such as $TiCl_4$ and a base such as a tertiary amine, followed by the addition of the electrophilic species **(Scheme 1)**.



Scheme 1. Classical two-step reactions

Due to the different electrophilic species available, enolates can participate in different types of reactions. For instance, enolates react with alkyl halides, forming a new carbon-carbon bond, in alkylation reactions. A second type is aldol reaction, in which enolates react with aldehydes to form β-hydroxycarbonyl compounds. Finally, a third example is the Michael reaction, where the

enolate acts as a nucleophile and the electrophilic species is an α,β-unsaturated carbonyl compound **(Scheme 2)**.[4]

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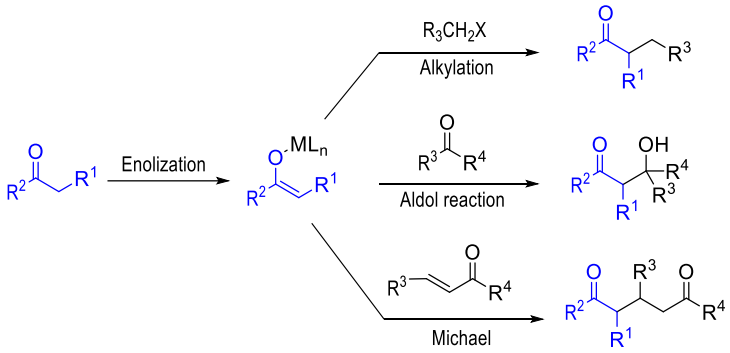


Scheme 2. Types of enolate reactions

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

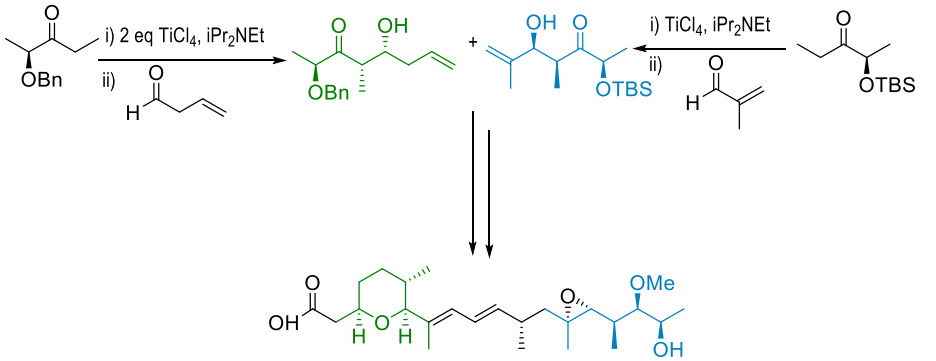
In the reaction for forming new carbon-carbon bonds, new stereocenters can be generated. There are two classical methods for controlling the configuration of the new stereocenters, which are substrate control and chiral auxiliary.[5]

3.2.1. Substrate control

One of the methods to control stereochemistry relies on the structure and properties of the substrate molecules which will keep the new stereocenters in the final product This means that the reaction conditions must be adapted to the substrate, as the latter plays an important role in determining the stereochemistry of the reaction.

The selectivity of a substrate-controlled reaction depends on the number and types of functional groups in the substrate molecule, and the configuration of the stereocenters in the substrate. This phenomenon can be clearly seen in the Felkin-Anh and Cram models. Both models account for the installation of a new stereocenter is depending on the substrate structure.

An example of a substrate-controlled reaction is shown in the synthesis of herboxidiene, where the configuration of the new stereocenters is controlled by the preexisting ones in the starting materials **(Scheme 3)**.[6]



Scheme 3. Substrate-controlled synthesis of the (+)-Herboxidine/GEX 1A

3.2.2. Chiral auxiliary control

A chiral auxiliary is an enantiomerically pure molecule that temporarily binds to the substrate to control the configuration of the new stereocenters. The new temporary stereocenter that is formed, either due to steric hindrance or through directing groups, forces the production of enantiomerically pure products. Once the desired product has been formed, the chiral auxiliary must be removed. 1,3-Oxazolidin-2-ones introduced by Evans are one of the most common chiral auxiliaries. Fujita-Nagao and Crimmins described similar auxiliaries**.** Other examples could be Oppolzer sulfonamides or Myer pseudoephedrines **(Figure 3)**. [7-11]

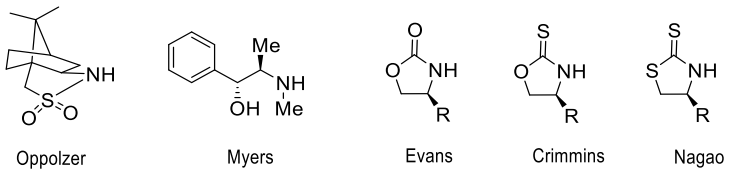
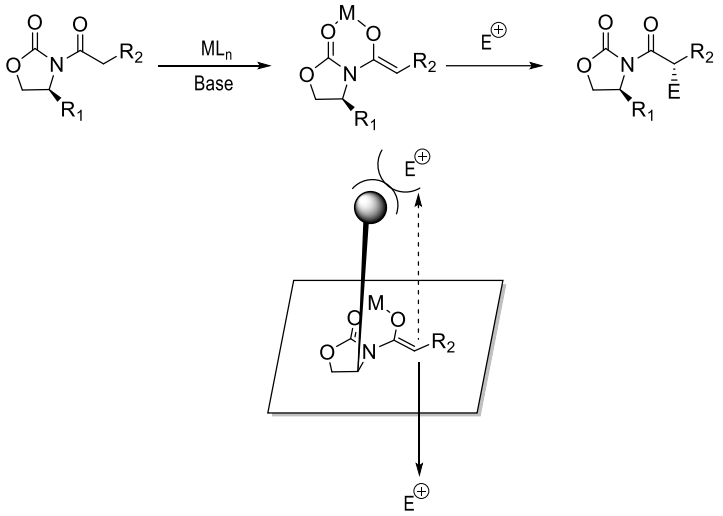


Figure 3. Different examples of chiral auxiliaries

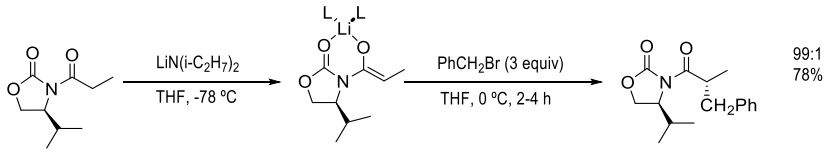
Enolates from *N*-acyl oxazolidinone can be generated with a strong base or a Lewis acid with a tertiary amine. The Lewis acid acts a coordinating agent, thereby generating chelation in the *N*-

acyl oxazolidinone group, which is a stable structure. This chelation generates a flat structure that blocks on π-face, causing the electrophile to approach from the opposite face, resulting in the desired stereochemical control **(Scheme 4)**. [12-13]



Scheme 4. Stereocontrol thanks to Evans auxiliary for the approach of the electrophile.

An example of stoichiometrically controlled reaction using a chiral auxiliary is the alkylation represented in **Scheme 5**, Evans scaffold is used to achieve high stereoselectivity and yield. [12]

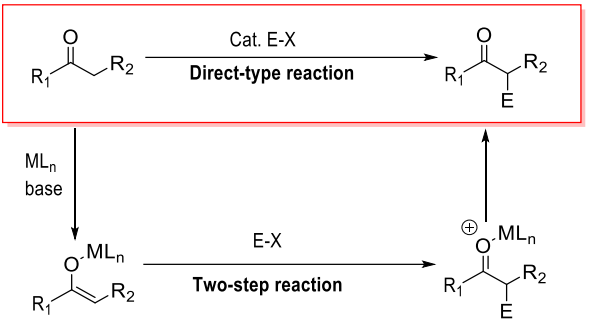


Scheme 5. Stereoselectivity of the alkylation reaction using a chiral auxiliary.

3.3. DIRECT AND CATALYZED REACTIONS

As seen in the previous section, the classical alkylation reaction is composed of two steps: first, the generation of the enolate, followed in a second step by the addition of the corresponding electrophile to generate the new carbon-carbon bond. However, over the years, this methodology

began to lose strength and gave way to the catalyzed direct reaction. As the name suggests, the direct reaction is a one-step reaction where both the nucleophile and the electrophile are added simultaneously with a catalyst. This direct reaction allows for the simplification of the process while obtaining good yields **(Scheme 6)**. [3,7]



Scheme 6. Comparison between the two-step reaction and the direct reaction.

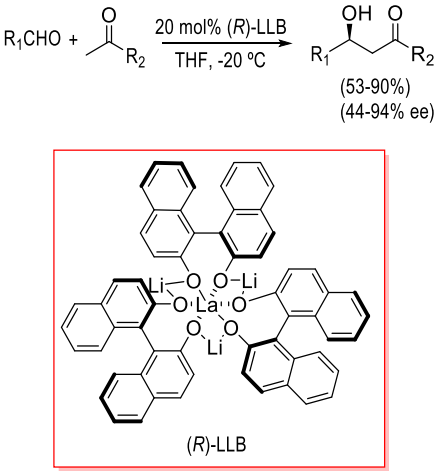
3.3.1. Metal enolates in direct reactions

One of the objectives in direct reactions in recent years has been to find catalytic systems for asymmetric aldol reactions.

Pioneering studies Evans involved *N*-acyl oxazolidinones and *N*-acyl thiazolidinethiones as chiral auxiliaries and magnesium halides as catalysts. Depending on the catalyst and chiral auxiliary used, either an anti-product or another one was obtained. In this case, the configuration is controlled by the chirality of the scaffold. This reaction exhibits good diasteroselectivity, yielding anti-products with high efficiency **(Scheme 7)**. [14-15]

Scheme 7. Control of diastereoselectivity through the chiral auxiliary and the metallic catalyst.

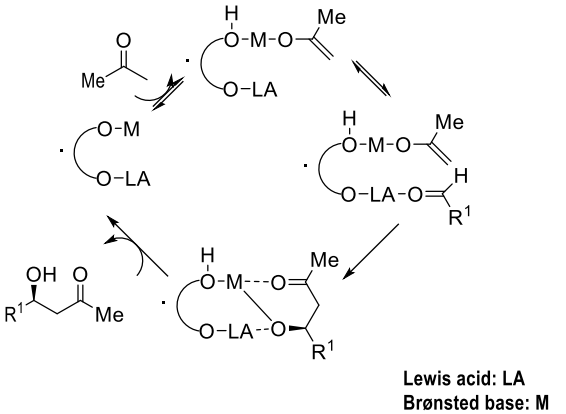
Alternatively, Shibasaki, who synthesized a direct asymmetric aldol reaction between an aldehyde and an acetone using a chiral catalyst. Therefore, the control of the configuration of the new stereocenters hinged on the use of a chiral catalyst instead of a chiral auxiliary covalently bound to the substrate. As seen in the **Scheme 8**, the (*R*)-LLB catalyst features a central Lanthanum atom. Experimentally, high yield ranging from 53% to 90% have been obtained with good enantiomeric control. [16-18]



Scheme 8. Direct asymmetric aldol reaction by Shibasaki.

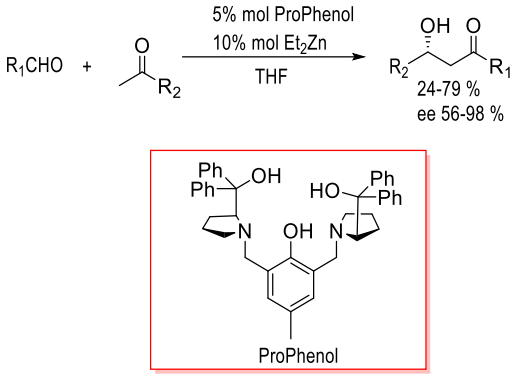
The catalyst contains both Lewis acid and Brønsted base functionalities. Thanks to this duality, the catalyst enables the aldol reaction to take place without the need for additional activation by other reagents.

The mechanism involves the deprotonation of the α-hydrogen of the ketone by the Brønsted base, while simultaneously the Lewis acid activates the aldehyde. With the metal of the Brønsted base, the aldol reaction between the aldehyde and the metal enolate occurs. Once the reaction is complete, the catalyst is regenerated. **(Scheme 9)**. [16-18]



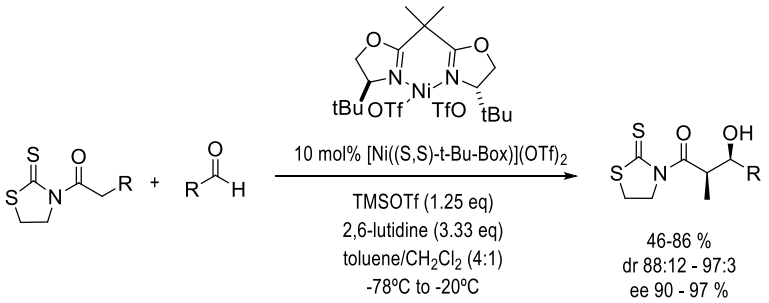
Scheme 8. The catalytic cycle of Shibasaki catalyst operation.

Another example of a reaction catalyzed by a metallic catalyst was described by Trost. In this case, the ligand Prophenol reacts with Et_2Zn to give rise to a metallic catalyst with two zinc atoms as central atoms. It has been used in asymmetric aldol reactions from α-hydroxyacetones. Thanks to its efficiency, just stoichiometric amounts of both reactants can be used, making it almost ideal and requiring less catalytic compound in this case **(Scheme 10)**.[16-18]



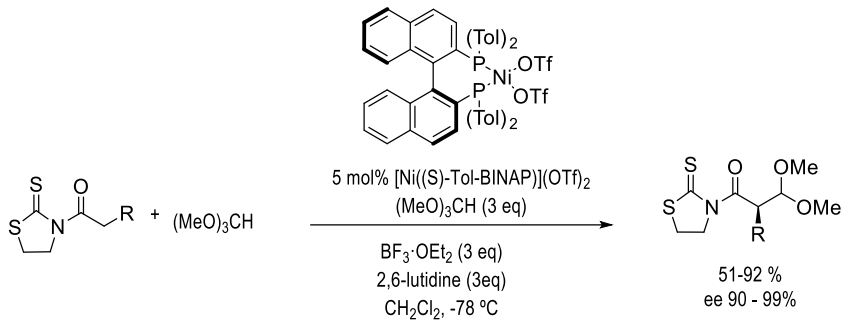
Scheme 10. Direct asymmetric aldol reaction by Trost.

Evans also devised a reaction where the starting materials are achiral and the stereochemical control depended on a chiral catalyst. An achiral thiazolidinethione propionamide reacts directly with an aldehyde, using 10% of the $Ni(OTf)_2$/(*S,S*)-tBuBox complex as a catalyst. The reaction yields a syn product with a good efficiency and excellent enantioselective control **(Scheme 11).**[17]



Scheme 11. Stereochemical control using a chiral nickel (II) catalyst.

Evans also reported a similar alkylation reaction, where the same scaffold is used, just varying the structure of the Ni(II) catalyst, resulting in a highly selective alkylation reaction. In this reaction trimethyl orthoformate reacts with $BF_3 \cdot OEt_2$ to generating the oxocarbenium cation, which reacts with the Z enolate. The product is obtained with good yield and excellent enantioselectivity. **(Scheme 12).**[19]

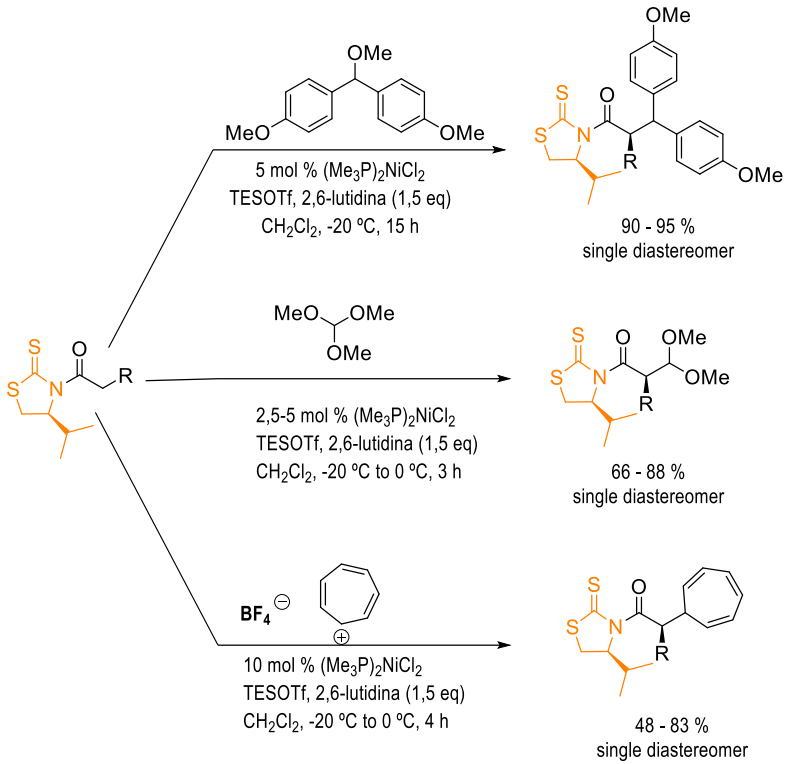


Scheme 12. Stereoselective control in an alkylation reaction using a chiral nickel (II) catalyst.

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

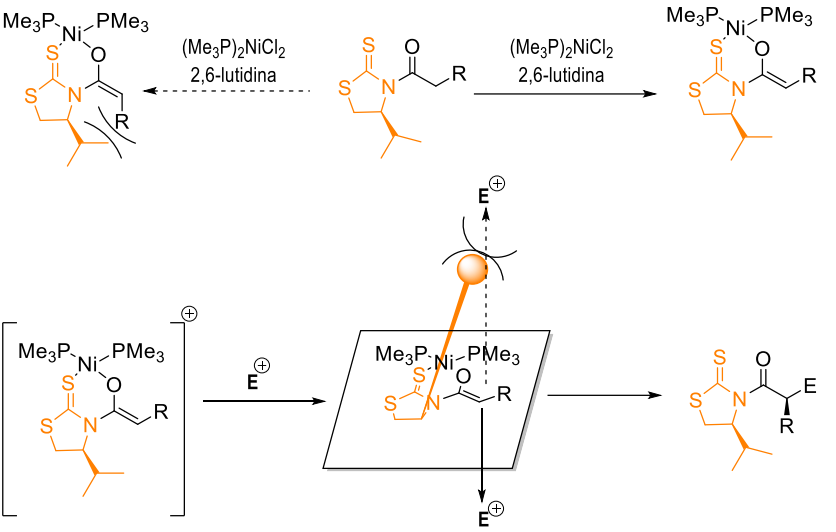
3.4.1. Direct reactions with achiral Ni(II) complexes

Taking advantage of these procedure, our group initially developed highly diastereoselective and catalytic direct alkylation reactions using achiral nickel (II) complexes and chiral auxiliaries such as (*S*)-4-isopropyl-1,3-thiazolidine-2-thione, which is the responsible for controlling the stereoselectivity. The use of *N*-acyl thiazolidinethiones allowed for the use of a variety of electrophiles as shown in **Scheme 13**. A simple mixture of thioamide, the electrophile, the nickel complex, 2,6-lutidine, and TESOTf led to the desired products with good yields and excellent stereoselectivity control **(Scheme 13).** [20-22]



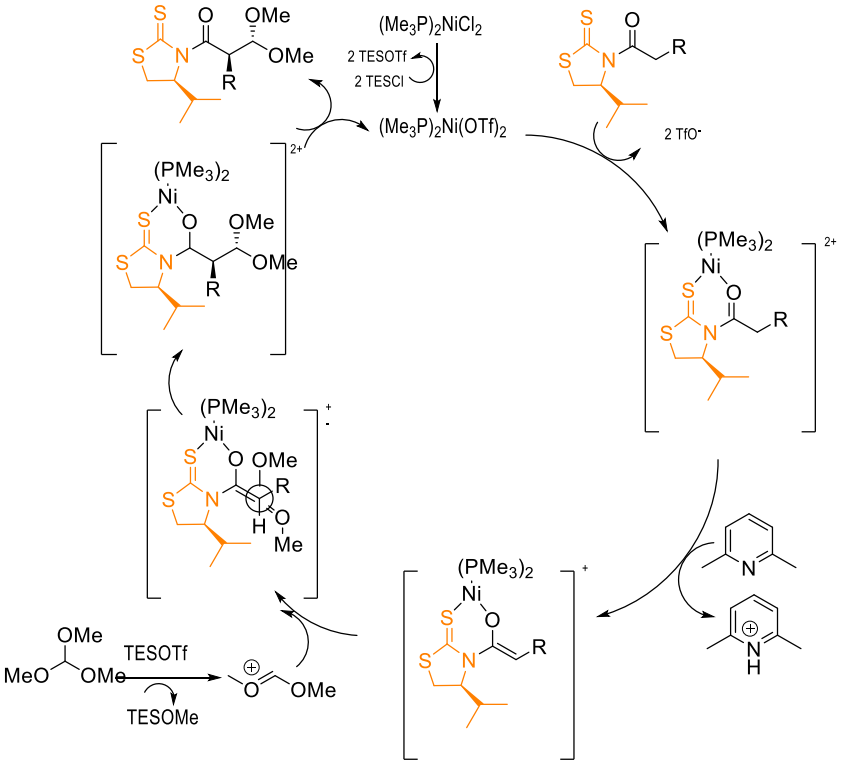
Scheme 13. Stereoselectivity control using N-acyl thiazolidinethiones for the generation of a single diastereomer.

The Lewis acid is very important. First it activates the electrophile and generates the real electrophilic species, the required cation for the reaction. Moreover, it also activates the precatalyst, which in this case is $(Me_3P)_2NiCl_2$, thereby generating the real catalyst $(Me_3P)_2Ni(OTf)_2$. The catalyst forms a chelate between the C=S group of the chiral auxiliary and the carbonyl which influences the C_α-H acidity. Then, the 2,6-lutidine act as a base, removing the α-proton which has some acidic character, to form the *Z*-enolate. Importantly, the *E* enolate is less stable because of A(1,3) and does not compete with the *Z* enolate (**Scheme 14)**. Finally, the chelated *Z* enolate reacts approaches to the cation from the less hindered π-face, the opposite face of the isopropyl group, thus generating a single diastereoisomer. This reaction creates a single stereocenter with a very good yield and high diastereoselectivity **(Scheme 14).** [7]



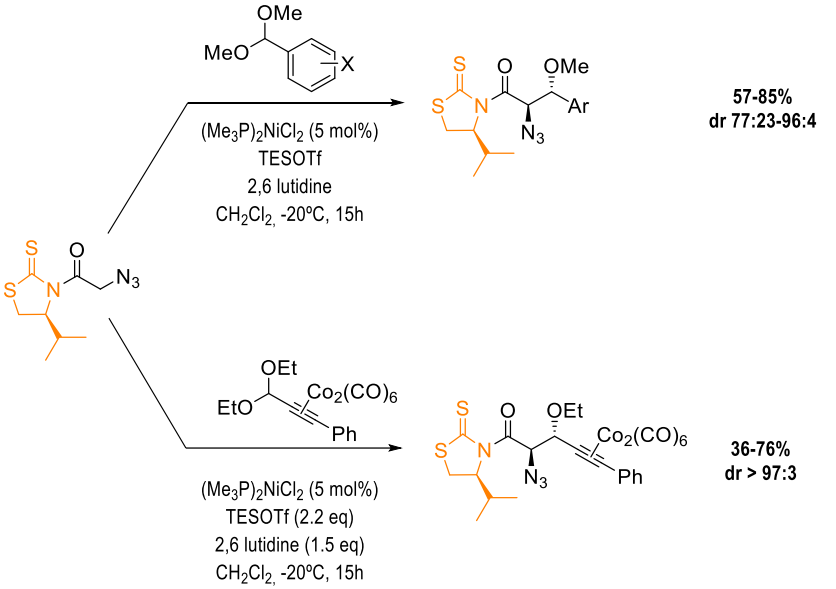
Scheme 14. Synthesis of the chelated Z enolate and further reaction with an electrophile.

The resultant catalytic cycle for the reaction with trimethyl orthoformate is represented below **Scheme 15**. Importantly, the real catalytic species, a highly electrophilic nickel(II) triflate, is formed at the beginning of the process. Then, it interacts with the thioimide to form a square planar complex. The enhanced acidity of this complex enables the formation of a chelated nickel *Z* enolate, the nucleophilic partner that reacts with the oxocarbenium cation through an open transition state in which the configuration of the C4 of the thiazolidinethione heterocycle determines that of the new stereocenter. Finally, the resultant adduct releases the product and the catalyst and a new cycle begins.[7]



Scheme 15. Catalytic cycle reaction of alkylation using an achiral catalyst.

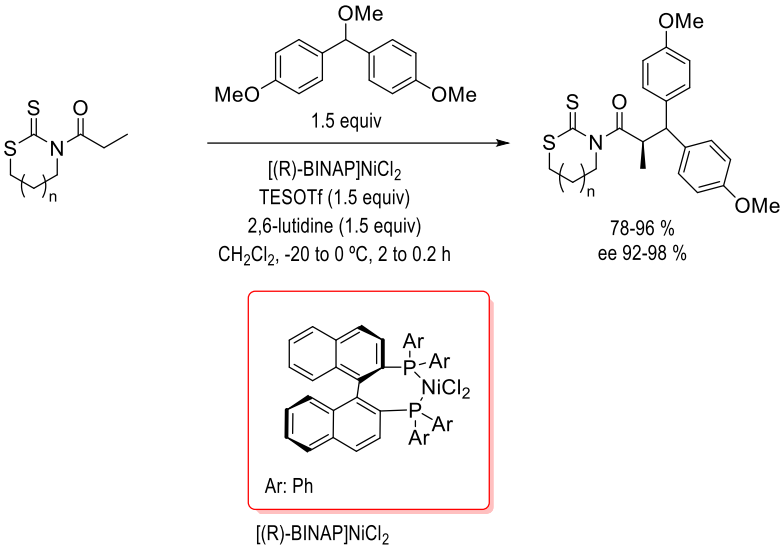
A similar reaction has been described that allows the introduction of two stereocenters using azidoacetyl thioimide as the nucleophilic partner and aromatic or propargylic acetals as electrophiles. This reaction gives very good yield and high stereoselectivity. These successful transformation fuelled our interest in more efficient processes on the use of chiral catalysts **(Scheme 16).** [23]



Scheme 16. Direct catalyzed reaction using aromatic and propargylic acetals as electrophiles.

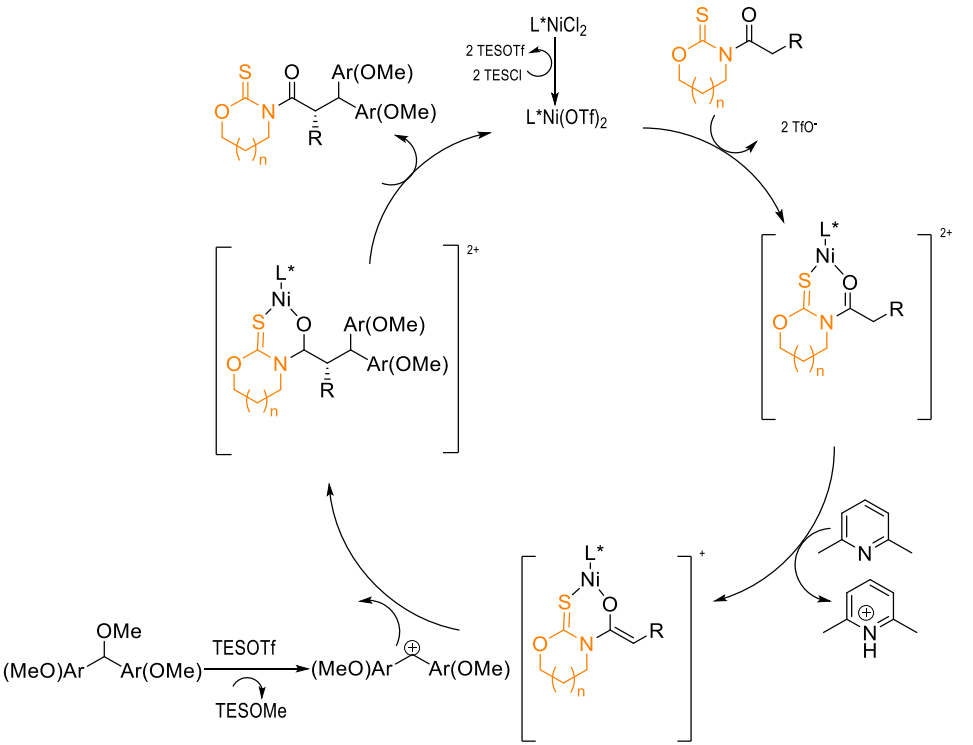
3.4.2. Direct reactions with chiral Ni(II) complexes

According to the former comments, an S_N1-type alkylation reaction in which the scaffold is achiral and therefore no longer responsible for enantioselective control was recently developed. Instead, the chiral Ni(II) complex acts as the catalyst. This direct reaction provides excellent enantiomeric control and high yields (**Scheme 17**).[24]



Scheme 17. Asymmetric and direct alkylation reaction using an achiral auxiliary and a chiral catalyst.

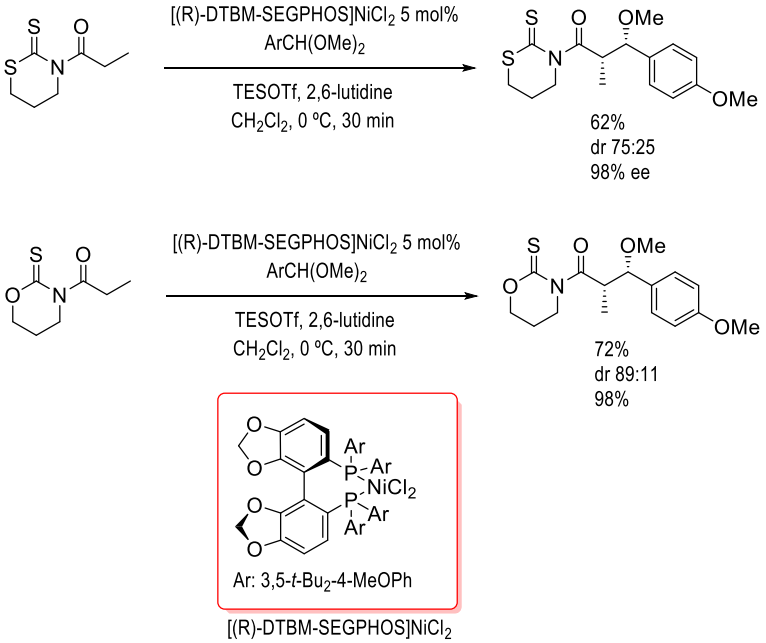
The mechanism of this reaction is similar to that shown in **Scheme 15**, the difference being that in this case the scaffold is achiral, so the ligands of the nickel (II) complex are responsible for controlling the stereochemical outcome of the reaction. The electrophile, due to steric hindrance, enters from the opposite side of the ligands **(Scheme 18)**. [24]



Scheme 18. Catalytic cycle reaction of alkylation using an achiral catalyst.

In turn, the generation of two new stereocenters using electrophiles such as acetals was also possible, with very good diastereoselectivities and excellent enantioselectivities. This new method allows for the generation of two stereocenters with great selectivity.

Finally, in order to improve the effectiveness of this reaction, some of the reagents have been varied, such as the scaffold, catalyst, and Lewis acid. Ultimately, this reaction has been arrived at, which shows better results, although the reason has not been determined **(Scheme 19)**. [24]



Scheme 19. Formation of two stereocenters through a reaction catalyzed by chiral nickel(II) complex.

4. OBJECTIVES

The first objective of this project is the synthesis of the scaffolds used in this kind of reactions in large quantities. In this case, 1,3-oxazinane-2-thione and 1,3-oxazolidine-2-thione have been synthesized.

1,3-oxazinane-2-thione 1,3-oxazolidine-2-thione.

Figure 4. Heterocyclic scaffolds

The second objective is the acylation of the previously synthesized scaffolds following different synthetic methodologies. Acylation is carried out using reagents such as propionyl chloride and 2-azidoacetic acid.

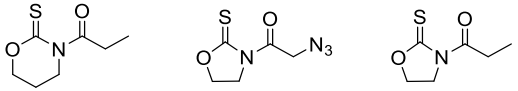
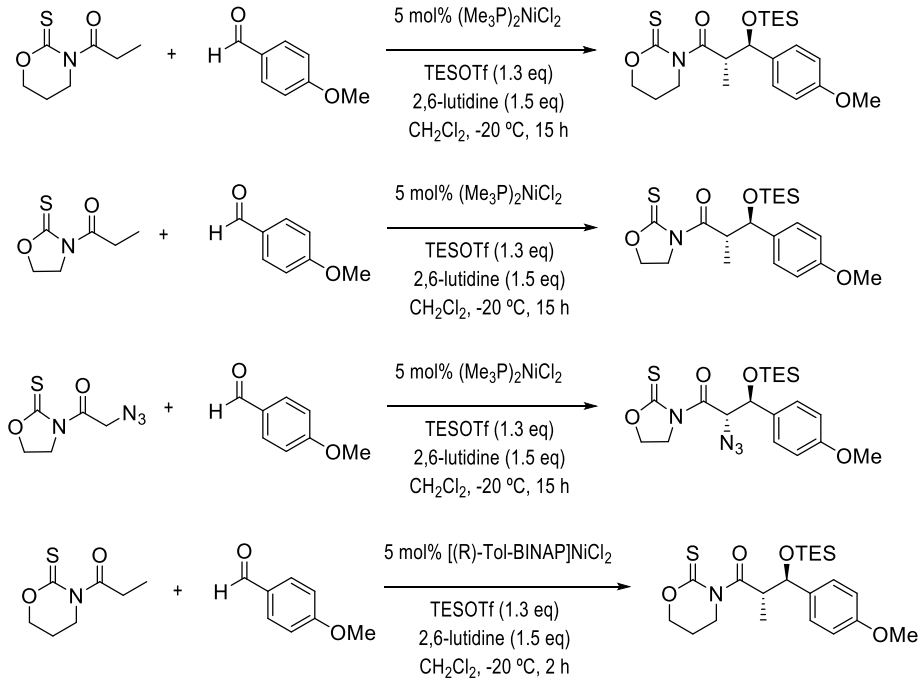


Figure 5. Acylated scaffolds

Finally, the third objective is the development of a direct asymmetric catalytic reaction between the acylated products and 4-methoxybenzaldehyde, where the latter acts as an electrophile. In this section, the influence of chiral and achiral catalysts will be tested. Additionally, the possible influence of the scaffold in this catalytic reaction will also be investigated **(Scheme 20)**.



Scheme 20. Direct reactions catalyzed by chiral and achiral nickel(II) complexes.

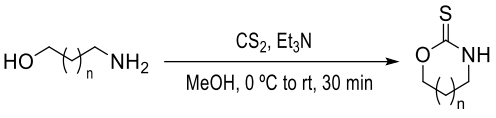
5. RESULTS AND DISCUSSION

5.1. SYNTHESIS OF THE SCAFFOLDS

As indicated in the previous section, the first objective is the synthesis of the scaffolds, to be used in various reactions within our group. Therefore, large quantities of scaffolds are synthesized, and the reproducibility, purity, and yields of the obtained products are checked.

5.1.1. Synthesis of 1,3-oxazinane-2-thione and 1,3-oxazolidine-2-thione.

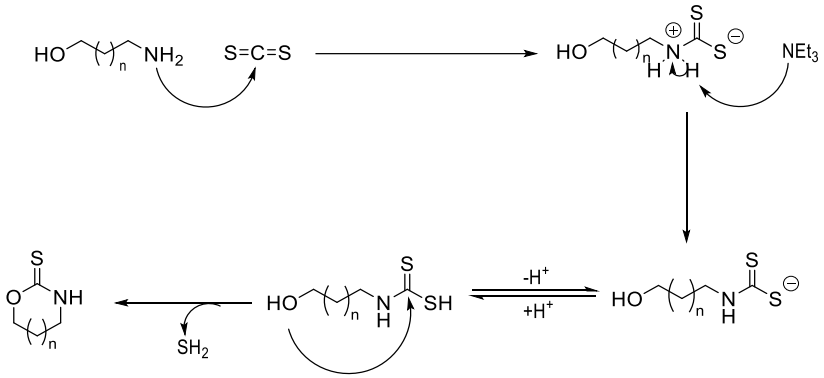
The scaffolds were prepared in a one-step reaction. Indeed, the aminoalcohol reacted with carbon disulfide and triethylamine in absolute methanol at 0 ºC **(Scheme 21)**.



1-2

Scheme 21. Synthesis of scaffolds.

Firstly, the aminoalcohol reacts with carbon disulfide, generating the dithiocarbamate intermediate under basic conditions provided by triethylamine. Triethylamine removes a hydrogen atom from the nitrogen of the dithiocarbamate intermediate, thus generating 3-hydroxypropyl carbamodithioic acid. The hydroxyl group of 3-hydroxypropyl carbamodithioic acid acts as a nucleophile and undergoes an intramolecular nucleophilic attack, resulting in the formation of the corresponding heterocycle **(Scheme 22)**.



Scheme 22. Mechanism of the synthesis of scaffolds **(1-2)** .

The synthesized products in this section are 1,3-oxazinane-2-thione **(**n=1, **1)** and 1,3-oxazolidine-2-thione **(**n=0, **2)**. The yields are summarized in Table 1. The yield obtained for **1** is similar to that reported by the group (52%).

Scaffold	Scale (mmol)	n	t (min)	Yield %
1	50	1	30	40
2	50	0	30	31

Table 1. Synthesis of scaffolds

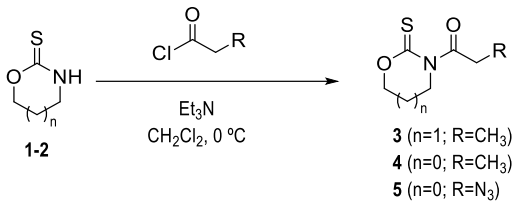
5.2. ACYLATION OF THE SCAFFOLDS

As mentioned earlier, the second objective of this project is the acylation of the previously synthesized scaffolds to determine which acylation method yields better results. This acylation can be carried out using carboxylic acids and acyl chlorides.

5.2.1. Acylation with acyl chlorides

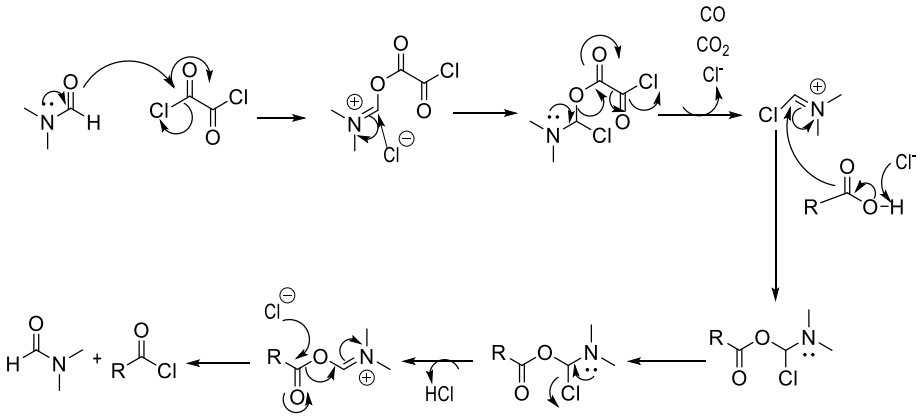
As the title suggests, this acylation reaction takes place with an acyl chloride. The acyl chloride is a commercially available product, but it can also be synthesized from the carboxylic acid. In this case the acylation reaction becomes a two-step reaction **(Scheme 23)**.

The thioimides synthesized in this section are *N*-propionyl-1,3-oxazinane-2-thione (**3**), *N*-propionyl-1,3-oxazolidine-2-thione (**4**), and *N*-(2-azidoacetyl)-1,3-oxazolidine-2-thione (**5**).



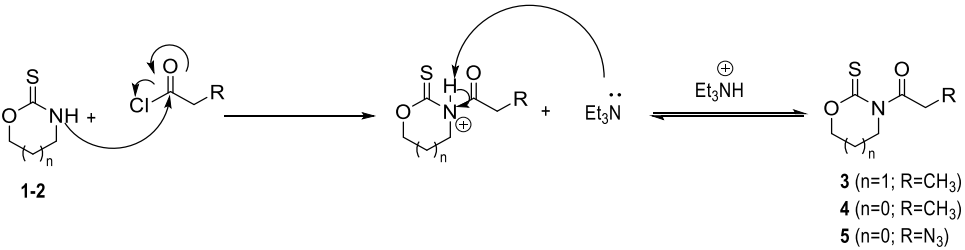
Scheme 23. The acylation of the previously synthesized scaffold.

In the synthesis of the acyl chloride from the carboxylic acid, an organic solvent such as DMF facilitates the overall process. The solvent reacts with oxalyl chloride, generating an electrophilic species that undergoes attack by the carboxylic acid group, as shown in the **Scheme 24**. This reaction with oxalyl chloride is necessary because the hydroxyl group is a poor leaving group.



Scheme 24. Mechanism of the acyl chloride formation.

Once the acyl chloride is generated, the acylation can begin. The scaffold reacts with acyl chloride, thus generating an addition-elimination reaction, where the nitrogen bonds to the carbonyl in a covalent bond, forming an *N*-acyl derivative **(Scheme 25)**.



Scheme 25. Acylation with acyl chloride.

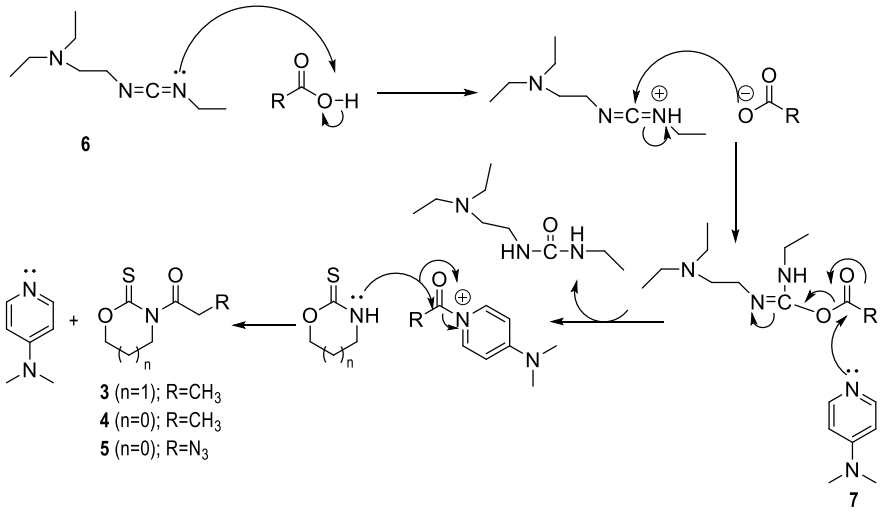
Scaffold	n	t (h)	Product	Scale (mmol)	Yield (%)
1	1	72	**3**	5	40
2	0	16	**4**	5	59
2	0	16	**5**	10	30

Table 2. The acylation of the scaffolds **(1-2)** with acyl chloride.

5.2.2. Acylation with carboxylic acids

In the case of acylation with carboxylic acids, an activating agent for carboxylic groups such as EDC and a nucleophilic catalyst like DMAP **(7)** are necessary **(Scheme 26)**. As mentioned in the previous section, the hydroxyl group is a poor leaving group, so a catalyst is needed to facilitate the reaction**.**

The mechanism of the reaction begins with the interaction of the activating agent with the carboxylic acid, followed by substitution by the nucleophilic catalyst.



Scheme 26. The mechanism of acylation using a carbodiimide nucleophilic catalyst.

Scaffold	n	t (h)	Product	Conc (mmol)	Yield (%)
2	0	16	**5**	10	53
2	0	16	**5**	3	31

Table 3. The acylation of the scaffolds **(1-2)** with carboxylic acid.

. The reader might wonder why the synthesis of the product *N*-(2-azidoacetyl)-1,3-oxazinane-2-thione (**8**) has not been attempted at any point. There is an explanation for this. Although it may seem that the only difference between *N*-(2-azidoacetyl)-1,3-oxazinane-2-thione (**8**) and *N*-(azidoacetyl)-1,3-oxazolidine-2-thione (**5**) is one carbon, suggesting that their reactivity should be

very close, the reality is different. The compound *N*-(2-azidoacetyl)-1,3-oxazinane-2-thione (**8**) is unstable due to potential interactions between the azide and sulfur, leading to the degradation. On the other hand, such interaction does not occur with the compound *N*-(azidoacetyl)-1,3-oxazolidine-2-thione (**8**) (**Scheme 27**).

8

Scheme 27. The interaction between the nitrogen and sulphur atoms in *N*-(2-azidoacetyl)-1,3-oxazinane-2-thione, which causes its instability

5.2.3. Comparison between the two acylation methods.

By examining the yields documented in **Table 2** and **Table 3**, it can be inferred that acylation with carboxylic acid using an activating agent and a nucleophilic catalyst yields better results. When DMAP reacts with the carbonyl, a very good leaving group is generated. Such a leaving group has a positive charge, and turns out to be better leaving group than the chloride, resulting in a higher yield. This phenomenon is evident when comparing the two yield values obtained for the N-acyl **(5)** product at 10 mmol.

In comparing the same acylation method, it can be observed from **Table 2** that the scaffold also plays a certain role in the reaction, as better results are obtained with scaffold (**2**) than with scaffold (**1**).

5.3. DIRECT ALDOL REACTIONS

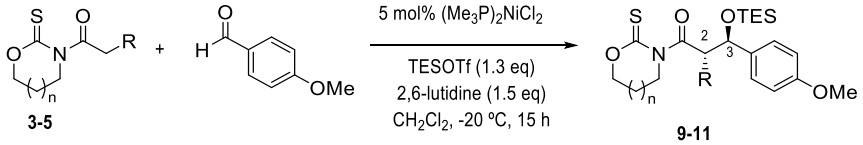
As mentioned earlier, a direct reaction is a reaction where a pronucleophilic substrate, a proelectrophilic substrate, and a catalyst are added simultaneously to generate the desired product.

In this section, acylated products were treated with 4-methoxybenzaldehyde, which acts as an electrophile, along with a Lewis acid and a nickel (II) complex that acts as a precatalyst, in CH_2Cl_2 at –20 ºC.

5.3.1. Aldol reactions catalyzed by an achiral Ni(II) complex

The acylated heterocycles previously synthesized have a pronucleophilic character and react with 4-methoxybenzaldehyde, which acts as a proelectrophile, along with TESOTf, 2,6-lutidine, and $(Me_3P)_2NiCl_2$. All the reagents are achiral, so a racemic mixture is obtained since both enantiomers are formed equally (**Scheme 28**).

The two diastereomers can be identified using NMR techniques as they have different chemical shifts. On the other hand, in HPLC, the two enantiomers can be differentiated by their retention time.



Scheme 28. Direct catalyzed reaction using achiral nickel (II) complex.

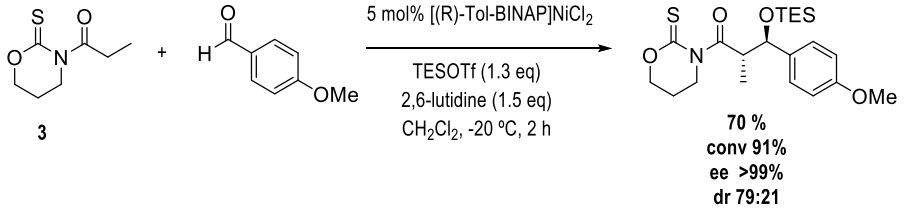
N-acyl	t (h)	Product	d.r (anti/syn)	Conv. [%]
3	15	**9**	86:14	>95
4	15	**10**	60:40	52
5	15	**11**	93:7	70

Table 4. Direct catalyzed reaction using an achiral nickel (II) complex.

Looking at the results obtained in **Table 4**, it can be inferred that the scaffold has a key influence on the conversion. The thioimide **(3)** yields the best result.

5.3.2. Aldol reactions catalyzed by a chiral Ni(II) complex

Based on the results obtained in the previous section **(Table 4)**, it was decided to perform this reaction using **3**. The only difference from the previous section is the use of a chiral nickel (II) complex as catalyst. Due to the achiral nature of the scaffold, the enantioselectivity is controlled by the chirality of the nickel (II) complex. To our delight, only one enantiomer of the major diastereomer was obtained since the nickel(II) provides an outstanding stereocontrol **(Scheme 29)**. Importantly, this reaction was only allowed to proceed for 2 hours, unlike the previous ones that were left overnight. In this case, the conversion was quite high (91%),



Scheme 29. Direct catalyzed reaction using a chiral nickel (II) complex.

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND METHODS

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

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

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

^{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 abbreviation: s, singlet; d, doublet, t, triplet; q, quadruplet; m, multiplet. The coupling constant (*J*) are quoted in Hz.

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

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. General procedure

The aminoalcohol (1 equiv) was dissolved in absolute methanol (2 equiv) in a previously dried flask equipped with a magnetic stir bar. Once the aminoalcohol dissolved, the solution was purged with N_2 and a balloon filled with N_2 was introduced to maintain an inert atmosphere. Triethylamine (1 equiv) was added dropwise with continuous stirring using a syringe, and the solution was immersed in a water bath at 0 ºC. Once the solution was cooled down, carbon disulfide (1.5 equiv) was slowly added drop by drop with constant stirring. After the addition of carbon disulfide was complete, the reaction was left stirring for 30 min at 0 ºC. The water bath was then removed, and the reaction was allowed to stir for an additional 30 min at room temperature. Then, 33% hydrogen peroxide (10 mL, 30 mmol) was slowly added to stop the reaction, resulting in a yellow-colored solution. The reaction was left stirring for 1 h at room temperature. The resulting solution was filtered and concentrated using a rotary evaporator. A 2M solution of sodium hydroxide (25 mL) was added, and the solution was acidified with 2M hydrochloric acid until reaching pH 1. The resulting mixture was extracted with dichloromethane (3 $\times$ 30 mL), the combined organic were dried with magnesium sulfate and concentrated using a rotary evaporator.

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

Following the general procedure 6.2.1, a 250 mL flask was equipped with a magnetic stir bar. 3-amino-1-propanol (3.8 mL, 50 mmol, 1 equiv) was added and dissolved in absolute MeOH (50 mL). The mixture was purged with N_2, and triethylamine (7 mL, 50 mmol, 1 equiv) was added. The solution was immersed in an ice/water bath, and carbon disulfide was added dropwise (4.5 mL, 75 mmol, 1.5 equiv). The reaction was allowed to proceed for 1 h, and then hydrogen peroxide (30% v/v in water, 10 mL) was added. Subsequently, the solution was filtered, and the resulting mixture was concentrated using a rotary evaporator. Finally, a solution of 2 M NaOH (25 mL, 50 mmol) and 2 M HCl (47 mL, 94 mmol) was added, followed by extraction with CH_2Cl_2 (3 $\times$ 25 mL), drying with $MgSO_4$, and concentrated to give 2.17 g (18.5 mmol, 38% yield) of **1**.

White solid. Mp 126-127 ºC. **Rf** 0,35 (hexanes/EtOAc 9:1)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H, NH), 4.42-4.35 (m, 2H, OCH_2), 3.40-3.37 (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): 3163, 2976, 2946, 1567, 1462, 1311, 1227, 1151 cm^{-1}
.

6.2.3. Synthesis of 1,3-oxazolidine-2-thione (2)

Following the general procedure 6.2.1, a 250 mL flask equipped with a Teflon magnetic stir bar, 2-amino-1-ethanol (3.12 mL, 50 mmol, 1 equiv) was added and dissolved in absolute methanol (50 mL). It was purged with nitrogen, and triethylamine (7 mL, 50 mmol, 1 equiv) was added. The solution was immersed in an ice/water bath, and carbon disulfide (4.5 mL, 75 mmol, 1.5 equiv) was added dropwise. It was allowed to react for 1 h, and hydrogen peroxide (30% v/v in water, 10 mL) was added. Then, the mixture was filtered and concentrated using a rotary evaporator. Finally, a solution of 2 M NaOH (25 mL, 50 mmol) and 2 M HCl (47 mL, 94 mmol) was added, followed by extraction with CH_2Cl_2 (3 × 25 mL). drying with $MgSO_4$ and concentrated to give 1.60 g (15.5 mmol, 31% yield) of **2**.

Yellow solid. Mp 98-99 ºC. **Rf** 0,35 (hexanes/EtOAc 9:1)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (s, 1H, NH), 4.73 (t, 2H, OCH_2), 3.84 (t, *J* = 8.6 Hz, 2H, $NHCH_2$)
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 188 (C), 69.4 (CH_2), 44.3 (CH_2).

6.3 ACYLATION

6.3.1. Acylation with acyl chlorides. General procedure.

In a flask with a single neck, previously dried in an oven and equipped with a magnetic core, the corresponding scaffold (**1-2**, 1 equiv), was added. The flask was sealed with a septum, the system was purged with N_2, and a balloon filled with N_2 was introduced to maintain the solution under an inert atmosphere. The scaffold was dissolved in anhydrous dichloromethane (40 mL), and the solution was submerged in a ice/water bath for cooling. After 3 min, triethylamine (1.3 equiv) was added dropwise, and the solution was stirred for 3 min. Then, acyl chloride (1.2 equiv) was added dropwise, thus avoiding a violent reaction. Once the addition was completed, the

water/ice bath was removed, and the solution was stirred overnight at room temperature with constant stirring.

The resulting solution was cooled in a water/gel bath and quenched with a saturated solution of ammonium chloride, stirring for 5 minutes. The solution was extracted with dichloromethane. The combined organic extracts were washed with a 2M sodium hydroxide solution dried with magnesium sulphate, filtered, and concentrated under pressure using a rotary evaporator.

Once the crude product was obtained, it was characterized using ^{1}H NMR and purified by flash column chromatography to obtain the pure product.

6.3.2. Acylation with carboxylic acids. General procedure.

In a single-neck dry flask previously heated in an oven and equipped with a magnetic core, the corresponding scaffold (1.1 mmol), DMPA (0.006 g, 0.05 mmol), and EDC·HCl (0.23 g, 1.2 mmol) were added. The flask was sealed with a septum, and the system was purged with N_2. A balloon filled with N_2 was introduced to maintain the solution under an inert atmosphere. The content of the flask was dissolved in dry dichloromethane (3 mL), and the solution was submerged in a water/ice bath at 0ºC.

In a second dry flask, the carboxylic acid (1 mmol) was added and purged with N_2 as indicated before. The acid was dissolved in dry dichloromethane (3 mL). Using a cannula, the carboxylic acid solution was added onto the previously prepared scaffold solution. The mixture was stirred for 15 min at 0 ºC, the water/ice bath was removed, and the mixture was stirred overnight at room temperature.

The reaction crude was diluted with dichloromethane (3.3 mL), and the organic layer was extracted with water (8 mL). The aqueous phase was extracted with dichloromethane (3×4 mL), the combined organic extracts were combined, dried with magnesium sulfate, filtered, and concentrated under rotary evaporation.

Once the crude was obtained, it was characterized by ^{1}H NMR and purified using flash column chromatography to obtain the pure product.

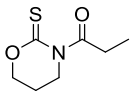
6.3.3. *N*-Propionyl-1,3-oxazinane-2-thione (3)

Following the general procedure 6.3.1, 1,3-oxazinan-2-thione (0.586 g, 5 mmol, 1 equiv) was added to a previously dried flask equipped with a magnetic stirrer. The flask was sealed with a

septum and purged with N_2. The scaffold was dissolved in dry CH_2Cl_2 (8.3 mL) and the solution was immersed in a water/ice bath. After a few minutes, triethylamine (0.9 mL, 6.5 mmol, 1.3 equiv) was added, followed by dropwise addition of propionyl chloride (0.52 mL, 6 mmol, 1.2 equiv). The ice bath was removed, and the reaction mixture was stirred overnight at room temperature.

To quench the resulting yellow solution, a saturated solution of NH_4Cl (4 mL) was added, and the solution was transferred to a separatory funnel. The aqueous phase was washed with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined organics extracts were combined and washed with a 2 M NaOH solution (16 mL, 32 mmol). Finally, the solution was dried with MgSO4, filtered, and concentrated under reduced pressure.

The crude was purified by flash column chromatography (3 cm Ø, h 22 cm) using a hexane/EtOAc mixture (7:3) as the eluent to obtain 0.344 g (2.0 mmol, 40% yield) of **3**.



White solid. Mp 59-61 ºC. **Rf** 0.30 (hexanes/EtOAc 7:3)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.34 (t, *J* = 7.1 Hz, 2H, $OC\underline{H_2}$), 3,75 (t, *J* = 7.1 Hz, 2H, $NC\underline{H_2}$), 3,16 (q, *J* = 7.3 Hz, 2H, $N(CO)C\underline{H_2}$), 2.23-2.20 (m, 2H, $OCH_2C\underline{H_2}$), 1,23 (t, *J* = 7.3 Hz, 3H, $OCH_2C\underline{H_3}$).
^{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}.

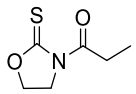
6.3.4. *N*-Propionyl-1,3-oxazolidine-2-thione (4)

Following the general procedure 6.3.1, 1,3-oxazolidine-2-thione (0.52 g, 5 mmol, 1 equiv) was added to a previously dried flask equipped with a magnetic stirrer. The flask was sealed with a septum and purged with N_2. The scaffold was dissolved in dry CH_2Cl_2 (8.3 mL) and the solution was immersed in a water/ice bath. After a few minutes, triethylamine (0.87 mL, 6.5 mmol, 1.3 equiv) was added, followed by dropwise addition of propionyl chloride (0.52 mL, 6 mmol, 1.2 equiv). The cooling bath was removed, and the reaction was stirred overnight at room temperature.

The resulting yellow solution was quenched with a saturated solution of NH_4Cl (4 mL), and the mixture was transferred to a separating funnel. The aqueous phase was washed with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined organics extracts were

combined and washed with a 2 M NaOH solution (16 mL, 32 mmol). Finally, the solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude was purified by flash column chromatography (3 cm Ø, h 22 cm) using a Hexane/ethyl acetate mixture (7:3) as the eluent, to obtain pure *N*-propionyl-1,3-oxazolidine-2-thione (**4**) as a white solid (0.47 g, 3 mmol, 59% yield).



White solid. Mp 47-49 ºC. **Rf** 0,30 (hexanes/ EtOAc 7:3)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.55 (t, *J* = 8.5 Hz, 2H, OCH_2), 4.24 (t, *J* = 8.5 Hz, 2H, NCH_2), 3.32 (q, *J* = 7.3 Hz, 2H, $COCH_2$), 1.20 (t, *J* = 7.3 Hz, 3H, OCH_2CH_3).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 185.5 (C), 175.2 (C), 66.4 (CH_2), 47.1 (CH_2), 31.1 (CH_2), 8.5 (CH_3).
IR (ATR): 2987, 2912, 1697, 1458, 1381, 1156, 930, 648 cm^{-1}.

6.3.5. *N*-(2-Azidoacetyl)-1,3-oxazolidine-2-thione (5)

In a previously dried and equipped flask with a magnetic core, 1,3-oxazolidine-2-thione (1.05 g, 10.2 mmol, 1 equiv) was added. The flask was sealed with a septum and purged with N_2. The heterocycle was dissolved in dry CH_2Cl_2 (40 mL), and triethylamine (1.42 mL, 10.2 mmol, 1 equiv) was slowly added dropwise at room temperature. The reaction was allowed to proceed for 15 min.

In another previously dried flask, azidoacetic acid was dissolved in dry dichloromethane (5 mL). The resultant solution was added to the other flask using a cannula. The resulting colorless solution was stirred overnight at room temperature.

Then, it was diluted with diethyl ether (67 mL). The solution was transferred to a separatory funnel and the organic layer was washed with water (40 mL) and the aqueous phase extracted with Et_2O (3 × 25 mL). The combined organic extracts were combined, dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude was purified by flash column chromatography (3 cm Ø, h 22 cm) using a hexane/EtOAc mixture (7:3) as the eluent, to obtain pure *N*-propionyl-1,3-oxazolidine-2-thione (**5**) as a white solid (0.59 g, 3.2 mmol, 31% yield).

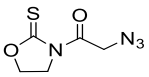
This product was also synthesized following general procedure 6.3.2. In a previously dried flask equipped with a magnetic core, 1,3-oxazolidine-2-thione (1.01 g, 10 mmol, 1 equiv), DMAP

(60 mg, 0.5 mmol, 0.05 equiv), and EDC·HCl (3.3 g, 12 mmol, 1.2 equiv) were added. The flask was purged with N_2, dissolved in dry dichloromethane (28 mL), and the solution was immersed in a water/ ice bath at 0°C.

In another previously dried flask, azidoacetic acid (1.01 g, 10 mmol, 1 equiv) was dissolved in dry dichloromethane (16 mL). The azidoacetic acid solution was added to the flask containing the heterocycle using a cannula, the water/ice bath was removed after 15 minutes, and the mixture was stirred overnight at room temperature.

The reaction crude was diluted with dichloromethane (33 mL), and the organic phase was extracted with water (40 mL). The aqueous phase was further extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator.

The crude was purified using flash column chromatography (3 cm Ø, h 22 cm) with a hexane/EtOAc mixture (7:3) as the eluent. Pure *N*-(2-azidoacetyl)-1,3-oxazolidine-2-thione (**5**) was obtained as a white solid (1.17 g, 6.3 mmol, 54% yield).



White solid. Rf 0,50 (hexanes/EtOAc 6:4)

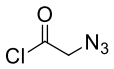
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.91 (s, 2H, $COCH_2$), 4.64 (t, *J* = 8.5 Hz, 2H, CH_2O), 4.29 (t, *J* = 8.5 Hz, 2H, CH_2N)
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 184.9 (C), 169.0 (C),54.5 (CH_2), 46.9 (CH_2).
IR (ATR): 2917, 2100, 1697, 1364, 1320, 1212, 1168, 1017, cm^{-1}.

6.3.5.1. Synthesis of 2-azidoacetyl chloride

In a previously dried flask equipped with a magnetic core, azidoacetic acid (1.5 g, 15 mmol, 1 equiv) was added, purged with N_2, and dissolved in dry dichloromethane (50 mL). Once dissolved, the solution was immersed in a ice/water bath at 0°C.

Oxalyl chloride (1.6 g, 18.8 mmol, 1.253 equiv) was added dropwise, followed by 10 drops of DMF. The water/ice bath was removed, and the reaction was stirred at room temperature for 4 h.

Finally, the solution was concentrated under pressure to obtain a colorless oil (1.71 g, 12 mmol, 81% yield).



Colorless oil. Rf 0,35 (hexanes/EtOAc 7:3)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.29 (s, 2H, $C\underline{H_2}N_3$)
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.5 (C), 67 (CH_2)
IR (ATR): 3048, 2100, 1788, 1723, 1406, 1269 cm^{-1}.

6.4. ALDOL REACTIONS

6.4.1. General procedure for diastereoselective reactions

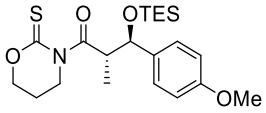
In a previously dried 5 mL flask equipped with a magnetic core, the corresponding *N*-acyl **3-5** synthesized previously (1 equiv) and the achiral catalyst $(Me_3P)_2NiCl_2$ (0.05 equiv) were added. The flask was sealed with a septum, purged with N_2, and a N_2-filled balloon was introduced to maintain the solution under an inert atmosphere. Anhydrous dichloromethane (1 mL) was added, and the resultant solution was immersed in a methanol/ice bath at -20 °C.

Using a Hamilton syringe, 4-methoxybenzaldehyde (1.1 equiv) was added to the solution. Then, TESOTf (1.3 equiv) was added as a Lewis acid, and the solution was stirred for 5 min. Next, 2,6-lutidine (1.5 equiv) was added. The solution was stirred overnight at -20 °C.

The reaction was quenched with a saturated solution of NH_4Cl (2 mL), and the mixture was transferred to a separating funnel. The organic layer was washed with water (15 mL) and the aqueous phase extracted with dichloromethane (3 × 15 mL). Finally, the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated under pressure.

6.4.2. *N*-[3-(4-Methoxyphenyl)-2-methyl-3-triethylsilyloxypropanoyl]-1,3-oxazinane-2-thione (9)

Following the general procedure 6.4.1, *N*-propanoyl-1,3-oxazinane-2-thione (95 mg, 0.5 mmol, 1 equiv), $(Me_3P)_2NiCl_2$ (7 mg, 2.5 μmol, 0.05 equiv), 4-methoxybenzaldehyde (67.5 μL, 0.55 mmol, 1.1 equiv), TESOTf (150 μL, 0.65 mmol, 1.3 equiv), and 2,6-lutidine (88 μL, 0.75 mmol, 1.5 equiv) were added and the reaction mixture was kept at –20 ºC overnight. The residue was purified by flash column chromatography (50:50 hexanes/DCM) to afford the anti-enantiomer **9** (179.4 mg, 0.42 mmol, 78% yield). HPLC characterisation was not required for the anti-diastereomer, as it was already available.[25]

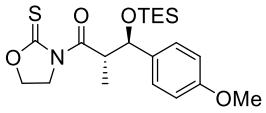


White solid. **Rf** 0.20 (hexanes/DCM 5:5)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.21 (m, 2H, ArH), 6.86-6.84 (m, 2H, ArH), 4.66 (d, 1H, *J* = 9.4 Hz, TESOCH), 4.50-4.45 (m, 1H, $COCHCH_3$), 4.18 (td, 1H, *J* =10.4, 3.7 Hz, OCH_xH_y), 4.07-3.99 (m, 1H, OCH_xH_Y), 3.90-3.85 (m, 1H, NCH_xH_Y), 3.81 (s, 3H, OCH_3), 3.62 (ddd, 1H, *J* = 12.7, 10.0, 8.3 Hz, NCH_xH_Y), 2.24-2.16 (m, 2H, OCH_2CH_2), 1,03 (d, 3H, *J* = 6.7 Hz, $CHCH_3$), 0.82-0.77 (m, 9H, $OSiCH_2CH_3$), 0.41-0.26 (m, 6H, $OSiCH_2CH_3$).

6.4.3. *N*-[3-(4-Methoxyphenyl)-2-methyl-3-triethylsilyloxypropanoyl]-1,3-oxazolidine-2-thione (10)

Following the general procedure 6.4.1, *N*-propanoyl-1,3-oxazolidine-2-thione (84 mg, 0.5 mmol, 1 equiv), $(Me_3P)_2NiCl_2$ (7 mg, 2.5 μmol, 0.05 equiv), 4-methoxybenzaldehyde (67.5 μL, 0.55 mmol, 1.1 equiv), TESOTf (150 μL, 0.65 mmol, 1.3 equiv), and 2,6-lutidine (88 μL, 0.75 mmol, 1.5 equiv) were added and the reaction mixture was kept at –20 ºC overnight.



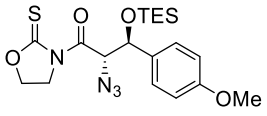
White solid. **Rf** 0.34 (hexanes/EtOAc 8:2)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.26 (m, 2H, ArH), 6.87-6.85 (m, 2H, ArH), 5.12 (dq, 1H, *J* = 9.5, 6.8 Hz, $COCHCH_3$) 4.76 (d, 1H, *J* = 9.5 Hz, TESOCH), 4.56 (td, 1H, *J* = 8.6, 6.6 Hz, OCH_xH_y), 4.49-4.42 (m, 1H, OCH_xH_Y), 4.26-4.21 (m, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 0.89 (d, 3H, *J* = 6.8 Hz, $COCHCH_3$), 0,78 (t, 9H, *J* = 7.9 Hz, $OSiCH_2CH_3$), 0.41-0.34 (m, 6H, $OSiCH_2CH_3$).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 185.1 (C), 176.4 (C), 159.0 (C), 135.1 (C), 127.9 (CH), 113.1 (CH), 76.4 (CH_2), 47.3 (CH_2), 47.2 (CH), 13.4 (CH_3), 6.7 (CH_2), 4.7(CH_3).
IR (ATR): 2958, 2930, 2869, 1701, 1610, 1518, 1460, 1365, 1307, 1255, 1160, 1069, 1038, 956, 940, 833 cm^{-1}.

6.4.4. *N*-[3-(4-Methoxyphenyl)-2-azido-3-triethylsilyloxypropanoyl]-1,3-oxazolidine-2-thione (11)

Following the general procedure 6.4.1, *N*-(2-azidoacetyl)-1,3-oxazolidine-2-thione (107 mg, 0.5 mmol, 1 equiv), $(Me_3P)_2NiCl_2$ (7 mg, 2.5 μmol, 0.05 equiv), 4-methoxybenzaldehyde (67.5 μL,

0.55 mmol, 1.1 equiv), TESOTf (150 µL, 0.65 mmol, 1.3 equiv), and 2,6-lutidine (88 µL, 0.75 mmol, 1.5 equiv) were added and the reaction mixture was kept at –20 ºC overnight.



White solid. **Rf** 0.33 (hexanes/EtOAc 8:2)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.03-7.01 (m, 2H, ArH), 6.93-6.91 (m, 2H, ArH), 4.99 (d, 1H, *J* = 8.6 Hz, $COCHN_3$) 4.49 (d, 1H, *J* = 9 Hz, TESOCH), 4.56 (td, 1H, *J* = 8.6, 6.6 Hz, OCH_xH_y), 4.49-4.42 (m, 1H, OCH_xH_Y), 4.23-4.20 (dd, 2H, *J* = 6 Hz, NCH_2), 3.9 (s, 3H, OCH_3), 0.82-0.77 (m, 9H, $OSiCH_2CH_3$), 0.41-0.26 (m, 6H, $OSiCH_2CH_3$).

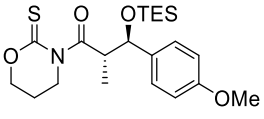
6.4.5. General procedure for enantioselective reactions

N-[3-(4-Methoxyphenyl)-2-methyl-3-triethylsilyloxypropanoyl]-1,3-oxazinane-2-thione (9)

In a previously dried 5 mL flask equipped with a magnetic core, the corresponding *N*-propanoyl-1,3-oxazolidine-2-thione synthesized previously (1 equiv) and the chiral catalyst [(R)-Tol-BINAP]$NiCl_2$ (0.05 equiv) were added. The flask was sealed with a septum, purged with N_2, and a N_2-filled balloon was introduced to maintain the solution under an inert atmosphere. Anhydrous dichloromethane (1 mL) was added, and the resultant solution was immersed in a methanol/ice bath at -20°C.

Using a Hamilton syringe, 4-methoxybenzaldehyde (1.1 equiv) was added to the solution. Then, TESOTf (1.3 equiv) was added as a Lewis acid, and the solution was stirred for 5 minutes. Next, 2,6-lutidine (1.5 equiv) was added. The solution was stirred for 2 h at -20 °C.

The reaction was quenched with a saturated solution of NH_4Cl (2 mL), and the mixture was transferred to a separating funnel. The organic layer was washed with water (15 mL) and the aqueous phase extracted with dichloromethane (3 × 15 mL). Finally, the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated under pressure. The residue was purified by flash column chromatography (50:50 hexanes/DCM) to afford the anti-enantiomer **9** (149.69 mg, 0.35 mmol, 70% yield). The anti-enantiomer was further characterised by HPLC to give 99% (column cellulose 5, 5% IPA concentration, flow rate 1 mL/min)



White solid. **Rf** 0.20 (hexanes/DCM 5:5)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.21 (m, 2H, ArH), 6.86-6.84 (m, 2H, ArH), 4.66 (d, 1H, *J* = 9.4 Hz, TESOCH), 4.50-4.45 (m, 1H, $COCHCH_3$), 4.18 (td, 1H, *J* =10.4, 3.7 Hz, OCH_xH_y), 4.07-3.99 (m, 1H, OCH_xH_Y), 3.90-3.85 (m, 1H, NCH_xH_Y), 3.81 (s, 3H, OCH_3), 3.62 (ddd, 1H, *J* = 12.7, 10.0, 8.3 Hz, NCH_xH_Y), 2.24-2.16 (m, 2H, OCH_2CH_2), 1,03 (d, 3H, *J* = 6.7 Hz, $CHCH_3$), 0.82-0.77 (m, 9H, $OSiCH_2CH_3$), 0.41-0.26 (m, 6H, $OSiCH_2CH_3$).

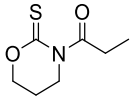
7. CONCLUSIONS

The first objective of this project was to prepare the described scaffolds on a large scale. By comparing the yield values obtained by the group, it can be concluded that in this case, the yield values obtained are slightly lower. One of the possible causes for this difference could be inexperience or potential cross-contamination.

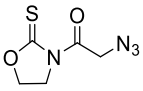
31%

40%

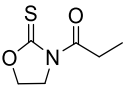
The second objective was the acylation of the previously prepared scaffolds with carboxylic acids and acyl chloride using different methodologies, aiming to observe the possible influence of leaving groups. Looking at the results, it has been observed that better results were obtained by using carboxylic acid for acylation, which was already anticipated.



40%

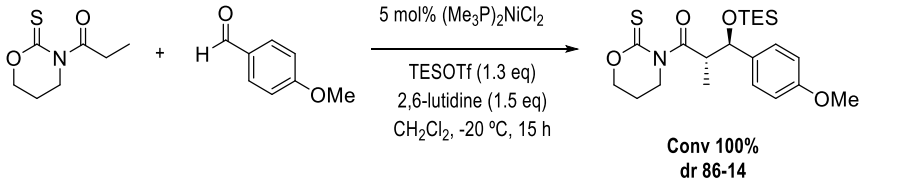


53%

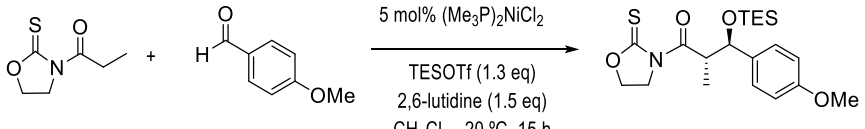


59%

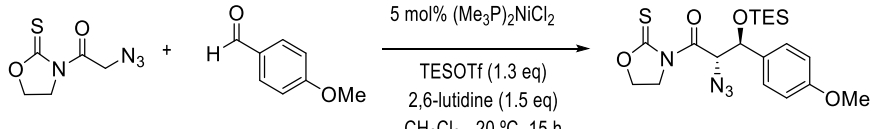
Finally, the last objective was the synthesis of a direct catalytic asymmetric alkylation reaction of the previously acylated products with 4-methoxybenzaldehyde, using chiral and achiral nickel (II) complexes and TESOTf as a Lewis acid to activate the aldehyde. In this case, it is observed that using the chiral catalyst resulted in high diastereoselectivity and excellent enantioselectivity.



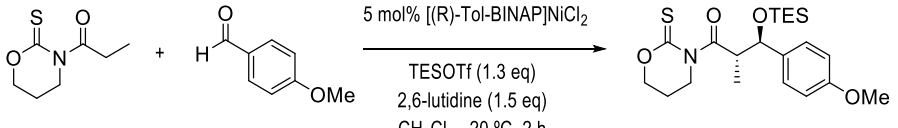
Conv 100%
dr 86-14



Conv 52%
dr 60:40



Conv 70%
dr 93:7



70% anti diastereomer
dr 71:29
ee > 99%

8. REFERENCES AND NOTES

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9. ACRONYMS

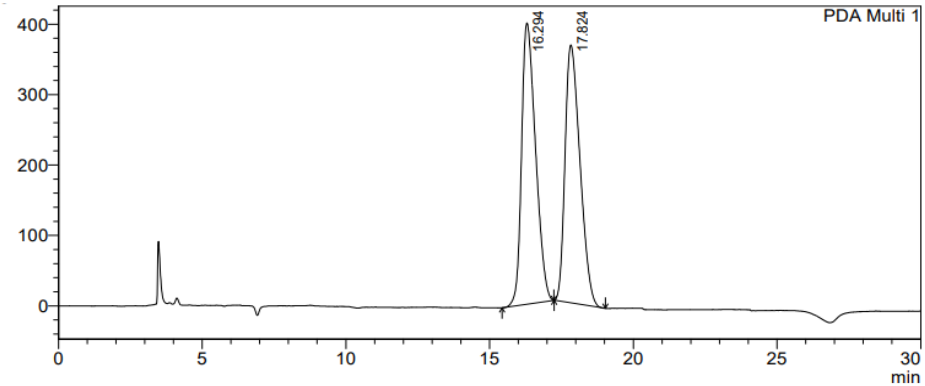
Ar	Aromatic
ATR	Attenuated Total Reflectance
δ	Chemical shift
DMAP	4-Dimethylaminopyridine
DMF	N.N-Dimethylformamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
E^+	Electrophile
EDC	1-Ethyl-3-(dimethylaminopropyl)carbodiimide
equiv	Equivalent(s)
Et	Ethyl
Et_3N	Triethylamine
EtAcO	Ethyl acetate
Et_2O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

rf	Room temperature
TESOTf	Trimethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl

APPENDICES

APPENDIX 1: HPLC COMPARISON IN CHIRAL AND ACHIRAL CATALYST REACTIONS

→ACHIRAL CATALYST (**9**)



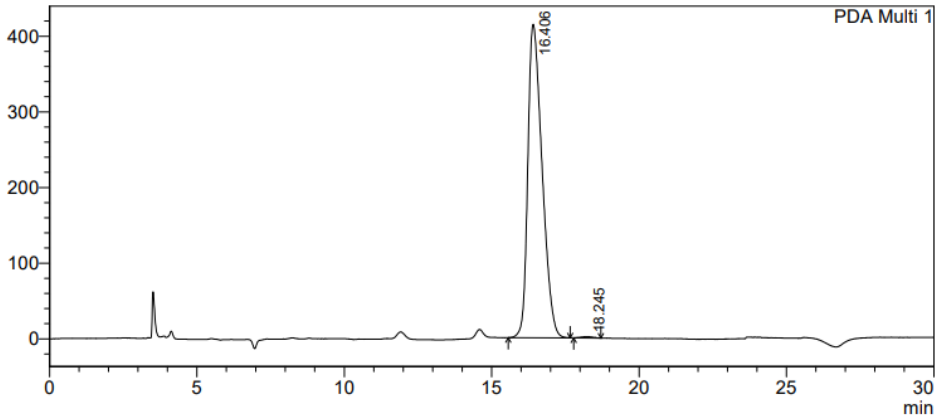
1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.294	13482286	399476	50.501	52.166
2	17.824	13214796	366304	49.499	47.834
Total		26697082	765781	100.000	100.000

→ CHIRAL CATALYST (**9**)



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.406	13947518	414359	99.625	99.550
2	18.245	52541	1875	0.375	0.450
Total		14000060	416233	100.000	100.000