NOVA SCHOOL OF SCIENCE & TECHNOLOGY

DEPARTAMENT OF CHEMISTRY

DIANA FILIPA LOPES ALVES

BSc in Applied Chemistry

STUDIES ON THE CURTIUS REARRANGEMENT OF PROLINE DERIVATIVES AND PREPARATION OF *N*-CARBAMOYL INDOLINE DERIVATIVES FOR ASYMMETRIC CATALYSIS

MASTER IN BIOORGANIC CHEMISTRY

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MASTER IN BIOORGANIC CHEMISTRY

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Studies on the Curtius rearrangement of proline derivatives and preparation of *N*-carbamoyl indoline derivatives for asymmetric catalysis

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ABSTRACT

In the synthesis of cernumidine (**1**) and its derivatives was previously developed in the research group, which involved the Curtius rearrangement as a key step. However, the compounds obtained showed some degree of racemization which was dependent on the substituents used in the trapping of the formed isocyanate.

In the first part of this work, *N*-pyrimidine, *N*-alkyl and *N*-acyl derivatives of proline were synthesized and subsequently subjected to Curtius rearrangement. The isocyanate was trapped with phenylmagnesium bromide to study the influence the substituents on the nitrogen atom can have on the observed racemization.

The *N*-pyrimidinyl proline (**8**) derivative was, after the Curtius rearrangement, trapped with benzylamine and cyclohexylamine both led resulted in racemic ureas (**9**) and (**10**), with 12% and 3% yield, respectively. The *N*-methyl (**4**), *N*-benzyl (**5**) and *N*-benzoyl (**7**) proline derivatives presented inconsistent results and resulted in complex mixtures of degraded starting material, while the *N*-acetyl proline (**6**) derivative afforded a complex mixture of compounds. Due to this, we weren't able to study the influence of the substituent on the nitrogen atom.

In the second part of this work, we worked on a synthetic route to synthesize guanidine pyrrolidine catalysts for the Michael addition reaction, between ethyl 2-oxocyclopentsnecarboxylate (**2**) and *trans*-β-nitrostyrene (**3**). The developed catalysts were (*S*)-indoline derivatives that were derivatized to amide derivatives and functionalized with a carbodiimide group on the nitrogen atom. The goal was to study their performance as bifunctional catalyst and to study the stereoselectivity induced in the reaction described above.

The synthesis of these compounds involved four steps in which the most challenging one was the last step, the guanylation. The guanylation was achieved using the guanylating agent 1,3-di-Boc-2-methylisothiourea and the catalyst SmI_2. Three different guanylated compounds were attained (**19**), (**20**) and (**21**), with 23%, 70% and 6% yield, respectively.

The Michael addition assays employing the synthesized compounds (**19**) and (**20**), didn't achieve satisfactory yields. The ^1H NMR of the assay using compound (**19**) revealed a diastereoisomeric excess of 59% for the *anti*-isomer, but the evolution of the reaction was very slow. The assay with compound (**20**) showed an excess of the *anti*-isomer, but the diastereoisomeric excess wasn't calculated due to the low resolution of the NMR spectrum and consequently the error associated with its calculation of the diastereoisomeric excess. It was not

possible to perform the analysis of the enantiomeric excess, because the HPLC equipment was not operational.

Keywords: Curtius rearrangement, L-proline, amino-pyrrolidine, S-indoline, guanidine, Michael addition

RESUMO

A síntese da cernumidina (**1**) e seus derivados previamente desenvolvida pelo grupo de investigação, envolveu o rearranjo de Curtius como passo chave da síntese. No entanto, os compostos sintetizados apresentaram algum grau de racemização dependendo dos substituintes utilizados na armadilha do isocianato formado.

Na primeira parte deste trabalho, foram sintetizados os derivados *N*-pirimidina, *N*-alquil e *N*-acil da prolina que foram posteriormente submetidos ao rearranjo de Curtius, e o isocianato armadilhado com diferentes nucleófilos para estudar a influência que os substituintes no átomo de azoto podem ter na racemização observada.

O derivado *N*-pirimidinil (**8**) da prolina foi, após o rearranjo de Curtius, armadilhado com benzilamina e ciclohexilamina, tendo-se obtido as ureias racémicas (**9**) e (**10**), com 12% e 3% de rendimento, respetivamente. Os derivados *N*-metilo (**4**), *N*-benzilo (**5**) e *N*-benzoilo (**7**) da prolina apresentaram resultados inconsistentes e resultaram em misturas complexas de material de partida degradado, enquanto que o derivado *N*-acetil (**6**) resultou numa mistura complexa de compostos. Devido a isto, não foi possível estudar a influência do substituinte no átomo de azoto.

Na segunda parte deste trabalho, desenvolveu-se uma via sintética para sintetizar catalisadores de pirrolidina guanilados para a reação de adição de Michael, entre etil 2-oxociclopentanocarboxilato (**2**) e *trans*-β-nitroestireno (**3**). Os catalisadores desenvolvidos foram derivados da (*S*)-indolina que foi derivatizada aos derivados amida e funcionalizados com um grupo carbodiimida no átomo de azoto. Era objetivo estudar a sua atuação como catalisador bifuncional e estudar a estereosseletividade induzida na reação atrás descrita.

A síntese destes compostos envolveu quatro passos, sendo o último passo sintético, a guanilação, o mais desafiante. A guanilação foi alcançada utilizando o SmI_2 como catalisador e o agente guanilante 1,3-di-Boc-2-metilisotioureia, obtendo-se três compostos guanilados diferentes (**19**), (**20**) e (**21**), com 23%, 70% e 6% de rendimento, respectivamente.

Os ensaios de adição de Michael utilizando os compostos sintetizados (**19**) e (**20**), não obtiveram rendimentos satisfatórios. O espectro de ^{1}H RMN do ensaio com o composto (**19**) revelou um excesso diastereoisomérico de 59% para o isómero *anti*, mas a evolução da reação foi muito lenta. O ensaio com o composto (**20**) mostrou excesso do isómero *anti*, mas devido à baixa resolução do espetro de RMN e consequentemente ao erro associado ao cálculo do excesso diastereoisomérico, este não foi determinado. Não foi possível realizar a análise do excesso enantiomérico, devido ao facto do equipamento de HPLC não se encontrar operacional.

Palavras-chave: Rearranjo de Curtius, L-prolina, amino-pirrolidina, S-indolina, guanidina, adição de Michael

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Nomenclature and Abbreviations

δ	Chemical shift
$\upsilon_{max.}$	Maximum wavenumber
^{13}C NMR	Carbon 13 nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
ACN	Acetonitrile
Boc	Tert-butyloxycarbonyl
br	broad singlet
Cbz	Carboxybenzyl
CDI	Carbonyl diimidazole
d	Doublet
DCC	Dicyclohexyl carbodiimide
DCM	Dichloromethane
dd	Doublet of doublets
DIPEA	Diethylpropylamine
Equiv.	Equivalent
EWG	Electron withdrawing group
EDC	Ethyl dimethylaminopropyl carbodiimide
IBCF	Isobutyl Chlorofomate
J	Coupling Constant
MTBE	Methyl tert-butyl ether
NMM	N-Methyl Morpholine
NMR	Nuclear magnetic resonance
PG	Protecting group
Ph	Phenyl
PTLC	Preparative thin-layer chromatography
ppm	parts per million
q	quadruplet
quint	quintuplet

t	Triplet
TEA	Triethyl amine
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
s	Singlet

1 INTRODUCTION

1.1 Insights over the synthesis of cernumidine and derivatives

Cernumidine (Figure 1.1) is a natural compound isolated from the ethanolic extract of leaves of *Solanum cernuum Vell*. The compound was isolated in 2011 and presented optical activity, with a specific optical rotation of $[\alpha]_D^{20}$ +10.9 (c 0.84, MeOH). Nevertheless, the X-ray analysis showed the presence of both enantiomers, which means that some racemization occurs either in Nature or after isolation [1].

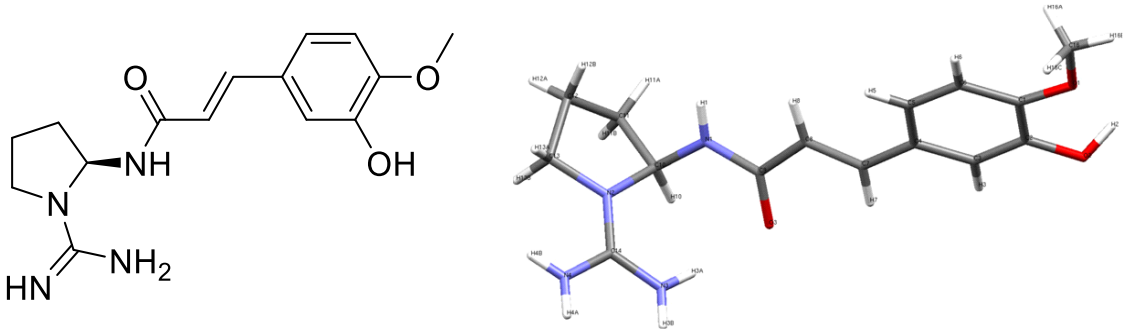
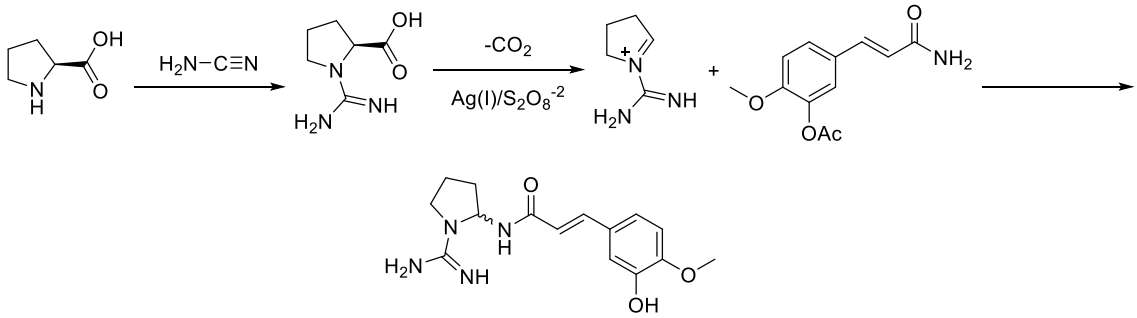


Figure 1.1 - Structure and X-ray crystal structure of cernumidine (**1**) [1]

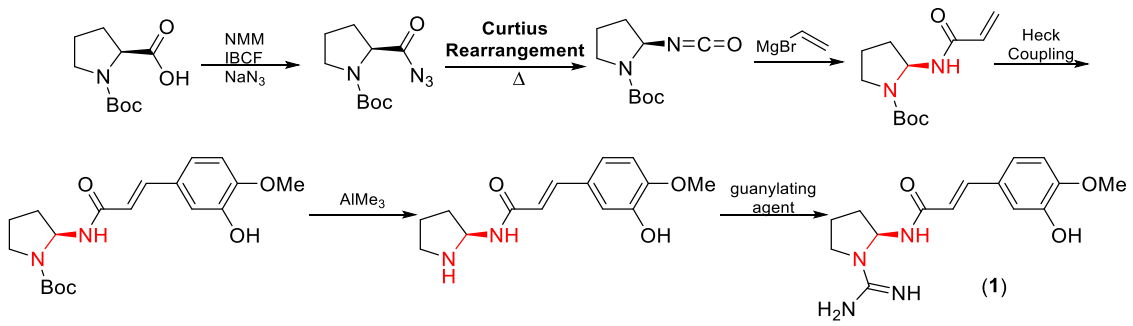
The first synthetic route reported for cernumidine was in 2020, in which it was obtained from proline with a 22% yield. This synthetic route employed the oxidative decarboxylation of guanylated *L*-proline using silver(I)/peroxydisulfate ($Ag(I)/S_2O_8^{2-}$), followed by the intermolecular trapping of the iminium with the acetylated isoferulic amide (Scheme 1.1). However, this route was not stereoselective and therefore cernumidine was obtained as a racemic mixture [2].



Scheme 1.1 - First synthetic route for the synthesis of cernumidine (**1**) [2]

New efforts to obtain an enantiomerically pure cernumidine have been made and a new synthetic route has been developed (unpublished results) (Scheme 1.2). The first step of this new route is the formation of the acyl azide moiety from commercially available *N*-boc *L*-

proline carboxylic acid, which is achieved by forming a mixed anhydride that then reacts with sodium azide. The next step is the key step of the synthetic route, the Curtius rearrangement. This rearrangement, which has been reported as a configuration retention step, consists in the thermal decomposition of acyl azide into isocyanate, releasing molecular nitrogen [3]. The isocyanate is a highly reactive specie and therefore can be trapped with different nucleophiles to achieve various functional groups [4]. To attain cernumidine (**1**) the isocyanate is trapped with vinyl magnesium bromide, which is followed by a Heck coupling reaction with the appropriated aryl bromide compound. Final steps are the deprotection of the nitrogen atom of the proline skeleton with trimethylaluminum, and its subsequent guanylation.



Scheme 1.2 - New synthetic route for cernumidine (**1**)

However, despite being this a stereospecific reaction it was not attained an enantiomerically pure cernumidine (**1**). Through this synthesis, cernumidine was synthesized with an enantiomeric excess of 82%. Later studies, led to the hypothesis that the racemization occurs through the opening and reclosing of the aminal core (highlighted in red in Scheme 1.2, unpublish results).

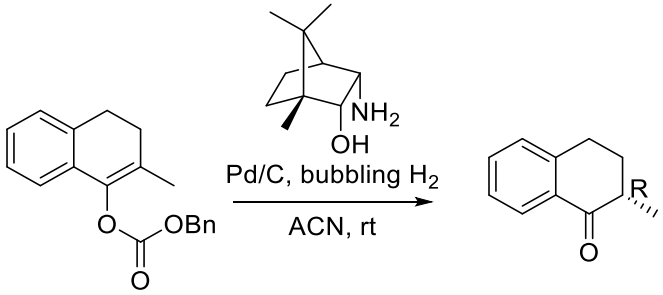
As mentioned, during the synthesis of cernumidine (**1**) the nitrogen atom of the proline skeleton is substituted with a boc protecting group. In this work, we intend to study the influence that different substituting groups on the nitrogen atom can play on the opening of the aminal core and understand if and how it affects the racemization of the of the aminal products of Curtius rearrangement.

1.2 Synthesis of guanidine based organocatalysts

1.2.1 Asymmetric Synthesis

Catalysis can be described as a process in which a substance, the catalyst, influences the rate of a reaction by lowering its activation energy, and/or the formed product through selectivity, while not being consumed during the reaction. Catalysis can be divided into three major groups: heterogenous, homogenous, and enzymatic.

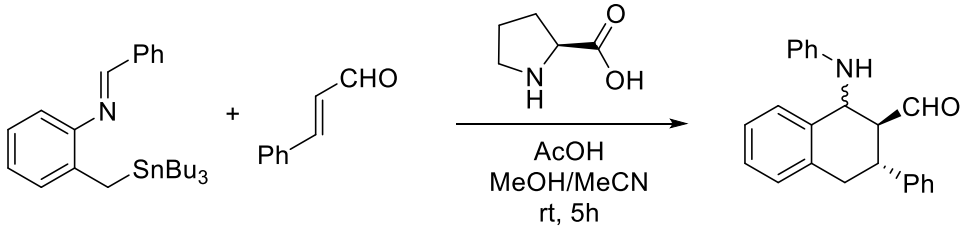
In heterogenous catalysis, the catalyst is in a different phase than the reagents of the reaction. Usually, the catalyst in this type of catalysis is in a solid state, typically adsorbed in a support, while the reactants are in a gaseous or liquid phase. Because of this dynamic, heterogenous catalysis is very appealing, not only due to the ease with which it is possible to separate the catalyst from the reactants and products of the reaction, but also because of the ability to recycle it [5]. As a result, this type of catalysis has been distinguished by its sustainability, which is especially important due the rising concerns and the efforts made aiming at the implementation of a green chemistry philosophy to reduce pollution and waste at its source. A common example of this catalysis is the enantioselective reaction of benzyl carbonate initiated by Pd/C leading to optically enriched 2-alkyl ketones (Scheme 1.3).



Scheme 1.3 - Example of a heterogeneous catalysis reaction: Enantioselective reaction of benzyl carbonate initiated by Pd/C leading to optically enriched 2-alkyl ketones [6]

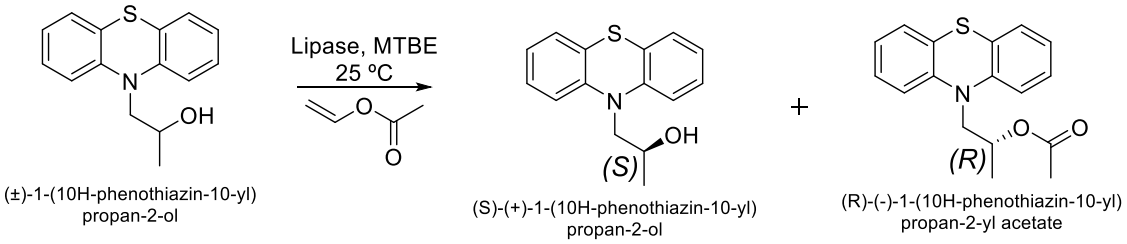
Homogeneous catalysis employs a catalyst, usually a small molecule, which is in the same phase as the reactants, facilitating the molecular collision between the two [5]. This generally leads to not only higher rates, but also higher selectivity. However, the homogeneity also poses disadvantages, such as difficulty in separation of the catalyst from the reactants, which leads to a reduced possibility of recycling of the catalyst [7]. An example of this type of

catalysis is the Diels-Alder asymmetric reaction of (*E*)-1-phenyl-*N*-(2-((tributylstannyl)methyl)phenyl)methanimine with cinnamaldehyde, catalyzed by proline (Scheme 1.4).



Scheme 1.4 - Example of a homogenous catalysis reaction: Diels-Alder asymmetric reaction catalysed by proline [8]

Finally, the enzymatic catalysis which involves the use of a protein as a catalyst. These catalyses are extremely specific since enzymes will only interact with certain substrates, or even only one stereoisomer [9]. An example is shown below, in which the enzyme, a lipase, only transfers the acetyl group to one of the alcohol stereoisomers, resulting in its esterification (Scheme 1.5).



Scheme 1.5 - Example of enzymatic catalysis: esterification of an alcohol by a lipase [10]

Some stereoisomers are enantiomers, compounds that exists in two forms that are non-overlapping mirror images of one another and can present optical activity, which means they each rotate the plane of a beam of polarized light (+/-). For a pair of enantiomers with same the concentration and under the same conditions, they rotate the plane of polarized light with the same angles but in opposite direction, one in clockwise and the other in counterclockwise. Because of this, when both enantiomers are present in equal quantities in a sample, the light rotation is 0º and the mixture is called a racemic mixture or racemate [11]. The chirality of a compound is very important because it can affect completely the way the compound interacts with other chiral environments like biological receptors. It is very common to see enantiomers with completely different biological activities, like for example ketamine where the one of the enantiomers is an anesthetic and the other is psychotic drug (Figure 1.2) [12].

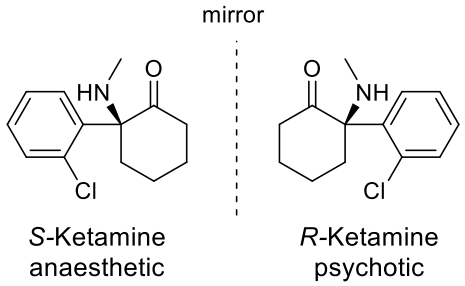


Figure 1.2 - Example of two enantiomers with different biological activities

This notion can introduce us to the concept of asymmetric catalysis, which consists of the use of a chiral catalyst that creates an effective asymmetric environment to enantioselective reactions, favoring the formation of a specific stereoisomer. These organocatalysts can be either be chiral organic molecules or metals with chiral ligands.

Guanidines have been an emerging organocatalyst in the last few years in organic synthesis. Their interest is not only due of their ability to operate as superbases, but also because they are structurally simple, have low toxicity and high efficiency and selectivity, making them very appealing to employ as chiral organocatalysts in enantioselective reactions [13].

1.2.2 Guanidines

Guanidines are a functional group in which a carbon atom is linked to three nitrogen atoms. This moiety can be found in nature in several organisms, from bacteria to marine sponges, terrestrial organisms, and plants, with the first three establishing the main biological source of natural guanidines [14], [15]. This functional group presents a high basicity, derived from its ability to stabilize its conjugated acids through resonance [16]. This basicity can be modified though the substitution of the nitrogen atom with electron-donating groups, like alkyls or heteroalkyls groups to slightly increase its basicity, or with electron-withdrawing groups, like OH or CN to lower it [17].

This moiety is present in catalysts of numerous reactions, like reduction reactions, epoxidations, sylilations of alcohols, aldol reactions, Diels-Alder reactions, epoxidations, Mannich reaction, enantioselective Steck reactions and enantioselective Michael addition reactions

among many others. In Figure 1.3 are presented several examples of compounds where the guanidine moiety is present and highlighted in red [16], [18], [19].

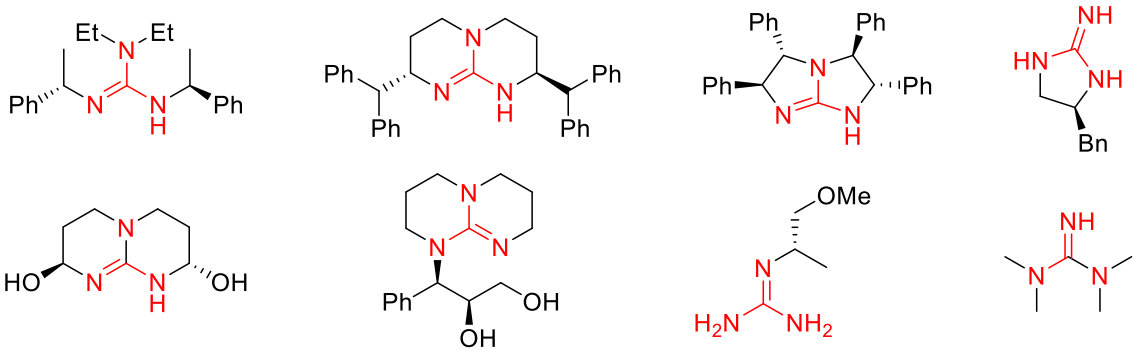


Figure 1.3 - Examples of guanidine based organocatalysts

This unique functional group can be found in many interesting compounds, presenting biological activity. They have known effects in the central nervous system, acting as inhibitors, ligands, or agonists in different receptors, showing usefulness in the treatment of neurodegenerative and neuropsychiatric conditions (Figure 1.4), as well as relevant effects as anti-inflammatory and anesthetic agents. Some of these compounds also present other types of biological activities, such as antibiotic, anti-viral, and anti-parasitic, among many others. However, perhaps the most relevant, is their anti-cancer activity, hindering tumor development and inducing metastasis suppression for cancer (Figure 1.4) [17].

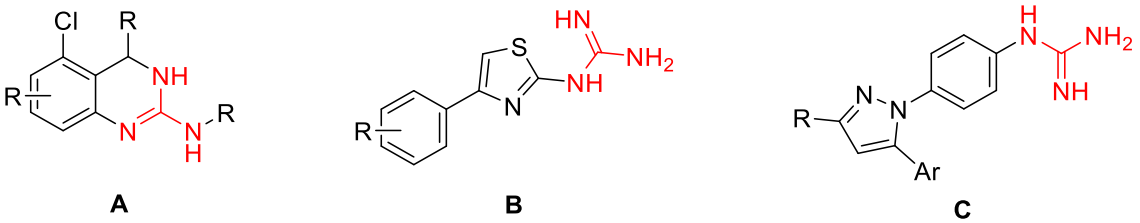


Figure 1.4 - Example of biologically active guanidine compounds. A: Neurodegeneration and dementia; B:Treatment of anxiety, sleeping disorders, pain, depression, and Parkinson's disease; C: Treatment and prevention of cancer [17]

Guanidines, are neutral compounds capable of exist in a cationic (guanidinium) and anionic (guanidinate) state, broadly recognized by chemists as a very strong base, being often described as superbases, due to their strong basic character, with a pKHa of 13.6 [20]. Free guanidines are both Lewis and Bronsted bases, as well as efficient hydrogen-bond donors and acceptors. On the other hand, guanidinium salts are bidentate, cationic hydrogen-bond donors

that present weak Bronsted acidity (Figure 1.5) [18]. These properties led to a growth in use this moiety as catalysts [21].

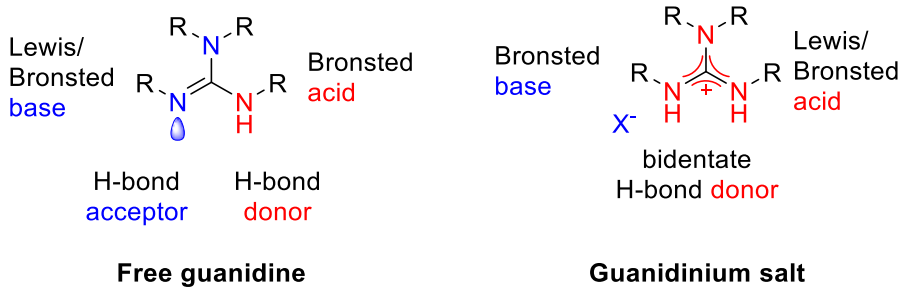
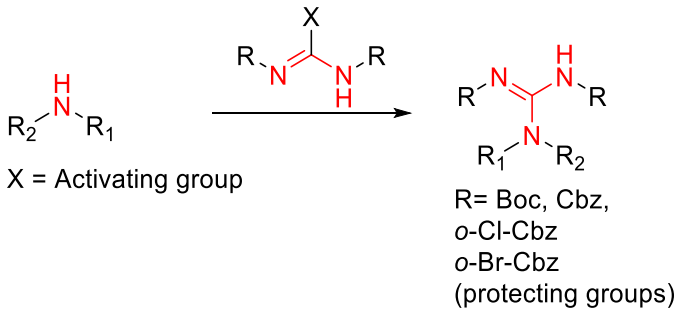


Figure 1.5 - Functionalities of free guanidine bases and guanidinium salts [21]

However, the synthesis of guanidine derived catalysts is known to be a challenging task, due to the high basicity and polarity of guanidines which complicates both the synthesis itself and also its purification process [21].

The synthesis of guanidines, designated as guanylation, is generally achieved through the reaction of an amine, primary or secondary, with a denominated guanylating agent (Scheme 1.6). The introduction of activating groups in the guanylating agents exhibited an improvement in the synthetic process and allowed the use of milder reactional conditions. The employment of protecting groups led to less polar and basic guanidines, facilitating both the handling and purification process [22].



Scheme 1.6 - General guanylation reaction

Several guanylating agents are present in Figure 1.6 [22]–[25]. As observable, they present a rather wide range of activating groups, like methyl sulphur, triflates, thioureas and pyrazole carboxamidine. This last activating group is reported to be among the most reactive, increased by the presence of the pyrazole ring which an electron withdrawing group. The protecting groups in the nitrogen atoms also affects the reactivity of the guanylating reagents. The

presence of electron withdrawing groups like Boc, Cbz, o-Cl-Cbz or o-Br-Cbz, bonded to the nitrogen atom also increase the reactivity of the guanylating agent [24].

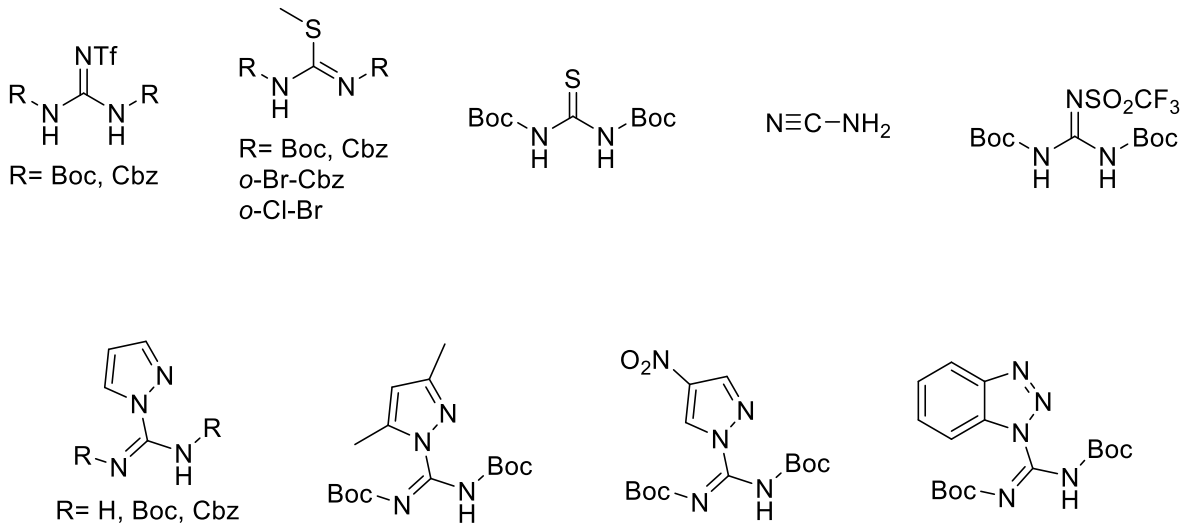
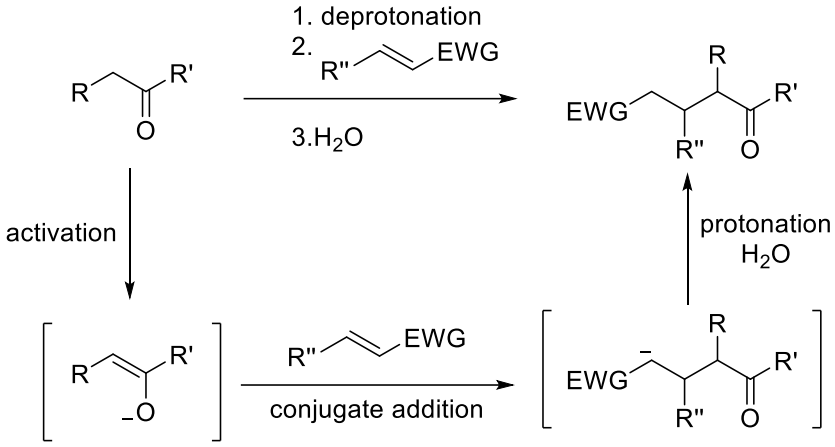


Figure 1.6 - Most commonly used guanylating agents

1.2.3 Michael Addition

The Michael addition, also known as 1,4 conjugated addition, is broadly known as one of the most important C-C bond formation reactions in organic synthesis in which there occurs an addition between nucleophiles and activated olefins and alkynes [26], [27]. This reaction, illustrated in Scheme 1.6, for the addition of a carbon nucleophile can be separated into three steps: the activation of the nucleophile, which generates an enolate or a nucleophilic species like an enamine or an enol; the conjugate addition; and finally the addition of a second electrophile, usually a proton, that results in a conjugate addition by reacting with the stabilized anionic intermediary (Scheme 1.7) [28].



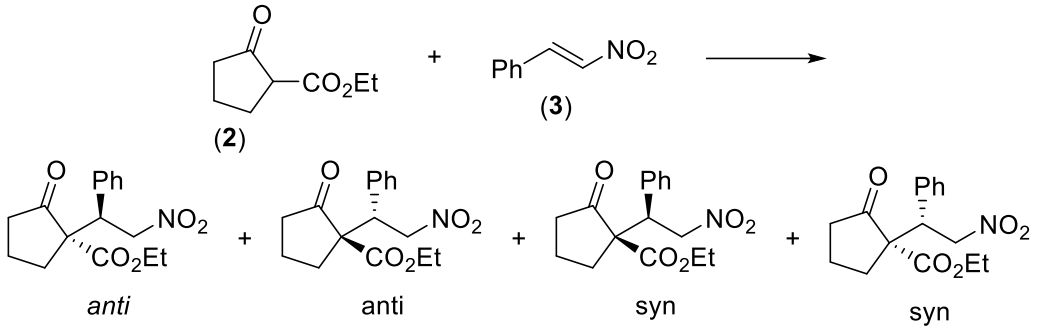
Scheme 1.7 – General Michael addition reaction

The reaction can lead to the formation of two new stereogenic centers, which means that we can obtain four different stereoisomeric compounds as reaction products. The predominance of one or another stereoisomer can be controlled, and the asymmetric catalysis can play here a vital role, through the introduction of a chiral catalyst. The enantioselective catalytic Michael reactions can be classified into two main groups, depending on the nature of the catalyst. These categories are metal catalysis, in which the catalyst used is a metal complex that interacts with the nucleophile and forms a chiral metal enolate; and organocatalysis, in which small organic molecules participate in the reaction, usually, by either activating the reagents through reversible covalent bonds, or through the effects, electrostatic or H-bonds, of the substrate-catalyst interaction [28].

The Michael addition of carbonyl compounds to nitro alkenes is recognized as a powerful carbon–carbon bond-forming reaction and affords the useful synthetic intermediates γ-nitro carbonyl compounds for example, for chiral pyrrolidines and γ-amino acids [29].

Numerous pyrrolidines or pyrrolidine derivatives have been developed over the years for Michael additions as bifunctional organocatalysts, with the ability to impose a specific orientation of the molecules during the transition state leading to stereospecific product [28], [30].

In this work, the organic catalysts developed are derived from the amino acid *L*-proline and employed in Michael reactions between ethyl 2-oxocyclopentane-carboxylate (**2**) and *trans*-β-nitrostyrene (**3**), in which we can obtain the formation of four stereoisomers (Scheme 1.8).



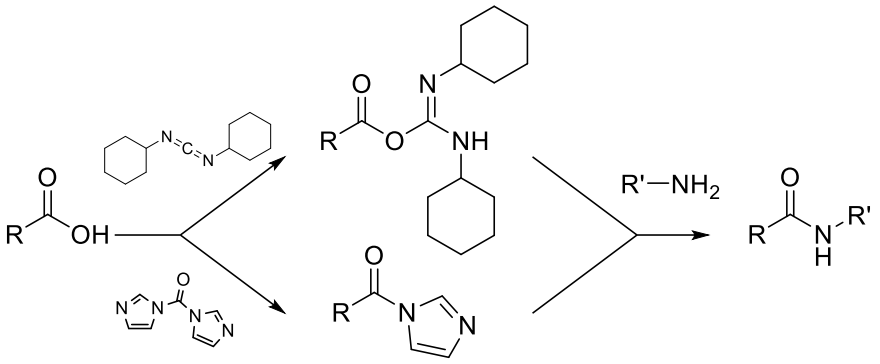
Scheme 1.8 – Michael addition reaction between ethyl 2-oxocyclopentane-carboxylate (**2**) and trans-β-nitrostyrene (**3**).

1.2.4 Amide Group

The amide groups are an essential functional group not only in organic synthesis, but across many other areas of chemistry, such as polymers, biochemistry, and drug discovery. The resonance of the amide bond, i.e. delocalization of the lone pair of electrons of the nitrogen atom to the carbonyl group, and the resulting stabilization and planarity of amides, has huge effect on the structure and reactivity of peptides and proteins, which is extremely important to all living organisms [31].

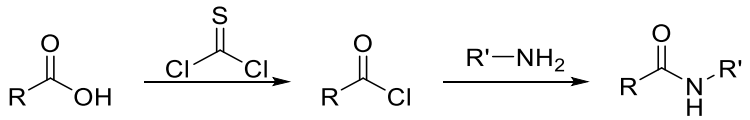
There are many procedures to obtain amides, with the most common ones being through the formation of an activated ester, the formation of an acyl chloride and finally, the formation of an anhydride [32].

The use of coupling reagents is a method involving the formation of an activated ester which then reacts with the amine to form the amide. This can be achieved with coupling reagents, such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and *N, N'*-dicyclohexylcarbodiimide (DCC), that lead to the formation of a reactive acyl isourea intermediary (Scheme 1.9, top). Another common coupling reagent is 1,1'-carbonildiimidazol (CDI) which forms an acyl imidazole intermediary (Scheme 1.9, bottom) which then reacts with an amine to form an amide [32], [33].



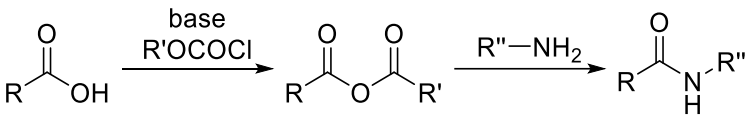
Scheme 1.9 - General reaction of amide formation using coupling reagents DCC (top) and CDI (bottom)

The formation of acyl halides as an intermediary to attain an amide is also very common. In this case, the carboxylic acid is activated using, for example, a thionyl chloride, which leads to the formation of the corresponding acyl halide. This forms a species that is much more reactive, the acyl chloride, which reacts easier with the amine, and results in the formation of the amide bond (Scheme 1.10) [33].



Scheme 1.10 - General reaction of amide formation through acyl halides

Another method is through the formation of an anhydride, specifically a mixed anhydride, as an intermediary which then reacts with the amine, leading to the formation of the amide. This is one of the oldest methods to obtain amides and typically use a base and an anhydride, such as acetic anhydride (Scheme 1.9). The formation of the mixed anhydride means that the carbonyls of the molecule are not equivalent, which usually results in the addition of the amine to the targeted carbonyl due to the lower electrophilicity of the undesired carbonyl [32].



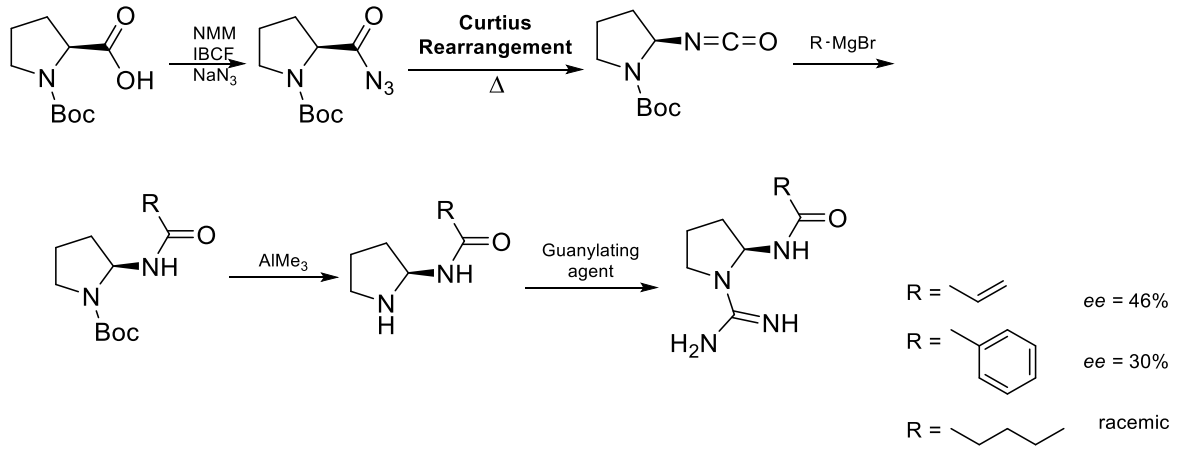
Scheme 1.11 - General reaction of amide formation through mixed anhydrides

In this work, we derived compounds from the (*S*)-indoline carboxylic acid amide derived compounds. This derivation was done through the formation of a mixed anhydride as an intermediary, which then reacted with the desired amine. The compounds synthesized were used as catalysts for Michael reactions between ethyl 2-oxocyclopentane-carboxylate (**2**) and *trans*-β-nitrostyrene (**3**).

2 Discussion

2.1 Preamble

The research group in which this work was developed has, in recent years, been dedicated to the synthesis of an alkaloid of natural origin, cernumidine (**1**). This was the principal compound isolated from the ethanolic extract of the leaves of *Solanum cernuum Vell*. In previous works of the group, the synthesis of cernumidine and its derivatives was developed, involving the Curtius rearrangement as a key step (Scheme 2.1). However, surprisingly the compounds obtained showed some degree of racemization which was dependent on the substituents used in the isocyanate trap (unpublished results).



Scheme 2.1 – Synthetic route for cernumidine derivatives

In the first part of the work here presented, *N*-alkyl and *N*-acyl derivatives of proline, as well as *N*-pyrimidine, were prepared to try to understand the influence that the substituent on the nitrogen atom can have on the observed racemization.

Thus, efforts were made in order to prepare the derivatives *N*-methyl-*L*-proline (**4**), *N*-benzyl-*L*-proline (**5**), *N*-acetyl-*L*-proline (**6**), and *N*-benzoyl-*L*-proline (**7**), as well as *N*-dimetoxypyrimidinyl-*L*-proline (**8**) and the compounds obtained were subsequently subjected to Curtius rearrangement and isocyanate trap with phenylmagnesium bromide.

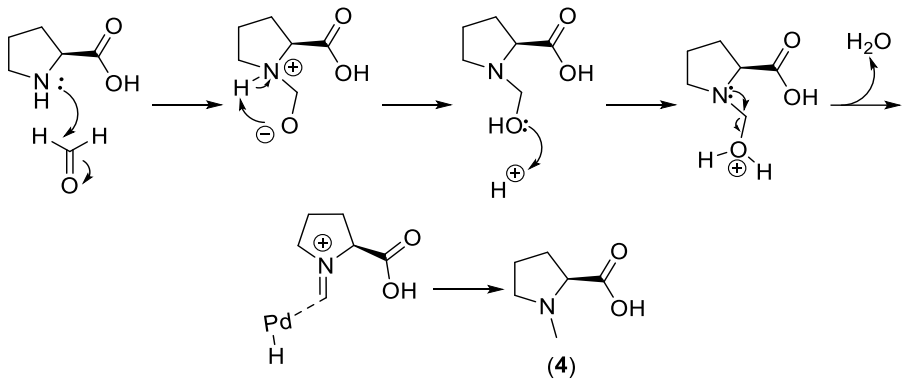
In the second part of this work, efforts are described in the preparation of *N*-carbamoyl derivatives of pyrrolidine and their application in asymmetric catalysis, namely in the preparation *N*-carbamoylindoline carboxylic acid. The developed compounds were applied as an organocatalyst in a condensation reaction between ethyl 2-oxocyclopentanecarboxylate (**2**) and trans-β-nitrostyrene (**3**).

2.2 The Preparation of *N*-Proline derivatives for the Curtius rearrangement

To study the influence that the substituent on the nitrogen atom can have on the observed racemization after the Curtius rearrangement of *N*-Boc-*L*-proline, it was outlined the preparation of the derivatives *N*-methyl-*L*-proline (**4**), *N*-benzyl-*L*-proline (**5**), *N*-acetyl-*L*-proline (**6**), and *N*-benzoyl-*L*-proline (**7**). The *N*-methyl and *N*-benzyl groups presents more electron donating properties than the previously studied carbamate groups (Boc group), unlike the *N*-acetyl and *N*-benzoyl groups, which are more electro withdrawing than the initial Boc protecting group.

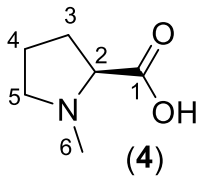
2.2.1 Preparation of *N*-methyl-*L*-proline (4)

This reaction was performed, as described in literature [34], using formaldehyde and Pd/C under H_2. The mechanism is presented in Scheme 2.2. In this reaction, the nucleophilic nitrogen atom of the proline attacks the electrophilic carbon of the carbonyl group of the formaldehyde, breaking the carbonyl double bond. The proton from the nitrogen atom is transferred to the oxygen atom creating an alcohol. The oxygen then captures another proton from the solvent, turning it into a good leaving group in the form of water. Finally, the catalytic hydrogenation with Pd/C and H_2 occurs by coordination of the iminium with the metal and insertion of the hydrogen into the carbon-nitrogen double bond leaving a methyl group attached to the nitrogen. The *N*-methyl-*L*-proline (**4**) was obtained with a yield of 90.5%.



Scheme 2.2 -Mechanism for the *N*-methylation of *L*-proline

The compound was confirmed through ^{1}H NMR spectroscopy in D_2O and the attained results were compared to literature [34].



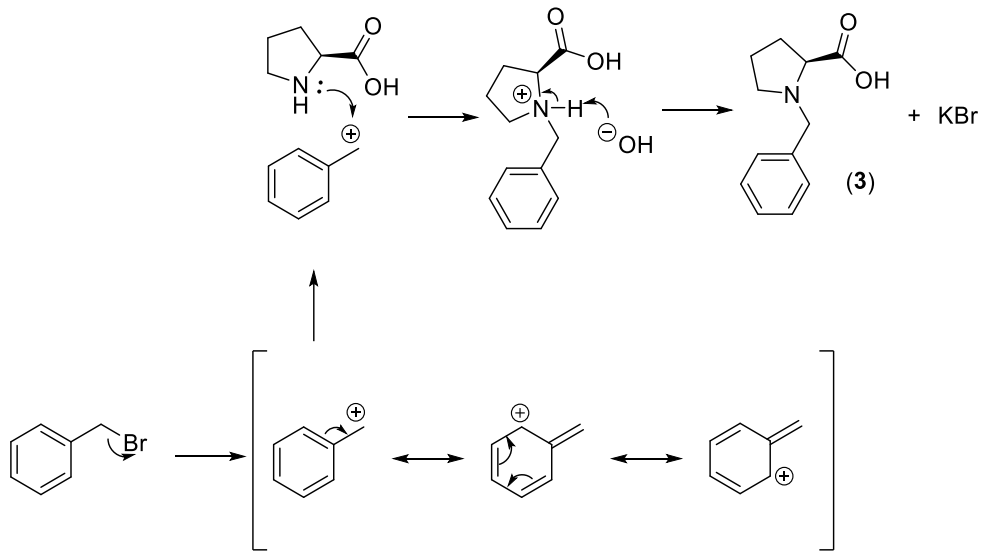
(**4**)

In the ^{1}H NMR spectrum of N-methyl-L-proline (**4**), we can confirm the presence of the methyl protecting group due to the singlet at 2.93 ppm integrating to three protons, which corresponds to the methyl group (H-6). The remaining signals correspond to the aliphatic protons of the proline skeleton. Among those signals, the most deshielded one at 3.88 ppm corresponding to stereogenic center (H-2), due to its proximity to the carboxylic acid group. The signals in the intervals of 3.76-3.71 ppm and 3.19-3.12 ppm correspond to the other protons adjacent to the nitrogen atom (C-5). This splitting happens due to the slightly different chemical environments the protons are in. Similarly, the signals corresponding to the protons of the carbon C-3 present in the interval of 2.54-2.46 ppm and 2.17-1.96 ppm. In this last multiplet, are also included the other aliphatic protons of the proline skeleton (C-4).

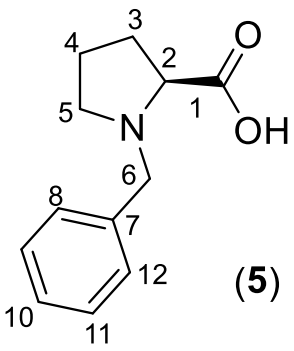
2.2.2 Preparation of *N*-benzyl-*L*-proline (5)

This reaction was performed using benzyl bromide as electrophile and isopropylic alcohol as the solvent, as so to attain *N*-benzyl-*L*-proline (**5**) [35]. The mention of the solvent is especially important in this reaction because it determines the type of mechanism it follows (Scheme 2.3). Nucleophilic substitution reactions with benzyl bromide can occur by both a S_N1

and a SN2 mechanism. However, in our case, as we mentioned before, the solvent of the reaction is isopropyl alcohol, which is a polar protic solvent and therefore favors the SN1 due to the stability of the benzylic carbocation. In this reaction the benzylic carbocation is attacked by the nucleophilic nitrogen atom of the proline [27]. The potassium hydroxide in solution captures the proton in the nitrogen atom and the *N*-benzyl-*L*-proline (**5**) was obtained in an 60% yield.



Scheme 2.3 - Mechanism for the *N*-benzylation of *L*-proline

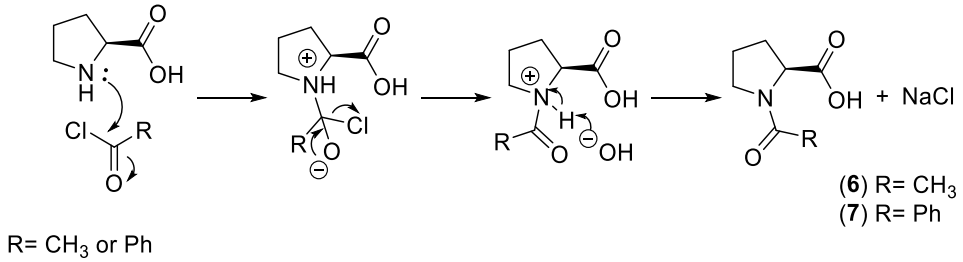


(**5**)

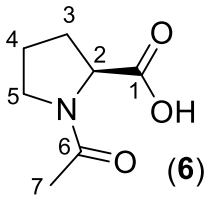
In the ^{1}H NMR spectrum of *N*-benzyl-*L*-proline (**5**), we can confirm the presence of the benzyl protecting group due to both the signal at 7.51 ppm, integrating to five protons, which corresponds to the aromatic protons of the phenyl group, as well as the signal at 4.39 ppm, integrating to two protons, that corresponds to the methylene protons. Like in the previous compounds, the remaining signals correspond to the aliphatic protons of the proline skeleton.

2.2.3 Preparation of *N*-acetyl-*L*-proline (6) and *N*-benzoyl-*L*-proline (7)

The preparation of *N*-acetyl-*L*-proline (**6**) and N-benzoyl-*L*-proline (**7**) was performed using in one case acetyl chloride and in the other benzoyl chloride [36].
The mechanism of the acylation of *L*-proline is presented in Scheme 2.4. In this reaction, the nucleophilic nitrogen atom of the proline attacks the electrophilic carbon of the carbonyl group of the acyl chloride, breaking the carbonyl double bond. In the next step this double bond is recovered by elimination of the chloride ion. The last step is capture of the proton in the nitrogen atom by the hydroxide. The *N*-acetyl-*L*-proline (**6**) was attained with a yield of 29% and *N*-benzoyl-*L*-proline (**7**) was obtained in 82% yield.



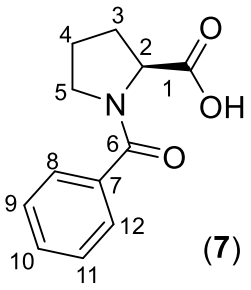
Scheme 2.4 - Mechanism for the N-acylation of L-proline



In the ^{1}H NMR spectrum of *N*-acetyl-*L*-proline (**6**), we can confirm the presence of the acetyl protecting group through the signal at 1.81 ppm, integrating to three protons, which corresponds to the methyl group. The proton of the stereogenic center (H-2) is the most deshielded proton of the aliphatic skeleton of proline, presenting its signal at 3.90 ppm. This signal is followed by the ones of the protons adjacent to the nitrogen atom (C-5), at 3.29 ppm and 3.12 ppm. The protons of the carbons C-3 are also split, as two multiplets at 2.23-2.14 ppm and 2.03-1.95 ppm. The protons of C-4 appear in a single multiplet at the interval of 1.91-1.85 ppm.

In the ^{1}H NMR spectrum of *N*-benzoyl-*L*-proline (**7**), we can confirm the presence of the benzoyl protecting group through the signals at 7.50 ppm and in the interval at 7.36-7.23 ppm that correspond to the aromatic protons (H-8 to H-12), integrating to two and three protons, respectively. The latter signal is a little bit inflated due to the overlap with the residual signal of deuterated chloroform.

When it comes to the protons of the aliphatic skeleton of proline both compounds present similar signals, as expected. The aliphatic protons of *N*-acetyl-*L*-proline more shielded than the protons of *N*-benzoyl-*L*-proline (**7**). The stereogenic center (H-2) is the most deshielded proton of the aliphatic skeleton of proline, presenting its signal at 4.46 ppm. This signal is followed by the ones of the protons adjacent to the nitrogen atom (C-5), which are split in the intervals of 3.59-3.52 ppm and 3.40-3.34 ppm. The protons of the carbons C-3 and C-4 also appear split and appear in succession, the intervals of 2.19-2.14 ppm (C-3), 2.06-2.02 ppm (C-3), 1.93-1.89 ppm (C-4) and 1.71-1.63 ppm (C-4).

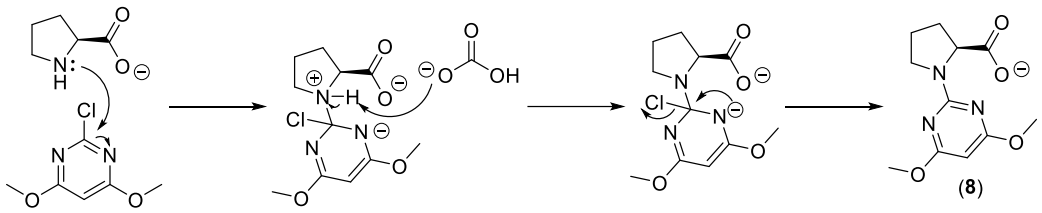


(**7**)

2.2.4 Preparation of *N*-pyrimidinyl proline derivative (8)

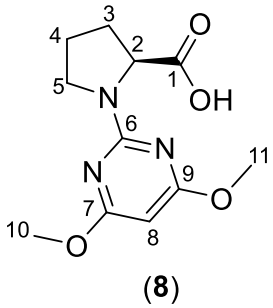
For the preparation of the *N*-dimetoxipyrimidine-*L*-proline derivative it was used the 2-chloro-4,6-dimethoxy pyrimidine, and sodium bicarbonate, in acetonitrile, through which we obtained (4,6-dimethoxypyrimidin-2-yl)-*L*-proline (**8**) [37].

In this reaction we have a standard nucleophilic aromatic substitution mechanism, as shown in Scheme 2.5. Due to the basic conditions, the carboxylic acid of the proline is deprotonated as a carboxylate. The nucleophilic nitrogen atom present in the pyrrolidine attacks the pyrimidine at the most electrophilic position, breaking the aromaticity of the ring and leaving a negative charge in the nitrogen atom of the pyrimidine. The HCO_3^- ion captures the proton of the nitrogen atom of the pyrrolidine. The next step is the recovery of the aromaticity through the elimination of the chloride atom. This reaction occurs in the presence of $NaHCO_3$ to neutralize the HCl that is formed. The compound (4,6-dimethoxypyrimidin-2-yl)-*L*-proline (**8**) was formed with a 74% yield.



Scheme 2.5 - Mechanism for the protection of *L*-proline

The structure of the compound was confirmed through 1H NMR spectroscopy in $CDCl_3$ and the results were compared with work done previously in the group.



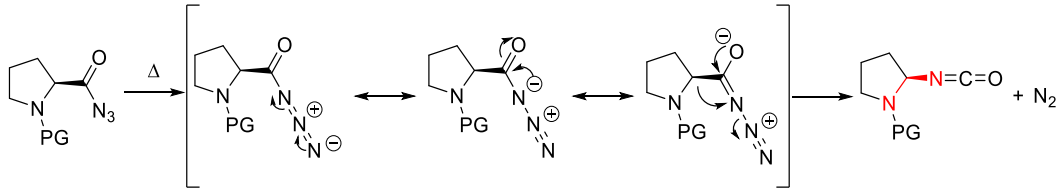
In the ^1H NMR spectrum of (4,6-dimethoxypyrimidin-2-yl)-*L*-proline (**8**), we can confirm the presence of the dimethoxy pyrimidine protecting group due to the singlet at 3.87 ppm integrating to six protons, which corresponds to the methoxy groups of the pyrimidine ring (H-10 and H-11), as well as the presence of the signal at 5.48 ppm, corresponding to the aromatic proton. The remaining signals correspond to the aliphatic protons of the proline skeleton. Among those signals, the most deshielded one at 5.53 ppm corresponding to the stereogenic center (H-2), due to its proximity to both the carboxylic acid group and the nitrogen atom. The multiplet in the interval of 3.69-3.57 ppm corresponds to the protons next to the nitrogen atom (H-5). The protons of the carbon C-3 appear split into two different signals because of the different chemical environments the protons are in, appearing one as a multiplet at the interval of 2.56-2.51 ppm, while the other can be found in the multiplet at 2.11-1.98 ppm. In this last multiplet, are also the last aliphatic protons of the proline skeleton (C-4).

2.3 Curtius rearrangement and trapping of the isocyanate with nucleophiles

The Curtius rearrangement is reported in literature [3] as proceeding with complete retention of configuration, which is why it is the key step for the attainment of an aminal moiety, while maintaining the configuration of the stereogenic center. The aminal moiety, *N, N*-acetal

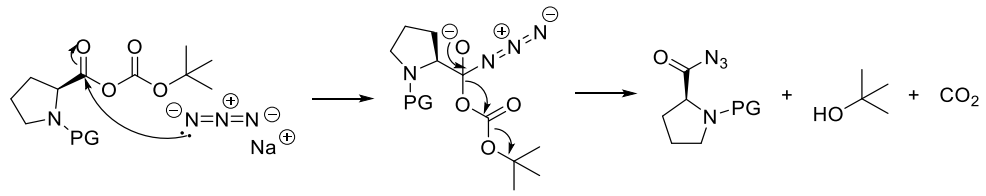
(highlighted in red in Scheme 2.6), is an analogue of *O*, *O*-acetals. They are usually attained through the condensation of diamines and aldehydes, which in most cases results in cyclic symmetric structures [38], [39].

Through this rearrangement it is envisioned to obtain the amide as well as the aminal moiety as are present in cernumidine (**1**), all while keeping the same configuration as in the asymmetric center of the starting material. In the proposed mechanism for Curtius rearrangement we have successive electronic movements leading into the elimination of molecular nitrogen as well as the formation of a reactive isocyanate species (Scheme 2.6). This reaction is carried thought the heating of an acyl azide, leading to its thermal decomposition, in an inert atmosphere.



Scheme 2.6 - Mechanism for the Curtius rearrangement

The isocyanate moiety is, like referred before, attained through a thermal decomposition of the acyl azide. The acyl azide is attained through the formation of a mixed anhydride (this reaction is further explained in the next chapter for the formation of amide), which then is attacked by sodium azide affording the acyl azide (Scheme 2.7).



Scheme 2.7 - Mechanism for the formation of the acyl azide

For the Curtius rearrangement, the acyl azide is dissolved in THF and placed in reflux under an inert atmosphere. This reaction is followed through IR spectroscopy since the bands of the acyl azide and the isocyanate are present in a characteristic area of the IR spectrum, being easily identifiable. The stretching of the acyl azide is around 2140 cm^{-1}, while the stretching for the isocyanate is around 2240 cm^{-1}. In figure 2.1A, we can observe the band of the acyl azide once the reaction is complete for the synthesis of compound (**9**). In figure 2.1B, during

the rearrangement of the same compound, we see the decrease of the acyl azide band and the increase of the isocyanate band, indicating that the acyl azide is decomposing into the isocyanate.

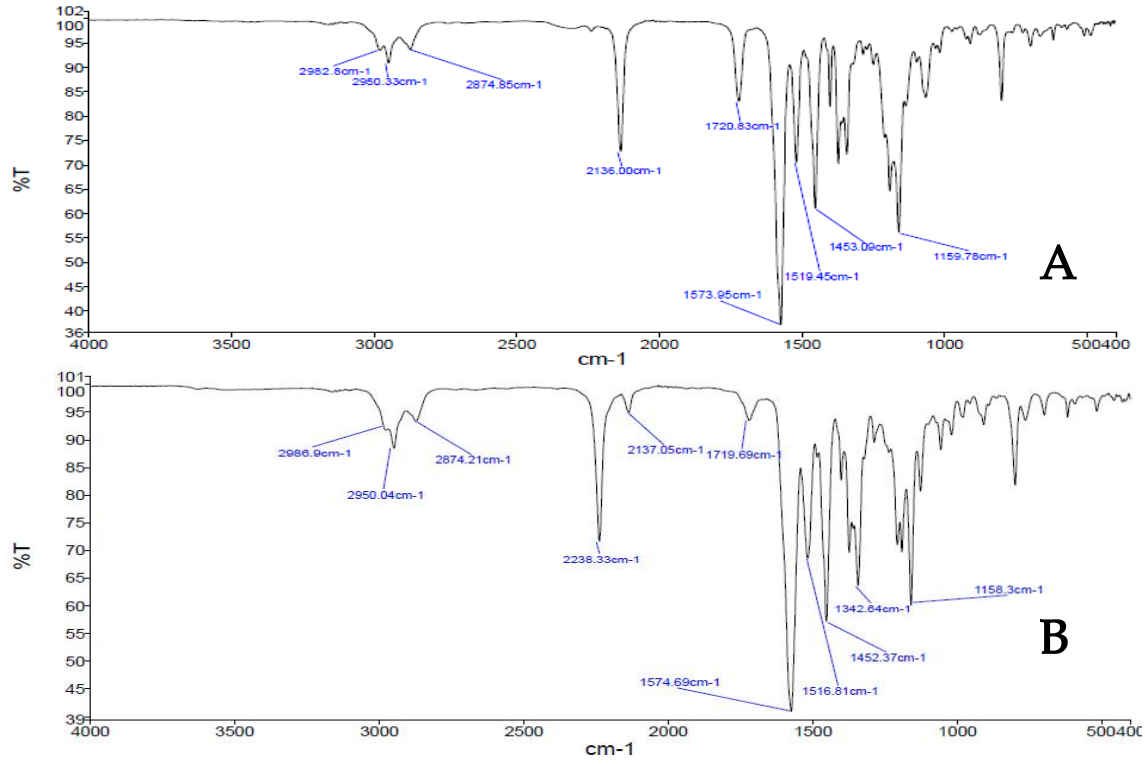
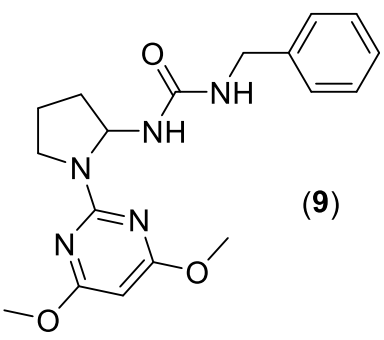


Figure 2.1 - IR of the Curtius rearrangement of compound (**9**). The band at 2136-7 cm^{-1} corresponds to the acyl azide, which thermally decomposes into isocyanate, originating the band at 2238 cm^{-1}. **A**: IR spectrum when the acyl azide formation was complete; **B**: IR during the rearrangement of the acyl azide into the isocyanate.

After the Curtius rearrangement is complete, the isocyanate is trapped with a chosen nucleophile to attain the desired compound. The isocyanate of the different synthesized derivatives was trapped with different nucleophiles. These assays are described next.

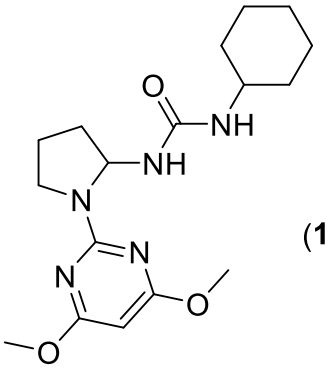


(**9**)

The rearrangement of acyl azide of (4,6-dimethoxypyrimidin-2-yl)-*L*-proline (**8**) proceeded in THF at room temperature and the isocyanate intermediate was trapped with benzylamine (Entry 1, Table 2.1) at -15 ºC. In this reaction, we were able to isolate the desired product (**9**), with a 12% yield. The measured optical rotation was of $[\alpha]_D^{20}$ 0.00 (c 0.29, $CHCl_3$), which showed a complete racemization of the

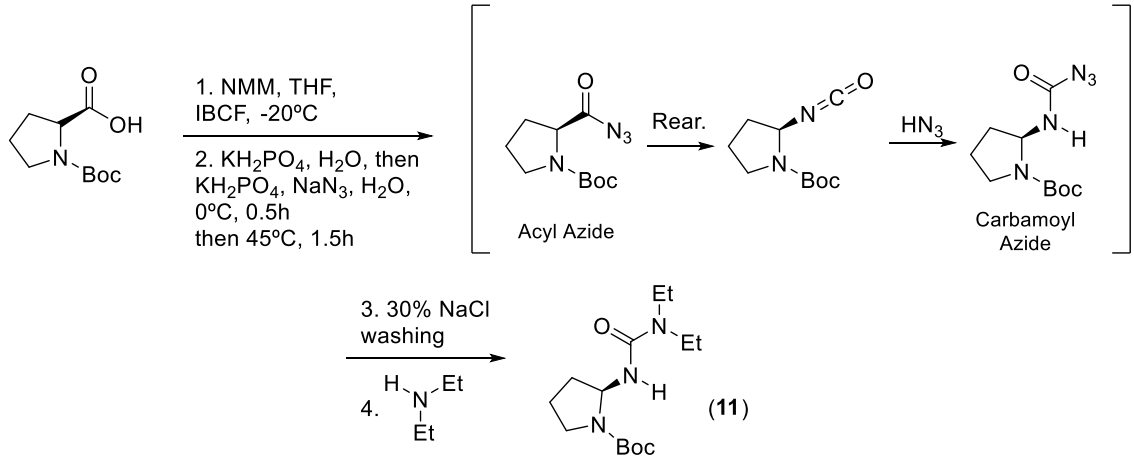
stereogenic center. This discovery made us question in which step of the synthesis this racemization had happened, so we decided to measure the optical rotation of the compounds along the synthesis. It is noteworthy to remember that the Curtius rearrangement is described as reaction in which it is achieved complete retention of configuration.

We can suppose that the *N*-dimetoxipyrimidinyl protected proline (**8**) maintains its enantiomeric purity since the reaction performed of *N*-protection does not affect the stereogenic center. Compound (**8**) presented a high rotation result with a specific rotation of $[\alpha]_D^{25}$ -222.9 (c 0.40, $CHCl_3$). The results of the next step, the acyl azide formation, could also indicate that the enantiomeric purity is maintained with a lower but still remarkably high, specific rotation of $[\alpha]_D^{25}$ -112.3 (c 0.39, $CHCl_3$). After the Curtius rearrangement, we proceeded to measure the specific rotation of isocyanate which was of $[\alpha]_D^{28}$ -11.0 (c 1.09, THF). The specific rotation of a compound can only give us such information if there is an established value for the specific compound we wish to compare it to, and since there isn't information in literature for these compounds we can only affirm that they are not racemic. In the next assay (Entry 2, Table 2.1), we used cyclohexylamine (CHA) to trap the isocyanate and we attained once again a racemic mixture of the compound (**10**) with a yield of 3%.



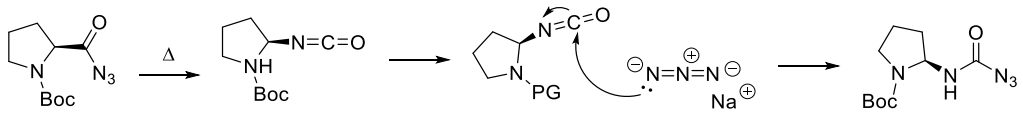
(**10**)

We tried a different approach after doing some research, through which we were able to find the synthesis of a similar compound (Scheme 2.8) [40] through the formation of a carbamoyl azide and trap with dietyhylamine. In this literature example the compound (**11**) presented a specific rotation of $[\alpha]_D^{20}$ -22.9 (c 14.3, $CHCl_3$). [40].



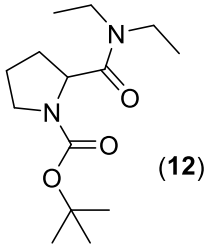
Scheme 2.8 – Synthesis of compound (**11**)

We repeated the literature conditions [40] (Entry 3, Table 2.1). Starting from Boc-*L*-Proline (**29**) the acyl azide was formed followed by the rearrangement to the isocyanate and then proceeded to the trap with sodium azide, leading to the formation of a carbamoyl azide (Scheme 2.9).



Scheme 2.9 - Mechanism of the formation of carbamoyl azide

We measured the specific rotation of the product, which was of $[\alpha]_D^{18}$ -34.9 (c 0.11, $CHCl_3$). The formation of the carbamoyl azide was, like the formation of the acyl azide, monitored through IR spectroscopy, in which we observed two stretches at 2137 cm^{-1} and 2022 cm^{-1}. In the course of time, we saw the decrease of the first band and the increase of the second band. Since we decided to replicate the literature in this assay, so we also trapped the carbamoyl azide with diethyl amine (DEA). After 40 h, we added an extra equivalent of the amine, and after 6 hours we saw the disappearance of the band at 2137 cm^{-1}. Initially, we thought we had obtained product (**10**). The specific rotation we obtained for the product was $[\alpha]_D^{20}$ -19.0 (c 0.74, $CHCl_3$), while it wasn't exactly the same as the one in literature ($[\alpha]_D^{20}$ -22.9 (c 14.3, $CHCl_3$)) [40], it was similar, and the ^1H NMR of the compound was according to the literature. However, our interpretation of the NMR spectrum and the knowledge already acquired in the group about the chemical shift of the alpha proton of the aminal (usually around 5.5 ppm) made us question the result obtained since the obtained compound had the aminal proton at a chemical shift 4.60-4.42 ppm. So, we decided compare compound (**10**) with literature of compound (**12**) and we confirmed they were indeed the same compound.



(**12**)

At this stage we could not use with confidence the results from literature in which concern the Curtius rearrangement with retention of configuration for proline derivatives. We continued the study of the Curtius rearrangement for other proline derivatives. We started with compound *N*-methyl-*L*-proline (**4**) and followed the standard procedure described to obtain the respective acyl azide. However, in this first attempt (Entry 4, Table 2.1) we discovered that the resulting acyl azide, due to the presence of *N*-methyl protecting group, was much more polar than before and therefore remained in the aqueous phase on the work up.

We then proceeded with compound *N*-benzyl-*L*-proline (**5**) (Entry 6, Table 2.1) and followed the standard procedure described to obtain the acyl azide moiety but used a lower excess of sodium azide to prevent the formation of the carbamoyl azide. Like the previous compound (*N*-methyl) the product of the reaction was very polar and remained in the aqueous phase of the work up (Entry 6, Table 2.1).

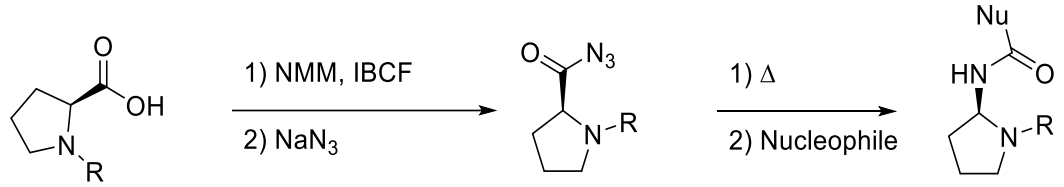
The second assays we did with *N*-methyl-*L*-proline (**4**) and *N*-benzyl-*L*-proline (**5**) (Entry 5 and 7, Table 2.1, respectively), were performed very similarly. We tried to work around the polarity problem by disregarding the work up step after the completion of the reaction and drying the water present in the reactional mixture, with Na_2SO_4 and filtrating it, with moderately positive results. In both assays, we observed the formation of bands at 2204 cm^{-1}, 2151 cm^{-1} and 1712 cm^{-1}. The first band was attributed as corresponding to the isocyanate, the second band corresponds to the azide stretching of acyl azide, and the last band is the carbonyl stretching of the acyl azide. During the rearrangement of both compounds (**4**) and (**5**), the band of the carbonyl decreased its intensity indicating that the acyl azide was disappearing and rearranging into the isocyanate. After the reactions showed no further evolution, they were left to cool to room temperature and then put in bath at -40 ºC for the addition of the Grignard reagent (PhMgBr). The IR analysis showed the appearance of two new bands at 2100 cm^{-1} and 2048 cm^{-1}, in addition to the disappearance of the isocyanate band. Once the reactions showed no further evolution, they were stopped through the quenching with MeOH. We were unable to attain the desired product and instead obtained a complex mixture in both cases, resulting from degradation of the starting material.

We tried repeat the assays in the same conditions using the same starting materials but were unsuccessful in all of them and obtained inconsistent results. In some cases the acyl azide stretching disappeared, but the isocyanate band did not appear, meaning that while the acyl azide was disappearing it was not decomposing into the isocyanate. In other cases, the band of the carbonyl decreased its intensity indicating that the acyl azide was disappearing and rearranging into the isocyanate, but the azide band of the acyl azide did not decrease in intensity. And in other cases, the band we attributed to isocyanate appeared during the acyl azide formation, then disappeared during the rearrangement and appeared again after the addition of the Grignard reagent, albeit with a much lower intensity. The problem seemed to occur in the rearranging step, as we were successful in obtaining the acyl azide, but then failed to either rearrange it into the isocyanate or in the trapping of the isocyanate with the Grignard reagent. We think that the isocyanate from the rearrangement of the *N*-methyl (**4**) and *N*-benzyl proline (**5**) derivative was very unstable and decomposed. Also, since we could not be effective in the complete removal of the water, the presence of a small amount could lead to the decomposition of the PhMgBr.

The next starting material we used on the Curtius rearrangement was compound *N*-acetyl-*L*-proline (**6**). With this compound, we ran into a problem right in the beginning, as it is poorly soluble in the solvent of the reaction (THF), taking over one hour to completely dissolve with the help of the NMM and the IBCF. However, after this mishap, we were able to follow the standard procedure to obtain the acyl azide moiety, including the work up after completion of the reaction. During the Curtius rearrangement we were able to clearly observe the decrease acyl azide band, at around 2140 cm^{-1}, accompanied by the appearance and increase of the isocyanate band, at around 2240 cm^{-1}. This was followed by the addition of PhMgBr at -40 ºC (Entry 8, Table 2.1). After the isocyanate band had disappeared, indicating that the Grignard reagent had reacted with all the isocyanate, the reaction was quenched, and the crude was sent to ^{1}H NMR for analysis. We were unable to attain the desired product and instead obtained a complex mixture. We repeated this assay, but this time trapping the isocyanate with DEA (Entry 9, Table 2.1). This assay was not successful and, like before, resulted in a complex mixture.

Finally, we tried this procedure with compound *N*-benzoyl-*L*-proline (**7**). The formation of the acyl azide occurred smoothly, and we were able to attain the acyl azide moiety successfully. As usual, the rearrangement was followed through IR and we observed the formation of the isocyanate and trapped it with aniline (Entry 10, Table 2.1). The rearrangement took much longer than usual, 4 h 30 min versus the usual 1 h to 2 h, without the complete disappearance of the acyl azide band. After the addition of the aniline and its complete reaction with the isocyanate, the reaction was quenched, the crude was purified, and the fractions were analyzed by ^{1}H NMR. The ^{1}H NMR spectrum revealed a degradation of the starting material, in which we were not able to identify the characteristic alpha proton of the starting compound or the end product. Moreover, the aliphatic protons of the proline skeleton had, much like the aromatic zone, shifted to higher field and also presented a different pattern, in comparison to the starting material (**7**).

Table 2.1 - Reactional conditions of the different *L*-proline derivatives for the Curtius rearrangement and trapping of the isocyanate



Entry	Starting Material (R group)	Nucleophile	Reactional Conditions		Yield (%)	Observations
			Acyl Azide production	Rearrangement and trapping of the isocyanate		
1	**8** (dimetoxi pyrimidine)	benzylamine	THF, -15 ºC, 1 h 30 min	THF, rt, 45 min	12	Racemic product (**9**)
2	**8** (dimetoxi pyrimidine)	cyclohexylamine	THF, -15 ºC, 1h30 min	THF, rt, 45 min	3	Racemic product (**10**)
3	**29** (Boc)	diethylamine	THF, -15 ºC, 4 h	THF, reflux, 1 h 50 min followed by THF, rt, 19 h	-	The product attained was compound (**13**)
4	**4** (methyl)	-	THF, -15 ºC, 2 h	-	-	The acyl azide stayed in the aqueous layer during work up
5	**4** (methyl)	PhMgBr	THF, -15 ºC, 2 h	THF, reflux, 1 h 15 min followed by THF, rt, 1 h 30 min	-	Complex mixture
6	**5** (benzyl)	-	THF, -15 ºC, 2 h	-	-	The acyl azide stayed in the aqueous layer of the work up

7	**5** (benzyl)	PhMgBr	THF, -15 ºC, 2 h 30 min	THF, reflux, 2 h followed by THF, rt, 19 h	-	Obtained a complex mixture
8	**6** (acetyl)	PhMgBr	THF, -15 ºC, 1 h 15 min	THF, reflux, 1 h 30 min followed by THF, rt, 1 h 30 min	-	Obtained a complex mixture
9	**6** (acetyl)	diethylamine	THF, -15 ºC, 1 h 30 min	THF, reflux, 1 h 30 min, followed by THF, rt, 2 h	-	Obtained a complex mixture
10	**7** (benzoyl)	aniline	THF, -15 ºC, 2 h	THF, reflux, 4 h 30 min followed by THF, rt, 30 min	-	Degradation of the starting material

This part of the work was developed with the intent of studying the influence of the *N*-substituting groups, pyrimidine, methyl, benzyl, acetyl, and benzoyl on the racemization of the Curtius rearrangement product. The main methodology used for this study was the formation of an acyl azide, which then was thermically decomposed into an isocyanate and then reacted with the nucleophile. We also tried to form a carbamoyl azide, by trapping the isocyanate with sodium azide, which then reacted with the nucleophile.

The assays with *N*-dimetoxipyrimidinyl proline (**8**) derivative trapped with benzylamine and cyclohexylamine both lead to the attainment of racemic products (**9**) and (**10**).

The *N*-methyl (**4**) and *N*-benzyl (**5**) proline derivatives were found to be much more hydrophilic than the *N*-acetyl (**6**), *N*-benzoyl (**7**) and *N*-pyrimidine (**8**) proline derivatives and required an adaptation of the work up in the acyl azide attaining step. In addition the reactions with *N*-methyl (**4**) and *N*-benzyl (**5**) proline derivatives showed inconsistent results and resulted in complex mixtures of degraded starting material.

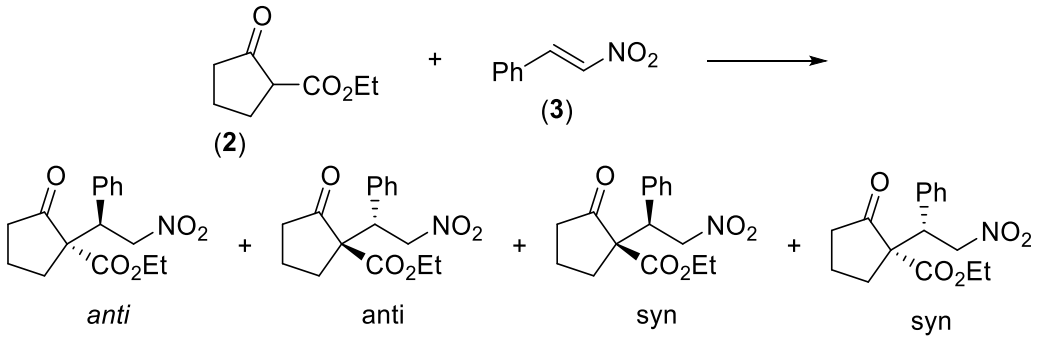
The assays with the *N*-acetyl proline (**6**) derivative had a problem with the solubility of the compound in the solvent, but after that the reaction progressed well. However, the assays with this derivative trapped with phenylmagnesium bromide did not afford the desired product and instead resulted in a complex mixture.

The assay with *N*-benzoyl proline (**7**) derivative took a significantly longer time to rearrange the acyl azide to isocyanate, which was then trapped with phenylmagnesium bromide, and afforded a degradation compound of the starting material which structure was impossible to determine.

Ultimately, we were unsuccessful in studying the influence of the *N*-substituting groups in the racemization of the Curtius rearrangement product.

2.4 Synthesis of amino-pyrrolidine guanidine catalysts

We prepared *N*-carbamoyl proline derivatives to be used as organocatalysts for enantioselective Michael's addition reactions between β-ketoesters and nitroalkenes. In this work was studied the stereoselective addition of 2-oxocyclopentanecarboxylate (**2**) to the *trans*-β-nitrostyrene (**3**) (Scheme 2.10).



Scheme 2.10 – Michael addition reaction between ethyl 2-oxocyclopentane-carboxylate (**2**) and trans-β-nitrostyrene (**3**).

Although proline and pyrrolidine derivatives are very useful and common catalysts, *L*-proline can be considered the starting point for the area of organocatalysis, namely since their use in aldol reactions [41].

In the past few years, chiral catalysts with guanidine moieties have become increasingly attractive in asymmetric organocatalysis. Compounds with rigid cyclic α-amino amides, such as those derived from *L*-proline or (*S*)-indoline carboxylic acid, are interesting possibilities because the chiral backbone they have can carry various sterically hindered amides simultaneously.

However, there are few examples of known chiral indoline organocatalysts. This knowledge encouraged us to synthesize new indoline derives with the ability to function as

bifunctional asymmetric organocatalysts, through the incorporation of H-bond donors and acceptors. We expected these catalysts to act as a highly successful bifunctional catalyst compounds class, which may afford excellent stereoselectivities as well as high reaction rates. The organocatalyst synthesized includes an amide functional group and a guanidine group. Both play important parts on the bifunctional organocatalyst because of their hydrogen bonding interactions, in addition to guanidines ability to function as a Lewis and Bronsted base (Figure 2.2) [21], [41]–[44].

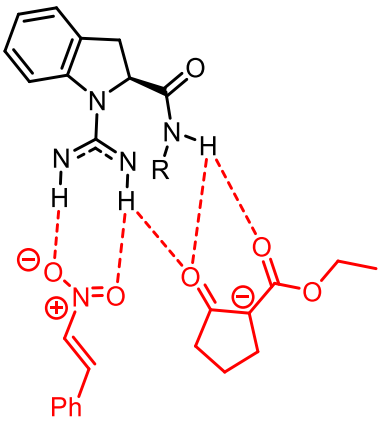
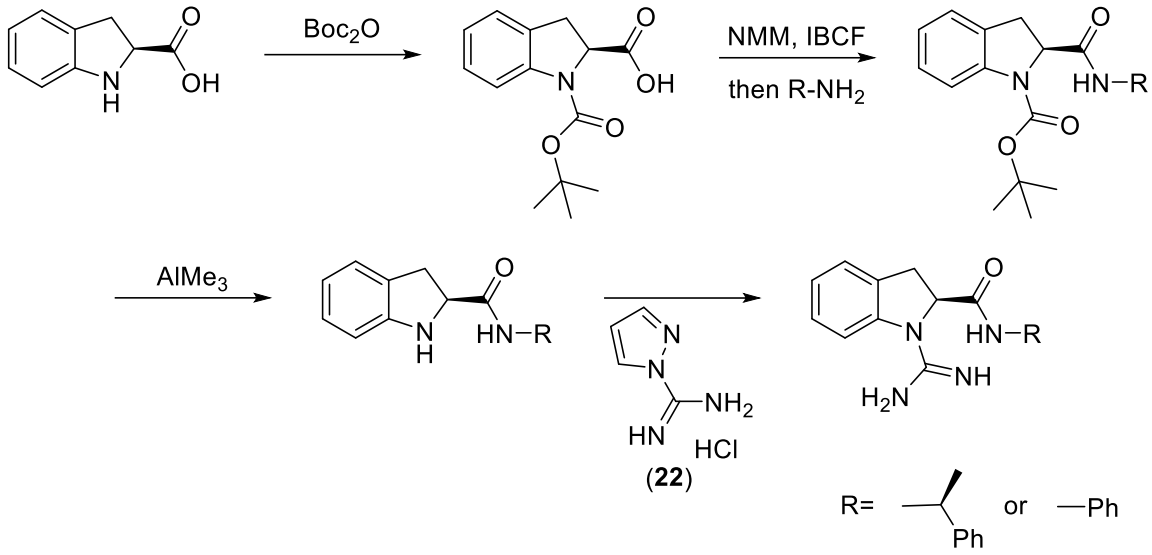


Figure 2.2 - Interactions of the proposed catalyst for the Michael addition reaction between ethyl 2-oxocyclopentsnecarboxylate (**2**) and trans-β-nitrostyrene (**3**).

The preparation of a family of indoline-based catalysts was envisioned in the following synthetic route presented below (Scheme 2.11). The synthesis of these compounds started with the protection of the nitrogen atom of enantiomerically pure (*S*)-Indoline-2-carboxylic acid, followed by the conversion of the carboxylic acid into an amide. This reaction was carried out through the formation of a mixed anhydride, followed by reaction with either aniline or the optically active amine, (*S*)-(-)-1-phenylethylamine. The following step was the deprotection of the nitrogen atom by trimethylaluminum, which was step optimized previously by the research group [45] and the final step of the synthetic route was the guanylation of nitrogen atom. For this step, it was employed the use of a guanylating agent, *1H*-pyrazole-1-

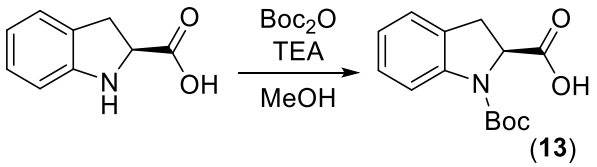
carboxamidine hydrochloride (**22**). This guanylation of the deprotected indoline after the formation of the amide, posed the biggest challenge in this synthesis.



Scheme 2.11 - Envisioned synthetic route for the proposed catalysts

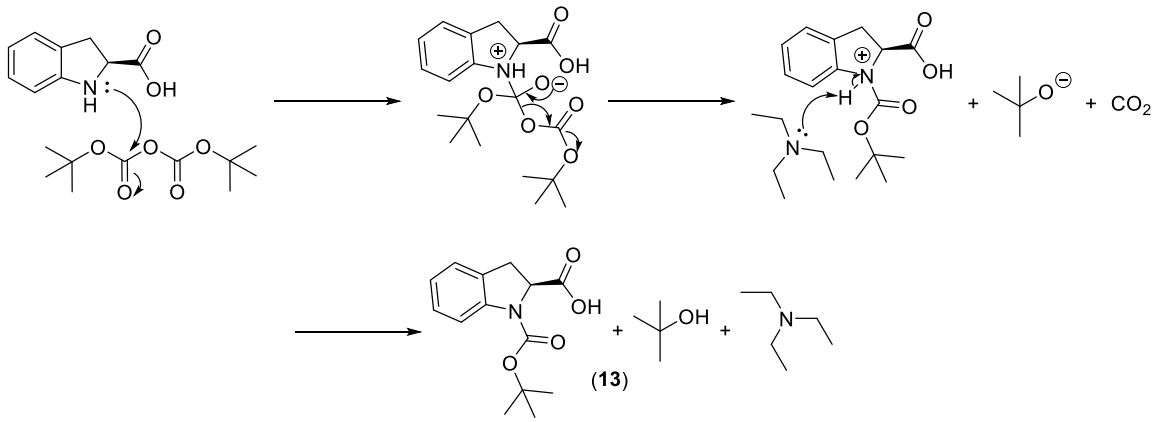
2.4.1 Preparation of *N*-Boc-(*S*)-Indoline carboxylic acid (13)

For the *N*-protection of indoline carboxylic acid we opted to use the commonly used amine protecting group Boc through the employment of the anhydride di-*tert*-butyl dicarbonate (Boc2O), following the procedures established in the literature [46] (Scheme 2.12). This procedure was used to prepare the (*S*)-1-Boc-indoline-2-carboxylic acid (**13**).



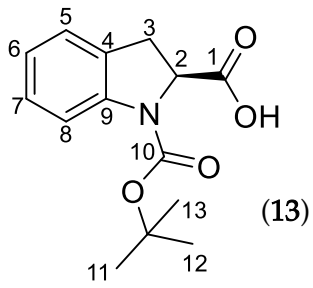
Scheme 2.12 - General scheme for the protection of (S)-indoline carboxylic acid

The mechanism of the protection of (*S*)-Indoline-2-carboxylic acid is presented in scheme 2.13. In this reaction, the nucleophilic nitrogen atom of the indoline attacks the electrophilic carbon of the carbonyl group of the anhydride, breaking the carbonyl double bond. This double bond is then restored and followed by the elimination of carbon dioxide and *tert*-butoxide. The last step is capture of the proton by the triethylamine, resulting in (*S*)-1-Boc-indoline-2-carboxylic acid (**13**). This compound was obtained with a yield of 90%.



Scheme 2.13 – Mechanism of the protection of (*S*)-indoline carboxylic acid (**13**)

The compound structure was confirmed through ^{1}H NMR spectroscopy in MeOD and these results were compared to literature [47].

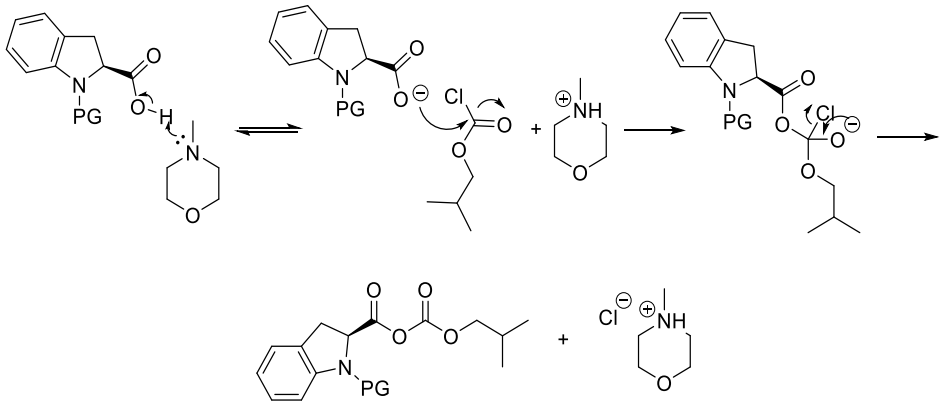


In the ^{1}H NMR spectrum of *(S)*-1-Boc-indoline-2-carboxylic acid (**13**), we can observe the presence of the Boc protecting group due to the singlet at 1.50 ppm integrating to nine protons, which corresponds to the three methyl groups of the Boc protecting group (H-10, H-11, H-12). The signals at 3.53 and 3.09 ppm correspond to the aliphatic protons (C-3). These protons display different coupling constants from each other due to the rigidity of the ring which results in slightly different chemical environments. Slightly hidden under the solvent signal, in the interval of 4.82-4.79 pm, we have the signal corresponding to the other aliphatic proton, which is also the proton of the stereogenic center (H-2). The remaining signals correspond to the aromatic protons of the indoline skeleton. The two triplets at 7.17-7.13 ppm and 6.95-6.91 ppm correspond to the protons H-5, H-6, and H-7. The most unshielded aromatic proton (H-8) is split into two signals at 7.77 ppm and 7.49 ppm because two different conformers resulted from limited movement of the Boc protecting present in the molecule.

2.4.2 Amide formation

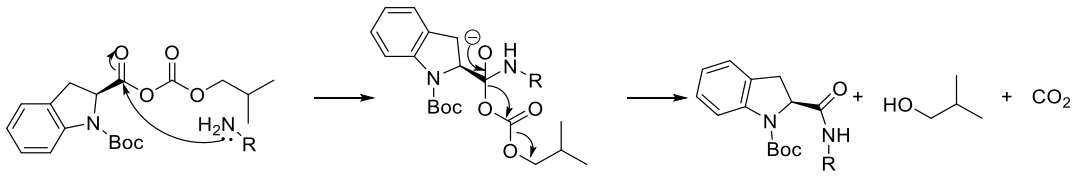
The amide formation is a reaction widely common and well-established. The transformation of the carboxylic acid of the starting material in amide was done through the formation of a mixed anhydride as a reactional intermediary, which is more reactive. This reaction followed the same procedure as the one we used for the formation of the acyl azide but swapped the nucleophile sodium azide for the desired amine. The starting material was reacted with isobutyl chloroformate (IBCF) and *N*-methyl morpholine (NMM) and is summarized in Table 2.2.

In the mechanism for the formation of the mixed anhydride (Scheme 2.14), the nucleophilic nitrogen of the NMM captures the proton of the carboxylic acid, leaving a carboxylate ion, which attacks the electrophilic carbon of the carbonyl group present in the IBCF. The double bond of the carbonyl group is broken, and then restored, eliminating the chloride ion, and leaving us with the mixed anhydride.



Scheme 2.14 - Mechanism for the formation of the mixed anhydride intermediary

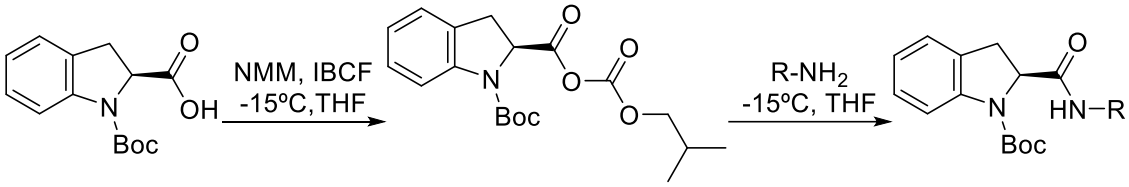
The following step corresponds to the attack of the amine to prepare different general amides. The mechanism for the formation of the amide is presented in Scheme 2.15. The nucleophilic nitrogen atom of the amine attacks the mixed anhydride moiety, breaking the carbonyl's double bond and leaving a negative charge in the oxygen. In the next step the double is restored, eliminating carbon dioxide and isobutanol.



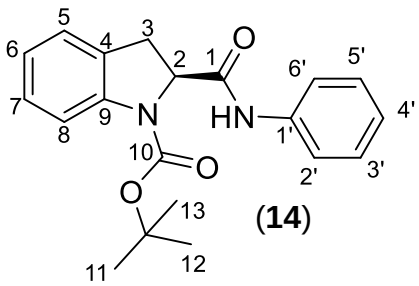
Scheme 2.15 - Mechanism for the attack of the amine to the mixed anhydride and formation of the amide

The pool of reactions conducted to obtain compounds (**14**) and (**15**) is summarized below in Table 2.2.

Table 2.2 - Reactional conditions to synthesis compounds (**14**) and (**15**)

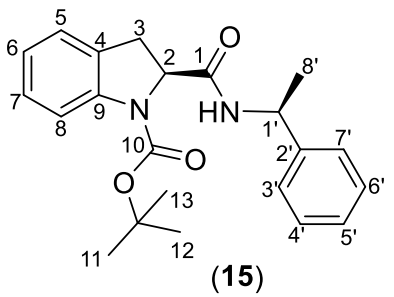


Entry	Amine (equiv.)	Temperature (ºC)	Reactional time (h)	Yield (%)
1	aniline (1.1)	Rt	24 h	29%
2	aniline (1.1)	Rt	48 h	63%
3	(*S*)-(-)-1-phenylethylamine (1.1)	Rt	24 h	43%
4	(*S*)-(-)-1-phenylethylamine (1.1)	Rt	72 h	74%



The anhydride intermediary of Boc indoline reacted with aniline (Table 2.2, Entry 1) and afforded the compound (**14**). The reaction was monitored through TLC, and after the reaction was stopped it went under a purification step to remove by-products of the reaction and attain compound (**14**). This assay was replicated under the same conditions (Table 2.2, Entry 2), but with a longer reactional time, in which resulted in a higher yield.

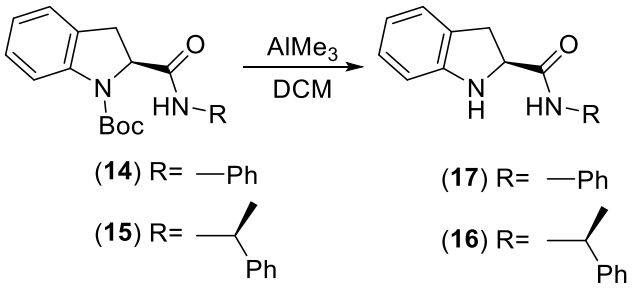
The anhydride intermediary of Boc Indoline (**13**) also reacted with a chiral amine, (*S*)-(-)-1-phenylethylamine (Table 2.2, Entry 3) to obtain compound (**15**). Similarly to the previous compound, this assay also went through a purification step, and higher yields were achieved while increasing the reactional time (Table 2.2, Entry 4) and maintaining all the other reactional conditions.



(**15**)

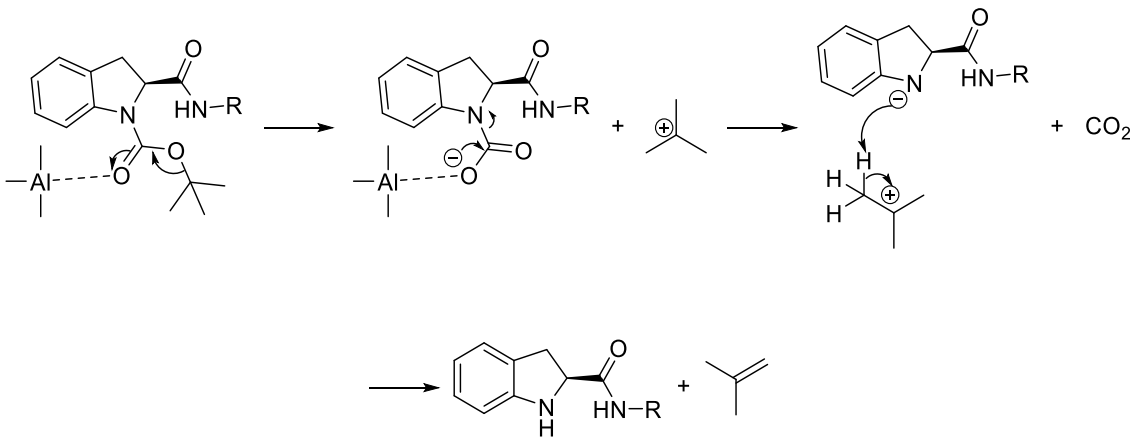
2.4.3 Indoline deprotection step

To attain the organocatalyst it was necessary to remove the Boc protecting group so that the carbodiimide could be introduced. The removal of the Boc protection group is an important step in this synthesis, which proved to be difficult. However, due to work done previously in the group [45], this step was quite straightforward. The removal of the Boc protection group was obtained using trimethylaluminum (Scheme 2.16). The reagent is added at a temperature of -78 ºC in inert atmosphere and the mixture is then left to reach room temperature.

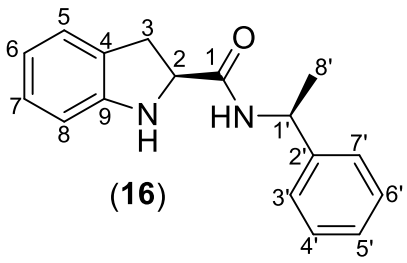


Scheme 2.16 - Deprotection of compounds (**14**) and (**15**)

The mechanism for the deprotection reaction is presented in Scheme 2.17. In this mechanism, there is a coordination of the aluminum with the oxygen atom of the carbonyl in the protecting group, which leads to the eliminations of the isobutane cation, followed by the elimination of carbon dioxide. The nitrogen atom, then captures a proton for the isobutane cation, originating the deprotected product, as well as isobutene.

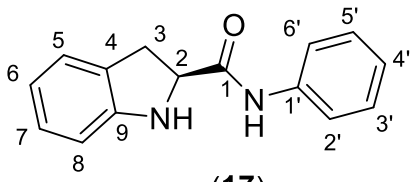


Scheme 2.17 - Mechanism of the deprotection reaction



(**16**)

In the ^{1}H NMR spectrum of compound (**16**), we can confirm the reaction was successful due to the absence of the characteristic signal of the *tert*-butyl group present in the Boc protecting group, which integrates to nine protons in the higher field of the spectrum, at around 1.50 ppm. The rest of the signals correspond to the indoline skeleton, as well as the phenyl group and ethyl groups, which means that the intended product was obtained with a 47% yield and without any kind of degradation in the rest of the molecule. We followed the same procedure for compound (**15**) and attained compound (**17**) with a 58% yield.

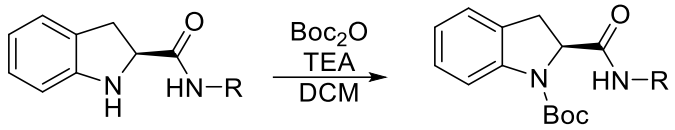


(**17**)

2.4.4 Indoline guanylation

The guanylation of the indoline derivatives was one of the biggest challenges in this work. The initial approach of this step was to react indoline-*(S)*-phenylethylamine with a guanylating agent, *1H*-pyrazole-1-carboxamidine hydrochloride, which proved to be unsuccessful. This maybe a result of the indoline skeleton stability due to the aromaticity, and therefore decreases the nucleophilicity of the nitrogen atom present in the indoline core. Indoline's pKaH of 4.9 can probably explain its decrease of nucleophilicity and also less basic nature,

especially when compared to pyrrolidine's pKaH of 11.2 [48]. We tested the nitrogen of the indole core to see if it could react at all, by trying to protect it once again, with Boc, after the formation of the amide (Scheme 2.18) and the reaction seemed to occur as well as it did in the beginning of the synthesis, because of the anhydride's reactive nature.



Scheme 2.18 - Protection reaction after amide moiety formation

In an attempt to obtain the guanylated derivative of the indolines (**16**) and (**17**), different guanylating reagents, with different reactivities, were employed. Therefore, we used the guanylating agents *1H*-pyrazole-1-carboxamidine hydrochloride (Figure 2.3, (**22**)), cyanamide (Figure 2.3, (**23**)), Boc-protected *1H*-pyrazole-1-carboxamidine (Figure 2.3, (**24**)), 1,3-Di-Boc-2-methylisothiourea (Figure 2.3, (**25**)), cyanogen bromide (Figure 2.3, (**26**)), *N,N'*-dicyclohexylcarbodiimide (Figure 2.3, (**27**)). The results are summarized on Table 2.3.

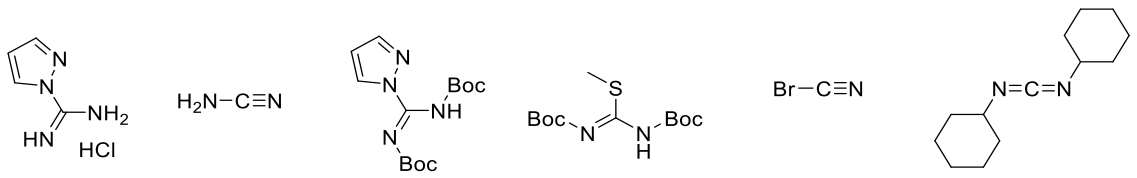
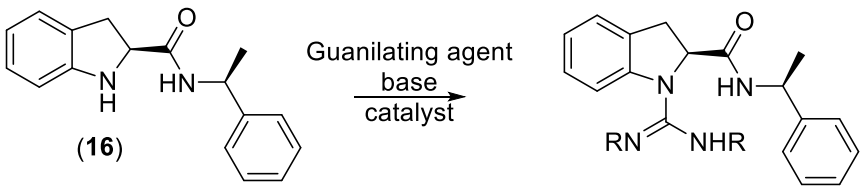


Figure 2.3 - Guanylating agents used

Table 2.3 - Guanylation conditions for compound (**16**)



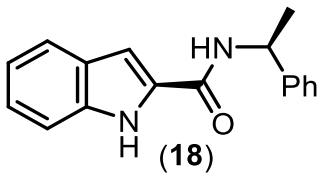
Entry	Guanylating agent (1.1 equiv.)	Base	Catalyst	Reactional Conditions	Yield (%)	Observations

1	**22**	DIPEA	-	ACN, Rt, 48 h	-	No reaction
2	**24**	DIPEA	-	ACN, Rt, 48 h	-	No reaction
3	**24**	NaH	-	THF, Rt, 48 h	-	No reaction
4	**24**	TEA	-	THF, Rt, 48 h	-	No reaction
5	**25**	TEA	-	THF, Rt, 48 h	-	No reaction
6	**26**	TEA	-	THF, Rt, 48 h	-	No reaction
7	**26**	TEA	-	THF, 40 ºC and then reflux, 48 h		Oxidation of the starting material: compound (**18**)
8	**23**	-	*p*-toluene sulfonic acid (3 mol%)	THF, Rt, 24h		Oxidation of the starting material: compound (**18**)
9	**26**	TEA	DMAP (20 mol%)	THF, Rt		Degradation of the starting material
10	**25**	-	I_2 TBHP	THF, Rt, 72 h		The ^{1}H NMR of the isolated compound from this reaction showed promising results, but it degraded in the tube
11	**27**	SmI_2	-	THF, 60 ºC, 72 h	-	No reaction
12	**23**	SmI_2	-	THF, 60 ºC, 72 h	-	No reaction
13	**25**	SmI_2 (3mol %)	-	Toluene (0.2M), 60 ºC, 48 h	12%	Compound (**19**) attained
14	**25**	SmI_2 (6mol %)	-	Toluene (0.2M), 60 ºC, 48 h	23%	Compound (**19**) attained
15	**25**	SmI_2 (3mol %)	-	Toluene (0.4M), 60 ºC, 48 h	70%	Compound (**20**) attained

16	**25**	SmI_2 (6mol %)	-	Toluene (0.4M), 60 °C, 48 h	39%	Compound (**20**) attained

The first guanylation assay was carried out using a methodology optimized by the research group for proline derived compounds. In the first attempt (Table 2.3, Entry 1), we used guanylating agent (**22**) along with a base (DIPEA), to remove the proton of the nitrogen in the indoline core. However, this reaction proved to be ineffective, leading to starting material remaining unreactive in the reactional mixture. We proceeded to try the guanylation with the guanylating reagent (**24**) (Table 2.3, Entry 2) which has a higher reactivity, still this attempt led to the same result as the first one. In the third attempt (Table 2.2, Entry 3), we tried with a stronger base (NaH), which was added at a much lower temperature (-78 °C), so we switched the solvent to THF. However, there was still no evolution in the reaction. In the following attempts (Table 2.3, Entry 4 and 5), in which there was also no evolution of the reactions, we used guanylating reagents (**24**) and (**25**), coupled with the use of the base TEA.

We proceeded with a slightly different approach through the attempt of a cyanation reaction, after which we could then react the nitrile with NH_3, achieving a guanylated product. Thus, we attempted using reagent (**26**) (Table 2.3, Entry 6), but there was still no evolution of the reaction. We replicated the conditions in the previous assay, but this time with heating (Table 2.3, Entry 7). We started by putting the reaction mixture at 40 °C, but after 24 h of no evolution in the reaction, we increased the temperature to reflux. This attempt led to the formation of compound (**18**), an oxidation product of the starting material (**16**). A new assay using the guanylating reagent (**23**) and *p*-toluene sulfonic acid as catalyst was attempted, but it also led to the formation of the indole (**18**).



(**18**)

Next, we attempted the cyanation reaction, by using once again the guanylating reagent (**26**), but this time with a catalyst (DMAP) while maintaining TEA as a base (Table 2.3, Entry 9). Here we tried to follow a reported procedure in literature [49]. This attempt seemed promising in the beginning through TLC due to what we thought to be a spot with a different shape (rounder than starting material), even though it had the same Rf as the starting material. This hope was also supported by H^1 NMR analysis, mainly because of the shifting of the signal of the alpha proton of the molecule to a lower field of the spectrum. However, the ^{13}C NMR disproved our suspicions. No signal could be attribute to the cyanide moiety and there had

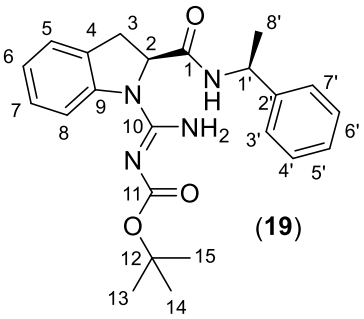
been the duplication of other signals, leading us to believe there had been a degradation of the starting material.

Since we were also using reagent (**25**), we tried an assay in which we used I_2 and an oxidizing agent (TBHP) [50] (Table 2.3, Entry 10), to help with the guanylation through desulfurization of the reagent. In this reaction, we were able to see a consumption of the starting material and a complex reaction mixture. After purification by PTLC, we were able to isolate a fraction that had promising, but confusing results. In the H^1 NMR spectrum, we observed a shift of the signal of the alpha proton of the molecule to a lower field of the spectrum.

In the ^{13}C NMR spectrum, we found that the spectrum of the starting material and isolated compound were mostly superimposable. However, while we observed a signal at 161.2 ppm that could correspond to the carbon of the guanidine, which we knew it appeared at around 159 ppm from previous works for compounds with a proline skeleton, we also observed the disappearance of a signal at 172.9 ppm in the spectrum of the isolated compound which corresponded to the carbon of the carbonyl of the amide. Unfortunately, due to a few technical issues, we were unable to obtain 2D NMR for this sample before its degradation.

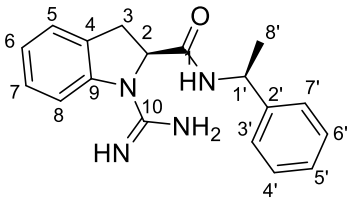
In a new approach, we tried to use a lanthanide, in this case (SmI_2), as a catalyst for the guanylation [51]. In a first attempt we used both reagent (**27**) (Table 2.3, Entry 11), which was the reported guanylating reagent for this reaction [51], and reagent (**23**) (Table 2.3, Entry 12). The reaction was carried at 60 ºC for 72 hours, but neither had any evolution.

Finally, we used the guanylating reagent (**25**) under the same conditions and were able to obtain a positive result. The reactions were monitored through TLC and purified through PTLC. We tried different conditions based on the reported literature. These conditions played with the concentration of the reaction and the catalyst (Table 2.3, Entry 13-16).



(**19**)

According to literature [51], a higher reactional concentration and catalyst concentration would result in a higher yield. In both of the assays with a lower reaction concentration (Table 2.3, Entry 13 and 14), we isolated a guanylated compound with one of nitrogen atom of the guanidine moiety protected by Boc (compound (**19**)). In these assays (Table 2.3, Entry 13 and 14), we obtained yields of 12% and 23%, respectively. While in the assays with a higher reaction concentration (Entry 15 and 16, Table 2.3), we obtained the guanylated compound without any Boc protecting groups (compound (**20**)), with yields of 70% and 39%, respectively. We

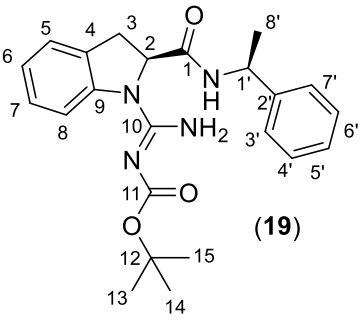


(**20**)

were unable to conclude if the increase of the concentration of the catalyst leads to higher yields as the results of the assays were contradictory.

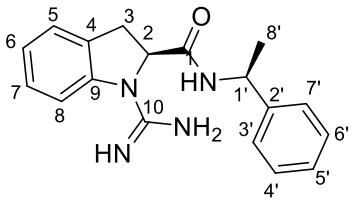
The assay in which the concentration of both the reaction and the catalyst was higher (0.4M and 6mol%, respectively) had a lower yield opposed to the assay with the higher reaction concentration and lower catalyst concentration (0.4M and 3mol%, respectively), while the assay with the lower concentration of the reaction and the catalyst was higher (0.2M and 6mol%, respectively) had a higher yield than the assay with the lower reaction and catalyst concentration (0.2M and 3mol%, respectively). We would need to repeat these conditions to identify a trend and be able to optimize the reactional conditions for this reaction. The fact that samarium iodide is a Lewis acid explains why we were observing the loss of the Boc protecting group in some cases. The concentration of the reaction could also have played a role, as the literature [51] reported that the higher the concentration of the reaction, the higher the yield of the reaction, which could result in the starting material being guanylated faster and then converted into the deprotected guanylated product.

In the ^{1}H NMR and ^{13}C NMR spectrum of the compounds confirmed the presence of the guanidine moiety in the molecule.



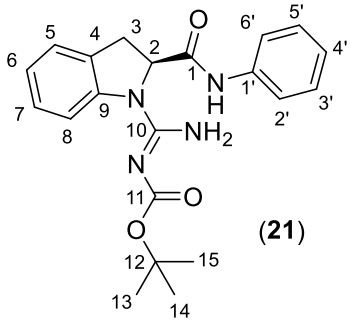
For compound (**19**), we observe two important signals immediately. The first one is the singlet at 1.45 ppm, which integrates to nine protons, a characteristic signal of the *tert*-butyl group, which confirmed the presence of the Boc protecting group attached to the guanidine moiety. The second signal was the proton of the stereogenic center (H-2), at 5.18-5.14 ppm, which shifted to lower field, relatively to the starting material, also indicates the presence of the guanidine group. The multiplets in the aromatic zone of the spectrum, 7.19-7.10 ppm and 7.01-6.96 ppm, corresponding to the aromatic protons of the phenyl group (C-3' to C-7') and the indoline skeleton (C-5 to C-8), integrating to nine protons. The signals at 3.57-3.47 ppm and 3.15-3.10 ppm correspond to the protons adjacent (H-3) to the stereogenic center in the molecule, and they too have shifted slightly towards the low field of the spectrum when compared to the starting material. The remaining signal at 5.02 ppm, corresponds to the methine proton, adjacent to phenyl group. The major reassurance that we had obtained the guanylated compound came from the ^{13}C NMR spectrum due to the presence of a signal at 159.0 ppm which was attributed to the guanidine carbon.

For compound (**20**), we observe immediately that the signal at 5.20 ppm, corresponding to the proton of the stereogenic center (H-2), has shifted to lower field comparatively to the starting material, indicating the presence of the guanidine group. The signals at 8.0 ppm, 7.24-7.10 ppm, and 7.0 ppm integrating to nine protons, corresponding to the aromatic protons of the phenyl group (C-3′ to C-7′) and the indoline skeleton (C-5 to C-8), show a different multiplicity pattern when compared to the aromatic zone of the starting material. The signals at 3.59-3.47 ppm and 3.28-3.18 ppm correspond to the protons adjacent (H-3) to the stereogenic center in the molecule, shifted slightly towards the low field of the spectrum comparatively to the starting material. Finally, the signal at 5.01 ppm, corresponds to the methine proton, adjacent to phenyl group. For compound, the ^{13}C NMR spectrum couldn't confirm the guanylation, as the carbons acquired in the lower field of the spectrum appeared with very low intensity, which could mean that the solution for NMR acquisition is not concentrated enough or the spectrum didn't acquire for enough time.



(**20**)

The procedure used for the attained of compound (**19**) was followed for compound (**17**) in order to attain the guanylated product (**21**). The ^{1}H NMR spectrum of the compounds indicated the presence of the guanidine moiety in the molecule.

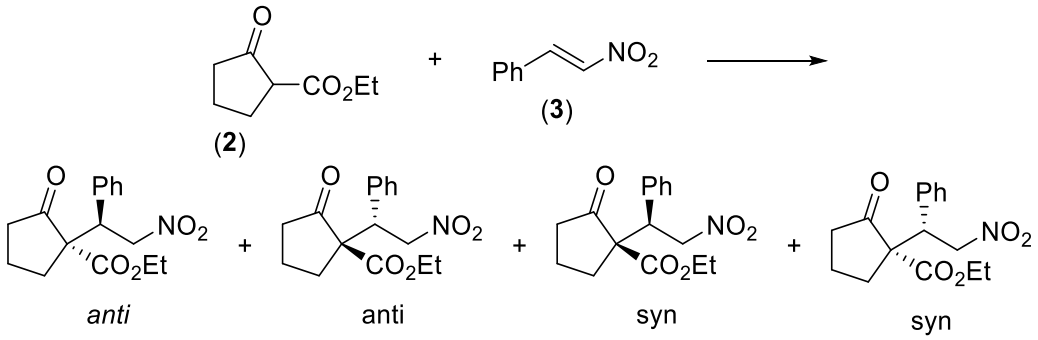


(**21**)

For compound (**21**), we once again observe the singlet at 1.45 ppm which, integrating to nine protons, and corresponding to the *tert*-butyl group, confirms the presence of the Boc protecting group attached to the guanidine moiety. We also observed the signal that corresponds to the proton of the stereogenic center (H-2), at 5.32-5.30 ppm, shifted to lower field, relatively to the starting material, indicating the presence of the of the guanidine. The multiplets in the aromatic zone of the spectrum, at 8.10-8.08 ppm, 7.90 ppm, 7.42-7.40 ppm, 7.30-7.20 ppm and 7.11-7.05 ppm, corresponding to the aromatic protons of the phenyl group (C-2′ to C-6′) and the indoline skeleton (C-5 to C-8), integrating to nine protons. The signals at 3.56-3.49 ppm and 3.46-3.38 ppm correspond to the protons adjacent (H-3) to the stereogenic center in the molecule, and they too have shifted slightly towards the low field of the spectrum when compared to the starting material. We were unable to attain a ^{13}C NMR spectrum due to the small quantity of isolated product and therefore, couldn't confirm the presence of the guanidine carbon, which could add more to prove the guanylation of compound (**21**).

2.5 Testing the catalysts on Michael's addition reaction

The effect of the synthesized catalysts in Michael's addition reaction between ethyl 2-oxocyclopentsnecarboxylate (**2**) and trans-β-nitrostyrene (**3**) was studied. In this reaction the two diastereoisomers that can be formed, anti and syn, are presented in Scheme 2.19. It was expected that compounds (**19**) and (**20**) would promote a diastereoisomeric excess and enantiomeric excess.



Scheme 2.19 - Michael addition reaction between ethyl 2-oxocyclopentane-carboxylate (**2**) and trans-β-nitrostyrene (**3**).

Between the two diastereoisomers, there is a preference for the formation of the *anti*-isomer. The identification of the two isomers is possible through ^{1}H NMR, due to the characteristic shift of the protons H-9, which appear in a zone of the spectrum that is clean in terms of overlap with other signals, allowing us to draw conclusions quickly (Figure 2.4). In Figure 2.4 are presented the signals of the *anti* and *syn* isomer which was attained from the assay using compound (**19**) as a catalyst for the reaction. The acquired spectrum is of the crude of the assay and, as mentioned before, it is possible to observe the signals of the *anti* and *syn* isomers without much overlapping of the signals. In this case, specifically, we can observe the proton H-1' of the catalyst (**19**) in between the protons of the *anti*-isomer.

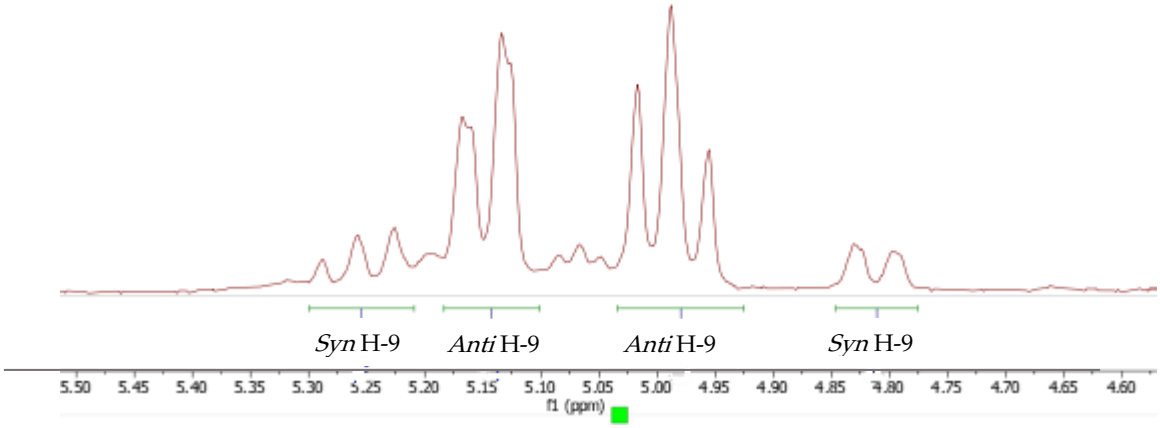
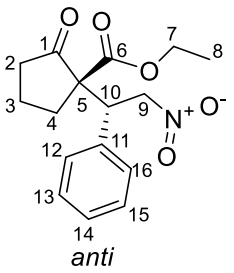
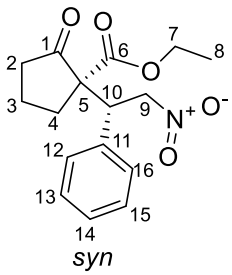
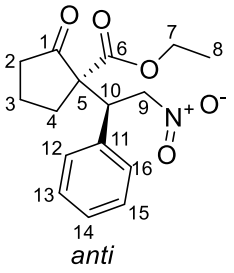
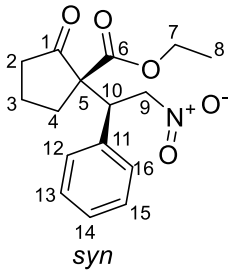


Figure 2.4 - ^{1}H NMR expansion of the signals of the protons that allow for the identification of the isomers from the assay using compound (**19**) as a catalyst.









The assays were performed in toluene and at room temperature for 24h, using 0.1 equivalents of the synthesized catalysts, compounds (**19**) and (**20**). The reactions employed *trans*-β-nitrostyrene (**3**) as the limiting reagent (1 equiv.) and ethyl 2-oxocyclopentsnecarboxylate (**2**) in excess (2 equiv.). In both assays, the TLCs of the reactions were inconclusive as they revealed the presence of compound (**2**) in the aliquot retrieved from reactional mixture, but the absence of compound (**3**) in the same aliquot. Therefore, after 48 hours, the reactions were stopped and the crude was sent directly to ^{1}H NMR without any purification.

In the first assay, we used compound (**19**) as the catalyst. The ^{1}H NMR of the reaction revealed the presence of both diastereoisomers with an excess of 59% of the *anti*-isomer. The signals the protons of the *anti*-isomer appeared as a duplet of duplets at 5.16 ppm (dd, J = 13.6 Hz, and 3.9 Hz) and 4.99 ppm (t, J= 12.2 Hz) and integrated to two protons each. The signals the protons of the *syn* isomer appeared at 5.26 ppm (dd, J = 12.1 Hz, and 25.0 Hz) and 4.81 ppm (d, J = 13.6 Hz and 3.12 Hz) and integrated to one proton each.

However, the reaction was not complete, as there was a doublet at 7.98 ppm (d, J = 13.7 Hz) which corresponds to the β proton of compound **3**, indicating the presence of the *trans*-β-nitrostyrene (**3**), which was limiting reagent of the reaction. In the NMR we can also

see the signal of proton H-1′ of the catalyst between the signals of proton H-7 of the *anti*-isomer.

In the second assay, we used compound (**20**) as the catalyst for the reaction. The ^{1}H NMR also revealed the presence of both diastereoisomers with an excess of the *anti*-isomer. However, the products attained were in such small quantity that it was not possible to do an accurate calculation of the diastereoisomeric excess. Like in the previous assay, we can observe the presence of the signal of the β proton of the *trans*-β-nitrostyrene (**3**) at 7.94 ppm (d, J = 13.7 Hz) in the ^{1}H NMR, which reveals that the reaction wasn't complete. Moreover, the intensity of this doublet wasn't proportional to the signal of proton H-1′ of the catalyst, and therefore presented a highly unsatisfactory yield. Like before, the signal of proton H-1′ of the catalyst appeared between the signals of proton H-7 of the *anti*-isomer.

Unfortunately and due to the limited time, it was not possible to repeat the synthesis to attain more catalysts so that it could be applied again to catalyze the Michael reaction between ethyl 2-oxocyclopentsnecarboxylate (**2**) and trans-β-nitrostyrene (**3**).

3

Conclusions and Future Perspectives

In the first part of this work, it was intended to study the influence of N-proline substituting groups such as pyrimidine, methyl, benzyl, acetyl, and benzoyl and the racemization observed on the Curtius rearrangement. The main used methodology used for this study was the formation of an acyl azide, which was rearranged into isocyanate through thermal decomposition and was then trapped with the chosen nucleophile.

The assays with the *N*-pyrimidinyl proline derivative trapped with benzylamine and cyclohexylamine both led to the attainment of racemic products (**9**) and (**10**), with low yields. The *N*-methyl (**4**) and *N*-benzyl (**5**) proline derivatives were found to be much more polar than the *N*-acetyl (**6**), *N*-benzoyl (**7**) and *N*-pyrimidine (**8**) proline derivatives and required an adaptation of the work up in the acyl azide attaining step, which still didn't produce satisfactory results. In addition, the reactions with *N*-methyl (**4**) and *N*-benzyl (**5**) proline derivatives presented inconsistent results and resulted in complex mixtures of degraded starting material.

The assays with the *N*-acetyl proline (**6**) derivative had a problem with the solubility of the compound in the solvent (THF), which were overcome with longer reaction times. The assays with this derivative trapped with phenylmagnesium bromide did not afford the desired product and afforded a complex mixture. The assay with *N*-benzoyl proline (**7**) derivative took a significantly longer time to rearrange the acyl azide to isocyanate and the trap with phenylmagnesium bromide, resulted in complex mixture.

Ultimately, we were unsuccessful in studying the influence of the proposed nitrogen-proline substituting group in the racemization of the Curtius rearrangement. Currently, computational studies are being carried out to understand how the racemization process works.

In the second part of this work, we developed the synthesis of new catalysts for the Michael addition reaction, between ethyl 2-oxocyclopentsnecarboxylate (**2**) and trans-β-nitrostyrene (**3**). The developed catalysts were based on the (*S*)-indoline carboxylic acid that were derivatized to amides and functionalized with the carbodiimide group at the indoline nitrogen atom.

Firstly, the nitrogen atom of the (*S*)-indoline carboxylic acid was protected with a Boc protecting group. Then, we proceeded to the amide formation, which was achieved through the formation of a mixed anhydride which reacted with aniline or (*S*)-(-)-1-phenylethylamine to afford the desired amides, compounds (**14**) and (**15**) respectively. These reactions presented higher yields with longer reaction times (24h *vs* 48h). Subsequently, the Boc protecting group from compounds (**14**) and (**15**) was removed with trimethylaluminum. Numerous assays were tested to guanylate the prepared indoline derivatives, with a wide variety of guanylating agents.

We successfully guanylated compound (**16**) using the lanthanide SmI_2 as a catalyst and 1,3-Di-Boc-2-methylisothiourea as a guanylating agent. Several assays for this reaction

were conducted to test different reactional conditions. The assays with lower concentration (0.19M) afforded a guanylated product with one Boc protecting group bonded to one nitrogen of the guanidine (compound (**19**)). The results were confirmed through ^{1}H and ^{13}C NMR. On the other hand, the assays with higher concentration (0.38M) afforded a guanylated product without Boc protecting groups (compound (**20**)). The guanylation of compound (**17**) was not achieved with complete certainty as we were not able to do an ^{13}C NMR analysis and confirm the presence of the carbon of the guanidine.

Finally, the assays of the Michael addition reaction employing the synthesized catalysts, compounds (**19**) and (**20**), were not satisfactory yield wise. The ^{1}H NMR of the assay using compound (**19**) revealed a diastereoisomeric excess of 59% for the isomer *anti*, however it also showed a high concentration of trans-β-nitrostyrene, which means that the evolution of the reaction was very slow. The assay employing compound (**20**) also showed an excess of the isomer *anti*, but due to the, virtually, non-evolution of the reaction, it was not possible to calculate the diastereoisomeric excess.

In the future, a new assay would need to be conducted to confirm the exact structure of compounds (**20**) and (**21**) through ^{13}C NMR and, if confirmed, apply it in catalysis assays. Another interesting study would be to use different amines to synthesize catalysts with different substitutes in the nitrogen atom of the amide and see if and/or how they would affect the Michael addition reaction. Finally, it would be interesting to see if the successful guanylation conditions of compounds (**16**) and (**17**) would be also successful if applied in an indoline compound derived from the Curtius rearrangement where the aminal group poses additional challenges.

4

EXPERIMENTAL SECTION

4.1 General Information

In this work were used general laboratory materials and procedures. All the reagents and solvents employed were used without further purification. The reagents were acquired from Sigma-Aldrich, TCI, and Alfa Aesar, and the solvents were acquired from Carlo Erba and Honeywell. When necessary, the solvents used in reactions were previously dried as described in the literature [52].

The reactions were followed by TLC on Merck Silica gel GF 254 0.2 mm plates supported on aluminium. Purifications on PTLC were performed on Merck Silica gel GF 254 0.2 mm plates supported on aluminium or Merck Silica gel GF 254 0.5 mm or 1 mm plates, supported on glass. Purifications made by column chromatography were performed with stationary phase Silica gel 60A (Carlo Erba) with granulometry 40-63 μm in normal phase flash chromatography. The revelation of TLCs was done using spraying reagents ninhydrin and Dragendorff.

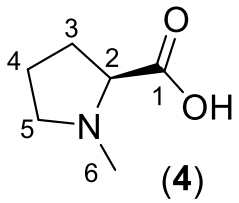
IR spectra were acquired using spectrophotometer *Perkin Elmer Spectrum two* in ATR mode between 4000 and 450 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were acquired with Bruker ARX 400, and were measured at 400 and 101 MHz, respectively.

The NMR signals are presented with chemical shift (, in ppm), correspondent proton and number of protons. NMR signals are described as singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), triplet (t), quintuplet (quint) and multiplet (m) with coupling constant (*J*) being given in Hz (Hertz).

Specific optical rotations were measured in the equipment *Bellingham + Stanley ADP410* using a 1 cm cell.

4.2 Synthesis of *L*-Proline derivatives

4.2.1 Synthesis of *N*-Methyl *L*-Proline (4)

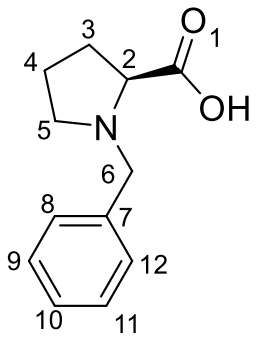


(**4**)

In a round bottom flask, 1g of *L*-proline (8.69 mmol) was dissolved in MeOH (0.9M) and formaldehyde (1.1 equiv.) was added, followed by Pd/C (10%) under H_2. The mixture was left to react overnight and monitored by TLC. After the starting material was completely consumed, the mixture was filtered through a silica pad with celite on top, and the filtered was concentrated and dried under vacuum. The solid was then dissolved in MeOH and was added diethyl ether until precipitation. The compound was filtered and dried under vacuum, affording 1.01g of a white solid, compound (**4**) [34] (7.86 mmol), with 91% yield.

^{1}H NMR (400 MHz, D_2O): 3.89 (t, *J*= 8.0 Hz 1H, H-2), 3.76-3.71 (m, 1H, H-5a), 3.19-3.12 (m, 1H, H-5b), 2.93 (s, 3H, H-6), 2.54-2.46 (m, 1H, H-3a), 2.17-1.96 (m, 3H, H-3b H-4).

4.2.2 Synthesis of *N*-Benzyl *L*-Proline (5)

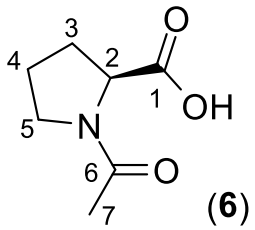


(**5**)

In a round bottom flask, 1g (8.69 mmol) proline was dissolved in *i*-PrOH (0.2M), followed by KOH (3 equiv.). The mixture was heated to 40 ^{O}C and benzyl bromide (1.2 equiv.) was added dropwise. The mixture was left to react overnight and monitored by TLC. After the starting material was completely consumed, the pH of the mixture was adjusted to 5 with HCl, followed by the addition of DCM while maintaining stirring. The mixture was left to rest overnight. The mixture was filtered, concentrated under vacuum and acetone was added. After a slow precipitation, the residue was filtered and dried under vacuum, affording compound (**5**) [35] as a white solid with 1.2g (5.21 mmol) and 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$): 7.51 (s, 5H, H-Ar), 4.39 (s, 2H, H-6), 4.01 (t, *J*=8.2 Hz, 1H, H-2), 3.67-3.61 (m, 1H, H-5a), 3.29 (q, *J*= 19.4 Hz e 9.2Hz, 1H, H-5b), 2.54-2.45 (m, 1H, H-3a), 2.16-1.92 (m, 3H, H-3b H-4).

4.2.3 Synthesis of *N*-Acetyl Proline (6)

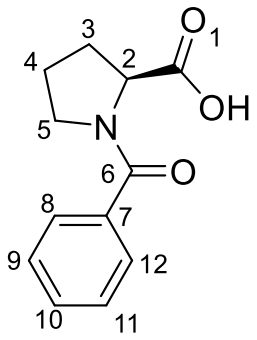


(**6**)

In a round bottom flask, 1.5g (13.03 mmol) of proline was dissolved in NaOH 1N (0.5 equiv.) and cooled to 0 C in an ice-water bath. The acyl chloride (1.1 equiv.) was dissolved in THF and NaOH 1N (0.5 equiv.) were added dropwise, while the temperature was maintained at 5-10 C. After the addition was complete, the mixture was allowed to warm up to room temperature and stirred overnight. The reaction was monitored by TLC and once it was complete, it was concentrated under vacuum and extracted with DCM. The organic layers were combined, dried over anhydrous $NaSO_4$, concentrated and dried under vacuum. Compound (**6**) [53] was attained as a white solid with 600mg (3.82 mmol) and 29% yield.

^{1}H(400 MHz, $CDCl_3$): 8.68 (bs, 1H, COOH), 3.90 (t, *J*= 12.1 Hz, 1H, H-2) 3.29 (d, *J*= 9.1 Hz, 1H, H-5a), 3.12 (d, *J*= 10.9 Hz, 1H, H-5b), 2.14-1.23 (m, 1H, H-3a), 2.03-1.95 (m, 1H, H-3b), 1.91-1.85 (m, 2H, H-4), 1.81 (s, 3H, H-7).

4.2.4 Synthesis of *N*-Benzoyl Proline (7)

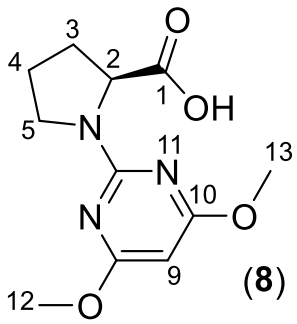


(**7**)

In a round bottom flask, 1g (8.69 mmol) of proline was dissolved in water (0.3M), followed by NaOH (2 equiv.). The mixture was cooled to 0º C and benzoyl chloride (1 equiv.) was added dropwise. The mixture was left to stir, at room temperature, overnight and monitored by TLC. After the starting material was completely consumed, the mixture was washed with water and diethyl ether. The pH of the aqueous phase was adjusted to 1 with HCl 1M and extracted with AcOEt. The organic phase was dried with Na_2SO_4, filtered, and concentrated under vacuum, affording a white solid as 1.55g (8.68 mmol) of compound (**7**) [36] and resulting in yield of 81%.

^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (d, *J*= 7.44 Hz, 1H, COOH), 7.50 (d, *J*= 7.26 Hz, 2H, H-Ar), 7.36-7.23 (m, 3H, H-Ar), 4.46 (bs, 1H, H-2), 3.59-3.52 (m, 1H, H-5a), 3.40-3.34 (m, 1H, H-5b), 2.19-2.14 (m, 1H, H-3), 2.06-2.02 (m, 1H, H-3'), 1.93-1.89 (m, 1H, H-4a), 1.71-1.63 (m, 1H, H-4b).

4.2.5 Synthesis of (4,6-Dimethoxypyrimidin-2-yl)-*L*-Proline (8)



(**8**)

In a round bottom flask, 500mg of 2-chloro-4,6-dimethoxypyrimidine (2.86 mmol) was dissolved in ACN (0.5M) and placed under inert atmosphere. The proline, dissolved in H_2O (0.2M) was added, as well as sodium bicarbonate (2equiv.). The mixture was left to react at 88 ^{O}C for 6h. The reaction was monitored by TLC. Once observed the starting material was completely consumed, the pH of the mixture was adjusted to 6 with HCl (1M) and then concentrated under vacuum. The crude was purified by flash chromatography with a mixture of DCM:MeOH to afford 531 mg (of a pale yellow solid, compound (**8**) [37], with a yield of 74%.

^{1}H NMR (400 MHz, $CDCl_3$): 5.53 (s, 1H, H-9), 4.53 (d, *J*=7,7 Hz, 1H, H-2), 3.87 (s, 6H, H-12 H-13), 3.69-3.57 (m, 2H, H-5), 2.56-2.51 (m, 1H, H-3a), 2.11-1.98 (m, 3H, H-3b H-4).

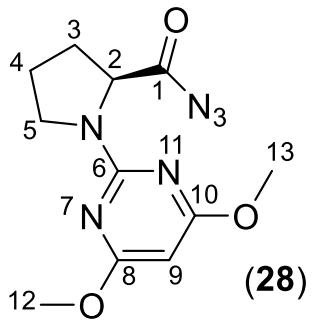
$[\alpha]_D^{25}$ -222.9 (c 0.40, $CHCl_3$)

4.3 General Procedure for the synthesis of acyl azides

In a round bottom flask, the starting material was dissolved in THF (0.2M) in an ice bath flask at -15 C under inert atmosphere. *N*-Methylmorpholine (1.1 equiv.) was added, dropwise, followed by Isobutyl Chloroformate (1.1 equiv.), after 5 minutes. The mixture was left to react and monitored by TLC. After no starting material was observed, an aqueous solution of sodium azide (2.4 equiv., 5M) was added, and the reaction monitored by TLC. After 1 hour, the reaction was complete, and the phases were separated. The organic phase was concentrated under vacuum, dissolved in ethyl acetate, and extracted with HCl (1M) and $NaHCO_3$

(saturated solution). The organic phase was filtrated with Na_2SO_4, evaporated and dried under vacuum.

4.3.1 Synthesis of (4,6-dimethoxypyrimidin-2-yl)-L-prolinoyl azide (28)



(**28**)

Following the general procedure previously described 434 mg (1.71 mmol) of (4,6-Dimethoxypyrimidin-2-yl)-*L*-Proline (**8**), compound (**28**) was attained as a colourless oil with 410 mg (1.47 mmol) and a yield of 86%.

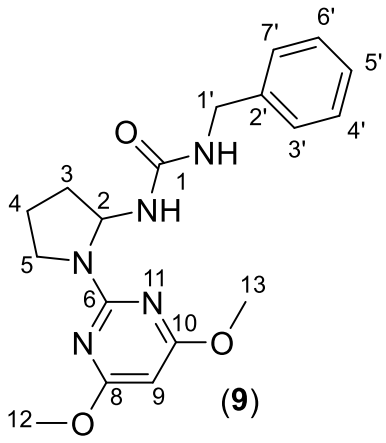
IR (ATR) υ_{max} (cm^{-1}): 2983, 2950 (C-H aliphatic), 2875, 2136 (N_3), 1720 (C=O), 1574, 1519, 1453, 1159.

$[\alpha]_D^{25}$ -112.3 (c 0.39, $CHCl_3$)

4.4 General procedure for Curtius rearrangement and isocyanate trapping with nucleophile

The acyl azide was dissolved in THF (0.2M) and to refluxed in an inert atmosphere for 40 minutes. The reaction was monitored by IR through the disappearance of the azide band, between 2126 cm^{-1} and 2140 cm^{-1}. After the reaction was completed, the mixture was allowed to cool to room temperature and placed in a bath (-41 ºC for the Grignard or -15 ºC for the amine) and the nucleophile was added. The reaction was once again monitored by IR through the disappearance of the isocyanate band, at 2240 cm^{-1}, was observed. Once the reaction was completed, MeOH was added, and the mixture was allowed to stir for 5 minutes. The mixture was then concentrated under vacuum and the crude obtained was purified by flash chromatography with mixtures of ether petroleum: ethyl acetate.

4.4.1 Synthesis of 1-benzyl-3-(1-(4,6-dimethoxypyrimidin-2-yl) pyrrolidin-2-yl)urea (9)



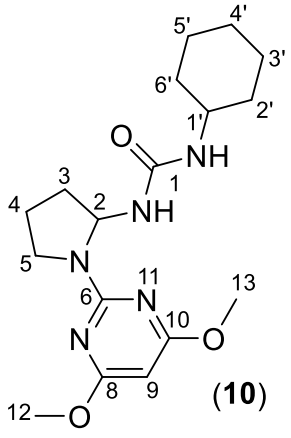
(**9**)

Following the general procedure previously described 410 mg (1.47 mmol) of (4,6-Dimethoxypyrimidin-2-yl)-*L*-Proline (**8**) and benzylamine, compound (**9**) was attained, after purification with 6:4 (petroleum ether:ethyl acetate), 62 mg (0.17 mmol) of a pale yellow solid with a yield of 12%.

^{1}H NMR (400 MHz, MeOD): 7.33-7.23 (m, 5H, H-2' H-3' H-3' H-4' H-6' H-7'), 5.87 (d, *J*= 5.5 Hz, 1H, H-2), 5.42 (s, 1H, H-9), 4.32 (s, 2H, H-1'), 3.81 (s, 5H, H-12 H-13), 3.74-3.59 (m, 1H, H-5a), 3.49-3.42 (m, 1H, H-5b) 2.16-2.00 (m, 4H, H-3 H-4).

^{13}C (101 MHz, MeOD): 173.4 (C-8, C-10), 160.8 (C-1), 160.2 (C-6) , 141.4 (C-2'), 129.4 (C-Ar), 128.2 (C-Ar), 128.0 (C-Ar), 79.3 (C-2), 66.7 (C-9), 54.1 (C-12, C-13), 47.5, 44.5, 35.2, 23.4.

4.4.2 Synthesis of 1-cyclohexyl-3-(1-(4,6-dimethoxypyrimidin-2-yl)pyrrolidin-2-yl)urea (10)



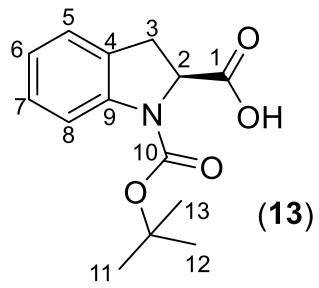
(**10**)

Following the general procedure previously described 410 mg (1.47 mmol) of (4,6-Dimethoxypyrimidin-2-yl)-*L*-Proline (**8**) and benzylamine, compound (**10**) was attained as pale yellow solid, after purification with 6:4 (petroleum ether:ethyl acetate), 14 mg (0.04 mmol) of a white solid with a yield of 3%.

^{1}H NMR (400 MHz, MeOD): 5.71 (t, *J*= 6.2Hz, 1H, H-2), 5.87 (d, *J*= 5.5 Hz, 1H, H-2), 5.43 (s, 1H, H-9), 3.86 (s, 5H, H-12 H-13), 3.67-3.62 (m, 2H, H-5), 2.57-3.43 (m, 1H, H-aliph) 2.01-1.10 (m, 14H, H-aliph).

4.5 Synthesis of amino-pyrrolidine guanidine catalysts

4.5.1 Synthesis of *N*-Boc-(*S*)-Indoline carboxylic acid (13)



(**13**)

In a round bottom flask, 1g (6.13mmol) of proline was dissolved in MeOH (0.2M), placed under inert atmosphere and cooled to 0^{O}C. Trimethylamine was added (2equiv.) followed by di-*tert*-butyl dicarbonate (1equiv.). The mixture was left to react at room temperature overnight. The reaction was monitored by TLC, and once observed the starting material was completely consumed, the mixture was concentrated under vacuum. The residue was dissolved in ethyl acetate and extracted with HCl (1M). The organic phase was dried with Na_2SO_4, filtered, and concentrated under vacuum, affording 1.45 mg (5.51mmol) of a pale-yellow solid, compound (**13**), with a 90% yield.

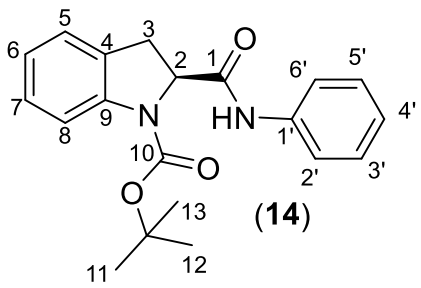
^{1}H(400 MHz, MeOD): 7.78 (d, *J*= 8.1 Hz, 1H, H-Ar), 7.15 (t, *J*= 7.9 Hz, 2H, H-Ar), 6.93 (t, *J*=7.4 Hz, 1H, H-Ar), 4.81-4.80 (m, 1H, H-2), 3.53 (dd, *J*= 16.8 Hz and 11.7 Hz, 1H, H-3a) , 3.09 (dd, *J*= 16.7 Hz and 4.5 Hz, 1H, H-3b), 1.50 (s, 9H, H-11, H-12 and H-13).

4.5.2 General procedure for amide synthesis

In a round bottom flask, the starting material was dissolved in THF (0.2M) in an ice bath flask at -15 C under inert atmosphere. *N*-Methylmorpholine (1.1 equiv.) was added, dropwise, followed by Isobutyl Chloroformate (1.1 equiv.), after 5 minutes. The mixture was left to react for 1h. The amine (1.1equiv.) was added, and the reaction monitored by TLC. After 48 hours, the reaction was stopped, and the phases were separated. The organic phase was

concentrated under vacuum, dissolved in ethyl acetate, and extracted with HCl (1M) and $NaHCO_3$ (saturated solution). The organic phase was filtrated with Na_2SO_4, evaporated and dried under vacuum. The crude was purified by flash chromatography using a mixture of mixture 9:1 (ether petroleum: ethyl acetate).

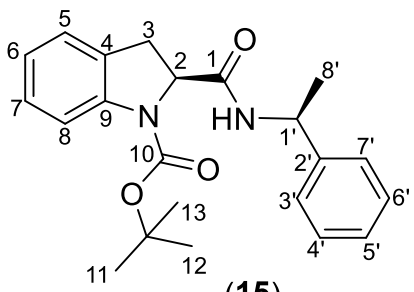
4.5.2.1 Synthesis of *tert*-butyl *(S)*-2-(phenylcarbamoyl)indoline-1-carboxylate (14)



Following the general procedure previously described a mixture of 100 mg (1.13 mmol) of *N*-Boc-(*S*)-indoline (**13**) and aniline were left to react for 48 hours. Compound (**14**) was obtained as 81 mg (0.24 mmol) of a white solid, after purification, with a 63% yield.

^{1}H NMR (400 MHz, $CDCl_3$): 7.66 (bs, 1H, H-Ar), 7.50 (d, *J*= 8.0 Hz, 2H, H-Ar), 7.30 (t, *J*= 8.0 Hz, 2H, H-Ar), 7.21 (t, *J*= 7.7 Hz, 2H, H-Ar), 7.10 (t, *J*= 7.5 Hz, 1H, H-Ar), 7.0 (t, *J*= 7.4 Hz, 1H, H-Ar), 5.01 (t, *J*= 7.0 Hz, 1H, H-2), 3.49 (d, *J*= 4.6 Hz, 2H, H-3), 1.57 (s, 9H, H-12 H-13 H-14).

4.5.2.2 Synthesis of *tert*-butyl *(S)*-2-((*(S)*-1-phenylethyl)carbamoyl)indoline-1-carboxylate (15)



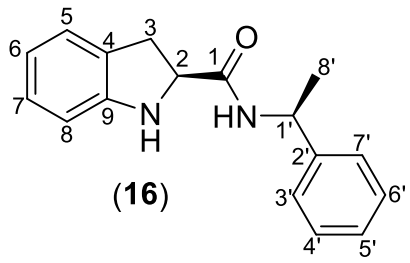
Following the general procedure previously described a mixture of 300 mg (1.13 mmol) of *N*-(*S*)-Indoline (**13**) and (*S*)-(-)-1-phenylethylamine were left to react for 72 hours. Compound (**15**) was obtained, after purification, as 303 mg (0.83 mmol) of a white solid with a 74% yield.

^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (bs, 1H, H-Ar), 7.30-7.12 (m, 7H, H-Ar), 6.98 (t, *J*= 7.4 Hz, 1H, H-Ar), 5.11 (quint, *J*= 5.7 Hz, 1H, H-1'), 4.91-4.87 (m, 1H, H-2), 3.47-3.35 (m, 2H, H-3), 1.55-1.53 (m, 9H, H-11 H-12 H-13), 1.49 (d, *J*= 7.0 Hz, 3H, H-8').

4.5.3 General procedure for deprotection

In a round bottom flask, the protected starting material was dissolved in DCM (0.2M), put under an inert atmosphere, and placed in a bath at -78 C. $AlMe_3$ (2M in heptane) was added dropwise and allowed to react reaching room temperature. The reaction was monitored by TLC. After the starting material was completely consumed, a solution of Sodium Potassium Tartrate was added at 0ºC was added dropwise and allowed to react for 5 minutes, leading to the formation two phases. These phases were separated, and the aqueous layer was washed several times with DCM. The combined organic layers were dried with Na_2SO_4, concentrated and dried under vacuum.

4.5.3.1 Synthesis of *(S)-N-((S)*-1-phenylethyl)indoline-2-carboxamide (16)



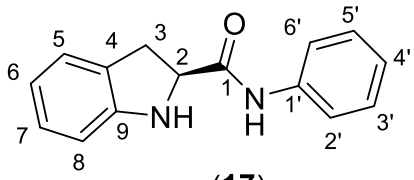
(**16**)

Following the general procedure previously described a mixture of 300 mg (0.82 mmol) of tert-butyl 2-(((S)-1-phenylethyl) carbamoyl)indoline-1-carboxylate (**15**) and trimethylaluminum were left to react for 1 hour. Compound (**16**) was obtained with a yield of 47%, as 103 mg (0.39 mmol) of a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): 7.89-7.84 (m, 1H, N-H), 7.63 (d, *J*=8 Hz, 1H, H-Ar), 7.28-7.08 (m, 7H, H-Ar), 7.94 (t, *J*= 7.4 Hz, 1H, H-Ar), 6.86 (d, *J*= 7.8 Hz, 1H, H-Ar), 5.84 (quint, *J*= 5.1 Hz, H-1'), 4.64 (t, *J*= 9.6 Hz, 1H, H-2) , 3.56 (dd, *J*= 16.4 Hz and 10.4 Hz, 1H, H-3a), 3.04 (dd, *J*= 16.3 Hz and 8.7 Hz, 1H, H-3b), 1.51 (d, *J*= 7 Hz, 3H, H-8').

^{13}C NMR (100 MHz, $CDCl_3$): 172.9 (C-1), 148.6 (C-Ar), 143.2 (C-Ar), 128.8 (C-Ar), 128.2 (C-Ar), 127.7 (C-Ar), 127.4 (C-Ar), 126.1 (C-Ar), 124.9 (C-Ar), 120.8 (C-Ar), 111.0 (C-Ar), 61.81 (C-2), 48.3 (C-1'), 35.6 (C-3), 22.0 (C-8').

4.5.3.2 Synthesis of *(S)*-*N*-phenylindoline-2-carboxamide (17)



(**17**)

Following the general procedure previously described a mixture of 48 mg (0.14 mmol) of tert-butyl (*S*)-2-(phenylcarbamoyl)indoline-1-carboxylate (**14**) and trimethylaluminum were left to react for 1 hour. Compound (**17**) was obtained with a yield of 58%, as 19.5 mg (0.08 mmol) of a pale yellow solid.

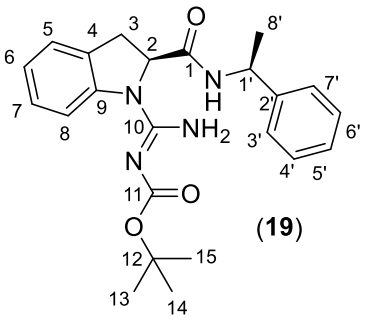
^{1}H NMR (400 MHz, $CDCl_3$): 7.59 (d, *J*= 7.5Hz, 2H, H-Ar), 7.33 (d, *J*=8.0 Hz, 2H, H-Ar), 7.15-7.10 (m, 3H, H-Ar), 6.89-6.82 (m, 2H, H-Ar), 4.32 (d, *J*= 6.1 Hz, 1H, H-2), 3.22 (dd, *J*= 16.4 Hz and 8.6 Hz, 1H, H-3a), 3.04 (dd, *J*= 16.3 Hz and 8.7 Hz, 1H, H-3b).

^{13}C NMR (100 MHz, $CDCl_3$): 172.9 (C-1), 149.1 (C-Ar), 137.5 (C-Ar), 129.2 (C-Ar), 128.4 (C-Ar), 127.9 (C-Ar), 125.1 (C-Ar), 124.6 (C-Ar), 121.4 (C-Ar), 119.8 (C-Ar), 111.6 (C-Ar), 61.8 (C-2), 35.6 (C-3).

4.5.4 General procedure for guanylation

In a round bottom flask, the deprotected starting material was mixed with SMI_2 (0.1M in THF) and allowed to react for 5 minutes under an inert atmosphere. The amine (1.1equiv.) was added to toluene. This solution was added to the flask, and allowed to react at 60º C. The reaction was monitored by TLC. After the 48 hours, the reaction was stopped, and the mixture was concentrated under vacuum. The crude obtained was purified by PTLC with mixtures of ether petroleum:ethyl acetate.

4.5.4.1 Synthesis of (tert-butyl (-amino((*S*)-2-(((*S*)-1-phenylethyl)carbamoyl)indolin-1-yl)methylene)carbamate (19)

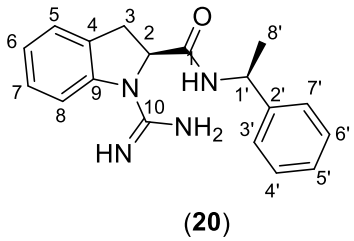


Following the general procedure previously described a mixture of 10 mg (1.13 mmol) of (S)-N-((S)-1-phenylethyl)indoline-2-carboxamide (**16**) and samarium iodide reacted for 5 minutes, followed by the addition of di-boc-methylisothiourea, and were left to react for 72 hours. Compound **19** was obtained, after purification with the mixture 6:4 (ether petroleum: ethyl acetate), as 3.5 mg (0.01 mmol) of a white solid with a 23% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.10 (m, 6H, H-Ar), 7.01-6.96 (m, 3H, H-Ar), 5.16 (dd, *J*= 11.4 Hz and 4.0 Hz, 1H, H-2), 5.02 (quint, *J*= 5.7 Hz, 1H, H-1'), 3.57-3.47 (m, 1H, H-3a), 3.12 (dd, *J*= 16.7 Hz and 3.9 Hz, 1H, H-3b), 1.45 (s, 9H, H-13 H-14 H-15), 1.34 (d, *J*= 6.9 Hz, H-8').

^{13}C (100 MHz, $CDCl_3$): δ 171.3 (C-1), 159.0 (C-10), 151.0, 142.7 (C-Ar), 141.8 (C-Ar), 130.4 (C-Ar), 128.8 (C-Ar), 127.9 (C-Ar), 127.4 (C-Ar), 125.9 (C-Ar), 125.1 (C-Ar), 124.4 (C-Ar), 116.6 (C-Ar), 83.5 (C-12), 63.5 (C-2), 48.6 (C-1'), 33.3 (C-3), 28.2 (C-13, C-14, C-15) , 22.0 (C-8').

4.5.4.2 Synthesis of *((S)*-1-carbamimidoyl-*N-((S)*-1-phenylethyl)indoline-2-carboxamide (20)

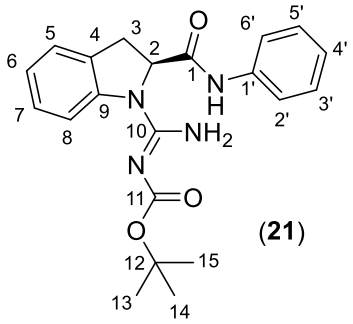


Following the general procedure previously described a mixture of 10 mg (1.13 mmol) of (S)-N-((S)-1-phenylethyl)indoline-2-carboxamide (**16**) and samarium iodide reacted for 5 minutes, followed by the addition of di-boc-methylisothiourea, and were left to react for 72 hours. Compound **20** was obtained, after purification with the mixture 6:4 (ether petroleum: ethyl acetate), as 8.1 mg (0.03 mmol) of a white solid with a 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, *J*= 8.2 Hz, 1H, H-Ar), 7.24-7.10 (m, 6H, H-Ar), 7.00 (t, *J*= 7.6 Hz, 1H, H-Ar), 5.20 (d, *J*= 8.2 Hz, 1H, H-2), 5.01 (quint, *J*= 5.7 Hz, 1H, H-1'), 3.59-3.47 (m, 1H, H-3a), 3.28-3.18 (m, 1H, H-3b), 1.44 (d, *J*= 6.8 Hz, H-8').

^{13}C (100 MHz, $CDCl_3$): δ 172.0 (C-1), 142.9 (C-Ar), 142.3 (C-Ar), 128.7 (C-Ar), 127.7 (C-Ar), 127.3 (C-Ar), 126.0 (C-Ar), 125.0 (C-Ar), 123.7 (C-Ar), 116.6 (C-Ar), 63.2 (C-2), 48.6 (C-1'), 33.0, 32.1 (C-3), 29.8, 29.5, 25.0, 22.8, 22.1 (C-8'), 14.3, 13.8.

4.5.4.3 Synthesis of *((S)*-1-carbamimidoyl-*N-((S)*-1-phenylethyl)indoline-2-carboxamide (21)



(**21**)

Following the general procedure previously described a mixture of 15 mg (0.06 mmol) of (S)-N-phenylindoline-2-carboxamide (**17**) and samarium iodide reacted for 5 minutes, followed by the addition of di-boc-methylisothiourea, and were left to react for 72 hours. Compound **21** was obtained, after purification with the mixture 6:4 (ether petroleum: ethyl acetate), as 1.5 mg (0.004 mmol) of a white solid with a 6.5% yield.

^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J*= 7.9Hz, 1H, H-Ar), 7.35 (d, *J*= 8.1 Hz, 2H, H-Ar), 7.21 (t, *J*= 7.8 Hz, 3H, H-Ar), 7.14 (d, *J*= 7.4 Hz, 1H, H-Ar), 7.04-7.02 (m, 2H, H-Ar), 5.25 (d, *J*= 9.6 Hz 1H, H-2), 3.57-3.47 (dd, *J*= 17.2 Hz and 10.9 Hz, 1H, H-3a), 3.40-3.32 (m, 1H, H-3b), 1.45 (s, 9H, H-13 H-14 H-15).

4.6 Testing of the catalysts in Michael addition reactions

4.6.1 General procedure for the Michael Additions

In a round bottom flask, 10 mg (0.07 mmol) of trans-β-nitrostyrene (**3**) was dissolved in THF, followed by the addition of the catalyst (0.1 equiv.) and then ethyl 2-oxocyclopentsnecarboxylate (**2**) (2 equiv.) at room temperature. The mixture was monitored through TLC and after 48 hours it was stopped. The crude was concentrated and dried under vacuum and sent to NMR.

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APPENDIX

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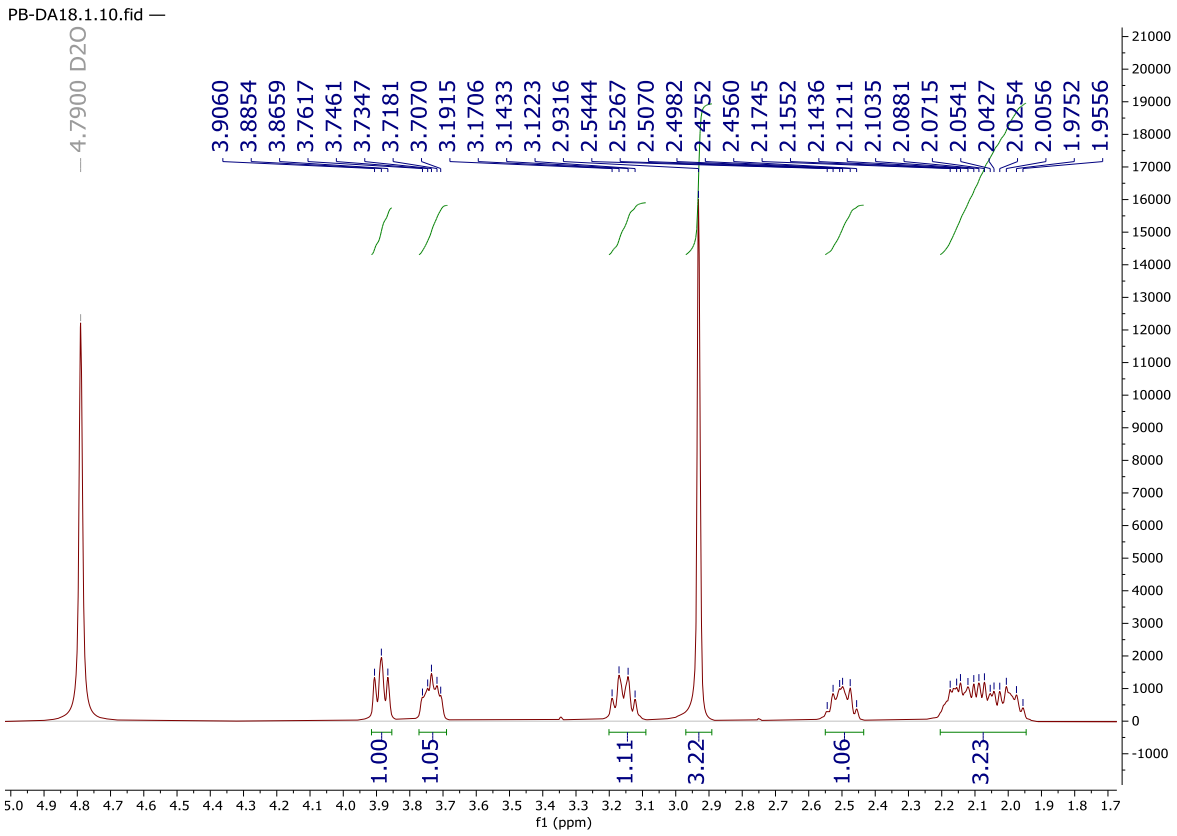
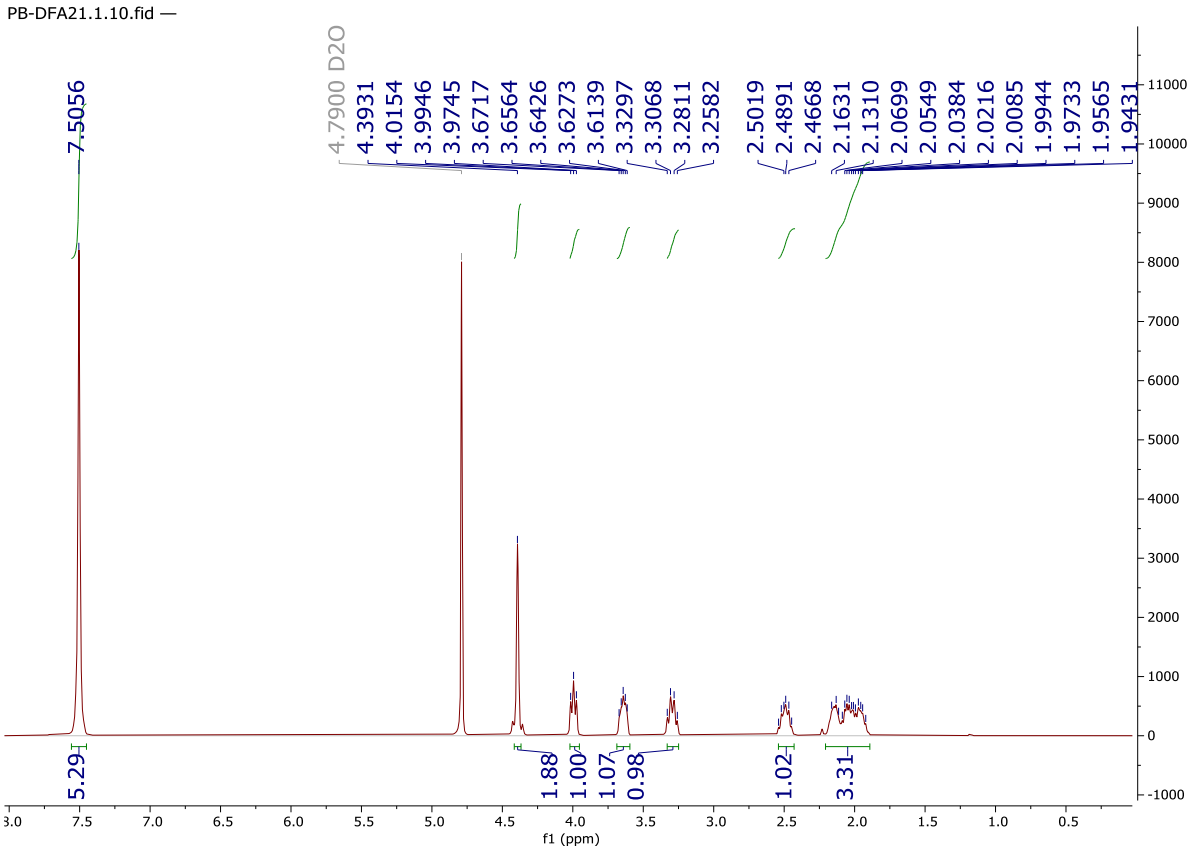
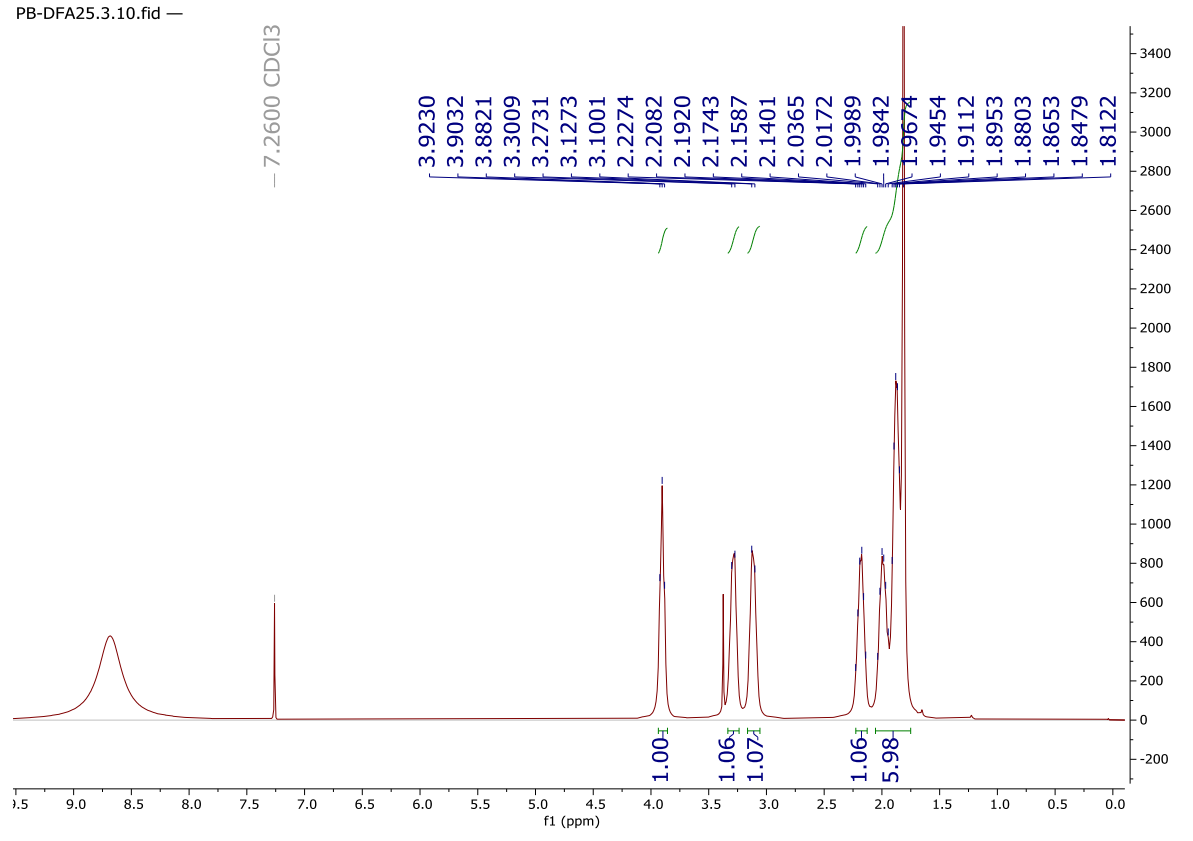
A.1 Study of the influence of the *N*-substituents in the Curtius rearrangement



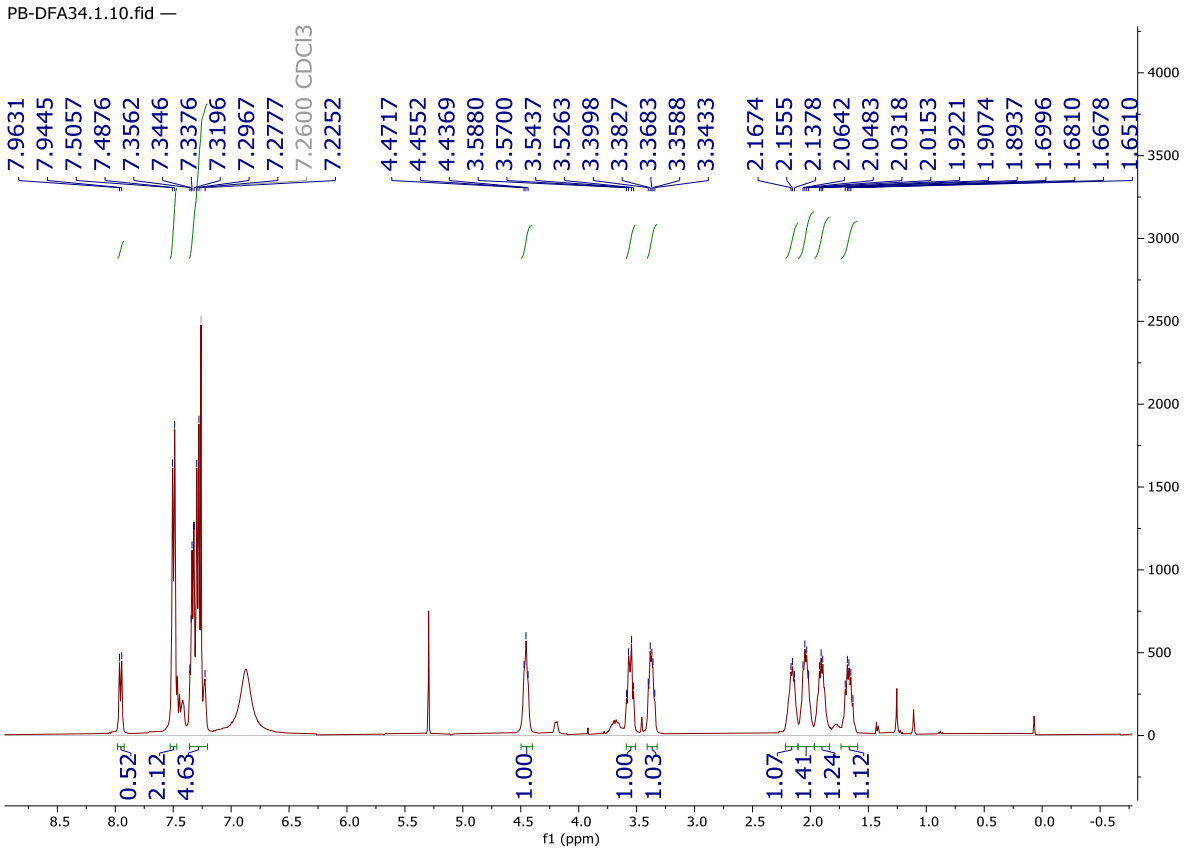
Appendix 1 - ^{1}H NMR spectrum of compound **4** in D_2O.



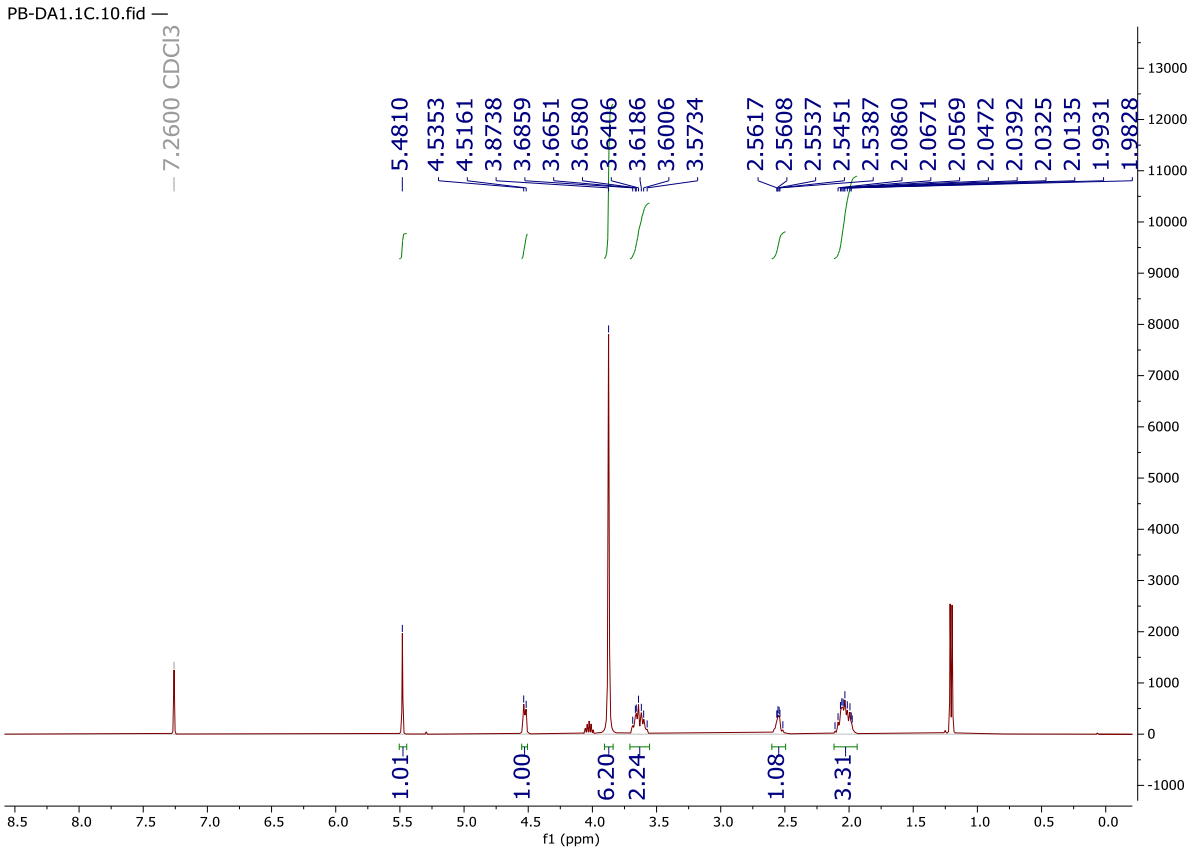
Appendix 2 - ^{1}H NMR spectrum of compound **5** in D_2O.



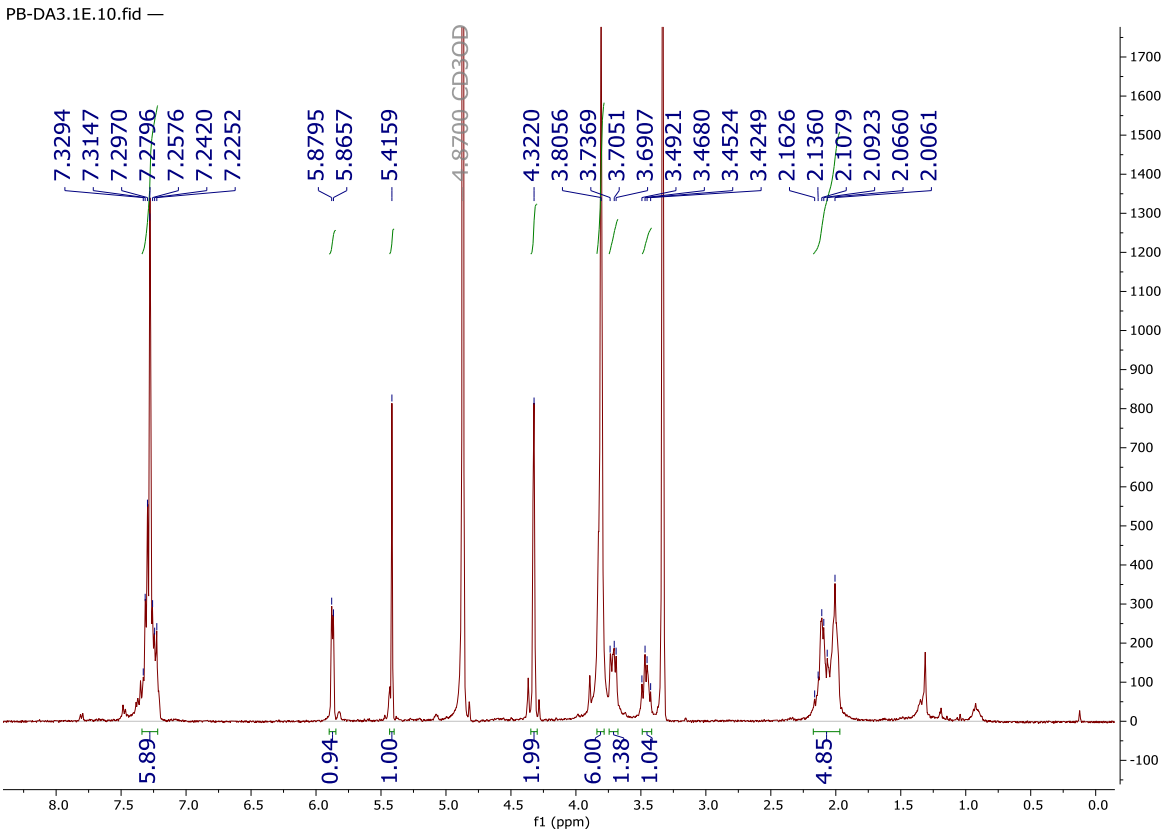
Appendix 3 - ^{1}H NMR spectrum of compound **6** in $CDCl_3$.



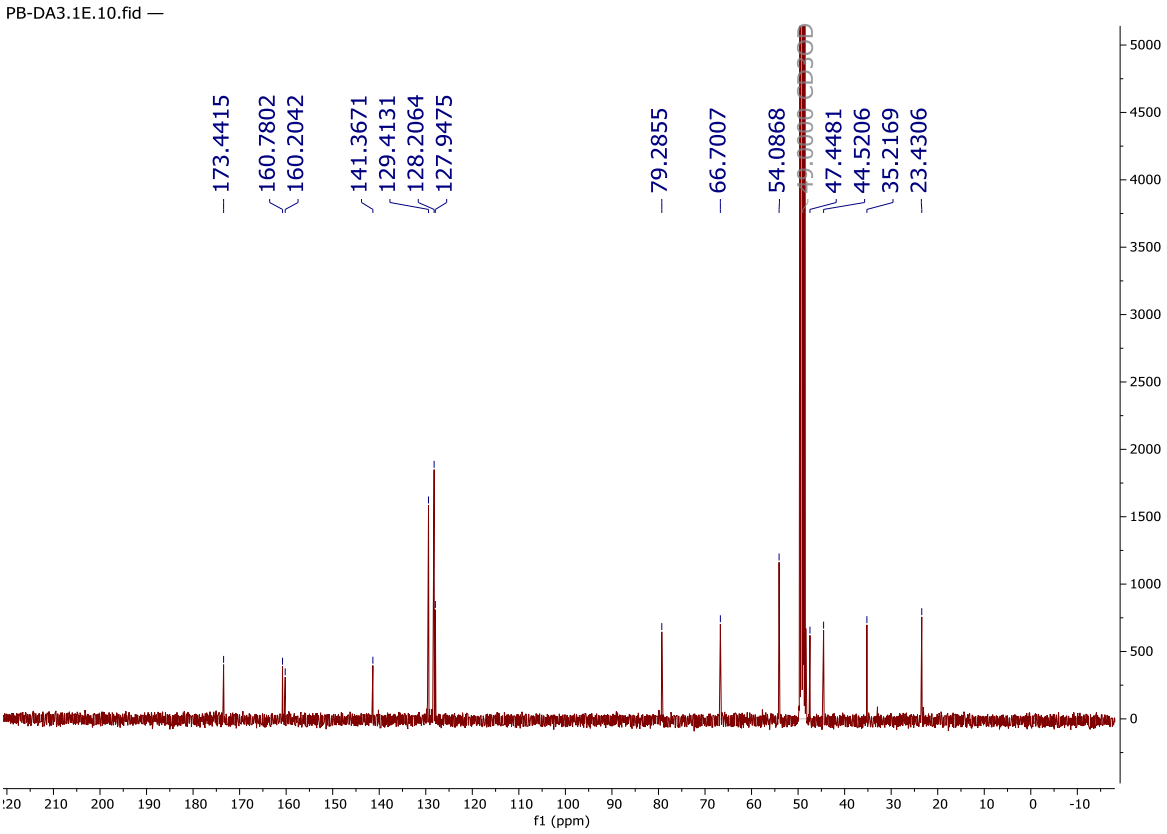
Appendix 4 - ^{1}H NMR spectrum of compound **7** in $CDCl_3$.



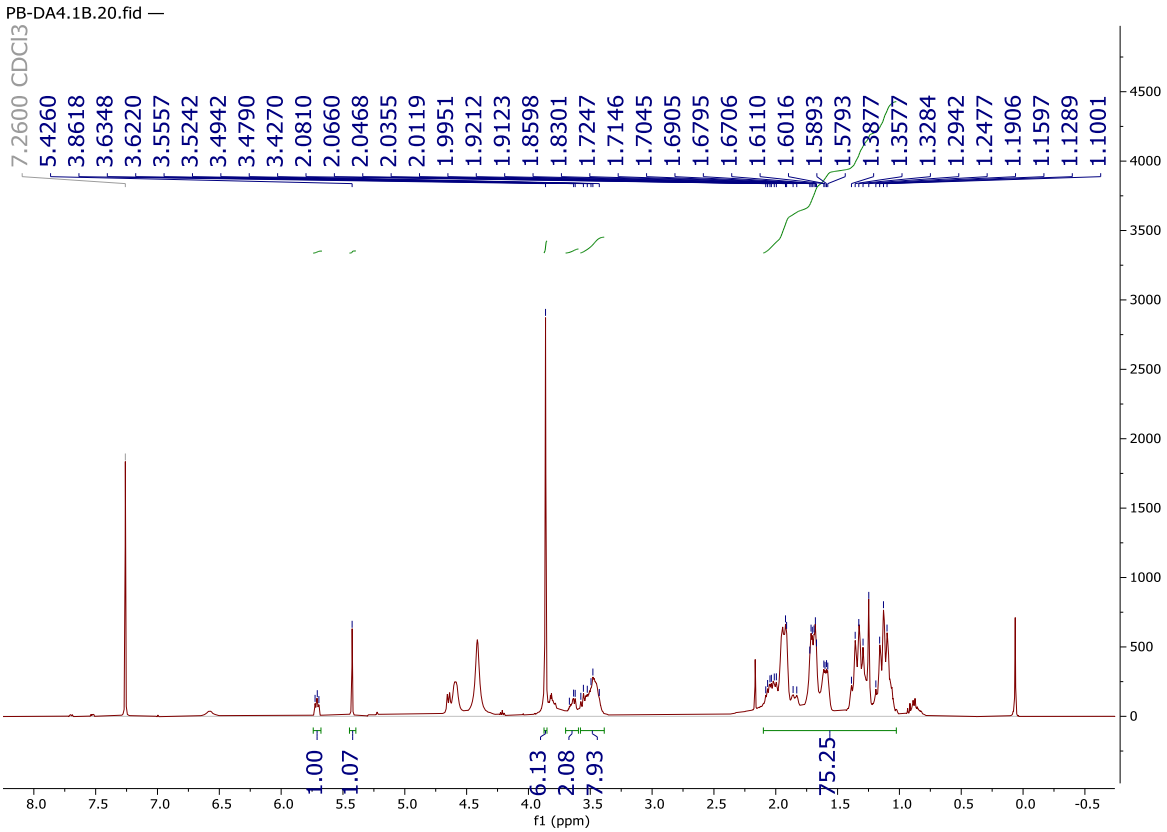
Appendix 5 - ^{1}H NMR spectrum of compound **8** in $CDCl_3$.



Appendix 6 - ^{1}H NMR spectrum of compound **9** in $CDCl_3$.

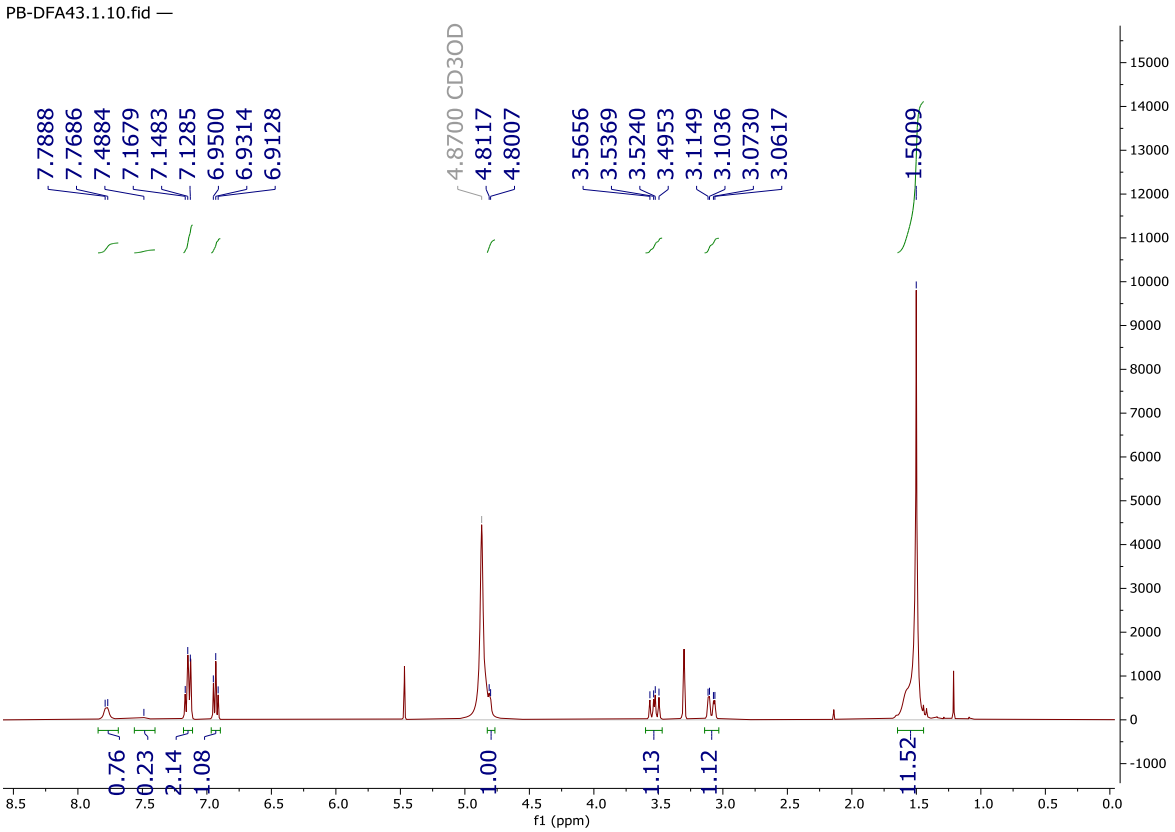


Appendix 7 - ^{13}C NMR spectrum of compound **9** in $CDCl_3$.

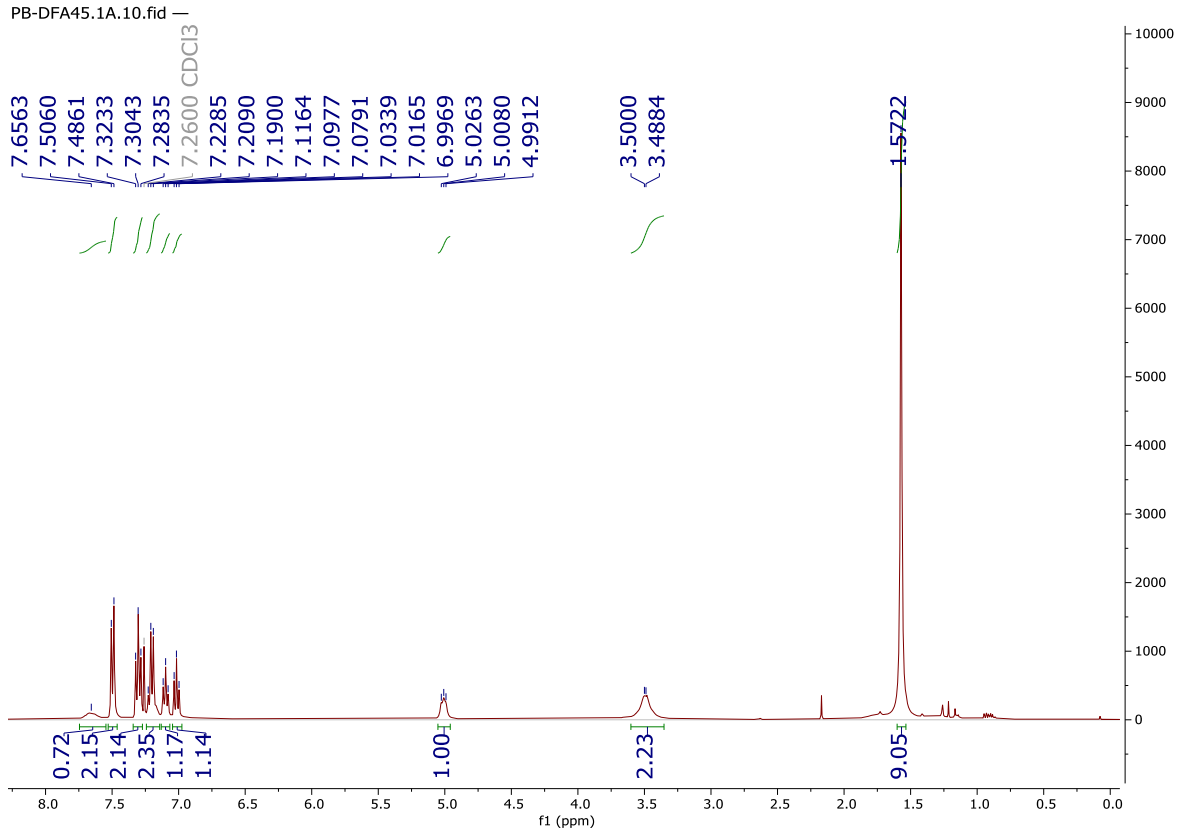


Appendix 8 - ^{1}H NMR spectrum of compound **10** in $CDCl_3$.

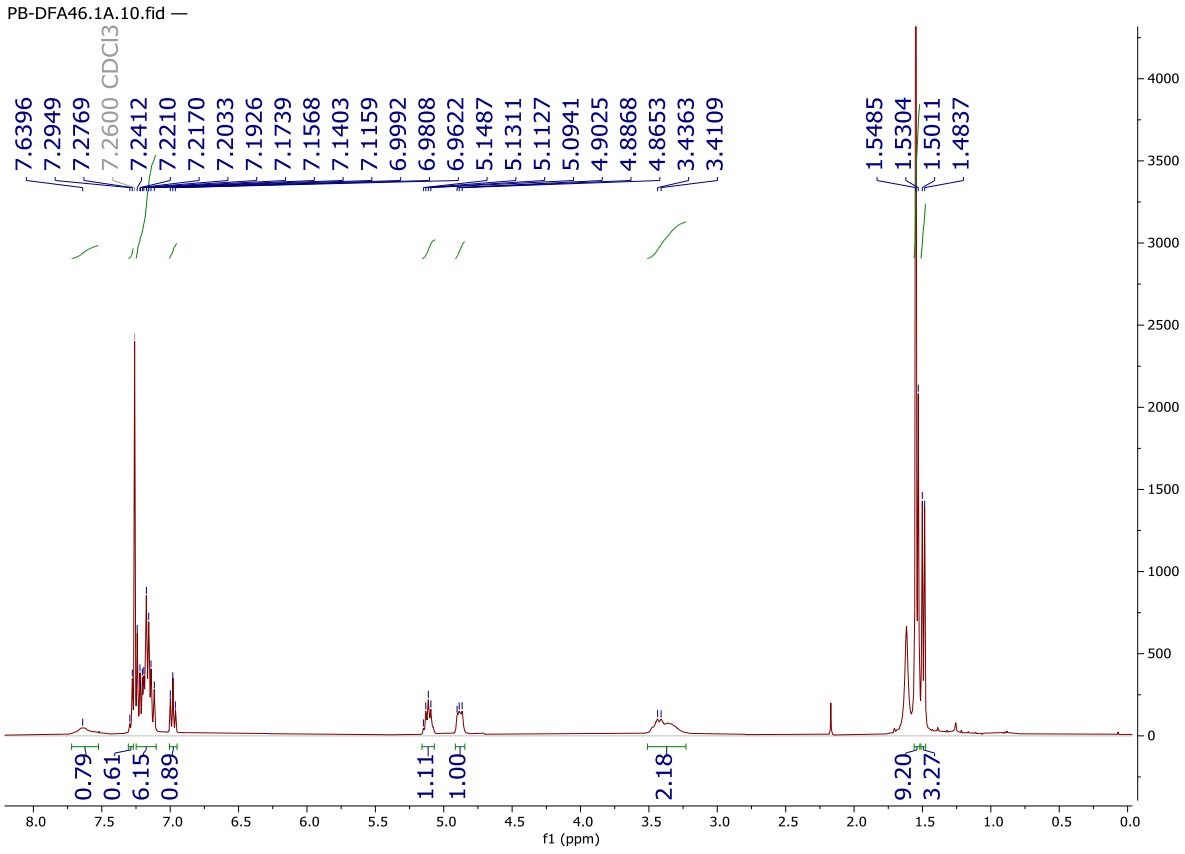
A.2 Synthesis of the guanidine amino-pyrrolidine catalysts



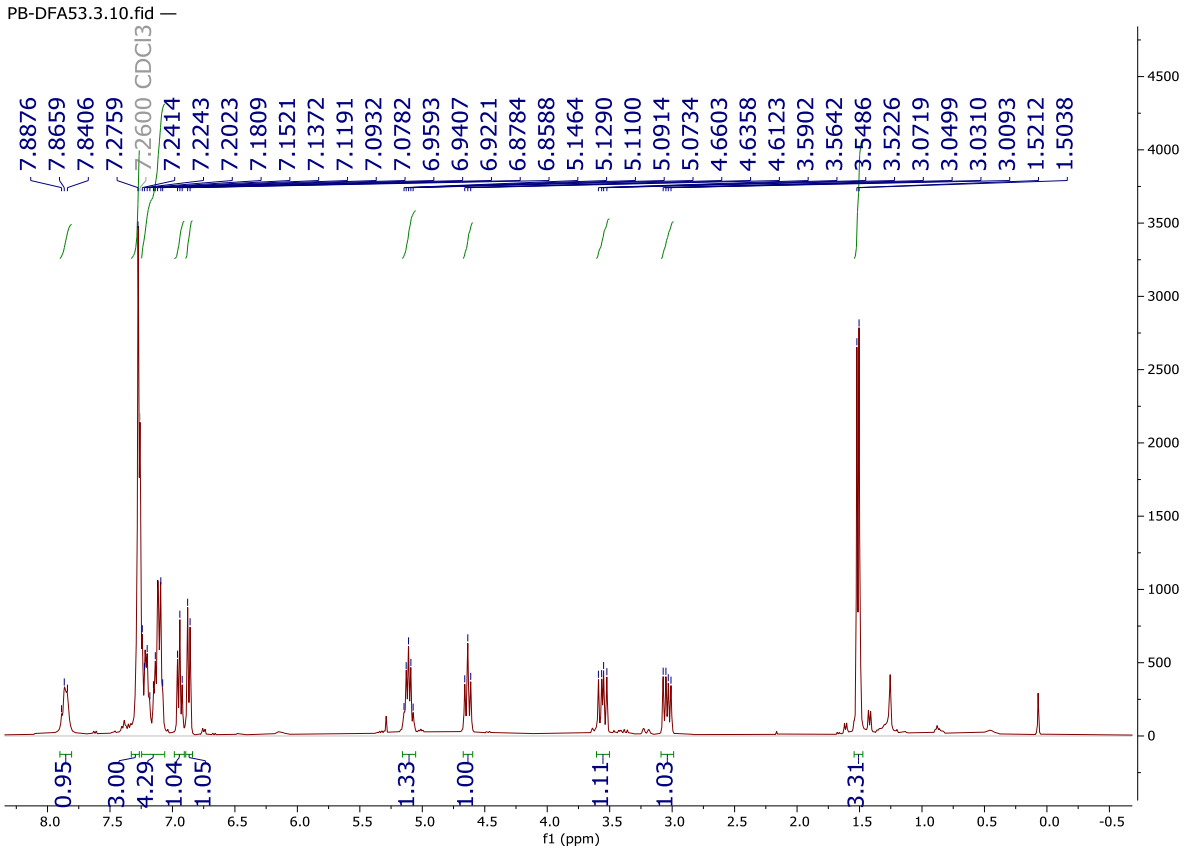
Appendix 9 - ^{1}H NMR spectrum of compound **13** in CD_3OD.



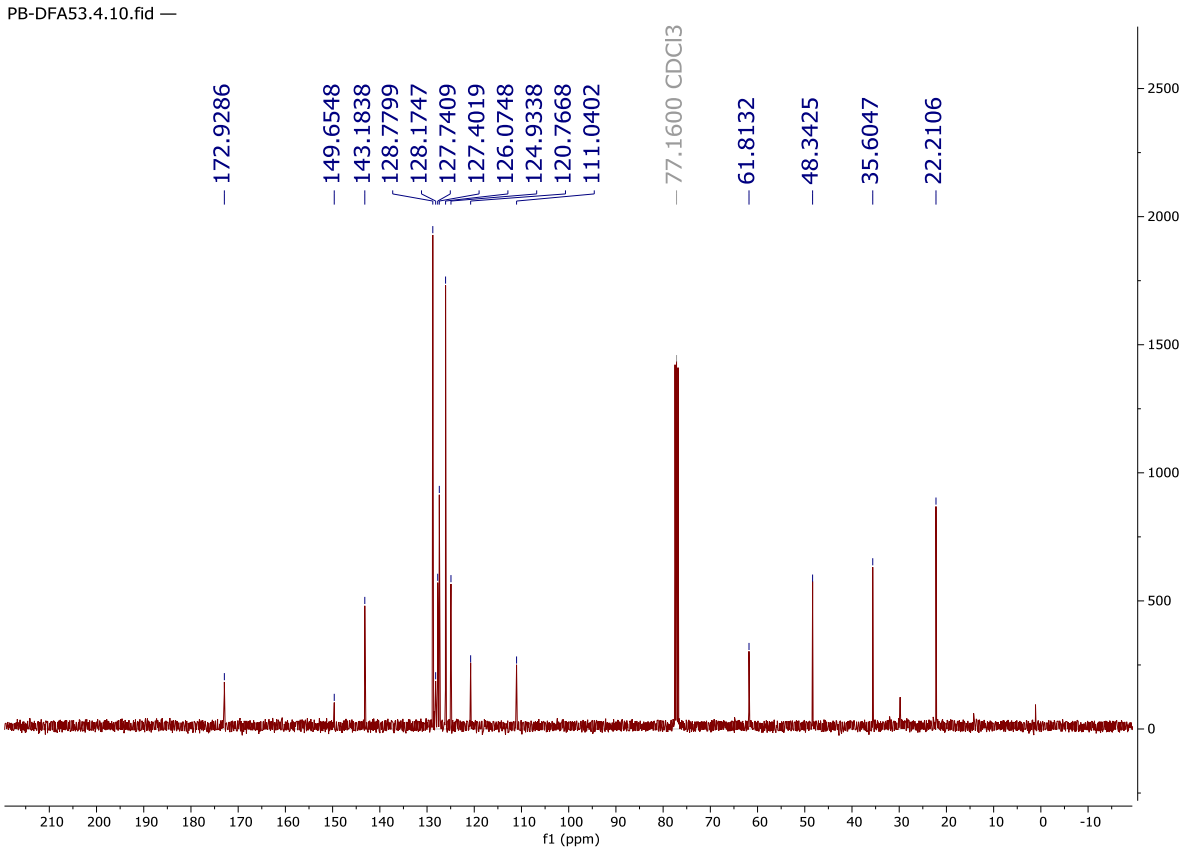
Appendix 10 - ^{1}H NMR spectrum of compound **14** in $CDCl_3$.



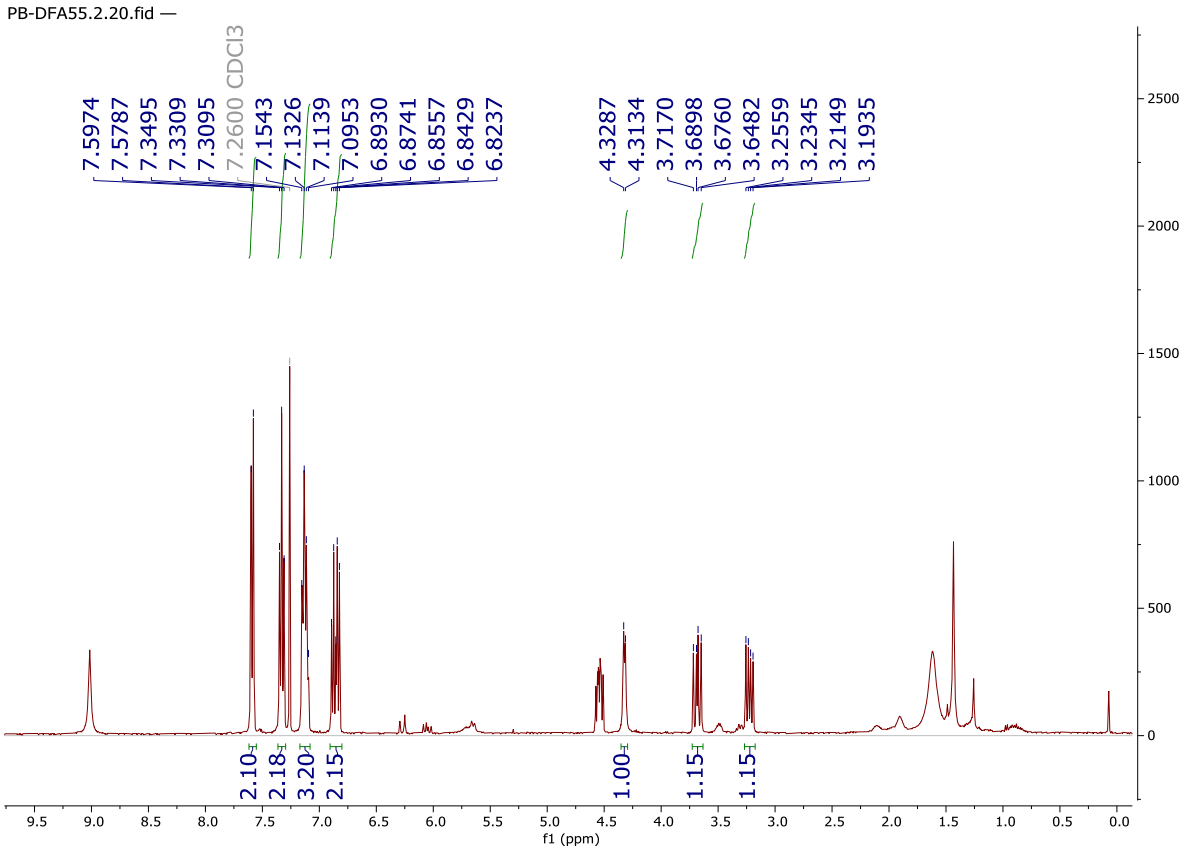
Appendix 11 - ^{1}H NMR spectrum of compound **15** in $CDCl_3$.



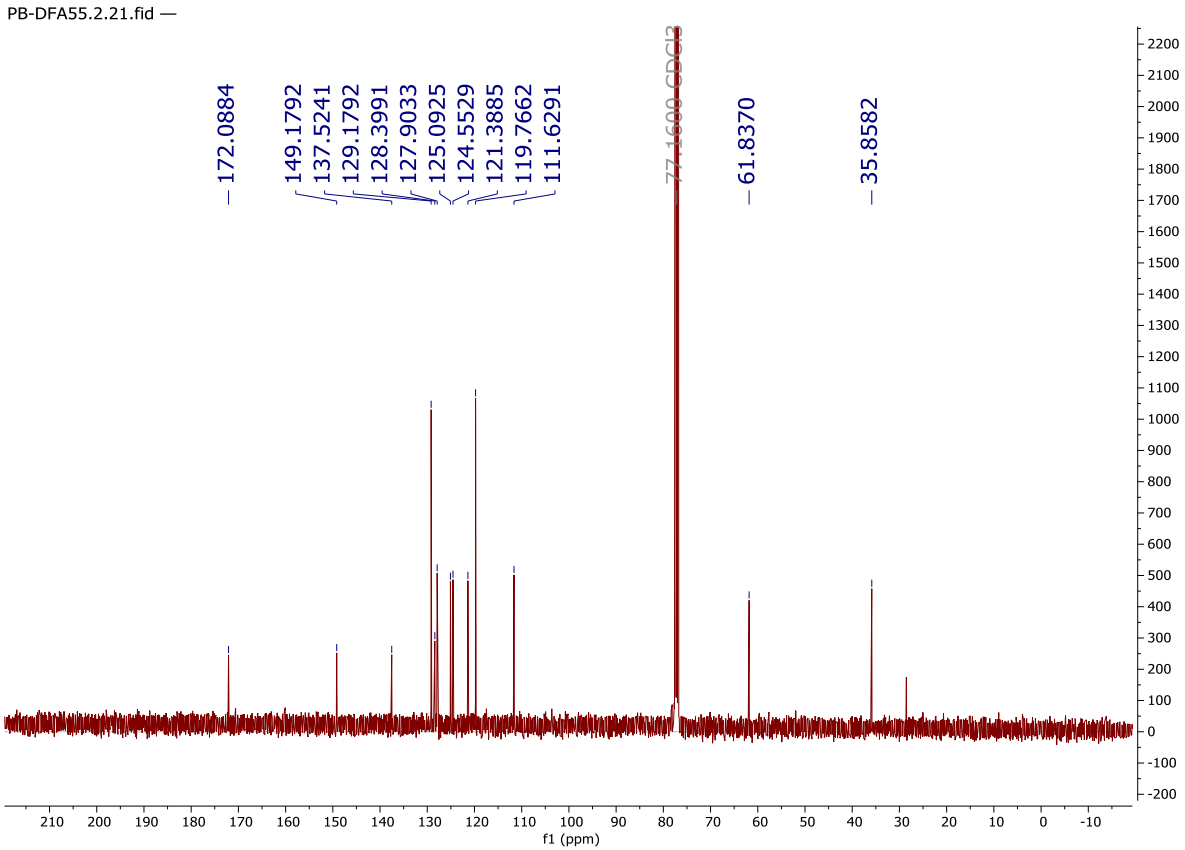
Appendix 12 - ^{1}H NMR spectrum of compound **16** in $CDCl_3$.



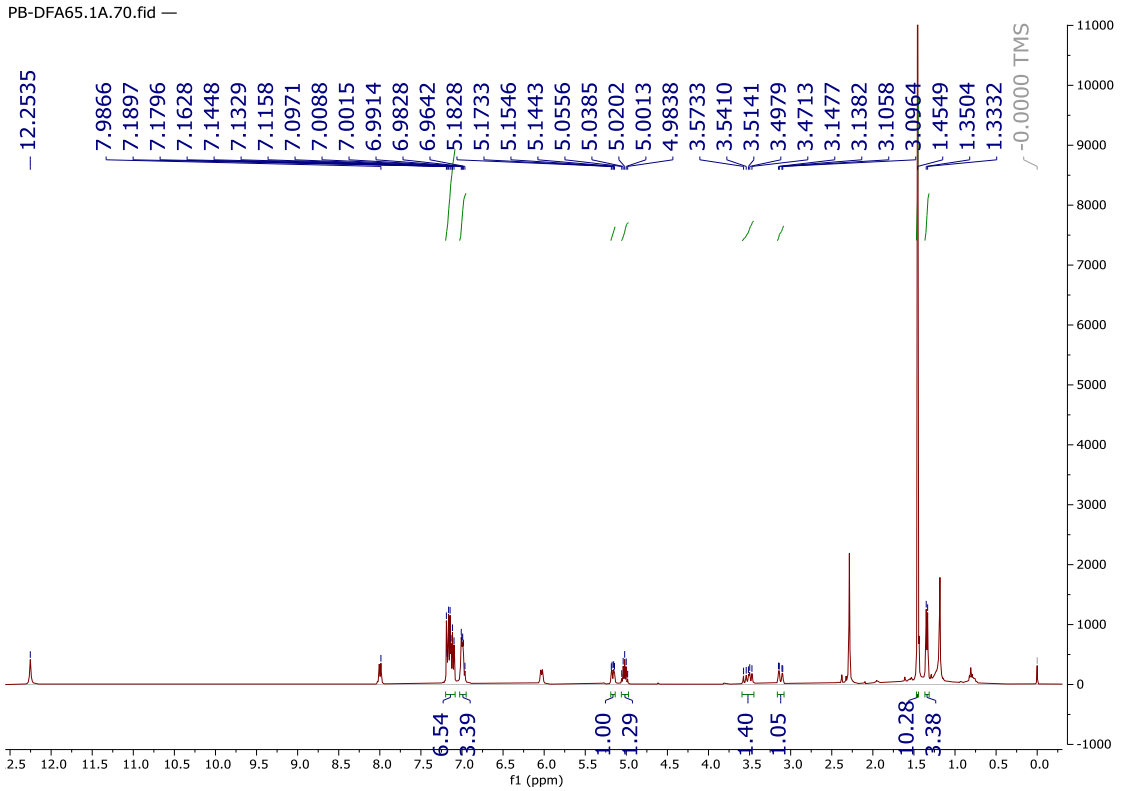
Appendix 13 - ^{13}C NMR spectrum of compound **16** in $CDCl_3$.



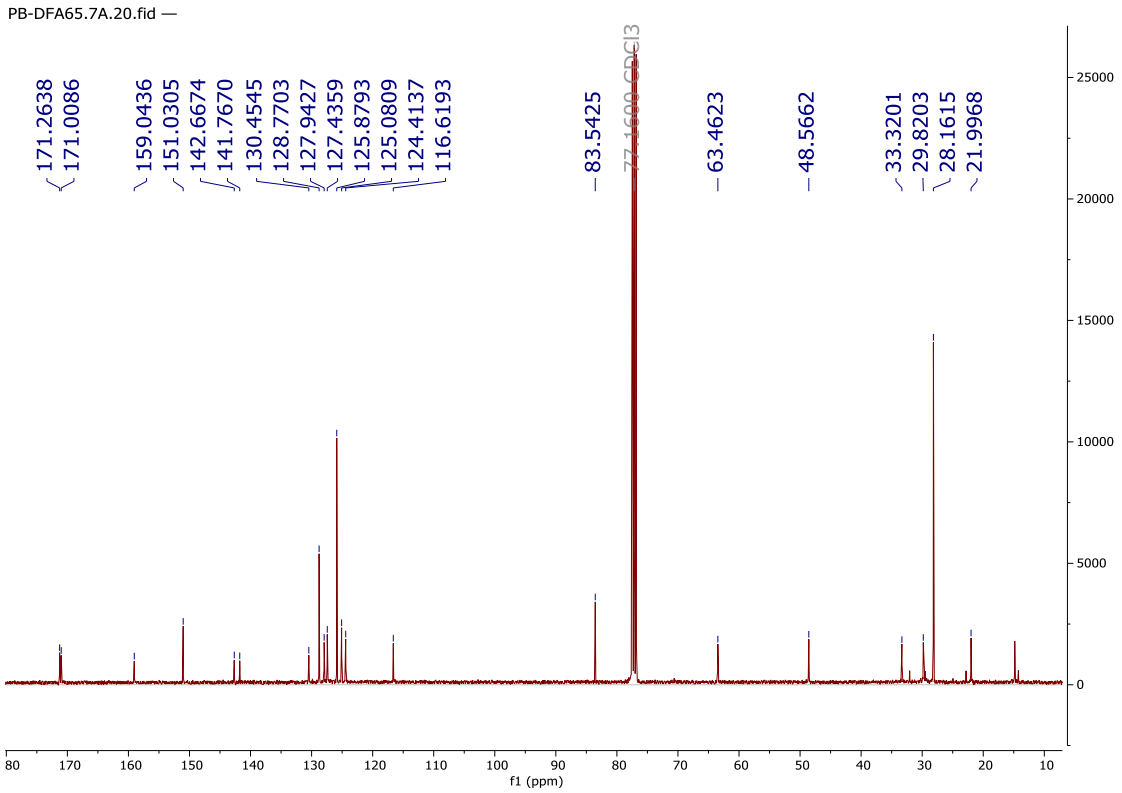
Appendix 14 - ^{1}H NMR spectrum of compound **17** in $CDCl_3$.



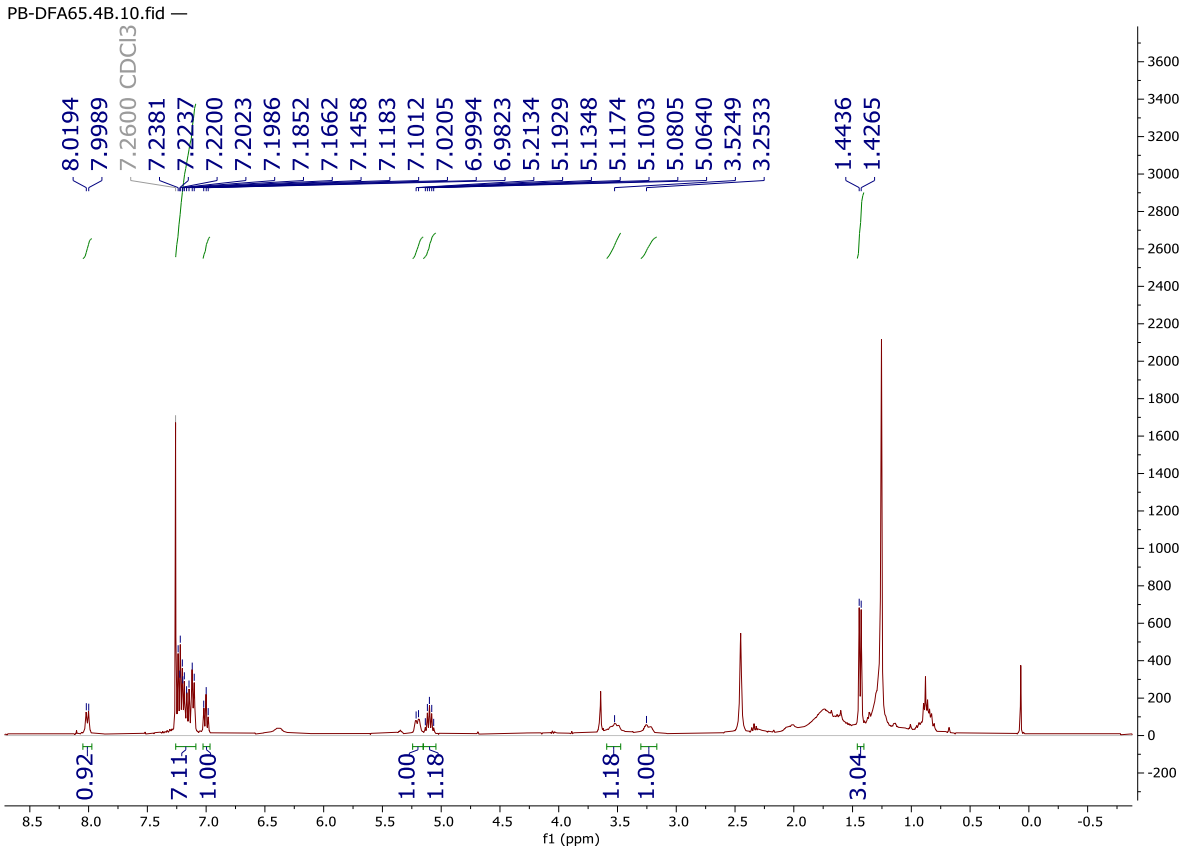
Appendix 15 - ^{13}C NMR spectrum of compound **17** in $CDCl_3$.



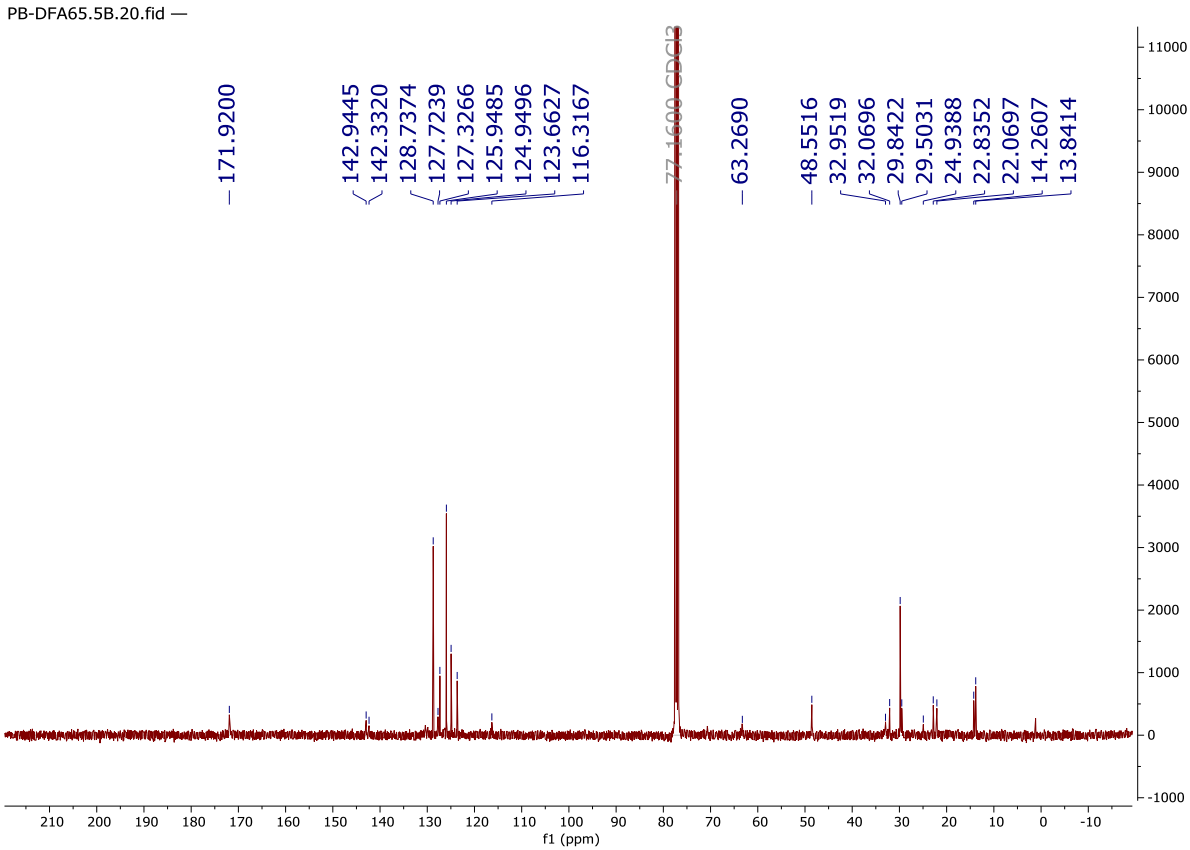
Appendix 16 - ^{1}H NMR spectrum of compound **19** in $CDCl_3$.



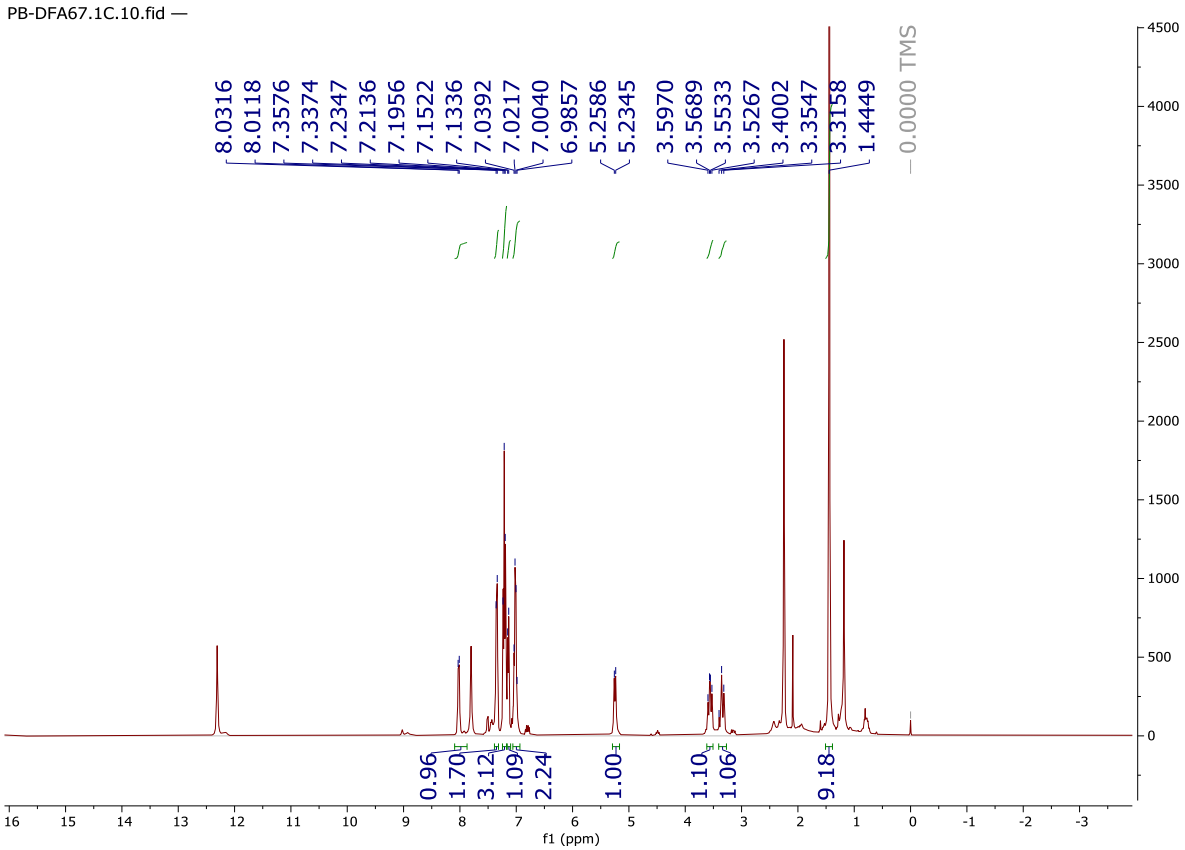
Appendix 17 - ^{13}C NMR spectrum of compound **19** in $CDCl_3$.



Appendix 18 - ^{1}H NMR spectrum of compound **20** in $CDCl_3$.

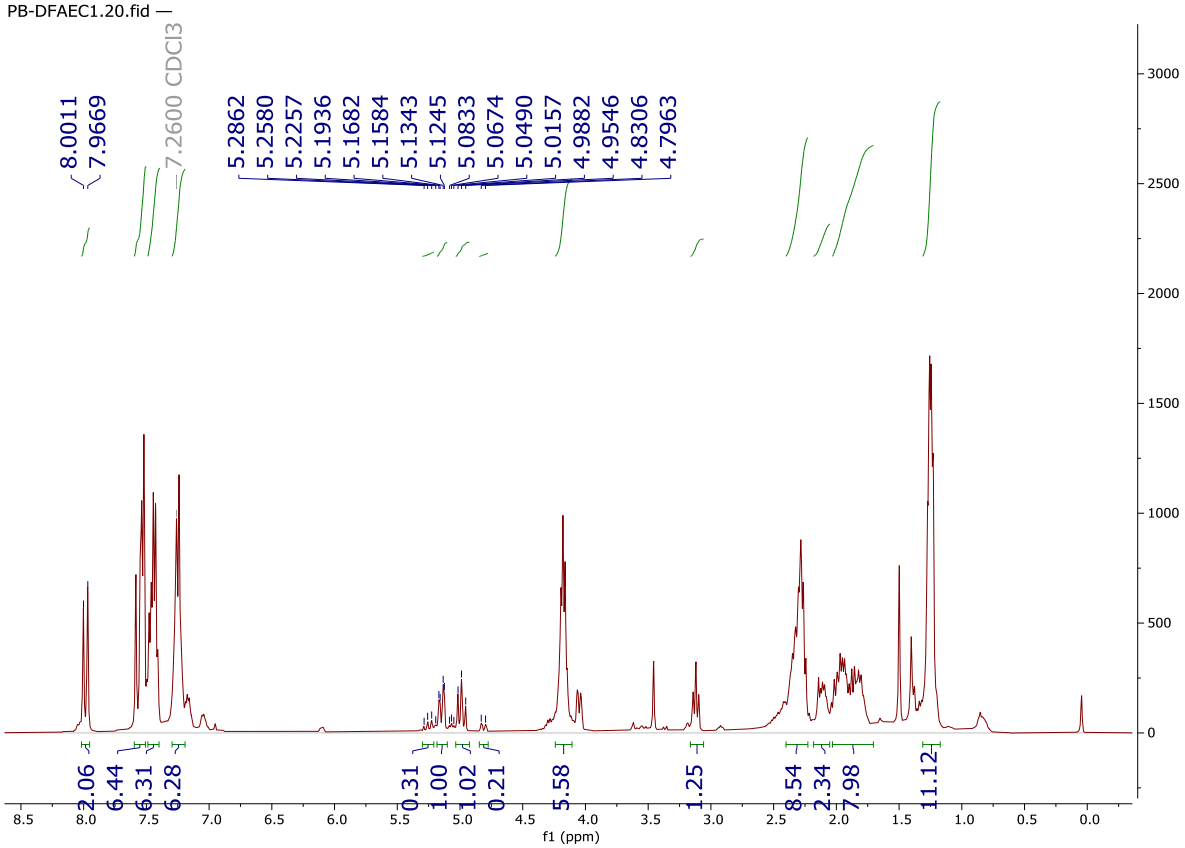


Appendix 19 - ^{13}C NMR spectrum of compound **20** in $CDCl_3$.

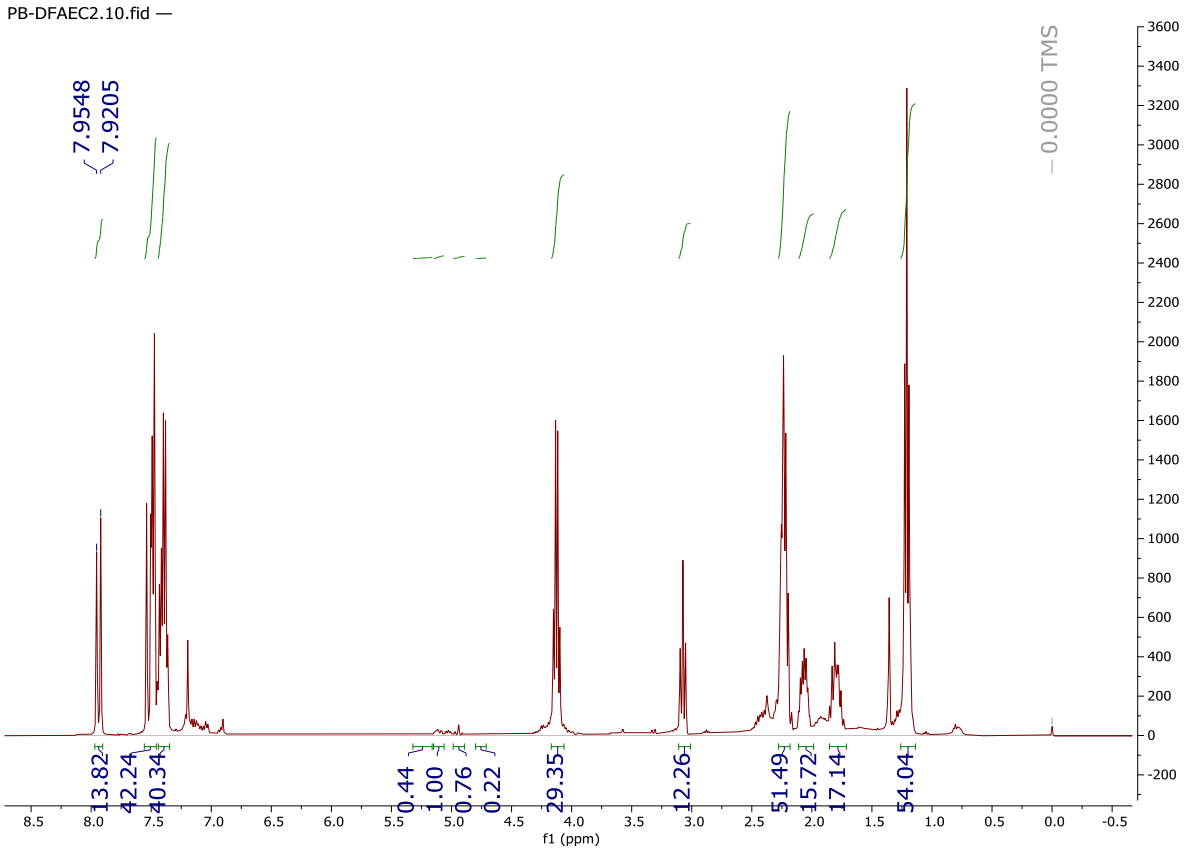


Appendix 20 - ^{1}H NMR spectrum of compound **21** in $CDCl_3$.

A.3 Testing of the synthesized catalysts



Appendix 21 - ^{1}H NMR spectrum of the Michaels addition reaction testing catalyst **19**.



Appendix 22 - ^{1}H NMR spectrum of the Michaels addition reaction testing catalyst **20**.