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THÈSE

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Présentée par

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Intitulée

New Michael and Aza-Michael reactions by asymmetric catalysis to obtain heterocyclic compounds "Pyrazolidine and Isoxazolidine"

Soutenue le : ……..... Devant le Jury composé de :

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Résumé

La synthèse des dérivés de la pyrazolidine et de l'isoxazolidine a attiré l'attention des biologistes et des chimistes pendant de nombreuses années parce qu'ils appartiennent à une classe de composés ayant une utilité réelle dans la chimie médicinale, en relation avec leur activité antimicrobienne, anti-inflammatoire, antioxydant, antidépresseur, antibiotique et anticancéreux. Dans cette thèse, nous avons optimisé des réactions Michael et Aza-Michael avec une synthèse résultante à de nouvelles molécules chirales de pyrazolidines et isoxazolidines substituées. En outre, l'environnement et les réglementations de Green Chemistry sont respectés.

La portée de cette thèse couvre les modèles synthétiques de la pyrazolidine et de l'isoxazolidine et crée une image d'une zone émergente d'organocatalytique. La voie réactionnelle est proposée pour la formation d'intermédiaires d'ions iminium à partir de la réaction de Michael/Aza-Micael entre les amines et α-enals substituées comme des accepteurs de Michael originaux. Nous avons étudié l'utilisation d'aldéhydes insaturés ramifiés en position α avec des chaînes aliphatiques et aromatiques comme des accepteurs nucléophiles de Michael pour 1-Boc-2- (4-nitrobenzènesulfonyl) hydrazine (2a) ou 1, 2-bis (p-toluènesulfonyl) hydrazine (2b) et N-Cbz-hydroxylamine (10), respectivement pour obtenir des dérivés de pyrazolidine et d'isoxasolidine.

Nous avons constaté que la réaction de Michael entre les α-enals substitués, tels que la méthacroléine, le 2-benzylpropenal et le 2-(n-hexyl)propenal avec les hydrazines actives a lieu avec de très bons rendements (83%-99,6%) en conditions très douces, en présence de la pyrrolidine / acide benzoïque pour donner des pyrazolidine-3-ol 4-substitués (sous forme de mélanges de diastéréomères), l'oxydation ultérieure avec le pyridinium chlorochromate (PCC) donne la 3-pyrazolidinone 4-substituée correspondante avec des rendements essentiellement quantitatifs. De manière similaire, des isoxazolidinones 4-substituées sont obtenues avec des rendements excellents de 87% au 93 % en présence de N-Cbz-hydroxylamine comme réactif nucléophile.

En synthèse asymétrique, l'utilisation d'éthers triméthylsilyliques de diarylprolinol chiral comme catalyseur permet la synthèse de plusieurs de ces composés optiquement actifs, dans certains cas avec une énantiosélectivité excellente arrive jusqu'à (96: 4 er).

Mots clés : *Pyrazolidine, Isoxazolidine, Réactions de Michael/Aza-Micael, Synthèse Asymétrique, Molécules Chirales.*

Abstract

The synthesis of pyrazolidine and isoxazolidine derivatives has attracted a great attention of biologists and chemists for many years because they belong to a class of compounds having a genuine usefulness in medicinal chemistry, such as antimicrobial, anti-inflammatory, antioxidant, antidepressant, antibiotic, and anti-cancer. In this thesis, we have optimized Michael and Aza-Michael reactions for the synthesis successively the new chiral molecules of 4-Substituted pyrazolidines and isoxazolidines. Furthermore, in this synthesis environmentally and Green Chemistry regulations are respected.

The scope of this thesis covered the synthetics models of "Pyrazolidine and Isoxazolidine" and creates a picture of an emerging area of asymmetric organocatalysis. A reaction pathway is proposed for the formation of iminium ion intermediates from the Michael reaction of amines with α-substituted enals as original Michael acceptors. We have investigated on the use of α-branched unsaturated aldehydes with aliphatic and aromatic chains as Michael acceptors for activated 1-Boc-2-(4-nitrobenzenesulfonyl) hydrazine (2a) or 1,2-bis (p-toluene sulfonyl) hydrazine (2b) and N-carbonyl (benzyloxy) hydroxylamine (10), respectively for obtaining pyrazolidine and isoxasolidine derivatives.

We found that the Michael reaction between the α-enals substituted, such as the methacrolein, 2-benzylpropenal and 2-(n-hexyl) propenal with activated hydrazines takes place in very good yields (83%–99.6%) under very mild conditions, in the presence of the pyrrolidine/benzoic acid to give 4-substituted pyrazolidin-3-ols (as diastereomer mixtures); subsequent oxidation with pyridinium chlorochromate (PCC) affords the corresponding-4-substituted-3-pyrazolidinones in essentially quantitative yields. Similary, 4-substituted isoxazolidinones are obtained in excellent yields (87% -93%) in the presence of N-Cbz-hydroxylamine as the nucleophilic reagent.

In asymmetric synthesis, use of chiral diarylprolinol trimethylsilyl ethers as catalysts allows the synthesis of several of these compounds in optically active form, in some cases with excellent enantioselectivity (up to 96:4 er).

Key words : *Pyrazolidine, Isoxazolidine, Michael/Aza-Micael Reactions, Asymmetric Synthesis, Chiral Molecules.*

ملخص الاطروحة

جذبت الاعدادات الكيميائية لمشتقات بيرازوليدين وازوقزازولدين انتباه البيولوجيين والكيميائيين الصيادلة لسنوات عديدة لأنها تنتمي إلى فئة من المركبات ذات فائدة حقيقية في الكيمياء الطبية، وفقا الانشطة المضادة للميكروبات، المضادة للالتهابات، المضادة الأكسدة، المضادة للاكتئاب، والمضادات الحيوية بالخص المضادة للسرطان. في هذه الأطروحة، قمنا بدراسة اعدادات كيميائية جديدة توافق على حد سواء اعداد مايكل وازا مايكل بتحضير منتج لجزيئات جديدة نشطة لكل من بيرازوليدين وازوقزازولدين. وبالإضافة إلى ذلك، هذه الاعدادات هي صديقة للبيئة من خلال احترام أنظمة الكيمياء الخضراء.

نطاق هذه الأطروحة يغطي الاعداد الكيمائي لنموذجين بيرازوليدين وازوقزازولدين، اذ يخلق صورة من مساحة الناشئة من التحضير الكيميائي المتسارع ويقترح مسار التفاعل الامنيوم أيون كشكل وسيط من تفاعل مايكل وازا مايكل بين الأمين ومشتقات الألدهيدات الفا، كمستقبلات اصلية لا عدادات مايكل وازا مايكل. لقد درسنا استخدام مشتقات الألدهيدات الفا الغير المشبعة المتشعبة والعطرية مع المركبات النشطة والمحبة لاعدادت مايكل وازا مايكل، خاصة 1-بوك-2-نيترو بنزانسلفونيل هيدرازين(I_2)، ثنائي بوكتوليان سلفونيل هيدرازين (ب $_2$) وازوت بنزيل هيدروكسي امين (10) على التوالي للحصول على المشتقات بيرازوليدين وازوقزازولدين.

وجدنا أن اعدادات مايكل كان لها رد ايجابي مع الألدهيدات الفا الغير المشبعة المتشعبة والعطرية خاصة ميتاكرولين، 2-بنزيلبروبنال وانهكزيل بروبنال مع الهيد رازين النشط بمردودات جيدة جدا تتراوح بين (83٪ -99.6 ٪) في ظروف معتدلة جدا في ظل وجود مجموعة المحفز الكيميائي بيروليدين / حمض البنزويك منحت فرصة الحصول على 3-بيرازوليدين مشعب عند 4 (في شكل خليط مقابل غير ضوئي)، والأكسدة لاحقة مع وجود مركب الاكسدة بيريلينيوم كلورو كرومات يعطي 3-بيرازوليدينون الموافقة دات تشعب عند 4 بعائدات كمية أساسا. وبالمثل، يتم الحصول على 3-ازوقزازولدينون مع عوائد ممتازة تتراوح بين (87٪ -93٪) بوجود ازوت بنزيل هيدروكسي امين (10) على شكل نواة محبة للتفاعل. في الاعدادات الغير متماثلة، واستخدام ثلاثي ميثيل سليل دياريلبرولين الاستر كمحفز كيميائي، افزا التفاعل على الحصول على العديد من هذه المركبات في شكل نشط ضوئيا، في بعض الحالات تصل جملة المركبات المميزة بنسبة تميز تصل (96: 4) للمركب الرئيسي.

الكلمات الدالة: بيرازوليدين، ازوقزازولدين، تفاعلات مايكل وازا مايكل، الاعدادات الغير متماثلة، جزيئات متناظرة.

Dedicate

To my mother, my father's memory and my wife.

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List of figures

List of tables

List of Schemes

List of abbreviations

F.D.A: Food and Drug Administration

DMSO: Dimethyl Sulfoxide

TFA: Trifluoroacetic acid

DCM: Dichloromethane

N-Boc: N-Tert-butoxycarbonyl

N-Cbz : N-Carbonyl Benzyloxy

Ns: Nitrobenzenesulfonyl

Ts: Toluene sulfonyl

PDC: Pyridinium dichromate

PCC: Pyridinium chlorochromate

HPLC: High-Performance Liquid Chromatography

HRMS: High-resolution mass spectrometry:

ESI-TOF: Electrospray ionisation time-of-flight mass spectrometry

NMR (^{1}H, ^{13}C): Nuclear Magnetic Resonance (1H NMR and 13C NMR)

Jørgensen catalysts: ((*S*)-diphenylprolinol trimethylsilyl ether) or ((*S*)-bis(3,5-trifluoromethylphenyl)prolinol trimethylsilyl ether)

Table of Contents

Chapter II: Pyrazolidine and Isoxazolidine Compounds

Chapter III: Section of Results and Discussion

Chapter IV: Experimental Section

Introduction

Introduction

Since Nature has provided a wide variety of chiral materials, they are obvious and usually inexpensive sources to generate new chiral auxiliaries as well as novel chiral compounds by asymmetric catalysis. The practical importance of asymmetric synthesis as a tool to obtain enantionmerically pure or enriched compounds has been fully recognized to date by chemists. Organic synthesis chemistry, medicinal chemistry, agriculture chemistry, naturel products, and pharmaceutical and Agricultures industries [1–3], approved the recommendation of F.D.A in 1992 the U.S about an encouraging the commercialisation of clinical drugs as single enantiomers [1–3].

In the present thesis, we concentrated on the asymmetric synthesis to prepare chiral compounds " Pyrazolidine and Isoxazolidine" by new Michael and Aza-Michael reactions as two of the most fundamental reactions in organic chemistry widely employed for the synthesis of bioactive molecules [4].

The pyrazolidine (pyrazolidin-3-one) moiety is an important structural motif that can be found both in natural products and in synthetic compounds with interesting pharmacological activities (analgesic, antibiotic, anticonvulsant, and with inhibitory cyclooxygenase, lipoxygenase, and γ-aminobutyrate transferase activity, among others) [5–14]. On the other hand, the selective oxidation of pyrazolidinones affords the corresponding pyrazolones (pyrazol-5-ones), a class of compounds that also exhibits very relevant pharmacological properties [15–22].

The isoxazolidine ring represents one of the privileged structures in medicinal chemistry. In particular, Isoxazolidinone have proven to be particularly useful synthetic intermediates for a variety of natural products including (alkaloids, β-amino acids, β-lactams, and aminosugars), unnatural biologically and medicinally important congeners [23–28]. To their importance in the both organic and medicinal chemistry with interest's applications in pharmaceutical industry [1–3], this thesis describes the preparation of Pyrazolidinone and Isoxazolidinone.

The first chapter gives an overview of asymmetric synthesis, state-of-the-art catalysis and the scope of Michael reaction as a tool for the modern chemist.

Reactions are discussed in terms of the catalytic mechanism and a selection of reactions catalysed by each route is included.

The second chapter discusses the design of two generations "Pyrazolidine and Isoxazolidine" as chiral components through important scientific work carried out over the last years, which are based on both reaction of Michael and Aza-Michael.

In the third chapter, included tow section experimental and practical section, were successfully discussed, prepared and characterised by a combination of NMR spectroscopy, HRMS and HPLC chiral separation of all new compounds described in this thesis.

Finally, a complete conclusion and bibliography of articles referred to in this thesis is included for each part.

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Bibliography part

Chapter I
Asymmetric aminocatalysis and Michael Reaction

I.1 Asymmetric Catalysis

The value of asymmetric catalysis to organic synthesis reflected in the awarding of the Nobel Prize in 2001 to *William S. Knowles*, *Ryoji Noyori*, and *K. Barry* Sharpless [1-3]. In a time when the pathway to chiral compounds involved biochemical processes or the synthesis of racemic compounds followed by laborious resolution, these laureates have shown that with a catalytic system comprising chiral ligands bound to metals a diverse range of organic transformations and industrial processes could be conducted with high levels of selectivity [4-8]. In 1992, the U.S. F.D.A issued a policy on stereo-isomeric drugs encouraging the commercialisation of clinical drugs in the form of optically compounds. From an economic standpoint, the synthesis of enantiomerically pure compounds minimises the losses incurred from making racemic compounds. In 2006, 80% of small drugs approved by the F.D.A with 75% of there are chiral and single enantiomers, for this reason, the space of organocatalysis has received much attention proven by the papers, books and reviews has been published in the area of asymmetric catalysis [9-11].

I.2 Organocatalysis

A goal in organic chemistry is to develop new and efficient methods to construct carbon-carbon and carbon-heteroatom bonds with complete control of the stereochemistry of the reaction. Chiral auxiliaries have partially solved this problem, but this approach requires a stoichiometric amount of the auxiliary and additional steps to remove and introduce the chiral unit [12]. The use of catalytic amounts of a catalyst, to obtain optically active molecules with one or more asymmetrical centres, is of utmost importance in organic synthesis. Organocatalysis fulfils these requirements and is today considered a field of central interest for the synthesis of chiral compounds [8, 13]. New and highly efficient ways of substrate activation have been achieved using simple chiral organic molecules that can now deliver unique and complementary selectivities to catalyzed processes. In addition, it offers some attractive benefits: The organocatalysis are generally nontoxic, readily available, and stable. These properties allow most reactions to be performed in wet solvent and in air, which

increases the reproducibility and operational simplicity. These methods allow the researcher to devise new multicomponent tandem sequences for the synthesis of useful building blocks and complex natural products [14].

Asymmetric organocatalysis is impressive because of its synthetic utility and because it gained its prominent role in such a short period from 2000 to now. Although it was known for a long time that chiral small organic molecules were able to promote different transformations in a stereoselective fashion, it was not until two seminal reports by List, Lerner and Barbas and MacMillan [8, 13, 15] and co-workers on catalysis by chiral secondary amines [16] that the potential of this approach was realized. Following these publications, numerous high quality studies on catalysis by chiral secondary amines or asymmetric aminocatalysis were reported [17]. This was quickly extended to different organocatalytic activation concepts [14, 18-19] and the "asymmetric aminocatalysis" was on.

The "asymmetric aminocatalysis» was started by a few leading research groups. Now, thousands of researchers from academia and the chemical industry are involved in this field, figure I-1[17, 20]. As a result, new ideas, new approaches, and creative thinking have flowed freely, substantially raising the level of quality.

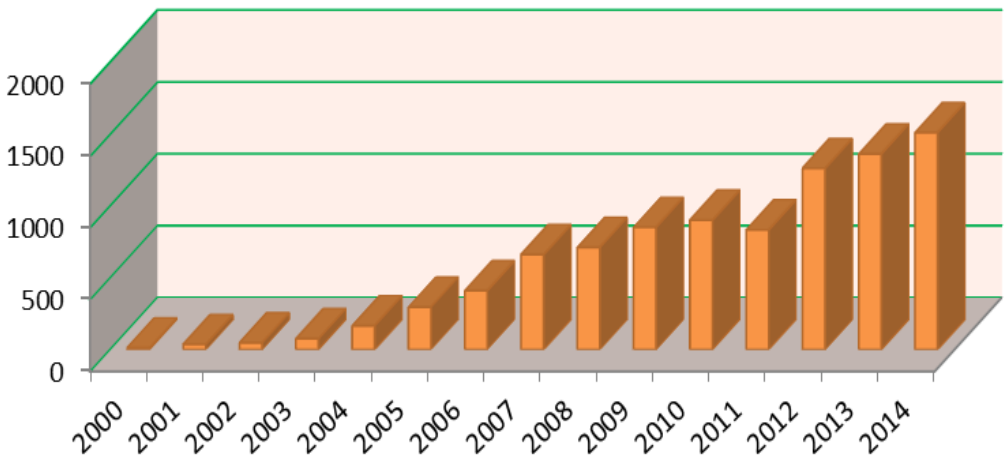
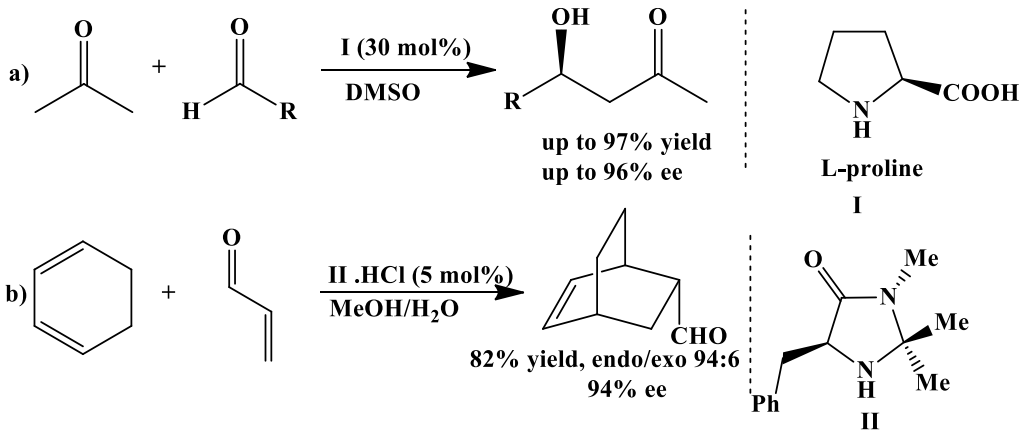


Figure I- 2. Numbre of the articles publised on organocatalysis source Scifinder scolar, the numbre has been calculeted until december 15th,2014.

This area of asymmetric amino catalysis give author excellent levels of development and opened up new synthetic opportunities that were considered inaccessible only a few years before. This "amino catalysis" emphasizes an important aspect of asymmetric chemistry.

I.3 Asymmetric Aminocatalysis

In 2000, two reports established the possibility of employing simple, chiral cyclic secondary amines to efficiently catalyze the asymmetric functionalization of carbonyl compounds. List, Lerner, and Barbas reported that a catalytic amount of the proteinogenic amino acid L-proline (I) was able to promote the enantioselective direct aldol reaction between an unmodified ketone, such as acetone, and a variety of aldehydes, scheme I-1a [21]. Soon after this publication, Mac-Millan and co-workers described the first amine-catalyzed asymmetric Diels–Alder reaction, and demonstrated the effectiveness of the newly designed imidazolidinone catalyst (II) in the activation of *α, β*- unsaturated ketone, scheme I-1b [22].



Scheme I-1. a) Proline –catalyst intermolecular aldol reaction beteen acetone donor and aldehydes acceptor II catalyzed asymmetric, b) Imidazolidinone II catalyzed asymmetric Deils-Alder reaction.

The pioneristic works of List, Lerner and Barbas and MacMillan Ahrendt and Borths, besides offering asymmetric and catalytic alternative methodologies at two fundamental C-C bond forming reaction, constituted the basis at two novel organocatalytic activation modes of carbonyl compounds, pinpointing the origin

of asymmetric aminocatalysis. In fact afterwards it was understood that it was possible to design an unlimited number of new reactions just using various electrophiles and nucleophiles for the functionalization of saturated ketones, aldehydes and enals en the presence of *(L)*-Proline as inducer of chirality, figure I-2 [23].

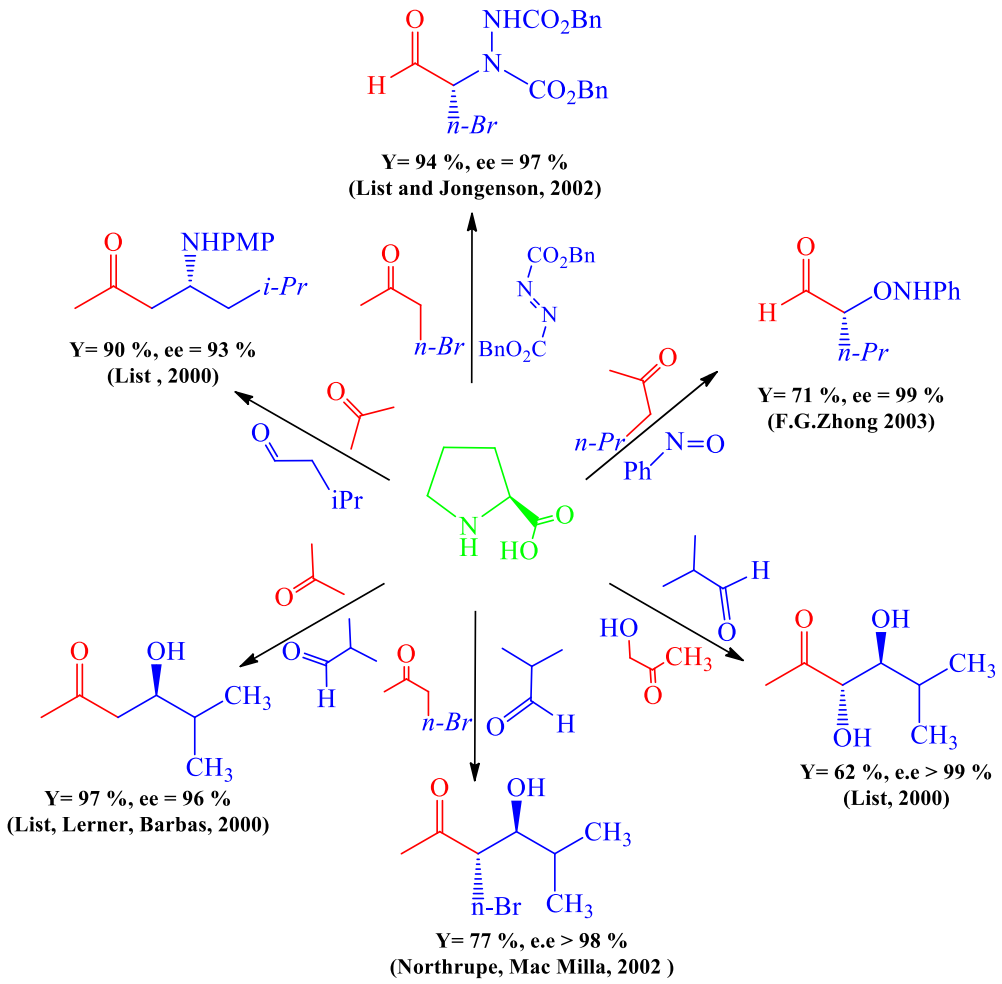


Figure I-2. A summary of the reaction catalyzed by *L*-proline published in the last decades.

In the recent years, the Asymmetric aminocatalysis with activation as enamines and iminium ions has resulted in a number of highly chemo and stereo selective α- and β- functionalizations of carbonyl compounds with electrophilic and nucleophilic reagents, respectively. The Michael addition is a particularly interesting reaction because induction proline may proceed by both

organocatalytic activation modes of carbonyl compounds of enamine and iminium catalysis [24]. The remainder of this chapter aims to give an overview of the scope of Aza-Micael /Michael reactions as tools for the modern synthetic of amino catalysis with different activation modes. The reactions discussed in terms of the catalytic mechanism and classified as follows:

(i) Amine Catalysis Involving Enamine Activation;

(ii) Amine Catalysis Involving Iminium Activation;

(iii) Amine Catalysis Involving Enamine and Iminium Activation.

For each activating mechanism, a basic background and description is included together with a selection of reactions that have catalysed by that particular route.

I.4 Amine Catalysis Involving Enamine Activation

I.4.1 Enamine Catalysis

Enamine catalysis described the catalysis, by primary or secondary amines, of electrophilic substitution reactions at the position of α-carbonyl compounds [25]. It has three historic roots [17]. The first is the chemistry developed by Stork and others, which outlines the general utility of enamines as nucleophiles in organic synthesis [15a-c, 18a-c]. The second is biochemical, with aldolases exploiting enamine catalysis as an approach to carbon-carbon bond-formation [26]. The third and final pillar of enamine catalysis builds on the Hajos-Parrish [19a] and Weichert [19b] explosive growth and there are a number of excellent reviews in this area [7, 8, 25, 17, 28-32, 13d]. The author has endeavoured to select a variety of synthetic transformations to demonstrate the power of enamine catalysis. The key to enamine catalysis is the increase in the nucleophilicity that ensues from the conversion of the carbonyl substrate to the enamine. This transformation results in an increase in the energy of the HOMO and is comparable to Lewis acid activation of carbonyl substrates in presence of (S)-proline catalyst, figures I-3, I-4a and I-4b.

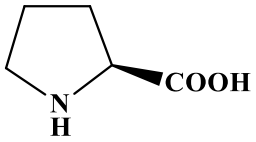


Figure I- 3. (S)-proline catalyst, (I).

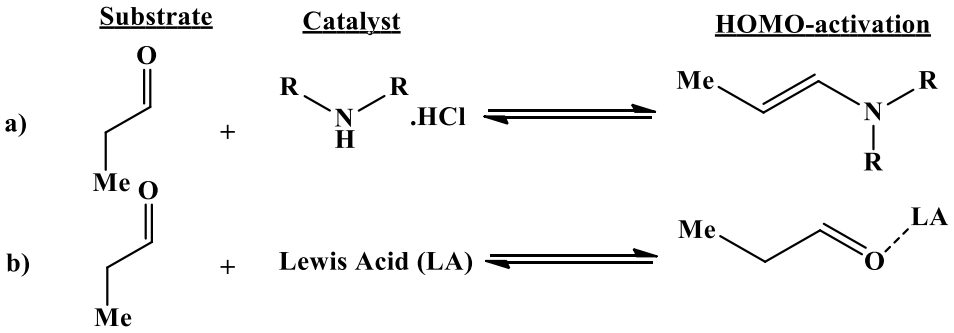


Figure I-4. Carbonyl groupe HOMO activation (a) by primary or secondry amine organocatalysts and (b) by lewis acids.

In this enamine catalysis area, we found one of the most important reactions in asymmetric synthesis "Michael reaction", which is based on the formation of the C-C and heteroatom bonds by the conjugated addition of electrophilic reagents to the *α, β*-unsaturated carbonyl compounds in the presence of chiral amine catalyst for the design of new families of chiral compounds [25, 33].

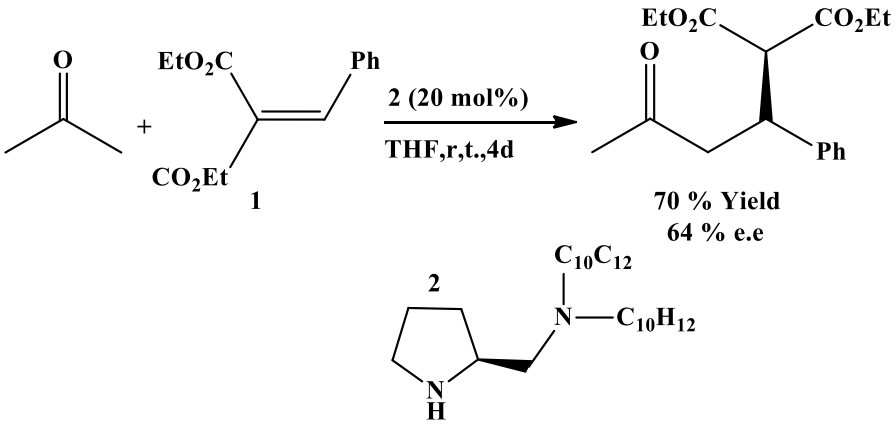
I.4.2 Enamine Catalysis of Michael Reactions

I.4.2.1 Introduction

Michael addition reaction subjected to formation of C-C bond formation by conjugate addition of nucleophiles to *α, β*-unsaturated carbonyl compounds. She is an important reaction in organic synthesis, versions of this reaction first reported in the 1900's involved catalysis by metalloprolinates [34-37]. This type of Michael addition chemistry with enamine catalysis has continued to be an active area of research and made recent significant contributions for the catalysis, which a few examples are included in the following section.

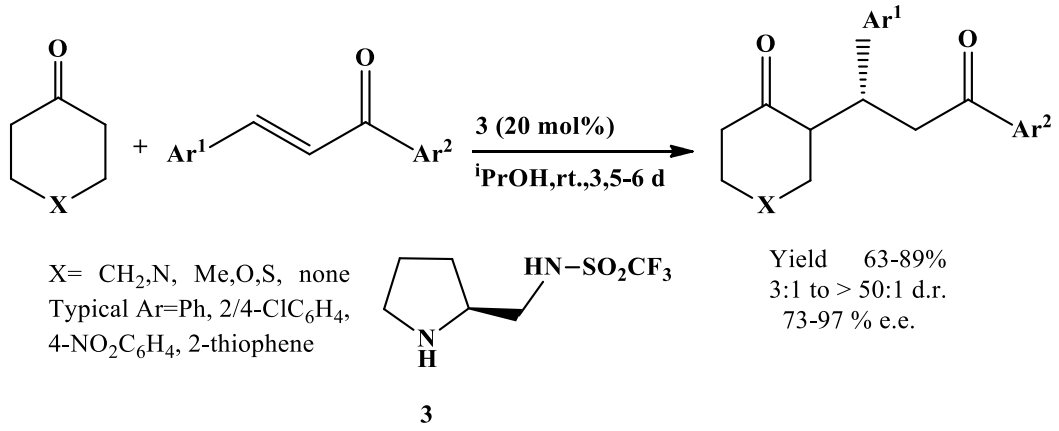
I.4.2.2 α, β-Unsaturated carbonyl substrates as Michael acceptors

Barbas and co-workers [38] adopted the addition of acetone to the highly activated Michael acceptor diethyl benzalmalonate, 1, in DMSO as a model addition reaction. (*S*)-Proline (*2*) found to catalyse the reaction; however, the product obtained in racemic form. Varieties of chiral amines subsequently screened in search of stereoselectivity and the hydrophobic diamine **2** was found to be the catalyst of choice yielding the product in 70% yield and with 64% ee, scheme I-2.



Scheme I-2. Organocatalysed Michael addition reaction between acetone and diethylbenzalmalonate.

Chiral diamines (3) have also been found to be optimal catalysts at the Michael addition of cyclic ketones to *α, β*-unsaturated ketones [39]. As shown in scheme I-3, the proline sulfonamide 3 promoted the formation of the 1, 5-dicarbonyl addition product with a high degree of stereoselectivity (>40:1 d.r. and up to 97% e.e.). Best results were observed for cyclic six-membered ketones and structural variation of the, *α, β*-unsaturated ketones was tolerated without affecting the stereoselection.



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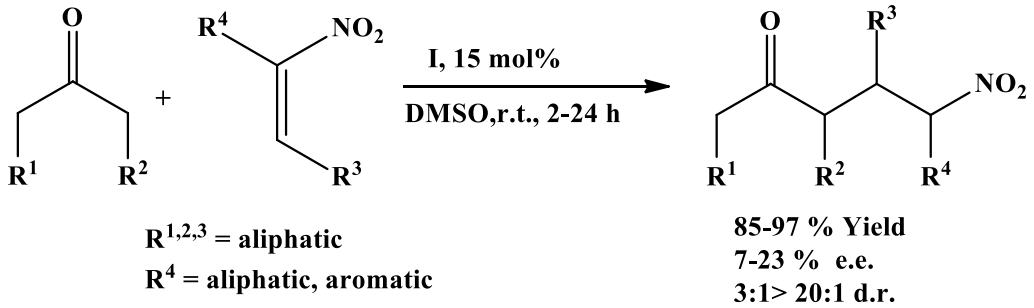
Scheme I-3. Organocatalyzed Michael addition of cyclic ketones to α, β unsaturated Ketones.

I.4.2.3 Nitro olefins as Michael acceptors

Indeed, List and al [40] as well as Barbas and co-workers [41] independently demonstrated that intermolecular Michael reactions between ketones and nitroolefins were also catalysed by (S)-proline (I), scheme I-4 [42].



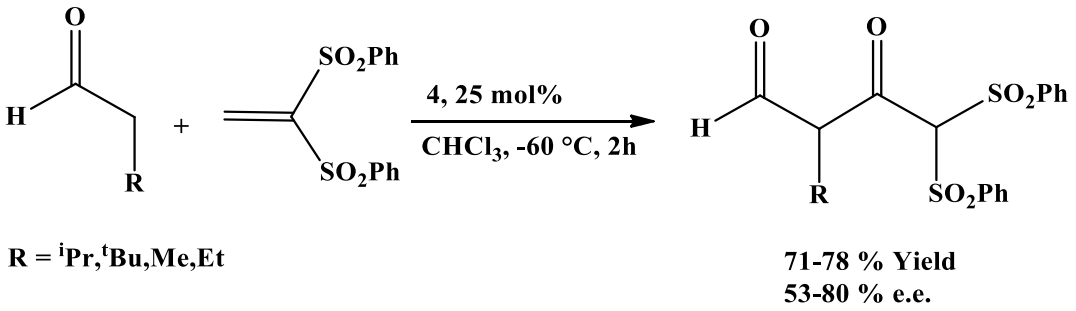
Scheme I-4. Intermolecular Michael reaction between Ketones and nitroolefins catalysed by (S)-proline.

Although the resulting γ-nitroketones are produced with low enantioselectivity, diastereoselectivity and yields were high. Protic solvents are most commonly used in proline-catalysed reactions thus it was anticipated that replacement of DMSO with an alcohol might increase the amount of dissolved proline and so promote the reaction. Accordingly, in methanol the selectivity were increased to 76% e.e. and up to 65:1 d.r [43].

I.4.2.4 Vinyl sulfones as Michael acceptors

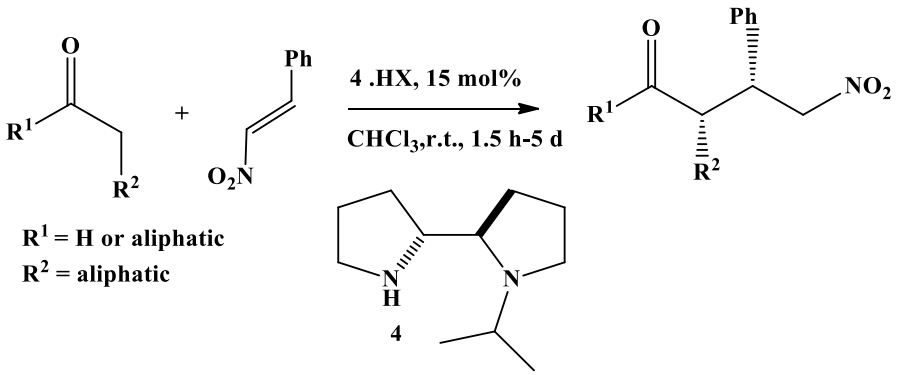
In 2005, Alexakis and Mossé reported the first asymmetric diamine (4) catalysed Michael addition of aldehydes to vinyl sulfones. The adducts obtained in good

yields had high enantioselectivities, scheme I-5. In general, the more encombred the aldehyde give the better of stereoisomerism [44, 45].



Scheme I-5. Diamine catalysed Michael addition of aldehyde to vinyl sulfones.

Moreover, Alexakis and Andrey employed the diamine as Michael addition catalysts [46, 47]. The catalyst 4 catalysed the addition of a range of aldehydes and ketones to trans-β-nitrostyrene, enantioselectivities and diastereoselectivities of the resulting products were modest for most of the acyclic and cyclic ketone substrates (23-76% e.e.), but were excellent for the aldehydes and the addition of an acid co-factor was observed to effect an increase in the rate of the reaction by facilitating enamine formation and suppressing side reactions [46], scheme I-6.

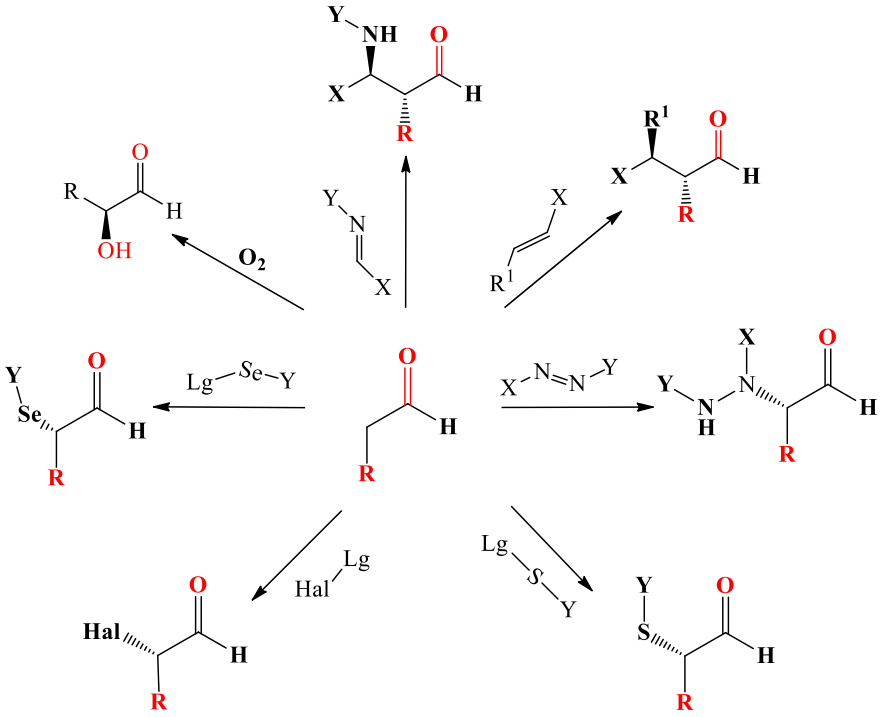


R^1	HX	% Yied	% e.e
H	None	99	61-66
H	HCl	86-99	67-79
Aliphatic	None	26-61	29-37
Aliphatic	HCl	55-95	25-76
Aliphatic	p-TsOH	74-99	23-48

Scheme I-6. Organocatalysed Michael addition of a range aldehydes and ketones to trans -β-nitrostyrene.

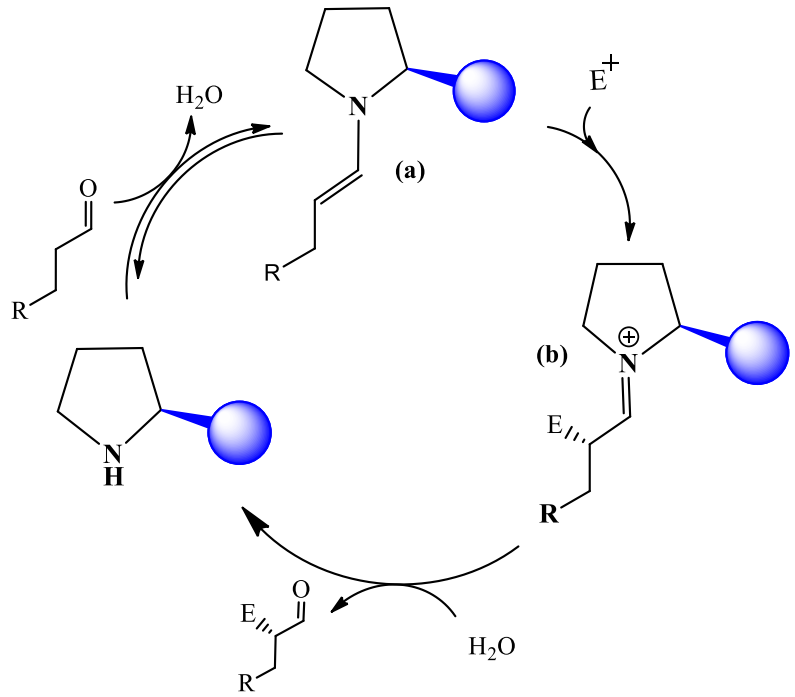
I.4.3 Catalytic cycle of enamine activation

Enamine activation can lead to a large variety of α-functionalized aldehydes and ketones. Many protocols have been developed in the last decade, the most important research in this area with aminocatalytic asymmetric Michael additions are regrouped in Scheme I-7 [48]. Carbon-carbon bond formation is easily achieved via Michael additions [49], the α- hetero functionalization can be achieved by α-amination[50], α-sulfenylation[51], α-halogenation[52], α-selenylation [53] and α- hydroxylation[54] using an appropriate electrophile.



Scheme I-7. Reactions involving enamine activation by a chiral amine catalyst.

In the amine catalysis involving nucleophilic enamine activation, the catalytic cycle starts with the formation of an iminium ion between a donor carbonyl compound and the amine of a secondary amine catalyst. The reversible formation of the correspondent iminium ion induces a fast deprotonation, which leads to the generation of the enamine (a) and a subsequent raise in energy of the highest occupied molecular orbital (HOMO).The enolate equivalent formed performs a nucleophilic attack on the electrophile generating an iminium intermediate (b). The final hydrolysis of the iminium intermediate releases the product and the catalyst for the next cycle, scheme I-8.



Scheme I-8. The catalytic cycle of Enamine activation by amine catalyst.

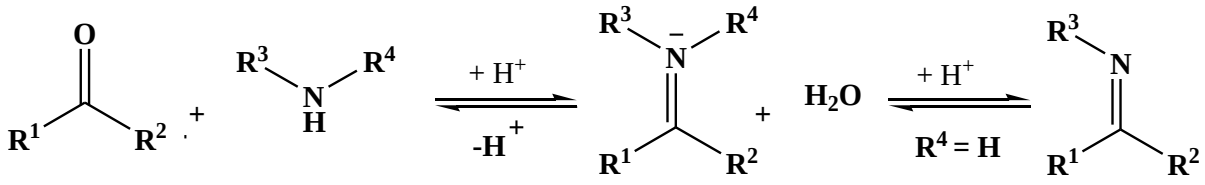
I.4.4 Concluding on Enamine Catalysis

The area of enamine catalysis has developed very significantly and in the recent past, (S)-proline is certainly part of this Noble catalyst [55, 56]. It has been defined as a "universal catalyst" [55, 56] because of its high utility especially in enantioselective enamine Michael reactions. The excellent results outlined in the above section confirm that enamine catalysis has indeed established itself as a powerful means and basic tool for the future application of pyrrolidine catalyst in asymmetric synthesis for next sections.

I.5 Amine Catalysis Involving Iminium Activation

I.5.1 Iminium Catalysis

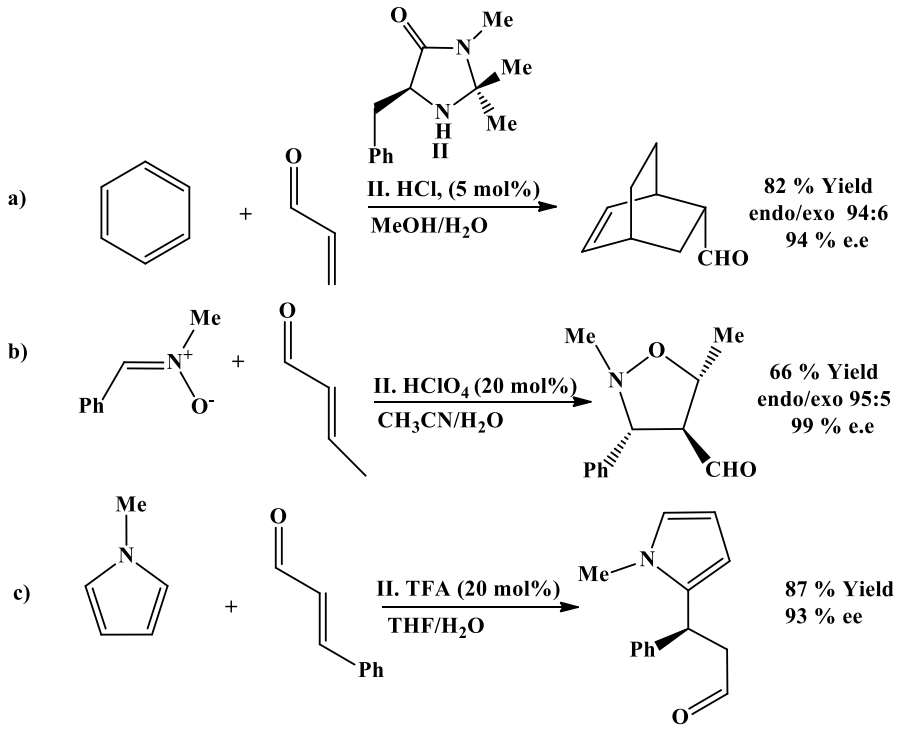
The reversible formation of an iminium ion by condensation of an amine catalyst with a carbonyl substrate is central to iminium catalysis. Schiff first discovered the reaction in 1864, and imines are referred to as Schiff bases, scheme I-9[58]. Primary amine-derived imines (R^4 = H) are basic (pKa = 7) and exist as iminium ions in acidic solution [59].



Scheme I-9. The formation of imines/Schiff bases.

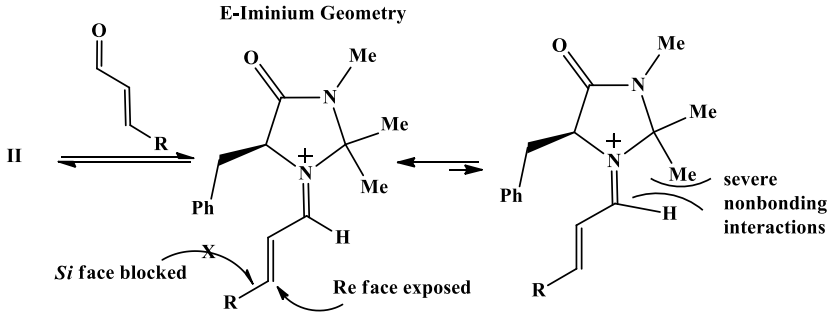
Aldehydes and ketones also condense with secondary amines to form iminium cations, which can only be isolated as salts of strong acids. In iminium catalysis, secondary amines tend to dominate the field, though catalysis by both primary and secondary amines has been demonstrated. For catalytic activity, primary amines always require an acid co-catalyst but co-factors are also very commonly employed with secondary amine catalysts.

In 2000, Mac Millan and co-workers [55] introduced this novel catalytic activation concept termed iminium catalysis, which led to the development of a large range of asymmetric transformations involving unsaturated carbonyl compounds. This organocatalytic activation mode exploits the reversible condensation of a chiral amine, substituted pyrrolidines such as imidazolinone II, with an unsaturated aldehyde to form an iminium ion intermediate. In this system, a rapid equilibrium exists between an electron deficient and an electron-rich state, which effectively lowers the LUMO energy of the *p* system and enhances its susceptibility toward nucleophilic attack [59]. Importantly, further studies on LUMO-lowering organocatalysis by MacMillan and co-workers established the effectiveness of the readily available chiral imidazolinone II to promote distinct transformations of *α, β*-unsaturated aldehydes in a highly enantioselective fashion, Scheme I-10 [60]. It is important to point out that the nature of the anion of the catalytically active salt is essential for modulating both the reactivity as well as the stereo selectivity of the process.



Scheme I-10. Asymmetric iminium catalysis by imidazolidinone II: a) Diels Alder reaction [22], b) [3+2] cycloadition with nitrones [61a] and c) frieldel-Crafts alkylation of pyrroles [61b].

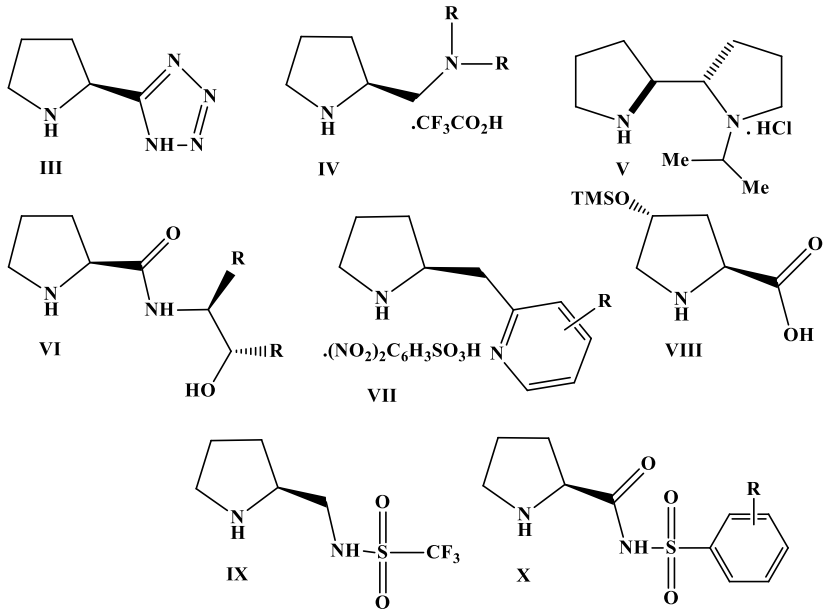
Central to the success of imidazolidinone (II) as a stereoselective iminium activator, its ability to effective and reversible form a reactive iminium ion intermediate with high levels of both configurational control and *p*-facial discrimination, Scheme I-11 [55].



Scheme I-11. Control of the configuration of the iminium ion and π –facial shielding by the imidazolidinone catalyst II.

The activated iminium intermediate predominantly exists in the E conformation to avoid problematic nonbonding interactions between the double bond of the substrate and the gem-dimethyl groups on the catalyst. The selective π-facial blocking of the imidazolidinone framework by the benzyl group leaves the re face of the iminium ion exposed for the nucleophilic attack, thereby resulting in a highly enantioselective bond formation **[55]**.

The iminium catalyst approach began with the derivatization of L-proline (I). The design of new catalysts has focused on the introduction of tunable hydrogen-bonding donor groups to improve the dual activation ability while preserving the molecular scaffold created by nature as a central design element. Different research groups [55] accomplished a series of modifications of the structure of L-proline (I) (Scheme I-12) who aimed mainly at improving the solubility and/or enhancing the acidity of the acid proton. In this research area, the aldol reaction and the conjugate addition of carbonyl compounds to nitro styrene derivatives were often chosen as benchmark reactions **[62]**. It is remarkable that these catalysts showed major improvements in terms of reactivity or enantioselectivity in some specific transformation, yet all lacked the generality of the natural proline (I). Iminium catalysis has been applied to a large range of reactions and the authors attempt to illustrate its scope in the following sections.

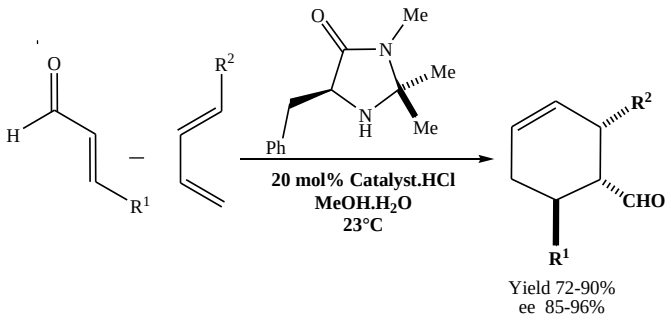


Scheme I-12. A series of modifications of the structure of proline (I) catalyst.

I.5.2 Cycloaddition Reactions

The range of cycloadditions can be attained through iminium catalysis covers conventional nitrone [4 + 2]**[63],** [3 + 2] **[64]** and [4 + 3] **[65]** processes, as well as intramolecular versions of some of these reactions. In general, the reactions tolerate a range of diene and dienophile components, which provides a reasonably broad scope for these catalytic cycloadditions, and the products are obtained in good yields, diastereoselectivities and excellent enantiomeric excesses. MacMillan reported that enals smoothly undergo [4 + 2] cycloadditions with substituted dienes with good endo control, Figure I-5a **[66]**. In addition, [3 + 2] cycloaddition of *1,3*-amino alcohols are readily formed from the products of nitrone cycloaddition with activated enals and can be used to form a range of functionalized products, Figure I-5b **[64]**.

a) Secondary amine-catalysed [4+2] cycloaddition of enals.



b) Secondary amine-catalysed [3+2] cycloaddition of enals.

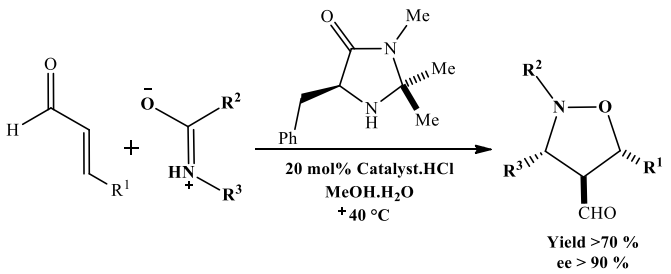


Figure I-5. [4+2] and [3+2] cycloadditions of enals.

Activation via iminium ion formation also renders facile conjugate addition processes with soft nucleophiles. A range of aromatic and hetero aromatic nucleophiles can be added to enals in high yields and enantiomeric excesses to

form many functionalities that are common in pharmaceutical compounds, figure I-6 [67].

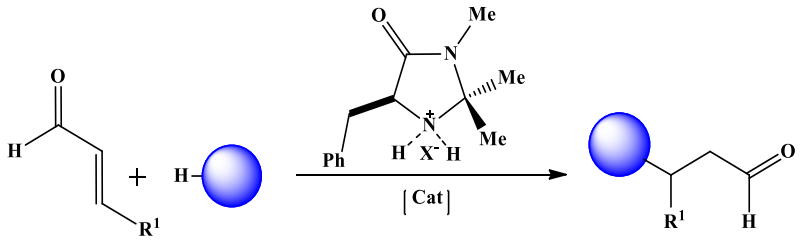


Figure I-6. Secondary amine-catalysed conjugate addition.

In particular, the indole and aniline motifs are readily incorporated into an asymmetric framework after modification, figure I-7 [68, 69].

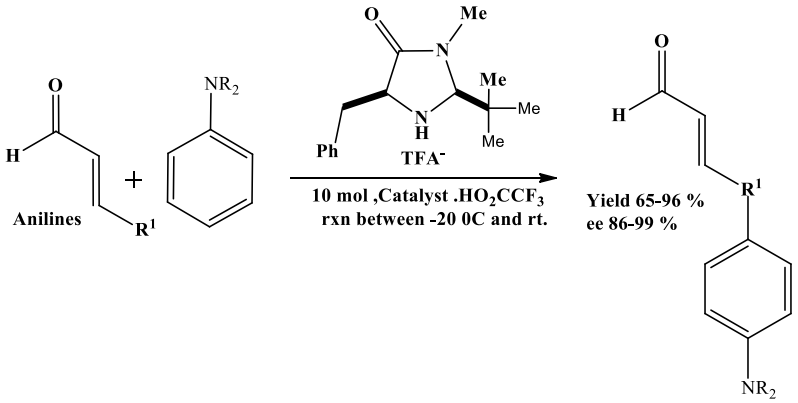
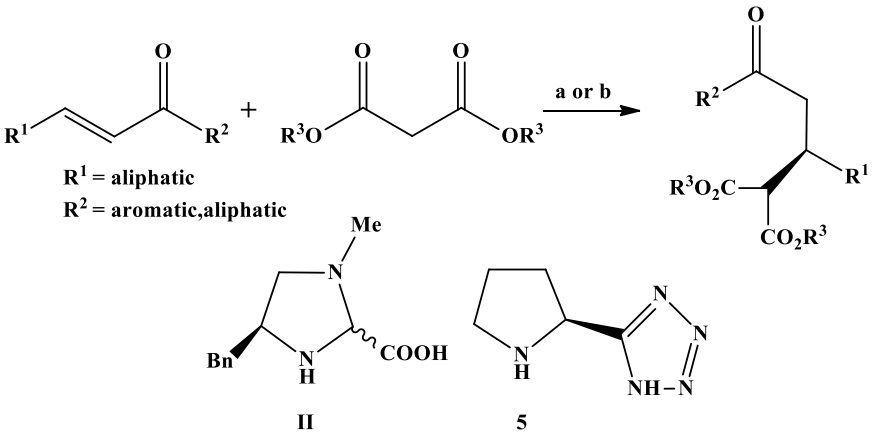


Figure I-7. Secondary amine-catalysed conjugate addition of indoles and anilines to enals.

I.5.3 Iminium Catalysis of Michael Addition Reactions

I.5.3.1 Dicarbonyl compounds as Michael donors

Although additions of malonate nucleophiles to iminium ions had been reported from as early as 1991, the first reaction was not reported until 2003 when Jørgensen and co-works demonstrated an imidazolidine II catalysed addition of malonates to acyclic enones, scheme I-13a [70-74]. It was observed that sterically hindered malonates afforded the addition products in low yields, whilst malonates free of steric impediments furnished excellent product yields with high enantioselectivities. Moreover, they identified the pyrrolidinyl tetrazole (5) as a suitable catalyst for the addition of dimethyl and diethylmalonates to a range of enones, scheme I-13b [73-75].

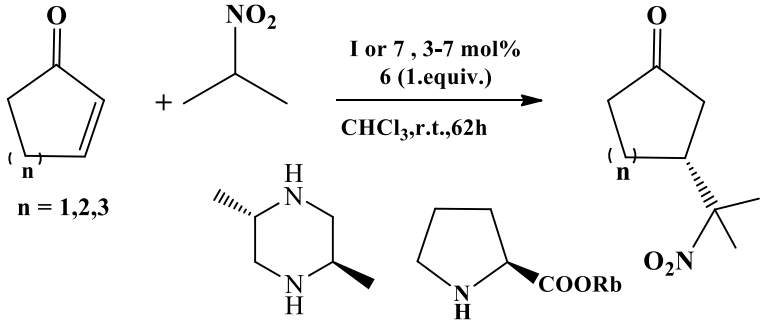


Conditions	% Yied	% e.e.
a. R^3 = Bn (8 equiv),II, 10 mmol , rt, 150-288 h	**33-99**	**59-99**
b. R^3 = Me(1.5 equiv),5, 5 mmol , piperidine (1 equiv.) rt, $CHCl_3$, r.t, 72 h.	**64-87**	**62-84**

Scheme I-13. Iminium ion catalysed addition of malonates to acyclic enones.

I.5.3.2 Nitroalkanes as Michael donors

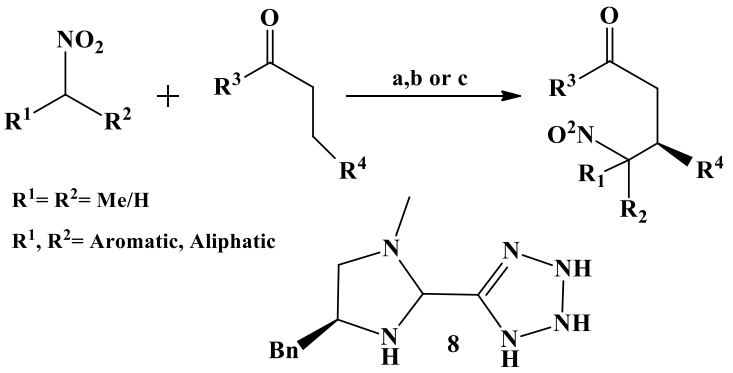
In 2000, Hanessian and Pham reported the first catalytic asymmetric of addition at nitroalkanes to cyclic enones. S-Proline (7) was the catalyst of choice and was used in conjunction with trans-2, 5-dimethylpiperazine, 6, as an additive. Products were obtained with high enantioselectivities and yields, well in excess of those results for the rubidium prolinate catalysis of the same reaction, scheme I-14 [37, 76].



	% e.e		
Catalyst	**n=1**	**2**	**3**
I	**75**	**93**	**86**
7	**12**	**59**	**73**

Scheme I-14. Organocatalytic asymmetric conjugate addition nitroalkanes to cyclcenones.

Addition of nitroalkanes to various cyclic enones was also reported to be catalysed by the pyrrolidinyl tetrazole 5 in the presence of the amine additive 6, scheme I-15a [77]. For example, reaction between cyclohexanone and 2-nitropropane yielded the addition product in 59% yield and 91% e.e. The yield of the addition product of nitroalkanes to acyclic substituted enones, catalysed by the chiral amine II, was shown to be strongly influenced by the size of the substitutent on the alkane [78]. The nitroalkanes were employed as the reaction solvent and were used in approximately twenty-fold excess, scheme I-15b. Three years later, Jørgensen reported the tetrazole appended imidazolidine catalyst 8 to be an equally viable catalyst for the addition of nitroalkanes to α, β-unsaturated enones[79]. The product yields a selectivity were similar to those observed in the presence of the pyrrodinyl tetrazole 5. However, the reaction times could be halved in most cases, scheme I-15c.

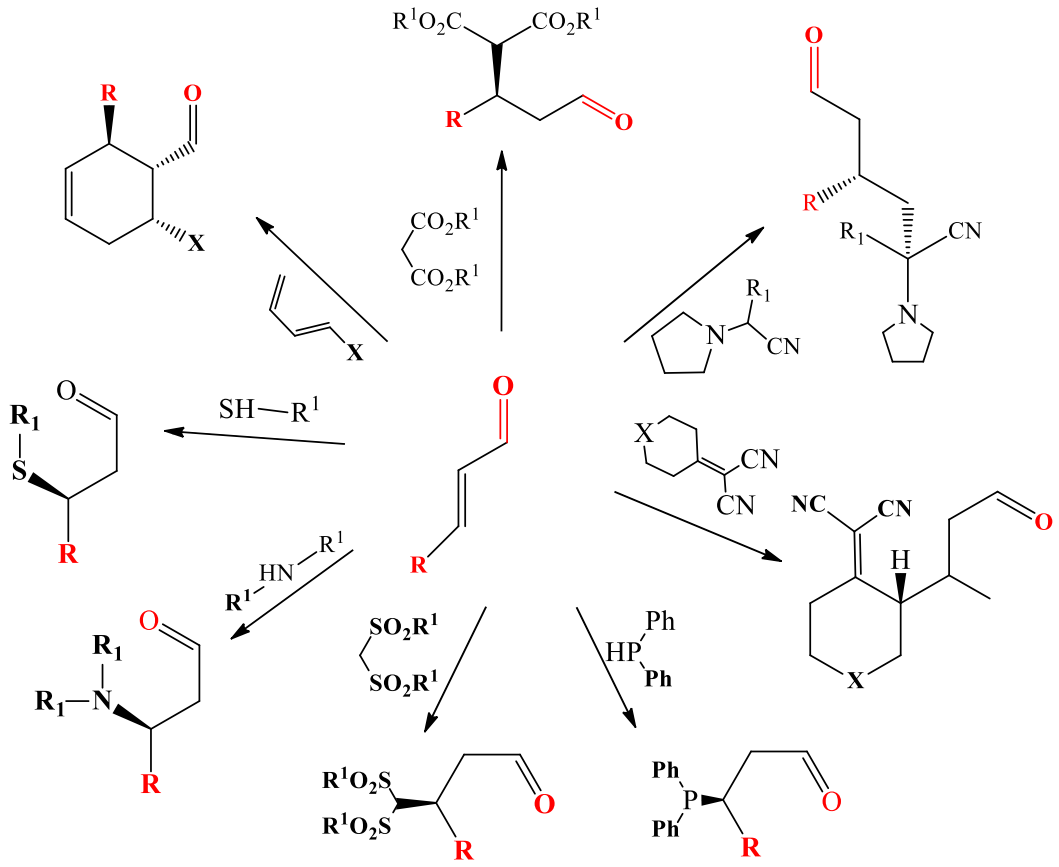


Condition	Yied%	% e.e
a. 5 , 15 % mmol , 6 (0.5 equiv.) , CH_2Cl_2, rt , 72 h	**21-88**	**54-83**
b. II, 10 % mmol, neat , rt , 80-300 h	**<5-100**	**35-86**
c. 8, 10 % mmol, neat , rt , 70-200 h	**83-97**	**64-86**

Scheme I-15. Conjugate addition of nitroalkanes to various cyclic enones.

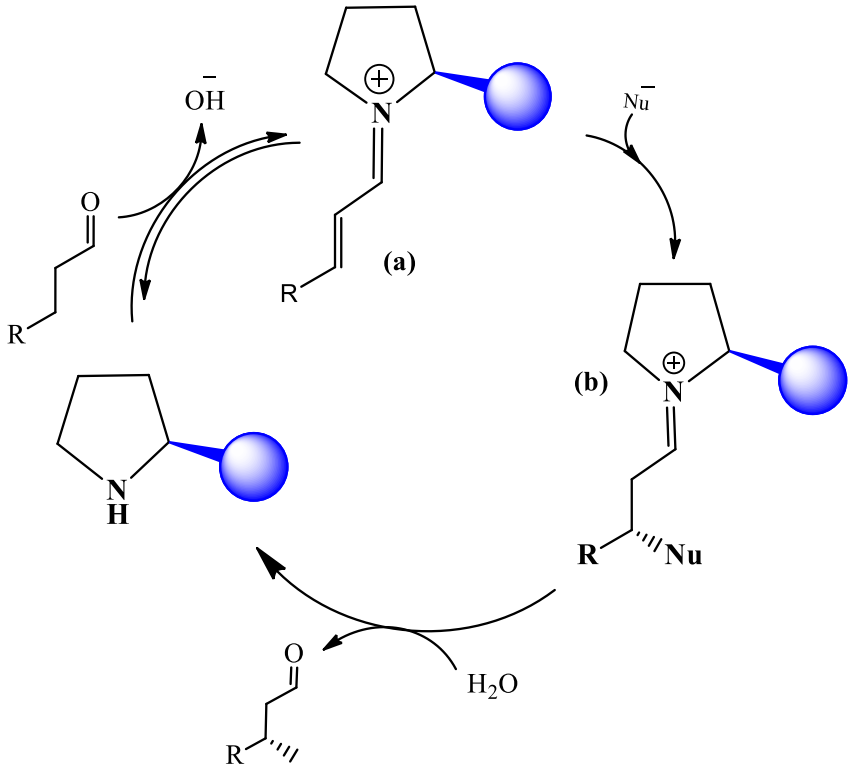
I.5.4 Catalytic cycle of iminium Activation:

The addition of a nucleophile to α, β-unsaturated aldehyde aided by the presence of an amine catalyst. The iminium activation of enals gives direct access to the β-position of carbonyl compounds. *β*-functionalizations of enals are carried out usually by 1, 4-additon at the double bond , scheme I-16.



Scheme I-16. Reactions involving iminium activation by a chiral amine catalyst.

Several types of nucleophiles can be used to form carbon-carbon bonds in the β-position, such as aminonitriles[80], dicyanoolefines[81], malonates[82] and arylsulfonyl methanes[83]. *β*-Heterofunctionalizations are reachable with oxa-[84], aza-[85], phos-[86] and sulfa-[87] Michael additions. The reversible formation of positively charged iminium intermediate (a) from the condensation of *α, β*-unsaturated aldehydes and chiral amines emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis. The catalytic cycle starts with the condensation of the amine with an *α, β*-unsaturated aldehyde (a). The energy of the lowest unoccupied molecular orbital (LUMO) of the system is lowered, making the *α, β*-unsaturated aldehydes more electrophilic. The iminium ion can now react with a nucleophile at the β-position forming an enamine intermediate (b). Hydrolysis of the enamine releases the product and the catalyst for the next catalytic cycle, scheme I-17.



Scheme I-17. The catalytic cycle of Iminium activation by amine catalyst.

I.5.5 Concluding on Iminium Catalysis:

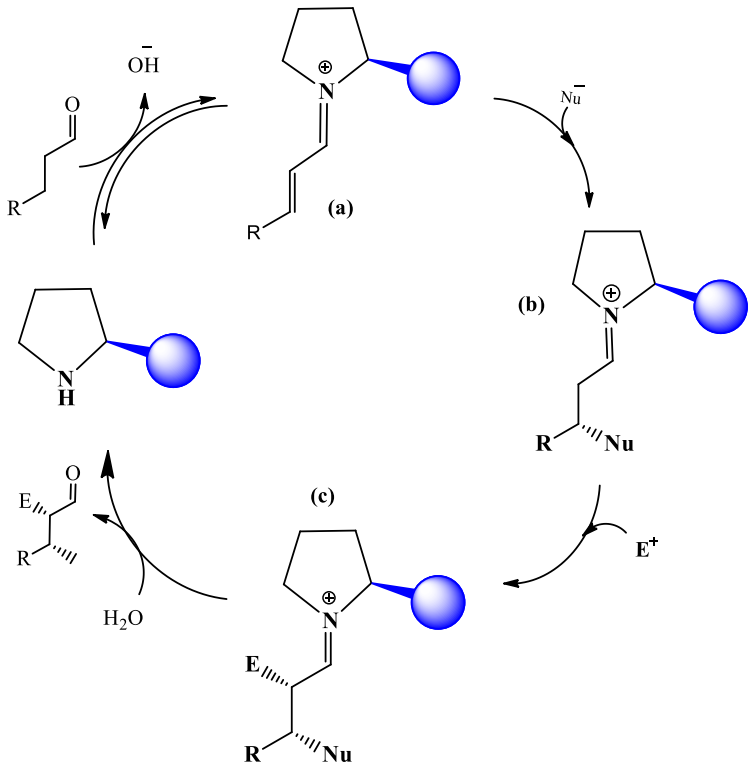
Iminium catalysis has been established as one of the key concepts in organocatalysis. The success of this approach can be garnered from the high yields and enantioselectivities of the products formed.

I.6 Amine Catalysis Involving Enamine and Iminium Activation:

Reduction of waste products and time optimization are of primary importance in chemical industry. The development of atom- and step-economic procedures is becoming the predominant goal for many research groups. "One-pot" procedures involving formation of two or more new chemical bonds, without any further addition of reagents or catalysts, are highly desirable [88]. In domino reactions, every step is a consequence of the functionality formed in the previous one. A careful retrosynthetic analysis of the desired product dictates the choice of suitable substrates. Combinations of iminium/ enamine activation allows for the creation of efficient "one-pot" protocols.

In the LUMO activation, it can be observed that as a consequence of the β-addition of a nucleophile to the iminium ion an enamine is formed, which is

HOMO activated. Next, a nucleophilic attack can be performed to an electrophile. Based on this strategy, it is possible to plan a two-component domino reaction. Michael-Michael[89], Michael-aldol[90], Michael/ Morita-Baylis-Hillman[91], Michael-Knoevenagel[92], Oxa-[93], Sulfa-[94], Aza-[95] Michael-heterocyclization and alkylation[96] domino reactions, aziridination, epoxidation[97] and cyclopropanation[98] give access to a wide variety of complex chiral molecules bearing different functionalities. Reactions with three or more substrates were developed in an extremely regio- and chemoselective fashion enabling for the synthesis of products that is often impossible to prepare with traditional "step by step" procedures [99]. The catalytic cycle starts with the condensation of *α, β*-unsaturated aldehyde with the chiral amine catalyst forming a labile iminium-ion intermediate (a). The nucleophile then adds to the activated electrophilic β-position generating the enamine (b). The resulting enamine can then undergo a second reaction with an electrophile (c) to afford, after hydrolysis, the product with two new stereocentres and the recycled catalyst, scheme I-18.



Scheme I-18. The catalytic cycle of Iminium ion and enamine intermidiates.

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Chapter II
Pyrazolidine and Isoxazolidine Compounds

II. 1 Introduction

Pyrazolidines and Isoxazolidines represent two important classes of five-membered *N*-heterocycles and *O*-heterocycles found in many natural products, agrochemicals and biologically active molecules. Over the past decades, tremendous efforts have been devoted to the development of efficient methods for efficient construction of these scaffolds. However, the catalytic asymmetric synthesis of pyrazolidines and isoxazolidines remains a challenging task for organic chemists. Recently, wide ranges of catalytic asymmetric cycloaddition, cyclization, cascade reactions and Michael addition have been developed to access these chiral compounds. The Michael reaction that was discovered few years ago has wide applicability in organic synthesis and attracted many researchers in medicinal chemistry [1]. Principally, Aza-Michael or hetero-Michael reactions are one of the widely used reactions for carbon-nitrogen bond formation in synthetic organic chemistry. Michael addition of various amines to α, β-unsaturated carbonyl compounds and nitriles provide the corresponding β-amino derivatives, which have attracted great attention for their use as important synthons for the synthesis of several nitrogen containing bioactive natural products [2], chiral auxiliaries [3], antibiotics [4], and a number of other drugs [5].

Due to the importance of pyrazolidine and isoxazolidine derivatives in both organic and medicinal chemistry, we have become interested in developing an efficient Michael and Aza-Michael reactions for the asymmetric synthesis of the pyrazolidine and isoxazolidines compounds through organocatalysis. In this chapter, we will survey the main recent advances of Aza-Michael and Michael reactions on the catalytic asymmetric synthesis of pyrazolidines and isoxazolidines derivatives and working models in the scientific world. Before that, it would really be interesting to know the rationale research position and the importance of these molecules to undertake these studies.

II.2 Asymmetric Synthesis of Pyrazolidines derivatives

II.2.1 Pyrazolidines, Pyrazolines and Pyrazolidinones

Pyrazolidines and Pyrazolines are two classes of privileged five-membered nitrogen-containing heterocycles with two adjacent nitrogen chiral centers [6]. They have been often utilized as valuable synthetic building blocks and chiral ligands in asymmetric catalysis [3,4a,7]. They can be easily converted to pyrazolidinones by oxidation of the hydroxyl group and to pyrazolines after dehydration under acidic conditions[5], which are also motifs of high relevance because of their presence in a wide range of biologically active molecules [5,8]. Pyrazolidines and pyrazolines, form an important group of heterocycles, with potentially important contributions to make to drug design by reason of their ability to form strong hydrogen bonds at either or both nitrogen atoms [9]. Pyrazoline shows various biological and pharmacological activities such as antimicrobial, anti-inflammatory, antitumor, antidepressant, antiamoebic, insecticides, antidiabetic, analgesic and anticancer activities [7, 10].

Pyrazolidines structure is present in many natural products and they are useful intermediates for the synthesis of important drugs with bioactivities such as antidepressant, antiviral, antimicrobial, immunosuppressive, anti-obesity, anti-inflammatory, psych analeptic, and anticonvulsant activities. Some examples of important compounds bearing a pyrazolidine [10-11] structure are depicted in figure II.1.

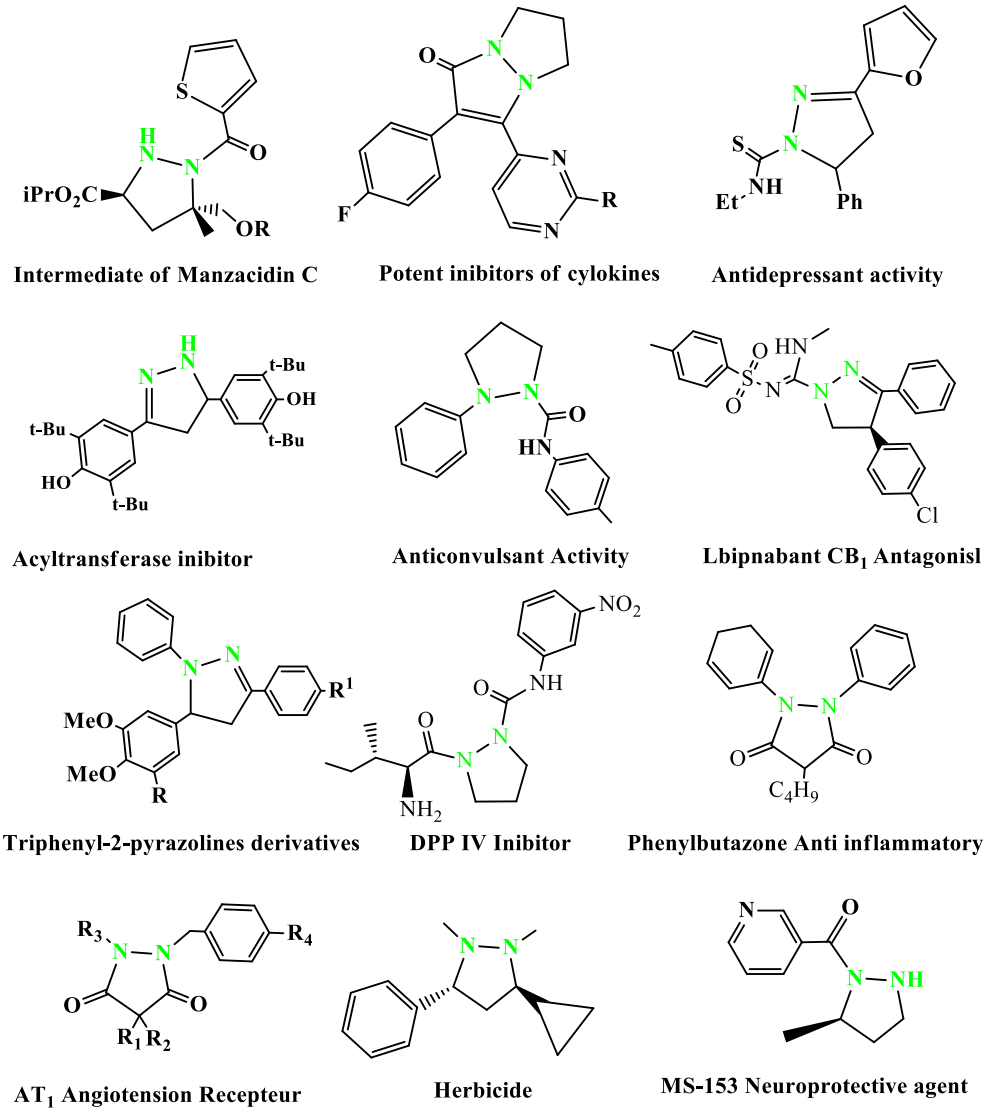


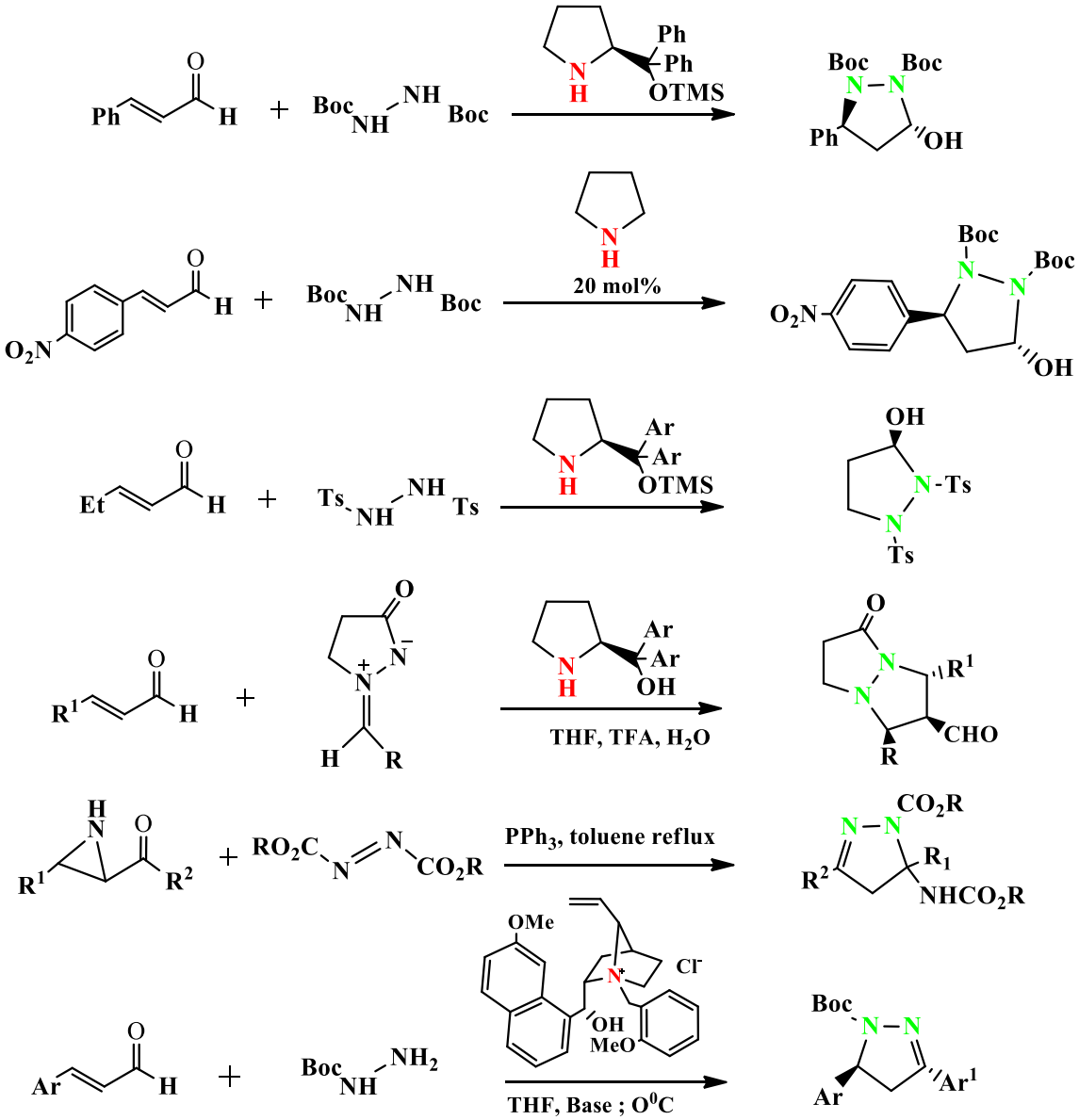
Figure II-1. Pyrazolidine, pyrazoline and pyrazolidinone drugs and natural products.

In their seminal 1887 work, Fisher and Knovenagel reported the first synthesis of pyrazolines using acrolein and phenylhydrazine under acidic conditions [12, 13]. However, it was not until 2000 that the first enantioselective synthesis of pyrazolines from acrylamides by means of metal-catalyzed enantioselective [1,3]-dipolar cycloaddition was disclosed [14]. Furthermore, despite their interest and potential as promising candidates in drug discovery programs, the number of available synthetic procedures for the stereoselective preparation of pyrazolidines and/or pyrazolines is still very limited. Most of the methodologies reported rely on the use of chiral Lewis acids, involving typically [3+2] cycloaddition using dipoles such as diazoalkanes [14-15] , nitrile imines[16] or hydrazones[17], or by

means of metal-catalyzed amination at allenes[18]. In this context, organocatalysis has emerged as a useful alternative tool for the development of enantioselective versions of certain transformations, which do not proceed efficiently with metal catalysis. The enantioselective synthesis of pyrazolines is a representative example of the complementary natures of these two different methodological approaches, with a couple of reports describing the access to these heterocycles under metal-free conditions. In 2009 and 2010, List et al. and the Brière group both reported, separately, the enantioselective synthesis of 2-pyrazolines starting from *α, β*-unsaturated ketones and phenylhydrazine or N-tert-butyloxycarbonylhydrazine in the presence of a chiral Brønsted acid or a phase-transfer catalyst [19-20]. Compared with monosubstituted hydrazines in organocatalytic asymmetric synthesis, disubstituted hydrazines were also explored by several groups [21, 22]. In 2007, Jørgensen et al. reported that the organocatalyzed asymmetric Aza-Michael addition of hydrazones to cyclic enones had been achieved in good yield and stereoselectivity [23]. In 2011, the Deng group developed a highly enantioselective organocatalytic synthesis of 2-pyrazolines using disubstituted hydrazines through an asymmetric addition followed by a deprotection–cyclization sequence [24].

In similar, the pyrazolidine structural unit is commonly constructed by [3 + 2] cycloaddition reactions using hydrazones [25-26] or azomethine amines [26-27] as dipoles. Moreover, it can also synthesized by catalysis metal and metal-free [29]. In 1980, Vladimir and Otto reported the first synthesis of pyrazolidine using the condensation between hydrazone benzene and aliphatic aldehydes [30]. After them, Robert et al. described a new pyrazolidine with interest antibacterial activity [31]. Recently in 2009, the Ma group and Toste et al. have produced efficient methods for the synthesis of pyrazolidine derivatives at metal-catalyzed aminations of allenes [32-33]. After this epoch, the research area of pyrazolidine organocatalysis has grown rapidly and become a third brand of catalysis besides the well-established biocatalysis and metal catalysis [34-35]. Particularly, organocatalytic Michael and Aza-Michael reactions have come into focus and become a powerful synthetic approach that allows the construction of structurally

diverse and complex molecules, in one-step, and saves time, effort, and production costs [35-38]. Thus, many nitrogen-containing heterocyclic compounds have been efficiently generated by means of organocatalytic Michael reactions [49-42]. In particular, Bharat Parashar [10a], Jose L. Vicario [5], Armando Córdova [41] and Zhi-Cong Geng [11] have investigated in the pyrazolidine organocatalysis and they contributed a lot in the evolution of Michael/Aza-Michael reactions between disubstituted hydrazines and α,β-unsaturated aldehydes or β-unsaturated aldehydes. Driven by our precedent studies on the synthesis of pyrazolidine compounds, we envisioned that the organocatalytic reaction between β-enals or α,β-enals and disubstituted hydrazine, as reactive substrates and interest factor for reaction efficiency, regio- and stereoselectivity[5], treated an efficient asymmetric route for the synthesis of 5 or 3-hydroxypyrazolidines and 5 or 3-pyrazolidinone. In the next part, we study these protocols thoroughly to produce the 3 and 4-Substituted pyrazolidine and pyrazolidinone, in particular that we have not found syntheses based of α-enals on the majority of bibliographic resources, as show in Scheme II-1.



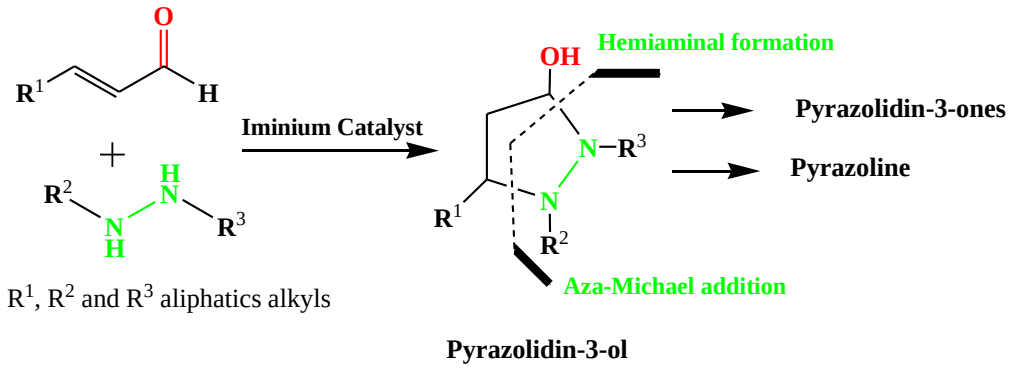
Scheme II-1. Synthetic routes for the synthesis of pyrazolidines and pyrazolines from α, β-unsaturated aldehydes [5, 10a, 11, 39-42].

II. 2.2 Direct Catalytic Synthesis of Pyrazolidine Derivatives

II. 2.2.1 Aza-Michael Reaction from aliphatic β-enals and *N,N'*-disubstituted hydrazines

Vicario and co-workers [5] have reported a related approach to the pyrazolidine heterocycle very recently in 2012. They have the possibility access to enantiopure pyrazolidines, pyrazolines and pyrazolidinones in a direct and efficient manner through an organocatalytic, enantioselective Aza-

Michael/hemiaminal formation cascade process using aliphatic *α, β*-unsaturated aldehydes and divers *N,N′*-disubstituted hydrazines under iminium activation with commercial chiral catalysts, scheme II-2. The process takes place with high regio and stereoselectivities and furnishes the target compounds in high overall yields by means of an operationally very simple methodology in which the pyrazolidine products easily transformed into the corresponding pyrazoline by sequential deprotection/dehydration or oxidised to the pyrazolidin-3-ones.

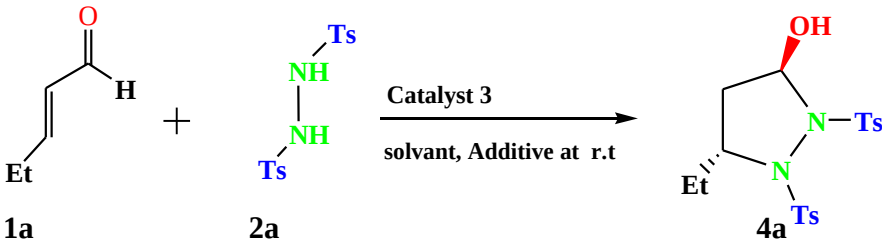


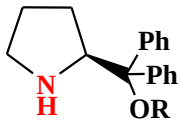
Scheme II-2. Direct organocatalytic enantioselective pyrazolidine synthesis through iminium activation.

In order to achieve these Aza-Michael reaction, Vicario initially started screening the viability of the chiral catalysts for the reactions between *N,N'*-bis-(*p*-toluene sulfonyl)hydrazide (2a) as model substrate for nucleophilic attack and the *β*-substituted enal as pent-2-enal (1a) using various solvents and working at room temperature, table II-1. In this situation, diphenylprolinol derivatives 3a and 3b delivered the waitly product 4a in high isolated yield and diastereoselectivity, although with low enantiocontrol (entries 1 and 2). In contrast, enantioselectivity was improved when the bulkier catalysts 3c and 3d were employed, although the yield was diminished (entries 3 and 4). Imidazolidinone 3e developed by MacMillan was also tested, providing 4a in good yield but low enantioselectivity (entry 5). Next, Vicario studied the effect of the solvent in conjunction with optimal catalyst 3c (entries 6–8), but he observed that the use of more polar solvents resulted in a less efficient reaction. In an attempt to improve the yield of the transformation, he also surveyed the incorporation of a base as a co-catalyst,

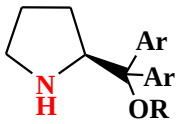
which was thought to activate the hydrazide by forming the corresponding anion for the iminium activation [5].

Table II-1. Screening for the best reaction conditions[a].

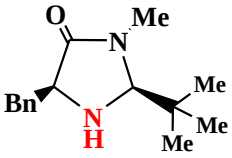




3a, R= TMS
3b, R= Me



3c, R= TMS
3d, R= Me
Ar = 3,5-$(CF_3)_2C_6H_3$



3e

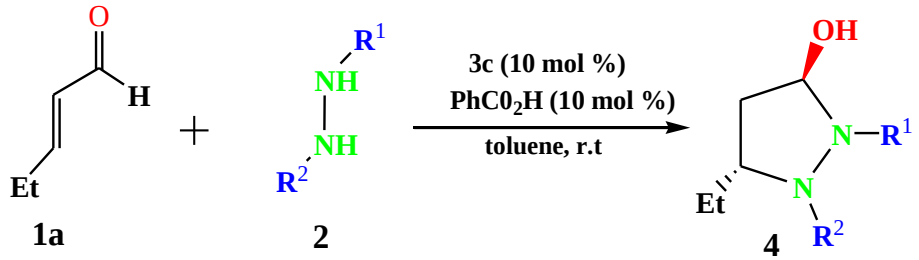
Entry	Solvent	3	Additive[b]	Yield of 4a [%][c]	dr[d]	e.e [%][e]
1	toluene	**3a**	$PhCO_2H$	83	>10:1	20
2	toluene	**3b**	$PhCO_2H$	80	>10:1	11
3	toluene	**3c**	$PhCO_2H$	54	>10:1	97
4	toluene	**3d**	$PhCO_2H$	30	>10:1	92
5	toluene	**3e**	TFA	67	10:1	45
6	CH_2Cl_2	**3c**	$PhCO_2H$	24	>10:1	38
7	CH_3CN	**3c**	$PhCO_2H$	38	>10:1	36
8	EtOH	**3c**	$PhCO_2H$	32	>10:1	39

[a] Reactions performed on a 0.2-mmol scale of 1a and 2a using 10 mol% of catalyst 3 in 2.0 mL of the corresponding solvent. 10 mol % used. [c] Isolated yield. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Determined by HPLC on a chiral stationary phase.

After this initial experiments, Vicario demonstrated the influence of the substitution pattern of the hydrazine reagent would have on the reaction using the conditions shown in entry 3 of Table II.1 and various models of hydrazine. In this context, Vicarion tested a family of different N, N'-disubstituted hydrazides which have diverse acidic character in the reaction, table II-2. After some experiments, Vicario demonstrated that the high reactivity and complete

regioselectivity Aza-Michael reaction observed when we have the higher acidity of the (N-H) group attached to the nosyl (Ns) substituent hydrazine, which presumably makes the nitrogen group more nucleophilic for the initial Aza-Michael process. The explanation of this theory paired clearly by the sets of results, the reaction between pent-2-enal 1a and the unsymmetrically substituted *N-Boc-N'-(p*-nitro benzene sulfonyl) hydrazide 2f , witch more nucleophilic, proceeded with creation pyrazolidin-3-ol (4f) in excellent yield, enantioselectivity and remarkably as a single regioisomer , entry 5. In contrary, no reaction was observed in the presence of the less acidic hydrazide 2b (entry 2). Moreover, no reaction was observed with hydrazides 2d and 2e due to presence of the strongly electron-withdrawing substituents such the tosyl, for which entries 4 and 5.

Table II-2. Effect of hydrazide substitution[a].



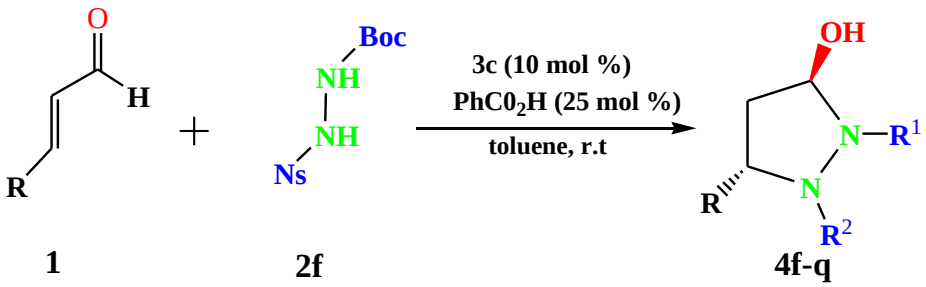
Entry	2	R^1	R^2	4	Yield of 4a [%][c]	dr[d]	e.e [%][e]
1	2a	Ts	Ts	4a	54	>10:1	97
2	2b	Boc	Boc	4b	< 5 %	-	-
3	2d	*p*-MeO-C_6H_4	Ts	4d	< 5 %	-	-
4	2e	*p*-N_2O-C_6H_4	Ts	4e	< 5 %	-	-
5	2f	Boc	Ts	4f	87	10:1	93

[a] Reactions performed on a 0.2-mmol scale of 1a and 2. [b] Isolated yield. [c] Determined by 1H NMR analysis of the crude reaction mixture. [e] Determined by HPLC on a chiral stationary phase.

After that, Vicario obtained the preparation of differently substituted pyrazolidin-3-ols using aliphatic α, β-unsaturated aldehydes with different substitution patterns in position *β*-enal and a nucleophile substrate of hydrazine 2 in order to survey the scope of the reaction, table II-3. Vicario acquired in majority of cases a both high yield and high levels of stereoselectivity for the pyrazolidin-3-ol with *α, β*-unsaturated aldehydes containing linear alkyl chains of different length and size (entries 1–8, table II-3). Furthermore, Vicario et al found very good results

with unsaturated β-alkyl in the reaction of (Z-EtCH=CHCH$_2$CH$_2$-, entries 9) and (*i-Pr*, entries 10), contrary to the negative reactions with *β*-Aryl-substituted enals reacted very slowly and he found in all cases yields below 15 % yield. Moreover, interest results obtained with nucleophilic hydrazine 2a, Vicario observed a relation between the reaction yields and the length of the *β*-alkyl substituent enals. Practically with enals (entries 13 and 14, table II-3), he found a very poor yields when longer substitubents were incorporated, although enantioselectivity remained high. In this section, it is remarkable that in our study with the same hydrazine 2a (1, 2-bis-(*p*-toluene sulfonyl) hydrazine) and Jørgensen-Hayashi catalyst (3c), we found the opposite relation between the yield and the length of the *α*-alkyl substituent, getting an excellent yields and high diastereoselectivity when longer substituents were combined, although enantioselectivity remained low (see the practical section).

Table II-3. Scope of Aza-Michael reaction[a] for pyrazolidi-3-ol.

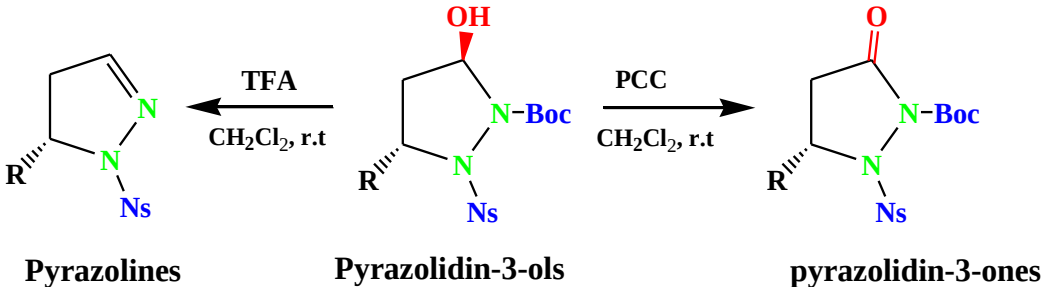


1 **2f** **4f-q**

Entry	1 (R)	4	Yield of 4a [%][b]	dr[c]	e.e [%][d]
1	**1a** *(Et)*	**4f**	87	>10:1	93
2	**1b** *(Me)*	**4g**	93	>10:1	85
3	**1c** *(n-Pr)*	**4h**	99	>20:1	92
4	**1d** *(n-Bu)*	**4i**	91	>20:1	94
5	**1e** *(n-C$_5$H$_{11}$)*	**4j**	95	>20:1	93
6	**1f** *(n-C6H13)*	**4k**	78	>20:1	93
7	**1g** *(n-C$_7$H$_{15}$)*	**4l**	78	>20:1	92
8	**1h** *(n-C$_8$H$_{17}$)*	**4m**	99	>20:1	94
9	**1i** *(Z-EtCH=CHCH$_2$CH$_2$-)*	**4n**	68	>20:1	90
10	**1j** *(i-Pr)*	**4o**	50	>20:1	97
11	**1k** *(CO$_2$Et)*	**4p**	65	20:1	89
12	**1l** *(CH(OM$_2$)*	**4q**	95	>20:1	> 99
13[f]	**1a** (Et)	**4a**	54	>10:1	97
14[f]	**1d** *(n-Bu)*	**4r**	21	>20:1	96

[a] Reactions performed on a 0.2-mmol scale of 1 and 2f using 10 mol% of catalyst 3c in 2.0 mL of toluene. [b] Isolated yield. [c] Determined by 1H NMR spectroscopy of the reaction mixture. [d] Determined by HPLC on a chiral stationary phase. [e] Reaction carried out at 4^{0}C. [f] Hydrazide 2a was used.

In conclusion, Vicario developed the first asymmetric aminocatalytic direct synthesis of pyrazolidin-3-ol, as a single a single regioisomers, based on the aza Michael/hemiaminalization reaction of aliphatic β-enals and hydrazides under iminium activation. The reaction was catalyzed by the commercially chiral catalyst and took place in very high yields (up to 99 %) and excellent stereoselectivities (up to 99 %), table II-3. Furthermore, He created other heterocyclic compounds of pyrazolidin-3-ones and pyrazoline in excellent results in both yields and stereoselectivities with simple transformations[5] using the oxidation process with pyridinium chlorochromate (PCC) and deprotection/dehydration reactions by Trifluoroacetic acid (TFA) respectively in CH_2Cl_2 at room temperature, Scheme II-3.



Scheme II-3. Synthesis of pyrazolines and pyrazolidinones.

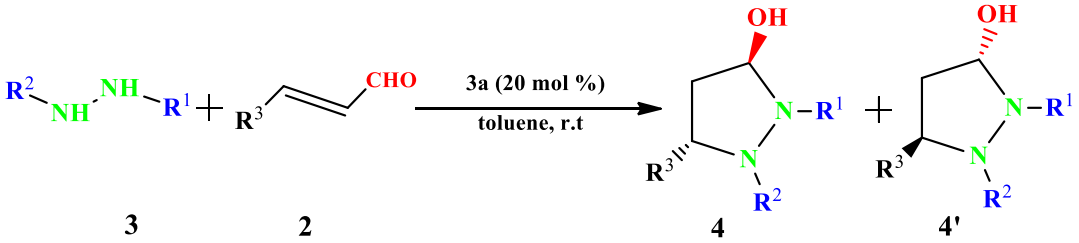
II. 2. 2.2 Aza-Michael Reaction from aliphatic β-enals and protected hydrazines

In the same period in 2012, Ya-Wen Zhang et al. and Armando Cordova et al. chose the downside of Aza-Michael pyrazolidinol preparation related to Vicario protocols , about the futility of the interaction between N,N'-bis(tert-butoxycarbonyl)-hydrazine protected hydrazine (2b) and aliphatic α, β-unsaturated aldehydes , as demonstrated previously. They considered this part as a fertile area for the Aza-Michael pyrazolidines reaction using the same protected hydrazine (2b) as a nucleophilic substrate but with aromatic α, β-unsaturated aldehydes in the presence of secondary amines as organocatalysts. Through their obtained results, we find that both of them have largely adjusted to the chosen aromatic α, β-unsaturated aldehydes series which are attached with an electron-deficient substituent on the aromatic ring as donor alkyl groups , ((table II-4,

column 3) [11] and (table II-5, column 2)) [41]. Moreover, we found great similarity in the methodology and interactions achieved for Michael reaction despite the different experimental conditions.

Firstly, Ya-Wen Zhang et al reported the racemic and asymmetric synthesis of pyrazolidine derivatives through the cascade Aza-Michael/hemiacetal reaction between disubstituted hydrazines (2c-2j) and aromatic *α, β*-unsaturated aldehydes (3) with chiral or achiral secondary amines as organocatalysts. The series of achiral pyrazolidine derivatives (4 and 4') were obtained with good yields (up to 90%) and high diastereoselectivities (>20:1) with pyrrolidine as an organocatalyst [11], and enantioenriched pyrazolidines are also obtained with good results (up to 86% yield, >10:1 regioselectivity, >10:1 dr, 99% ee) in the presence of Jørgensen catalyst (3a). Its Aza-Michael preparations obtained with two (0.5 mmol), three (0.25 mmol), and 3a (0.05 mmol) in toluene (0.5 mL) at room temperature with four days as typical reaction time, table II-4.

Table II-4 . Scope of Aza-Michael reaction[a] for pyrazolidi-3-ol from aromatic α, β-unsaturated aldehydes 2 and hydrazine 3 en the presence of Jøngensen catalyst 3a.

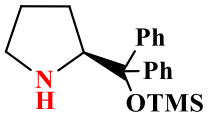


3 2 4 4'

2c: $R^1 = R^2$ = Boc **2d:** $R^1 = R^2$ = CooiPr

2g: R^1 = Boc , R^2 = Ph **2h:** R^1 = Boc , R^2 = *p*-ClPh

2i: R^1 = Boc , R^2 = *p*-BrPh **2j:** R^1 = Boc , R^2 = *p*-MeOPh



3a =Jongensen catalyst

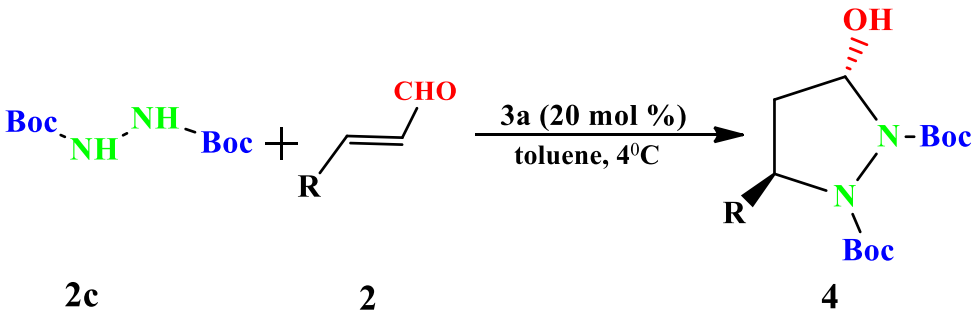
Entry[a]	Donor	R^3	Time (d)	Yield [%][b]	Ratio[c]	ee [%][d]
1	**2c**	4-$NO_2C_6H_4$ **(3a)**	**4**	**4a**/80	-	92
2	**2c**	3-$NO_2C_6H_4$ **(3b)**	2	**4b**/83	-	91
3	**2c**	4-CNC_6H_4 **(3c)**	4	**4c**/86	-	89
4	**2c**	4-ClC_6H_4 **(3d)**	4	**4d**/61	-	74
5	**2c**	4-BrC_6H_4 **(3e)**	4	**4e**/62	-	77
6	**2c**	4-$MeOC_6H_4$ **(3f)**	4	**4f**/<5	-	-
7	**2c**	4-MeC_6H_4 **(3g)**	4	**4g**/<5	-	-
8	**2d**	4-$NO_2C_6H_4$ **(3a)**	**2**	**4h**/60	-	72
9	**2g**[e]	4-$NO_2C_6H_4$ **(3a)**	**4**	**4n**/58 (**4n'**/32)	1.8 :1	88/55
10	**2h**[e]	3-$NO_2C_6H_4$ **(3b)**	**4**	**4o**/60	3.2:1	88
11	**2h**[e]	4-$NO_2C_6H_4$ **(3a)**	**4**	**4p**/72	4.5:1	99
12	**2h**[e]	4-CNC_6H_4 **(3c)**	**4**	**4q**/65	4.7:1	93
13	**2h**[e]	3-$CF_3C_6H_4$ **(3h)**	**4**	**4r**/53	–	81
14	**2i**[e]	4-$NO_2C_6H_4$ **(3a)**	**4**	**4s**/74	6.4:1	99
15	**2i**[e]	4-CNC_6H_4 **(3c)**	**4**	**4t**/72	4.0:1	90
16	**2j**[e]	4-$NO_2C_6H_4$ **(3a)**	**4**	**4u'**/75	1:9.0	-/11
17	**3h**[f]	Me **(3i)**	**2**	**4v**/78	>10:1	72
18	**2i**[f]	Me **(3i)**	**2**	**4w**/83	>10:1	74
19	**2h**[f]	Et **(3j)**	**3**	**4x**/<10	–	-

[a] Unless noted, the reaction was run with **2** (0.5 mmol), **3** (0.25 mmol), and **1m** (0.05 mmol) in toluene (0.5 mL) at room temperature. [b] Isolated yield of pure isomer **4** (the data in parentheses is related to the isolated yield of the **4'**). [c] The ratio based on isolated yield of pure **4** and **4'**. [d] Determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H, AD-H or AS-H), >20:1 dr. eThe ratio of **2**/**3** is 1.2:1. [f] The reaction was run with **2** (0.25 mmol), **3** (0.38 mmol), and **3a** (0.05 mmol) in toluene (0.5 mL) at room temperature.

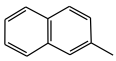
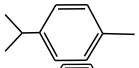
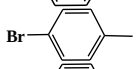
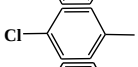
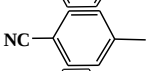
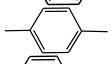
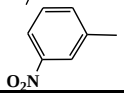
Secondly, Armando Cordova and al follow the same strategy about a choosing of aromatic *α, β*-unsaturated aldehydes series witch are attached with an electron deficient substituent on the aromatic ring as donor alkyl groups. In this context, Cordova founded that the substituents on the aromatic ring influenced the reactivity of Michael reaction between *N,N'*-bis-(tert-butoxycarbonyl) hydrazine protected hydrazine (2c) and aliphatic *α, β*-unsaturated aldehydes in the presence

of asymmetric catalysts[41-42] as Jøngensen catalyst (3a) under iminium activation . The pyrazolidinol products were obtained in moderate yields for the aldehydes bearing electron with drawing groups (entries 4-7, Table II-5) and in modest yields for β-enals bearing electron donating groups (entries 2, 3, 8, TableII-5). In addition, it was able to achieve the Michael asymmetric synthesis in douse conditions without co-catalyst substances such as bases or acids contrary to previous settings. The series of aromatic pyrazolidine (4) obtained by Cordova characterised with moderate yields (up to 77%) and excellent enantionselectivity in majority of case (up to 99 %) using a mixture of hydrazine 2c (0.3 mmol), aromatic aldehyde 2 (0.25 mmol), catalyst 3a (20 mol%) in toluene (0.5 mL) was stirred at 4^{o}C at for four days, table II-5.

Table II-5. Asymmetric synthesis of aromatic pyrazolidines[a].



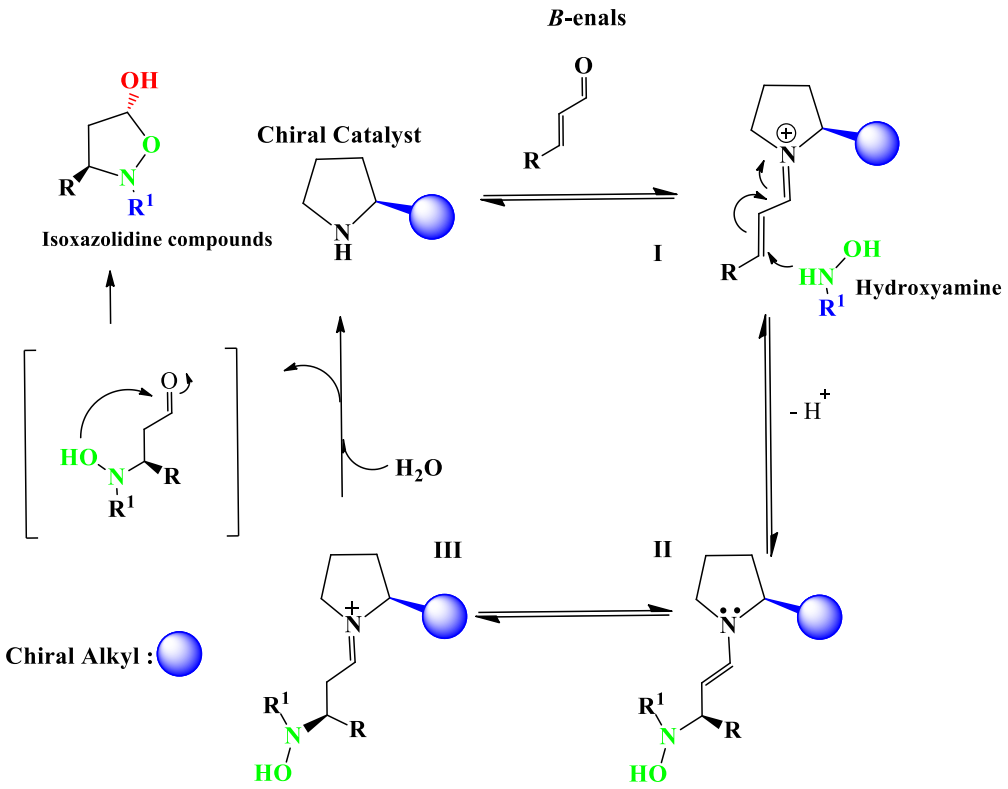
2c **2** **4**

Entry	R	Yield [%][b]	ee [%][c]
1		64	**99**
2		48	**98**
3		47	**99**
4		62	**99**
5		59	**99**
6		68	**99**
7		**77**	**99**
8		45	**99**
9		68	**99**

[a] Experimental condtions: a mixture of hydrazine **14a** (0.3 mmol), aldehyde **1** (0.25 mmol), catalyst **3f** (20 mol%) in toluene (0.5 mL) was stirred at 4 oC for 144 h. [b] Isolated yield after silica-gel column chromatography.
[c] Determined by chiral HPLC analysis. The α:β ratio of **15** was always >20:1 as determined by 1H NMR analysis of the crude reaction mixture. [d] Reaction time was 92 h.

II.3 Aza-Michael Reaction Mechanism of 4-Substituted pyrazolidines obtained for β-unsaturated aldehydes

We have offered the most important researches related to Aza-Michael reaction between aromatic or aliphatic *α, β*-unsaturated aldehydes and various hydrazine under iminium activation. According to Cordova and Wang [11-41], the iminium activation started with the formation of delivers iminium intermediate (I) by the condensation of *β*-enals (aromatic or aliphatic alkyls) and the organocatalyst. Next, a nucleophilic Aza-Michael attack performed by hydrazine on the Si-face of the iminium intermediate gives an enamine intermediate (II). The hydrolysis on the iminium ion (III) regenerates the catalyst to afford the pyrazolidinol product, Scheme II-4.



Scheme II-4. Catalytic cycle of iminium activation of Michael reaction.

II. 4 Asymmetric Synthesis of Isoxazolidine derivatives

II. 4.1 Isoxazolidines derivatives and their biological importance

Isoxazolidines and Isoxazolidinones are five-membered heterocyclic systems with one oxygen and one nitrogen atom at adjacent positions. The great interest associated with this class of compounds is based on their versatility as key intermediates in the synthesis of a variety of natural compounds, including (alkaloids, *β*-amino acids, *β*-lactams, and amino sugars) and as unnatural biologically and medicinally important congeners [43-48]. They used as biologically active compounds, such as antifungal [49], anti-tuberculosis [50], antiviral [51], and cytotoxic agents [52]. In addition, they are core structures in biologically active compounds such as Pyrinodemin [53a], PR967-234FB [53b, c], and Arenediyne [54-5], figure II-2 [47, 49]. These compounds exhibit cytotoxicity, anti-fungal activity, anticancer and can serve as transcriptional activators [53] respectively, may be ascribed to the easy cleavage of the N—O bond with formation of more reactive species, for example the chiral *β*-amino alcohols[56-57] and homonucleosides witch have a potential antiviral capabilities [58].

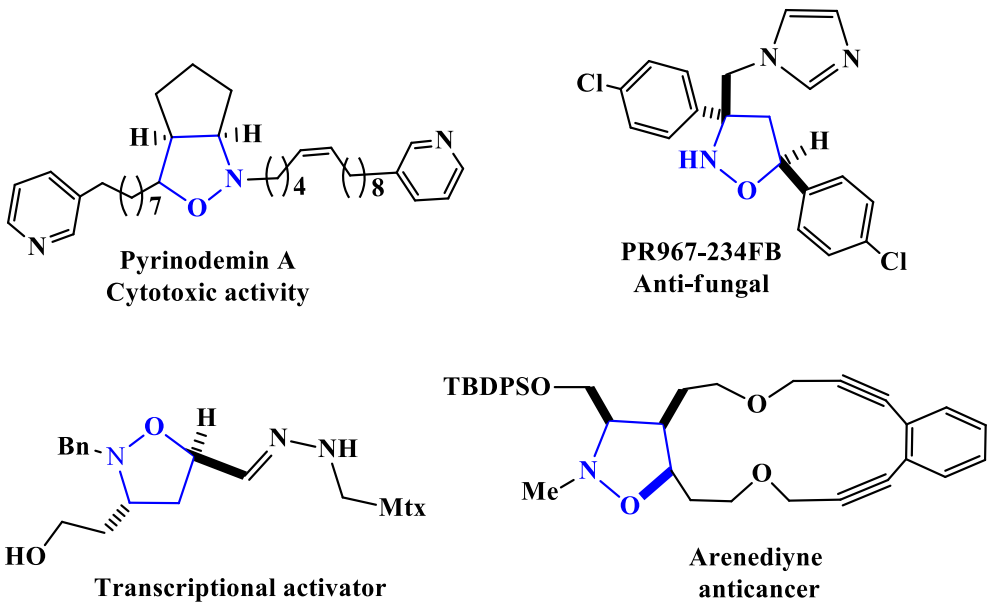


Figure II-2. Biologically Active Isoxazolidines.

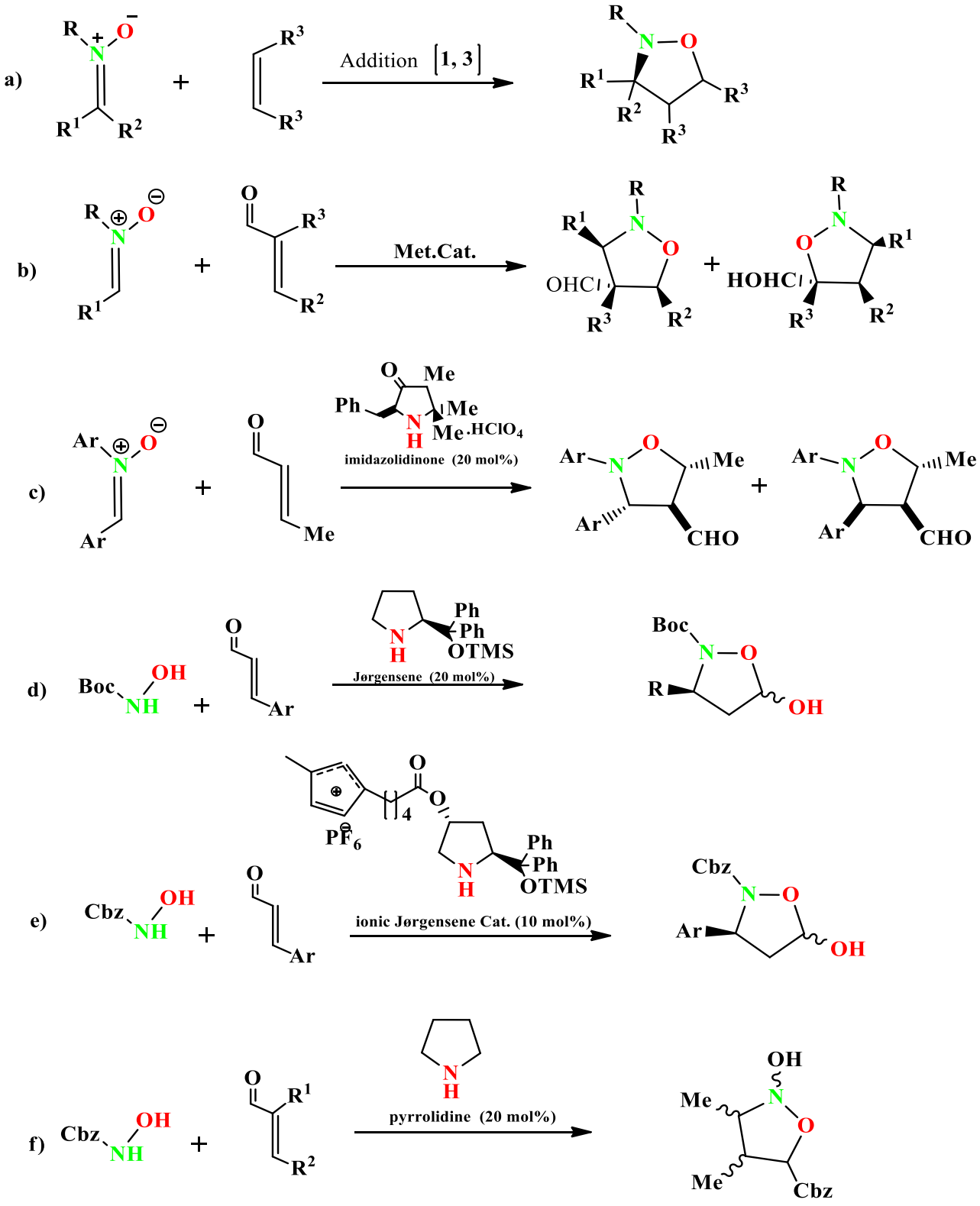
II.4.2 Direct Catalytic Synthesis of Isoxazolidine Derivatives

Despite the interest and potential of isoxazolidine compounds as promising candidates in organic synthesis [58] and drug discovery [59], the number of available synthetic procedures for the stereoselective preparation of isoxazolidine and/or isoxazolidinone is still very limited. Over the last 20 years, the 1,3-dipolar cycloaddition of nitrones is the most-versatile and reliable synthetic route to isoxazolidines [61,62], on the base of α, β-unsaturated aldehydes dipolarophiles and new chiral metal and amino organic catalysts have allowed the synthesis of a plethora of densely substituted diastereomeric and enantiomerically pure isoxazolidines [62d], scheme II-5a .

In 2010, Nàjera and Sansano [62d] and later Hashimoto and Maruoka [63] performed an in depth analysis of the papers devoted to the synthesis of 5-Substituted isoxazolidines from α, *β*-enals by means of the metal catalyst space, Scheme II-5b. Coincident with this area, asymmetric amino catalysis also began gathering momentum. Its versatile options have been strikingly demonstrated in the synthesis of isoxazolidines through the [3+2] cycloaddition of *α, β*-enals and nitrones. In 2000, MacMillan and co-workers employed the Brønsted acid salts of imidazolidinone in this reaction, scheme II-5c. After these works and in 2007, Michael/Aza-Michael organocatalytic have come into focus and become a powerful synthetic approach that allows the construction of structurally diverse isoxazolidines, in one step, and saves time, effort, and production costs by the use of hydroxylamine derivatives and α, β-unsaturated aldehydes as key synthons in the presence of several amino catalysts [64-67]. In particular, Jørgensen catalysts have gained considerable attention were found to be owing to the reversible activation of an *α, β*-unsaturated aldehyde by an enamine [68-69, 73] and an iminium ion [68, 70, 71] activations.

Principally, Sergei Zlotin [71], Armando Córdova [64] and Jung Woon Yang [65] and Abert .Moyano [67] have investigated in the isoxazolidine with Jørgensen orgnocatalysts, they contributed a lot in the evolution of Michael reaction between substituted hydroxylamine and *α, β*-unsaturated[67] aldehydes or *β*-

unsaturated aldehydes [64-65] as reactive substrates and interest factor for reaction efficiency, regio- and stereoselectivity [64, 67]. In the next part, we study these protocols systematically to produce the 3 and 4-Substituted isoxazolidines and isoxazolidinones. In particular, as in pyrazolidine part, that we have not found syntheses based of α-enals on the majority of bibliographic resources, such as show below in Scheme II-5d-f.



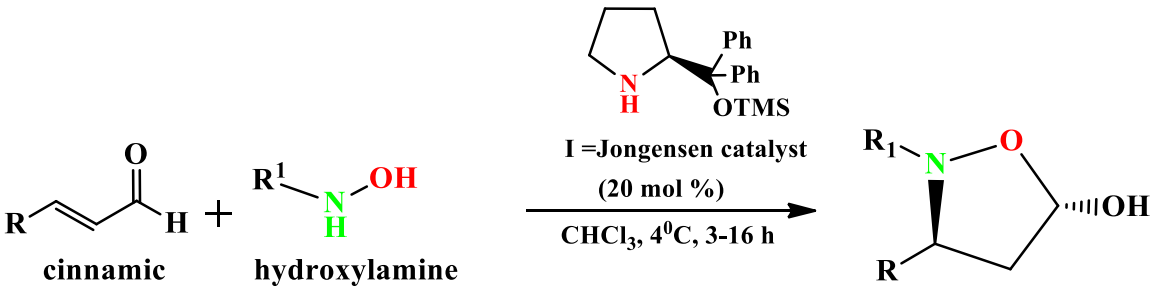
Scheme II-5. Synthetic routes for the synthesis of 3 and 4-Substituted isoxazolidines and isoxazolidinones from α, β-enals or β-enals.

II.4.3 Michael/Aza-Michael Reactions from aliphatic α, β-enals and substituted hydroxylamine

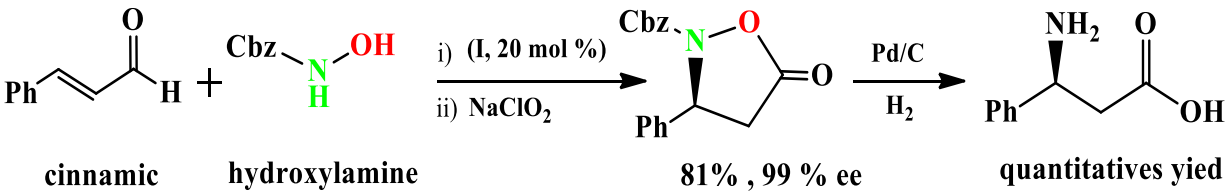
Practically, A. Córdova [64] and A. Moyano [67] provided the most attractive synthesis of isoxazolidine compounds based of the substituted hydroxylamine and *α, β*-unsaturated aldehydes in the presence of secondary amines as organcatalysts via Aza-Michael/cyclization reaction under iminium activation. Across their results, we find that both of them have largely adjusted to the chosen of the substituted hydroxylamine as nucleophile substrate, but with two various models of unsaturated aldehydes, as shown below. Moreover, we found great similarity in the general methodology and the interactions achieved for Michael reaction despite the different experimental conditions.

Firstly in 2006, Armando Córdova et al reported the asymmetric synthesis of isoxazolidine derivatives through the Aza-Michael reaction between cinnamic as aromatic *β*-unsaturated aldehydes and *N*-Boc-protected-hydroxylamine or benzyloxycarbonyl-hydroxylamine in the presence several organocatalysts. Their final chiral 3-Substituted 5-hydroxyisoxazolidines were obtained in good yields (up to 94%) and excellent enantioselectivity (up to 99%ee) in the presence of Jørgensen catalyst (3a), which are converted in one-pot to N-protected 5-oxazilidinones (up to 90%ee) by oxidation using the $NaClO_2$ or in two steps to β-amino acids (up to 99% ee), table II-6 and scheme II-6.

Table II-6. Scope of the organocatalytic Michael reactions to the 3-Substituted 5-hydroxyisoxazolidines**.**



Entry	R	R^1	Yield (%)	ee (%)
1	Ph	Boc	80%	99%
2	Ph	Cbz	94%	99%
3	4-Br-C_6H_4	Boc	80%	97%
4	4-NO_2-C_6H_4	Boc	75%	98%
5	CO_2Et	Cbz	85%	97%
6	n-Bu	Boc	94%	91%

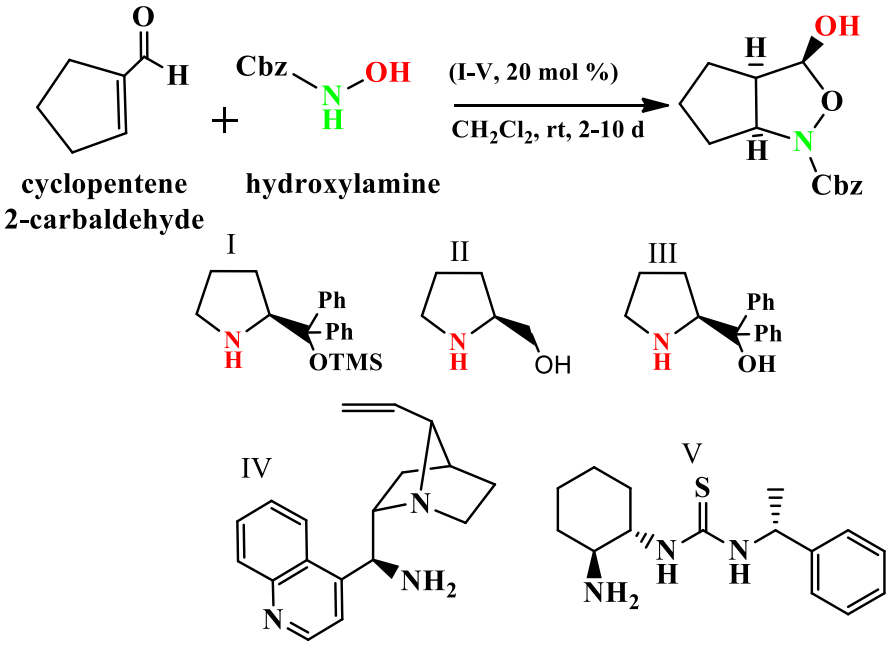


Scheme II-6. Asymmetric synthesis of β-amino acid.

Secondly, in 2016, Albert Moyano followed the same strategy with (benzyloxycarbonyl) hydroxylamine as nucleophilic substrate but with *α*-branched *α, β*-unsaturated aldehydes and used chiral amine catalysts in order to develop an original catalytic asymmetric version of Michael addition/cyclization. In this context, Albert selected the cyclopentene-2-carbaldehyde as an acceptor of Michael and used Jørgensen catalyst (S-diphenylprolinol trimethylsilyl ether) as a chiral amine catalyst. Their final chiral and achiral 4-Substituted 5-hydroxy isoxazolidines were obtained in moderate yields (up to 90%) and excellent enantioselectivity (up to 92% er). Which are converted in one-pot to 4-Substituted isoxazilidinones (up to 92% er) by oxidation using pyridinium

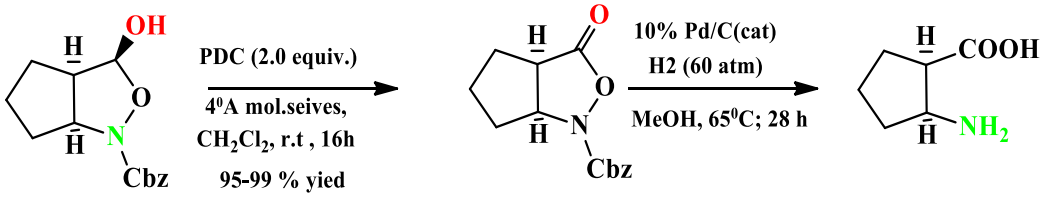
dichromate (PDC) in the presence of 4 Å molecular sieves, or in two steps to give racemic cispentacin quantitative yield, table II-7 and Scheme II-7.

Table II-7. Scope of the organocatalytic Michael reactions to the 4-Substituted 5-hydroxyisoxazolidines.



Entry	Catalyst	Time[d][a]	Yield(%)[b]	er[c]
1	I	10	80%	91:9
2	II	5[a]	94%	38:62[e]
3	III	6[f]	80%	-
4	IV	4	75%	38:62[e]
5	V	8	85%	26:74[e]
6[g]	V	2	94%	33:67[e]

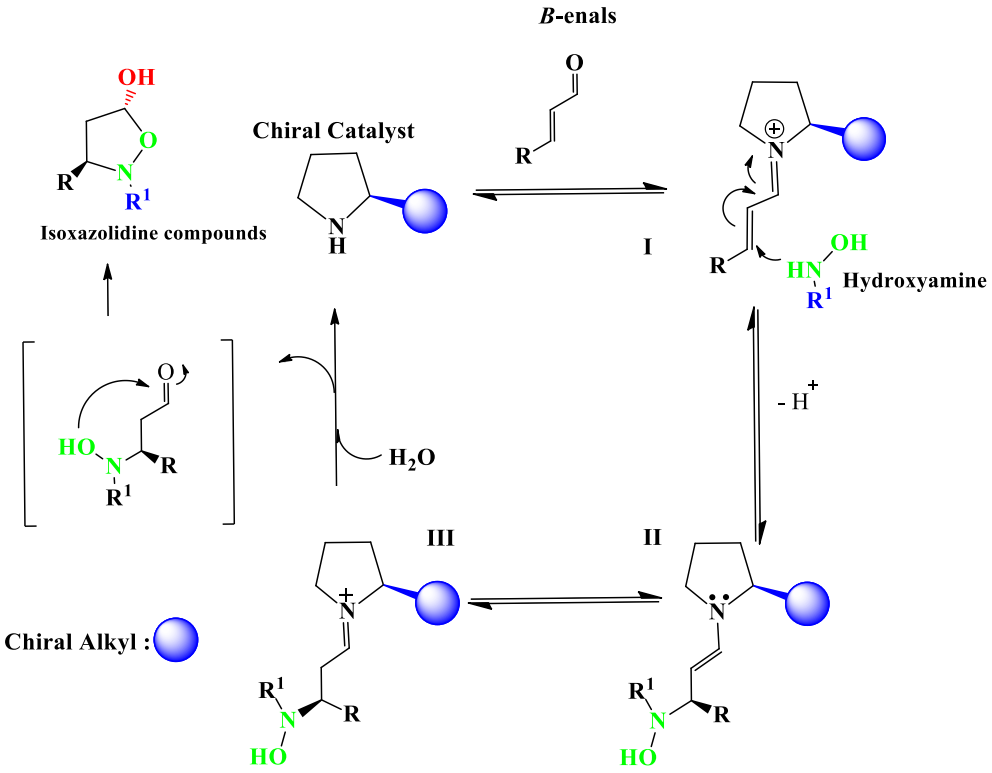
[a]Time necessary for consumption of 3, monitored by ^{1}H NMR spectroscopy.[b]Yield of isolated 4 after chromatographic purifica- tion. [c] Determined by chiral HPLC analysis of 5. [d] Reaction stopped before completion. [e] The major enantiomer had the con- figuration (3aR, 6aS). [f] No reaction was observed after 6 d at room temperature. [g] Reaction performed in toluene in the presence of water (2.0 equiv.) and acetic acid (0.15 equiv.).



Scheme II-7. Synthesis of 4,5-disubstituted N-Cbz-isoxazolidinones and racemic cispentacin.

II.5 Michael Reaction Mechanism of 4-Substituted Pyrazolidines obtained by *β*-unsaturated aldehydes

In summary, the precedent part select the most important researches related to Michael reaction between α, β-unsaturated aldehydes or *β*-unsaturated aldehydes and various hydroxylamine under iminium activation. According to A. Cordova and A. Moyano [64, 67], the iminium activation started with the formation of delivers iminium intermediate (I) by the condensation of *β*-enals or *α, β*-enals and the organocatalyst. Next, a nucleophilic Aza-Michael attack performed by hydrazine on the Si-face of the iminium intermediate gives an enamine intermediate (II). The hydrolysis on the iminium ion (III) regenerates the catalyst and to afford the isoxazolidine products, Scheme II-8.



Scheme II-8. Catalytic cycle of iminium activation of Michael reaction from *β*-enals.

II.6 Our strategy

In conclusion, the organocatalytic Michael and Aza-Michael reactions of amines with *α, β*-unsaturated aldehydes has attracted our attention as one of the most effective methods for the synthesis of chiral heterocyclic structures with C-N, N-N and O-N bonds. We decided to investigate new protocols of Michael and Aza-Michael reactions for the synthesis successively the new chiral molecules of 4-substituted Pyrazolidines and Isoxazolidines. we use of α-branched unsaturated aldehydes with aliphatic and aromatic chains as original Michael acceptors for activated 1-Boc-2-(4-nitrobenzenesulfonyl)hydrazine (2a) or 1,2-bis-(p-toluenesulfonyl)-hydrazine (2b) and N-carbonyl (benzyloxy) hydroxylamine, respectively for obtaining pyrazolidine and isoxasolidine derivatives.

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Practical section

Chapter III

Section of Results and Discussion

III.1 Section of Results and Discussion

III.1.1 Introduction

The organocatalytic Michael and Aza-Michael reactions of amines with α, β-unsaturated aldehydes has attracted much attention as one of the most effective methods to prepare the chiral heterocyclic structures with C-N, N-N and O-N bonds [1-2]. The aim of this thesis is to investigate new protocols of Michael and Aza-Michael reactions for the synthesis successively the new chiral molecules of 4-Substituted pyrazolidines and isoxazolidines. Furthermore, these synthetic protocols are environmentally friendly and comply with the regulations of Green Chemistry.

We have used of α-branched unsaturated aldehydes with aliphatic and aromatic chains as original Michael acceptors for activated 1-Boc-2-(4-nitrobenzene sulfonyl) hydrazine (**2a)** or 1,2-bis(p-toluenesulfonyl) hydrazine (**2b)** and N-carbonyl (benzyloxy) hydroxylamine (**10)**, respectively for obtaining pyrazolidine and isoxasolidine derivatives. We have found that the pyrrolidine/benzoic acid-catalyzed reaction of α-substituted propenals such as methacrolein, 2-benzylpropenal and 2-(n-hexyl)propenal with activated hydrazines takes place in very good yields (83%–99.6%) under very mild conditions to afford 4-substituted pyrazolidin-3-ols (as diastereomer mixtures); subsequent oxidation with PCC affords the corresponding-4-substituted-3-pyrazolidinones in essentially quantitative yields. In a similar way, 4-substituted isoxazolidinones are obtained with N-Cbz-hydroxylamine as a reagent. The use of chiral diarylprolinol trimethylsilyl ethers as catalysts allows the synthesis of several of these compounds in optically active form, in some cases with excellent enantioselectivity (up to 96:4 er).

III.1.2 Strategy of investigation work

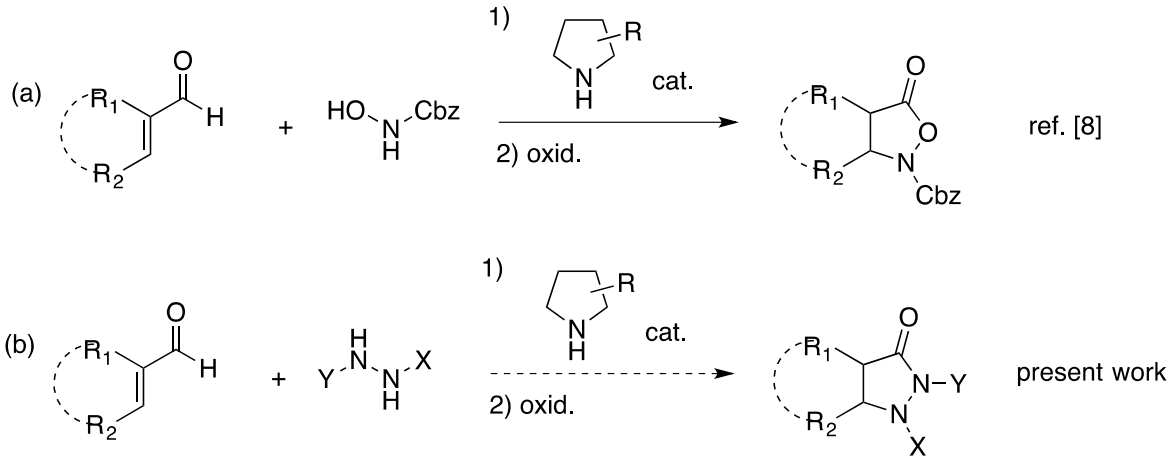
III.1.2.1 Introduction

The organocatalytic approaches to the synthesis of pyrazolidine compounds, based either on the amine-catalyzed **[1a, 2]** or on the carbene-catalyzed **[3]** reaction of α, β-unsaturated aldehydes with hydrazine derivatives and subsequent oxidation of the intermediate pyrazolidinols, have been described, enabling their preparation in optically active form **[4–6]**. Although these approaches are highly interesting, all of

them have the common limitation that they have been applied only to β-substituted enals, so that they can exclusively lead to 5-substituted-3-pyrazolidinones.

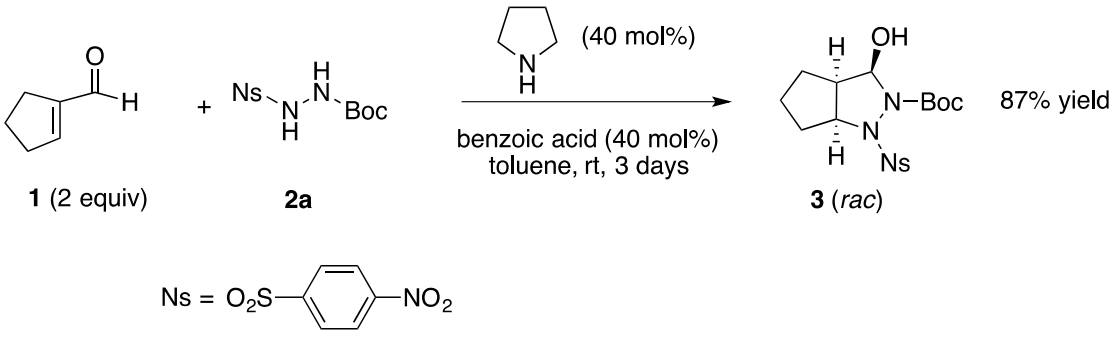
III.1.2.2 Racemic synthesis of Pyrazolidinol 3 and 5-forum hydrazine 2a

In the framework of Albert Moyano and al on the organocatalytic synthesis of *α, β*-disubstituted-β-amino acids, we had found that the pyrrolidine-promoted Aza-Michael addition/cyclization of N-protected hydroxylamines to acyclic *α, β*-unsaturated *α, β*-disubstituted enals took place in several instances with excellent yields and good diastereoselectivities [1b]. So, we set out to investigate if the pyrrolidine (1) secondary amine-catalyzed reaction of these branched enals with substituted hydrazines, followed by oxidation of the resulting pyrazolidin-3-ols, would provide a general route to *4, 5*-disubstituted-*3*-pyrazolidinones , scheme III-1.



Scheme III-1. Background (**a**) and goals (**b**) of the present work.

We began our research by examining the pyrrolidine-catalyzed addition/cyclization of cyclopentene-1-carboxaldehyde (**1**) with 1-*Boc*-2-(4-nitrobenzenesulfonyl) hydrazine (**2a**) [1a] using benzoic acid as a co-catalyst. After some experiments, we found that by using 40 mol % of both pyrrolidine and benzoic acid the expected bicyclic pyrazolidin-3-ol **3** was obtained in excellent yield (87% isolated yield after chromatographic purification) and as a single isomer (dr > 30:1), after three days in toluene at room temperature (r.t.), Scheme III-2.



Scheme III-2. Synthesis of the bicyclic pyrazolidinol **3**.

The ^{1}H and ^{13}C NMR spectral data for bicyclic pyrazolidinol 3 are shown in figure III-2 and III-3. In the ^{1}H NMR is characterized by the appearance of two doublet picks at 3.38 ppm which correspond to the proton of the OH group and a multiple picks for the proton H-8 at 5.42 ppm. Protect group (-boc) of hydrazine reagent 2a resonate with single pic at 1.24 ppm and the two proton in the position 9 and 10 resonates respectively at 2.72–2.77 ppm and 4.73–4.78 ppm as a multiples peaks. Bicyclic pyrazolidinol 3 (figure III-1) formation is confirmed by the disappearance of the signal at 9.78 ppm of carbonyl group **[13]** for the premier reagent cyclopentene-1-carboxaldehyde (1) and the appearance of OH group as a doublet signals. More there, the phenyl group appearance in the aromatic area with the resonance of 8.11 ppm and 8.29 ppm. In ^{13}C NMR, the signal of the group C-OH observed at 91.89 ppm and the two equivalent carbons of phenyl group resonate at 123.71 ppm and 131.1 ppm.The diastereomeric ratio (dr > 30:1) was obtained in the position of proton 8 for the two diastereomeric compounds of pyrazolidinol 3.

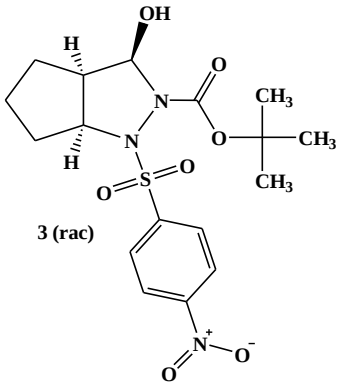


Figure III-1. *Tert-Butyl* (3*RS*, 3a*RS*, 6a*SR*)-3-Hydroxy-1-((4-nitrophenyl) sulfonyl) hexahydrocyclopenta [*c*] pyrazole-2(1*H*)-carboxylate, **3**.

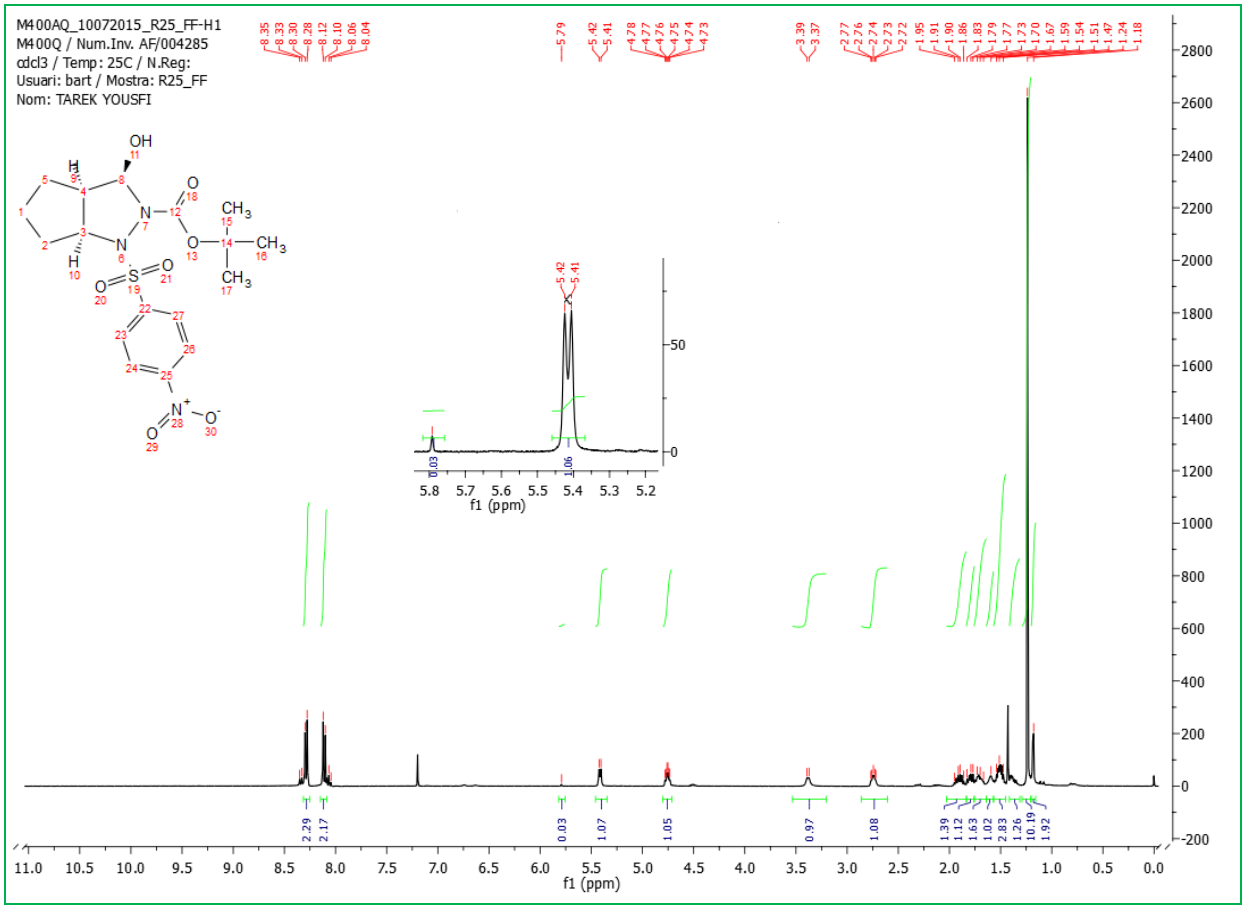


Figure III-2. ^{1}H-NMR of (400 MHz) *tert*-Butyl (3*RS*,3a*RS*,6a*SR*)-3-Hydroxy-1-((4-nitrophenyl) sulfonyl) hexahydrocyclopenta [*c*] pyrazole-2(1*H*)-carboxylate, **3**.

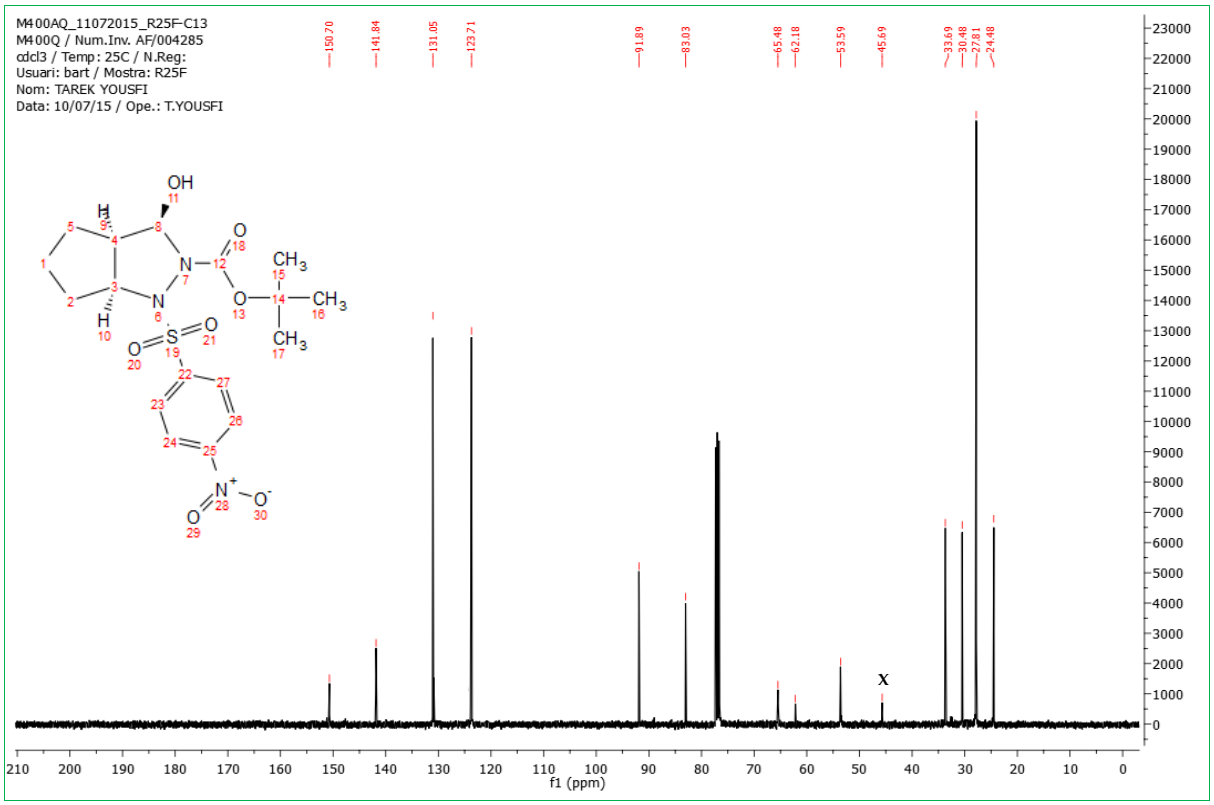
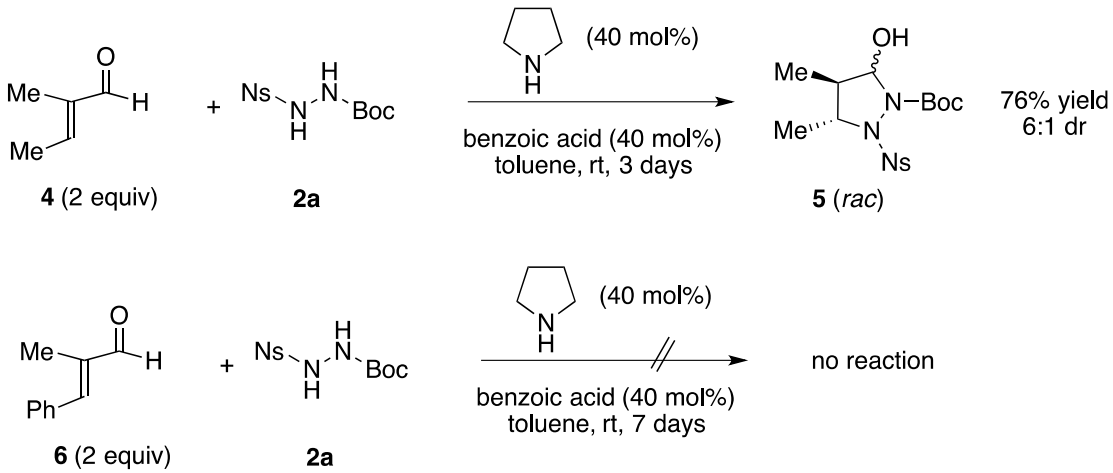


Figure III-3. ^{13}C-NMR (100.6 MHz) of *tert*-Butyl (3*RS*, 3aRS,6aSR)-3-Hydroxy-1-((4-nitrophenyl)sulfonyl) hexahydrocyclopenta [*c*] pyrazole-2(1*H*)-carboxylate, **3**.

Next, we tried the same reaction conditions with acyclic α, β-substituted enals. While the reaction with tiglic aldeyhyde ((E)-2-methylbutenal, 4) led to the formation of the pyrazolidinol **(5)** (76% yield, 6:1 dr) after 3 days, we found that (E)-2-methyl-3-phenylbutenal 6 was completely unreactive, no product being detected after 7 days of stirring at r.t., scheme III-3.



Scheme III-3. Reaction of hydrazine **2a** with the acyclic α, β -disubstituted enals **4** and **6**.

The ^{1}H and ^{13}C NMR spectrum data for pyrazolidinol **5** are shown in figure III-5 and III-6. In the ^{1}H NMR is characterized by the appearance of two doublet picks at 2.86-2.87 ppm, which correspond to hydroxyl group at position 5 of pyrazolidine ring. A multiple picks at 5.46–5.48 ppm related to neighbor proton H-5 of hydroxylamine, the Boc- group resonates with single peak at 1.26 ppm and the two protons of pyrazolidinol ring in the position 1 and 2 resonates respectively at 1.80–1.87 ppm and 3.72–3.79 ppm with multiples pics. Bicyclic pyrazolidinol **5** (figure III-4) conceptions is confirmed by the disappearance of corresponding signal of carbonyl group at 9.68 ppm [13] related to tiglic aldeyhyde 4 and the appearance of hydroxyl group. In addition, the appearance of the methyl groups separately resonates at 1.00 and 1.36 with doublet signal and density of 6 protons.In ^{13}C NMR, the corresponding carbon 5 connected to hydroxyl group observed at 86.6 ppm and the last two-methyl groups vibrates 11.1 and 20.7 ppm, figure III-6. The diastereomeric ratio (dr = 6:1) was calculated in the position of proton 5 and in the position of Boc- group for the two diastereomeric compounds of pyrazolidinol 5 as shows in ^{1}H-NMR , figure III-5.

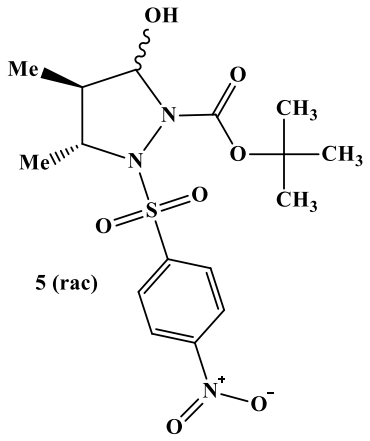


Figure III-4. *tert*-Butyl 3,4-*trans*-5-Hydroxy-3,4-dimethyl-2-((4-nitrophenyl)sulfonyl)-pyrazolidine-1-carboxylate, **5**.

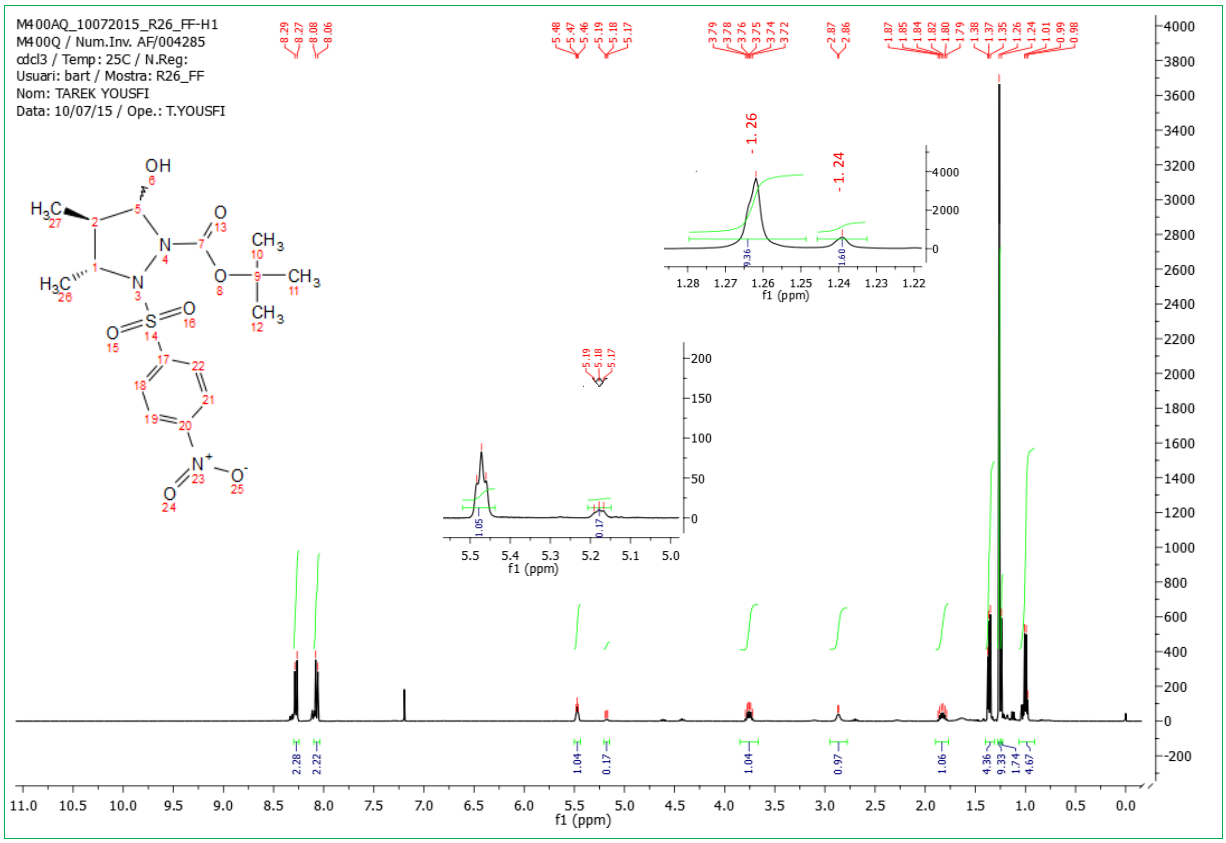


Figure III-5. ^{1}H-NMR (400 MHz) of *tert*-Butyl 3, 4-*trans*-5-Hydroxy-3,4-dimethyl-2-((4-nitrophenyl)sulfonyl)-pyrazolidine-1-carboxylate, **5**.

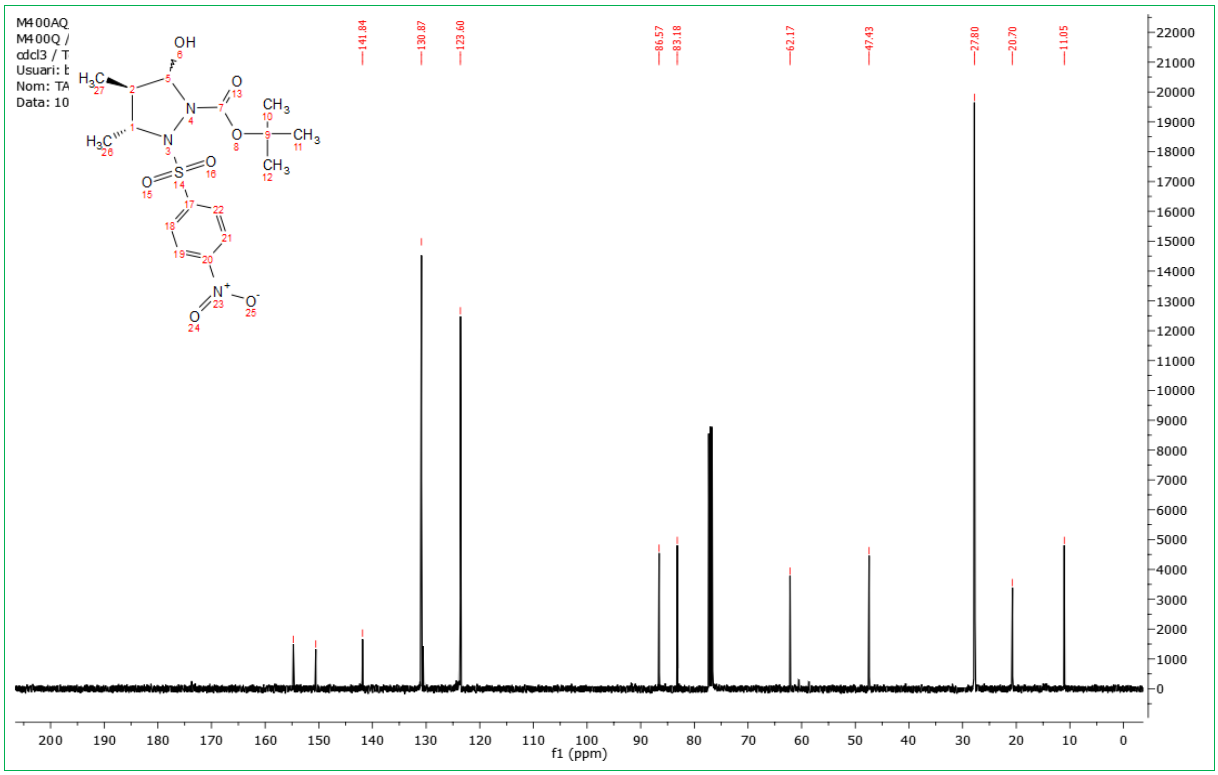


Figure III-6. ^{13}C-NMR (100.6 MHz) of *tert*-Butyl 3, 4-*trans*-5-Hydroxy-3, 4-dimethyl-2-((4-nitrophenyl) sulfonyl)-pyrazolidine-1 carboxylate, **5**.

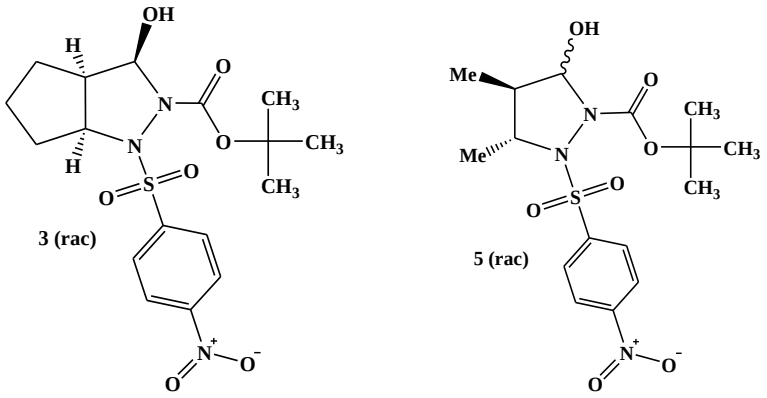


Figure III-7. Pyrazolidinol 3 and 5.

Table III-1. Primaries pyrazolidin-3-ols **3 and 5** obtained with hydrazine 2a and acyclic α, β-disubstituted enals **4** and cyclic aldehyde **1**.

Pyrazolidinol	Reactants	Brute formula	M gr.mol $^{-1}$	Reaction Time (d)	Yield [1]	dr [2]	Fusion point °C
3	1, 2a	$\mathbf{C_{17}H_{23}N_3O_7S}$	413.23	3	**87 %**	>30:1	**83–85 °C**
5	4, 2a	$\mathbf{C_{16}H_{23}N_3O_7S}$	401.26	3	**76 %**	6:1	**71–73 °C**

[1] Yield of isolated product after chromatographic purification; [2] By ^{1}H-NMR.

The reaction yields of pyrazolidinol 3 and 5 were heavily dependent on the substitution pattern of the enals and we found that both reactions are slows which are stayed three days at room temperature. Pyrazolidinol 3 and 5 were obtained as inseparable mixtures of diastereomers and after recrystallization in the ratio of (1:9, chloroform/hexanes); as a colorless solid for the both products. Good yield were obtained with cyclopentene-1-carboxaldehyde as cyclic aldehyde 1 ((1,2a), table III-1, entry 1) but we can see a monthly yield and with Tiglic aldehyde 4 ((4, 2a), table III-1, entry 2) as acyclic with α, β-branched enals. These primaries results confirmed the theoretical of MacMillan and co-workers [7-8], this organocatalytic activation mode of Aza-Michael addition/cyclization exploits the reversible condensation between a chiral amine catalyst as pyrrolidine (scheme III-1, III-2) and an unsaturated aldehyde 1 and 4 to form an iminium ion intermediate. In this system, a rapid equilibrium exists between an electron deficient and an electron-rich state, which effectively lowers the LUMO energy of the *p* system and enhances its susceptibility toward nucleophilic attack [8], which explains the case of good yield for the pyrazolidinol (3) reactions between

hydrazine (2a) and cyclopentene-1. Importantly, central to the success of pyrrolidine catalyst as an iminium activator system is its ability to effectively and reversibly form a reactive iminium ion intermediate but these reactivity depend the steric limitation and the configuration of the substrate of α, β-branched enal [7], that explained by the reactivity of the pyrazolidinol (5) reaction in the presence of the tiglic aldeyhyde ((E)-2-methylbutenal, 4) with E confirmation as a favorably configuration for nucleophilic attack of hydrazine 2a, Scheme III-3. In addition, the low steric limitation in the presence of two methyl groups in position α, β-branched enal of tiglic aldeyhyde 4 positively influences the reaction route of pyrzolidinol (5).Contrary, the supplementary steric limitation with methyl and phenyl groups in (E)-2-methyl-3-phenylbutenal phenylbutenal 6 was completely unreactive and no product being detected after 7 days of stirring at r.t., scheme III-3.

III.1.2.3 Oxidation of pyrazolidinol 3 and 5

We found that the two mild oxidizing agents PCC and PDC carried out the oxidation reaction of pyrazolidine derivatives[1], we have repeatedly tried oxidation reaction but it was completely unreactive, no product being detected after 4 days of stirring at r.t in DCM as solvent. We have introduced molar excesses to 5 equivalent for the both oxidizing agents PCC and PDC. Contrary to what we had observed for the corresponding isoxazolidinols [1b], attempted oxidation of both (3) and (5), either with pyridinium chlorochromate (PCC), or with pyridinium dichromate (PDC), failed to cleanly give the desired pyrazolidinones and the spectral data ^{1}H and ^{13}C NMR confirmed these results by obtaining the same significant spectras shows in the figures (III-2 and III-3) and (III-5 and III-6) correspondingly for the pyrazolidinols (3) and (5) primers.

In addition to these fallouts, we have established the 2D ^{1}H NMR (NOSY) analysis in order to confirm the relationship between the neighboring proton and the hydroxyl group of the pyrazolidinol (3). In the 2D ^{1}H NMR (NOSY, figure IV-8) is illustrated the existence of different protons in the positions 9, 10 and 8 at 2.74 ppm, 4.73 ppm and 5.42 ppm respectively (figure III-8), which forms covalent bonds (C-H) separately in the pyrazolidinol ring of the pyrazolidinol structure (3) isolated after oxidation. Also, the NOSY NMR analysis supported the presence of hydroxyl group at

position 8 and confirmed the inactivity oxidation reaction by PCC and PDC according to the steric hindrance around the hydroxyl group, which related to the presence of protect group (Boc).

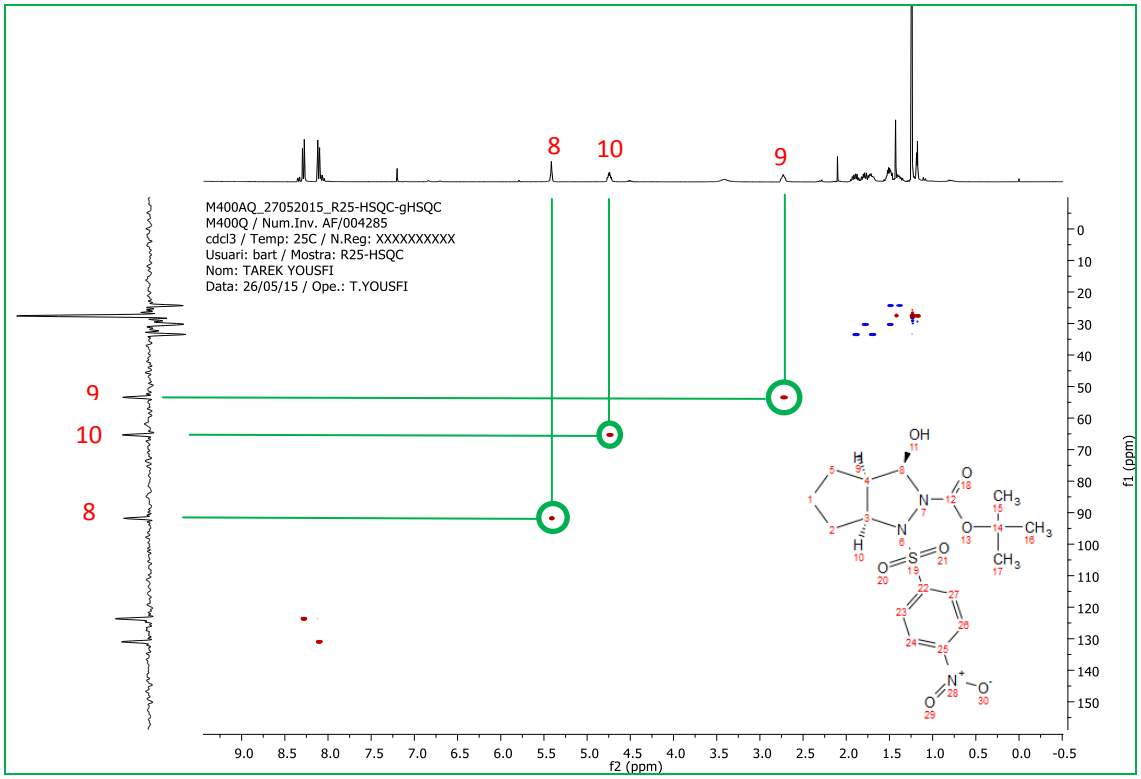


Figure III-8. NOSY-NMR (100.6 MHz) of *tert*-Butyl (3*RS*, 3aRS, 6aSR)-3-Hydroxy-1-((4-nitrophenyl)sulfonyl) hexahydrocyclopenta [*c*] pyrazole-2(1*H*)-carboxylate, **3**.

We then turned our attention to the oxidation possibility of the pyrazolidinol 3 by the pyridinium chlorochromate (PCC) as shown by the existence of traces corresponding to the oxidizer products that are present in very small quantities and they are not identified in the ^{1}H and ^{13} H NMR analysis. Contrary in HRMS analysis, as show in figure III-9 and table III-2, they are characterized by minor molecular fragments corresponding to the oxidized product $C_{17}H_{25}N_4O_7S = [M_1 + NH_4^+]^+$ and $C_{17}H_{21}N_3NaO_7S = [M_1 + Na^+]^+$ presented with the molecular fragmentation of starting pyrazolidinol (3), $C_{17}H_{27}N_4O_7S = [M_3 + NH_4^+]^+$ and $C_{17}H_{23}N_4NaO_7S = [M_3 + Na^+]^+$. Finally, we concluded that pyrazolidinol (3) is resistant to oxidizing agent PCC.

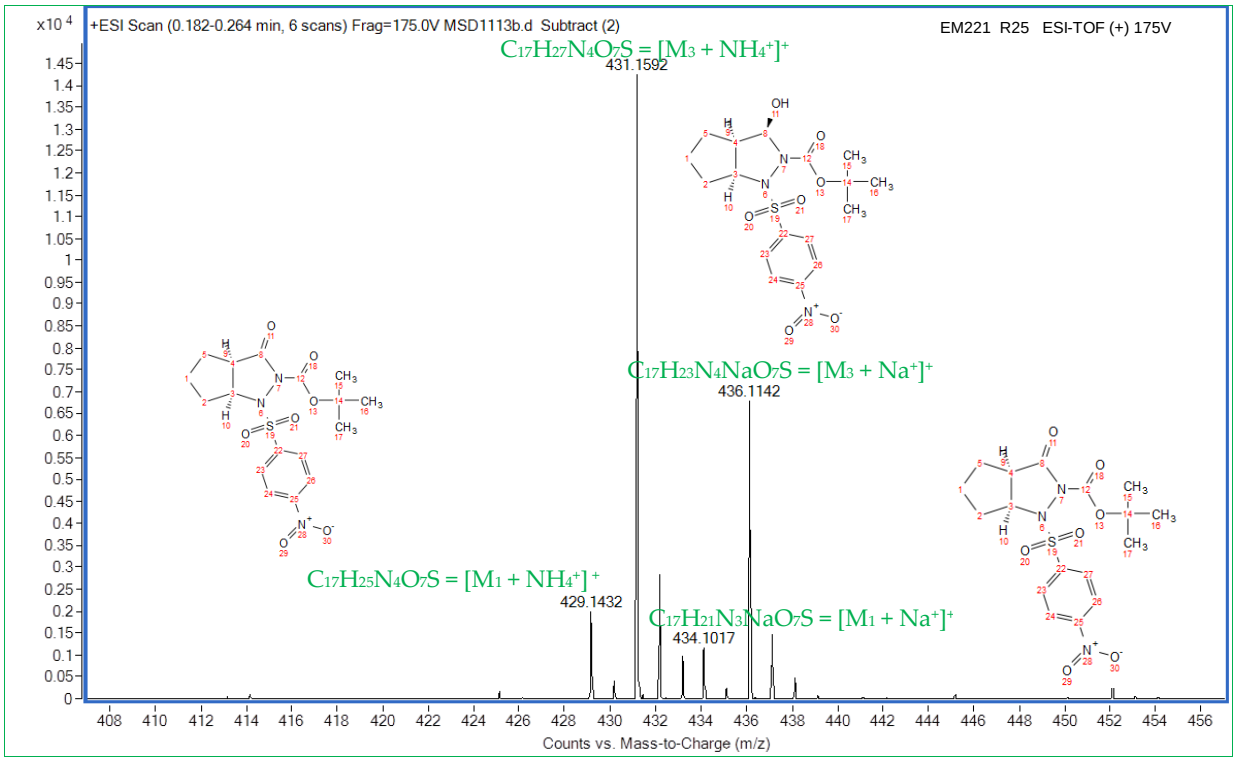


Figure III-9. HRMS analysis of bicyclic pyrazolidinol, **3.**

Table III-2. MS formula results of bicyclic pyrazolidinol **3** obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{17}H_{27}N_4O_7S$	98.94	431.1592	431.1595	97.19	0.3	0.71	$[M_3 + NH_4^+]^+$
TRUE	$C_{17}H_{23}N_3NaO_7S$	96.18	436.1142	436.1149	99.04	0.64	1.48	$[M_3 + Na^+]^+$
TRUE	$C_{17}H_{25}N_4O7S$	70.95	429.1432	429.1438	49.2	0.68	1.6	$[M_1 + NH4^+]^+$

III.1.2.4 Concluding of primaries reactions

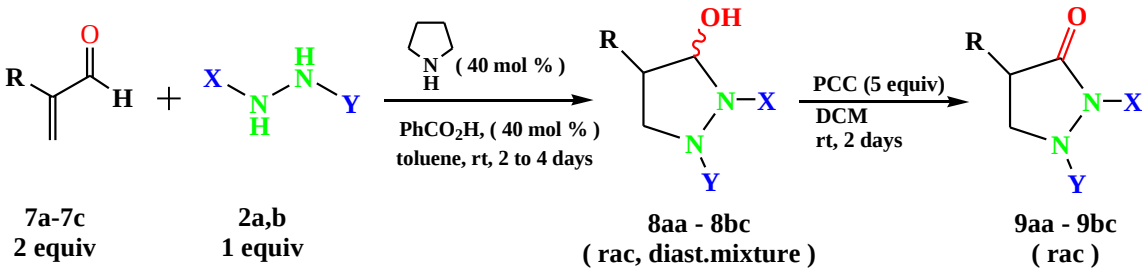
After these experiments, we have tired some preliminary decisions, in particular that the steric hindrance affects the activation mode of Aza-Michael addition/cyclization between a chiral amine catalyst as pyrrolidine and *α, β*-branched enal. In addition, the steric hindrance affects the oxidation reaction by pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC). So, we decided to reduce the steric hindrance of the intermediate pyrazolidinols by suppressing the β-substituent in the starting enals in order to increase the efficiency of Aza-Michael addition/cyclization and to reduce the reaction time , we have been applied only to α-substituted enals such as methacrolein (**7a**), 2-benzylpropenal (**7b**), and 2-(*n*-hexyl)propenal (**7c**). In our strategy, we have

investigated on the Michael and Aza-Michael reactions between the α-branched unsaturated aldehydes such as methacrolein, 2-benzylpropenal and 2-(n-hexyl) propenal as Michael acceptors to activate the 1-Boc-2-(4-nitrobenzenesulfonyl) hydrazine (2a), 1,2-bis-(p-toluenesulfonyl) hydrazine (2b), and N-carbonyl (benzyloxy) hydroxylamine (10), respectively for obtaining originals pyrazolidine and isoxasolidine derivatives.

III.1.3 Organocatalytic synthesis of pyrazolidine derivatives

III.1.3.1 Racemic 4-substituted pyrazolidin-3-ols

We were found that the pyrrolidine/benzoic acid-catalyzed reaction of the α-substituted enals methacrolein (7a), 2-benzylpropenal (7b), or 2-(n-hexyl)propenal (7c) with the activated hydrazines (2a) and 1,2-bis(p-toluenesulfonyl) hydrazine (2b) took place in very good yields (83% – 99.6%), affording the 4-substituted pyrazolidin-3-ols (8aa–8bc) as diastereomer mixtures. Without further purification, oxidation with PCC was performed to afford the corresponding-4-substituted-3-pyrazolidinones 9aa–9bc in essentially quantitative yields (94 %–99 %), scheme III-4 and table III-3.



Scheme III-4. Organocatalytic synthesis of pyrazolidin-3-ones from α-substituted enals.

Table III-3. Pyrrolidine-catalyzed synthesis of pyrazolidin-3-ols (8aa–8bc) from α-substituted enals 7a–7c and hydrazines 2a and 2b, and oxidation to the corresponding pyrazolidin-3-ones **9aa–9bc.**

Entry	Reactants	R	X	Y	Pyrazolidinol	Yield [1]	Reaction Time (d)	dr [2]	Pyrazolidinone	Yield [1]
1	**7a**, **2a**	Me	Ns	Boc	**8aa**	93%	4	4:1	**9aa**	94%
2	**7b**, **2a**	$PhCH_2$	Ns	Boc	**8ab**	83%	2	>20:1	**9ab**	98%
3	**7c**, **2a**	*n-Hexyl*	Ns	Boc	**8ac**	99.6%	2	5:1	**9ac**	99%
4	**7a**, **2b**	Me	Ts	Ts	**8ba**	88%	2	8:1	**9ba**	98%
5	**7b**, **2b**	$PhCH_2$	Ts	Ts	**8bb**	85%	2	9:1	**9bb**	97%
6	**7c**, **2b**	*n*-Hexyl	Ts	Ts	**8bc**	98%	2	10:1	**9bc**	98%

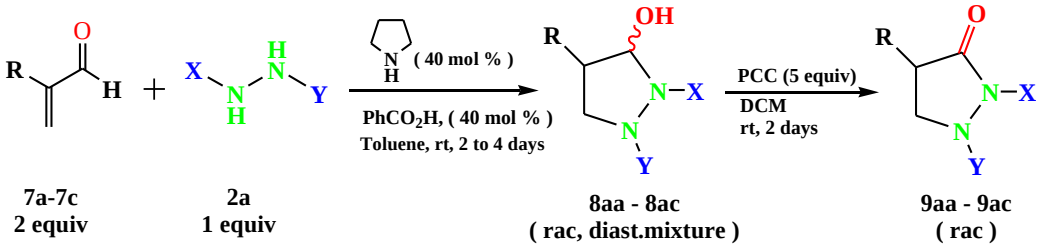
[1] Yield of isolated product after chromatographic purification; [2] By ^{1}H-NMR.

As it can be seen in the Table III-3, the Aza-Michael addition/cyclization step took place in excellent yield and high diastereoselectivity, irrespective of the nature of the hydrazine (2a or 2b) and of the acrolein substituent (methyl, benzyl, or n-hexyl). It

should be noted however that when the more hindered α-isopropyl acrylaldehyde as (3-methyl-2-methylenebutyraldehyde (7d)) was used under the same conditions, no reaction with hydrazine (2a) was observed after 7 days at rt. In our hands, *N, N'*-bis-(tert-butoxycarbonyl) hydrazine (2c), reported to give good yields of pyrazolidin-3-ols upon pyrrolidine-catalyzed reaction with cinnamaldehyde derivatives [2], failed to react with the α-substituted enals 1, 4, and 7a–7d.

III.1.3.1.1 Racemic 4-substituted pyrazolidin-3-ols from hydrazine 2a

On the light of preliminary results of phyrazolidinols (3) and (5), we started the optimization reactions between 1-Boc-2-(4-nitrobenzenesulfonyl) hydrazine (2a) as a chiral substrate for nucleophilic attack and the α-substituted enals such as methacrolein (7a), 2-benzylpropenal (7b), and 2-(n-hexyl)propenal (7c).



Scheme III-5. Organocatalytic synthesis of pyrazolidin-3-ones from hydrazine **2a** and α-substituted enals.

We found the perfect conditions for Aza-Michael addition/cyclization system, that by using 40 mol % of both pyrrolidine and benzoic acid with the presence of a molecular equivalent 2: 1 for (α-aldehydes / hydrazine 2a) in toluene at room temperature give the excellent yields 93%, 83% and 99.6% respectively for the phyrazoldinols **8aa**, **8ab** and **8ac** after chromatographic purification by column chromatography (silica gel; hexane/ethyl acetate mixtures of increasing polarity) with remarkable reduction in reaction times from three days with α,β-unsaturated aldehydes (1, 4) to two days with α -unsaturated aldehydes 7b and 7c, (figure III-10, table III-4). More, we established a good diastereoselectivity as a single isomer (dr > 20:1, entry 2, table III-4) with pyrazolidinol **8ab** as a single isomer synthesized forum a cyclic aldehyde 2-benzylpropenal (7b).

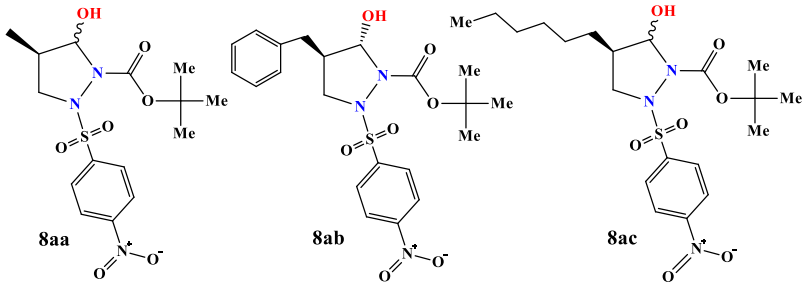


Figure III-10. Pyrazolidin-3-ols structures **(8aa–8ac)** from α-substituted enals 7a–7c and hydrazines **2a.**

Table III- 4. Pyrazolidin-3-ols products (8ba–8bc) from α-substituted enals 7a–7c and hydrazines **2a.**

Pyrazolidinol	Brute formula	M gr.mol $^{-1}$	Reaction Time ^{d}	Yield ^{1}	dr ^{2}	Fusion point °C
8aa	$C_{15}H_{21}N_3O_7S$	387.24	4	**93%**	4:1	111–114°C
8ab	$C_{21}H_{25}N_3O_7S$	463.3	**2**	**83%**	**>20:1**	122–126 °C
8ac	$C_{20}H_{31}N_3O_7S$	457.29	**2**	**99.6%**	5:1	83–85 °C

^{1} Yield of isolated product after chromatographic purification; ^{2} By ^{1}H-NMR.

The structures of compounds obtained was inferred from the ^{1}H and ^{13}C NMR and High-resolution mass (HRMS) spectroscopies, the ^{1}H NMR spectra of substituted pyrazolidinols 8aa, 8ab and 8ac (figure III-11, III-14 and III-17) confirmed the existence of hydroxyl group (–OH) in the position 5 at pyrazolidinol ring witch resonate at 3.23-3.26 ppm showed by double peaks . In the vicinity of hydroxyl group, we find the proton as a triples resonate at 5.21-5.22 ppm, 5.25-5.28 and 5.39-5.41 ppm, this confirms the blinding phenomenon of the hydroxyl group due to the presence of alkyl groups methyl, hepthyl and benzyl corresponding to the compounds 8aa, 8ac et 8ab respectively. Also, we observed the protect group (–Boc) with single pic vibrate at 1.33 and 1.36 ppm for the major isomer for these products with total integration of nine protons, this group clearly presents at 27.88 ppm and 27.90 ppm on the ^{13}C NMR spectrum of the two compounds 8aa and 8ab as shown in the two figures III-12 and III-15.

About the specific groups for each compound, we can see the methyl group of compound 8aa in the area of 1.09 -1.10 ppm as a doublet peak with three protons as the total density integration and this group visibly present at 15.04 ppm on the ^{13}C NMR spectrum, figure III-12 . In HRMS analysis confirmed the attendances of the molecular pics $[M_{8aa}+Na^{+}]^{+}$, $[2M_{8aa}+Na^{+}]^{+}$ and $[M_{8aa}+K^{+}]^{+}$ relates to the molecular

fragment of 8aa through a calculation error < 5ppm with identification success greater than 93 % , as shown in figure III-13 and table III-5. More there, the ^{1}H NMR spectrum (figure III-11) presented the presence of two sets of signals assigned to two stereisomers (cis and trans) with respect to the substituents orientation at positions 1, 4 and 5 of the pyrazolidine ring. The diastereomeric ratio (dr = 4:1) was calculated in the two positions 4 and 5 corresponding to protect group and the adjacent proton for hydroxyl group.

- ***Product 8aa***

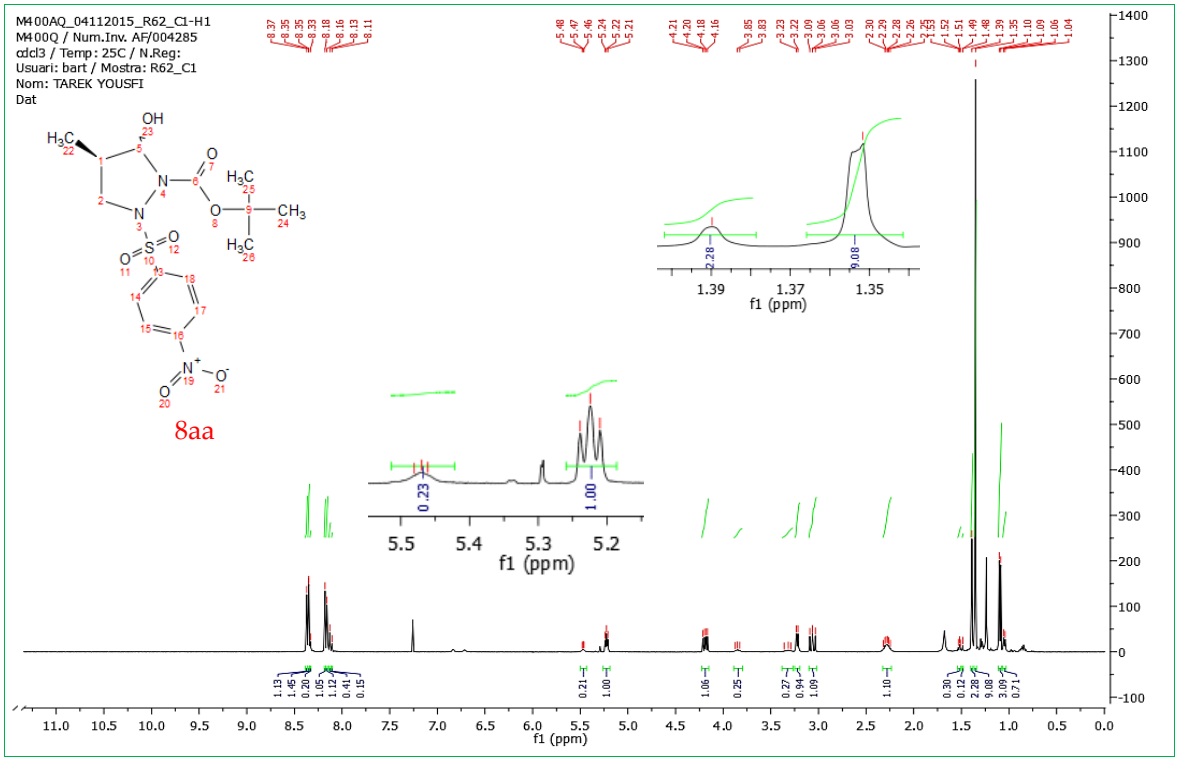


Figure III-11. ^{1}H-NMR (400 MHz) of *tert*-Butyl 5-Hydroxy-4-methyl-2-((4-nitrophenyl)sulfonyl)-pyrazolidine-1-carboxylate, **8aa**.

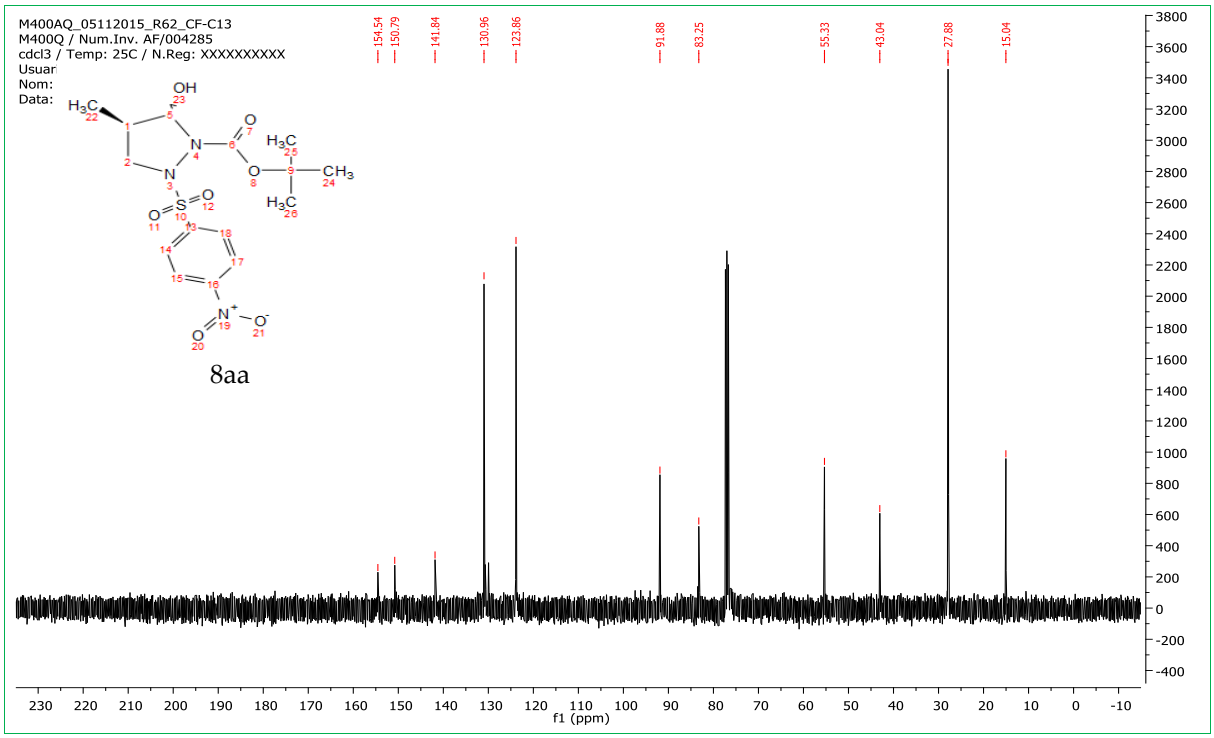


Figure III-12. ^{13}C-NMR (100.6 MHz) of *tert*-Butyl 5-Hydroxy-4-methyl-2-((4-nitrophenyl) sulfonyl) -pyrazolidine-1-carboxylate, **8aa**.

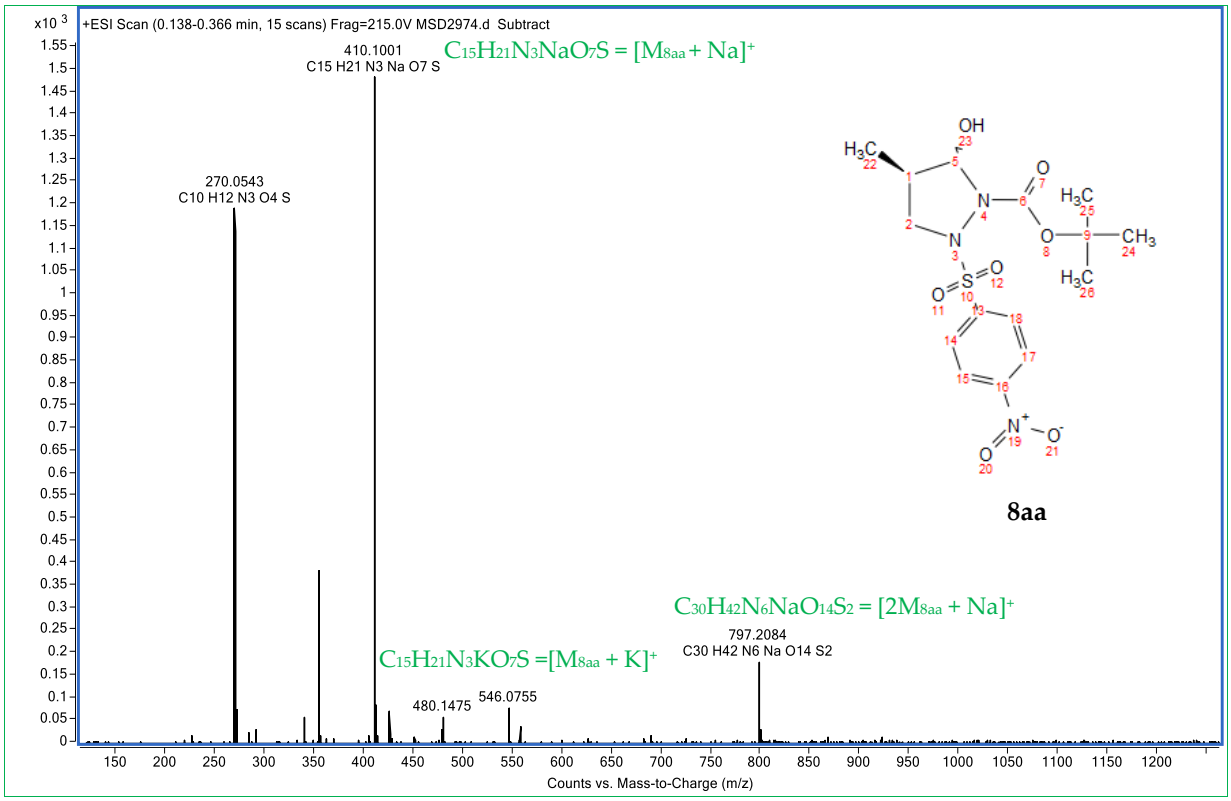


Figure III-13. HRMS analysis of pyrazolidinol, **8aa.**

Table III-5. MS formula results of pyrazolidinol **8aa** obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{15}H_{21}N_3NaO_7S$	93.76	410.1001	410.0992	94.2	-0.84	-2.05	$[M_{8aa}+ Na^+]^+$
TRUE	$C_{30}H_{42}N_6NaO_{14}S_2$	93.11	797.2084	797.2093	83.34	0.82	1.03	$[2M_{8aa}+ Na^+]^+$

We have recrystallized perfectly the pyrazoldinol 8ab in the ratio from (1:2:7, dichloromethane/chloroform/hexanes) as a colorless solid characterized by the fusion point 122–126 °C. We can see the phenyl aromatic groups at the aromatic area, each one resonate at 7.24-7.33 ppm and 7.08-7.10 ppm with total integration of nine protons. In addition, the two protons adjacent of phenyl group resonate at 2.53–2.58 ppm as exposed on ^{1}H NMR spectrum, figure III-14. This group (-CH_2-) in position 22 evidently presents at 36.65 ppm on the ^{13}C NMR spectrum, figure IV-15. In HRMS analysis confirmed the appearances of the molecular pics $[M_{8ab} + Na^+]^+$ and $[2M_{8ab} + Na^+]^+$ accorded to the molecular fragment of 8ab structure, figure III-16 and table III-6.

- ***Product 8ab***

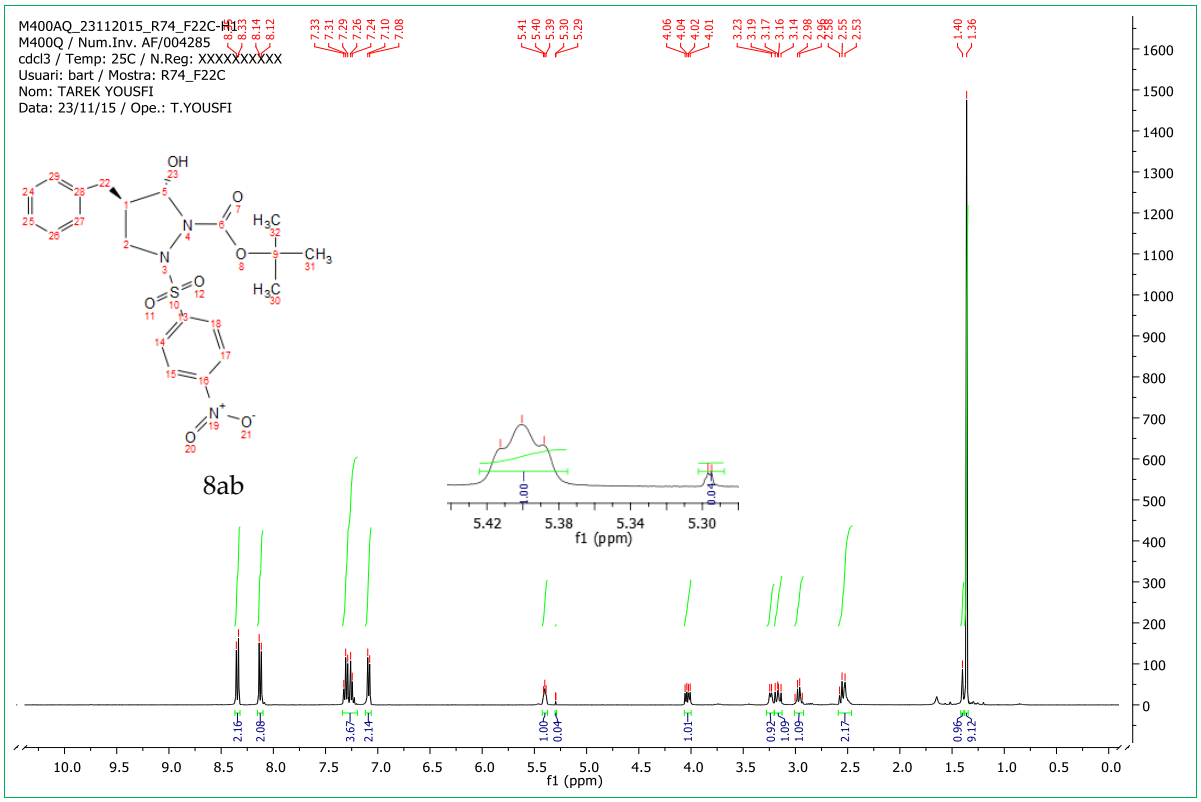


Figure III-14. ^{1}H-NMR (400 MHz) of *tert*-Butyl 4-Benzyl-5-hydroxy-2-((4-nitrophenyl) sulfonyl)-pyrazolidine-1-carboxylate, **8ab**.

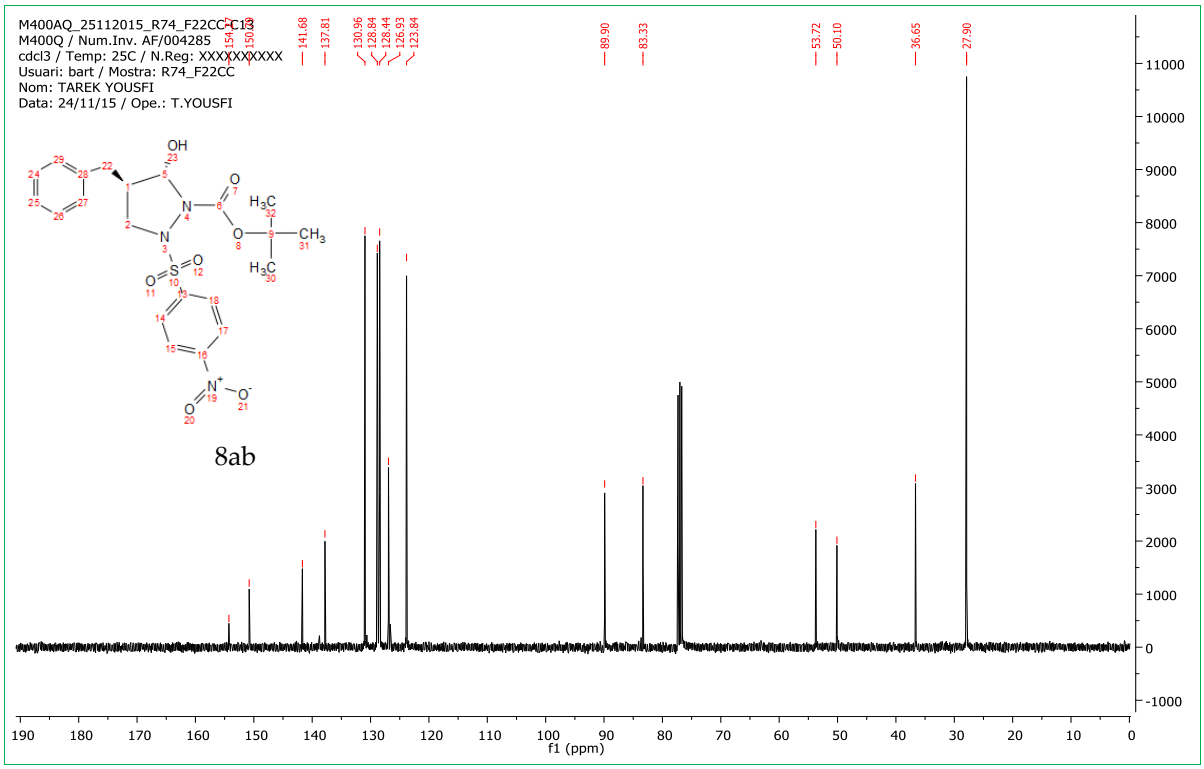


Figure III-15. 13C-NMR (100.6 MHz) of tert-Butyl 4-Benzyl-5-hydroxy-2-((4-nitrophenyl) sulfonyl)-pyrazolidine-1-carboxylate, **8ab.**

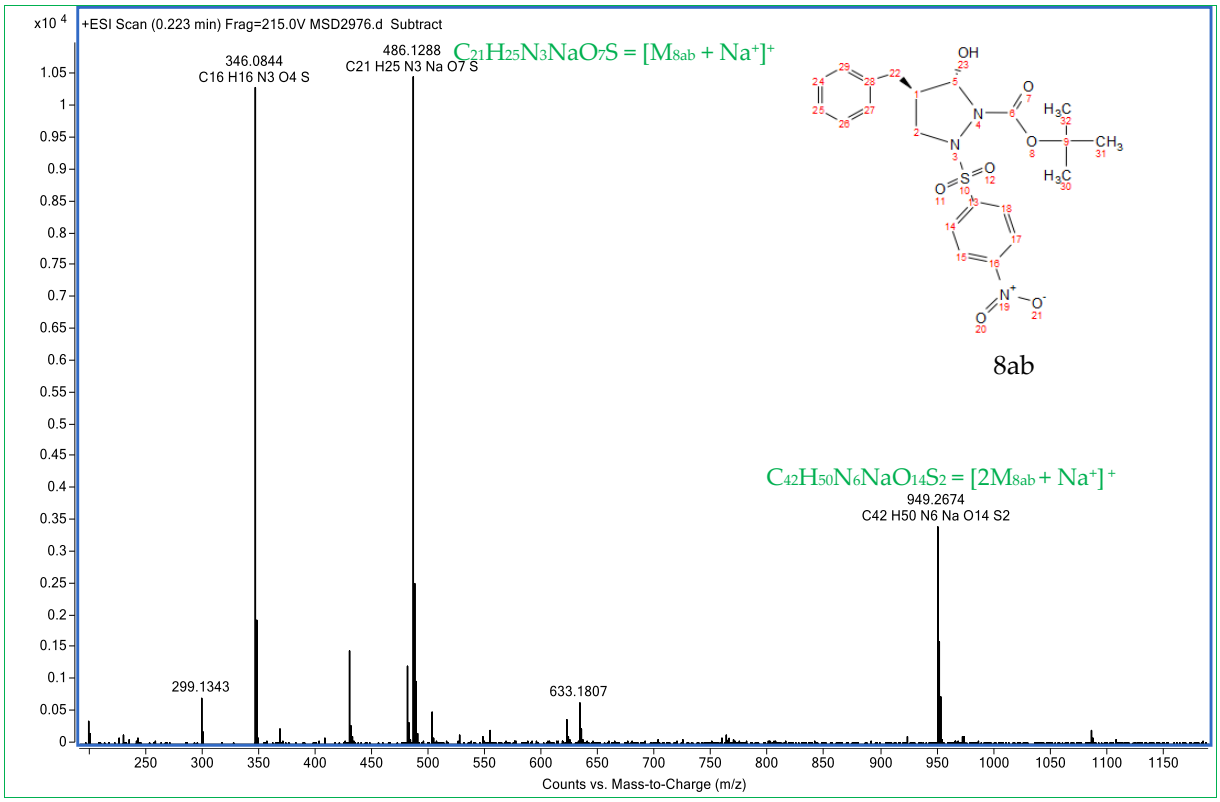


Figure III-16.HRMS analysis of pyrazolidinol, **8ab.**

Table III-6. MS formula results of pyrazolidinol 8ab obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{21}H_{25}N_3NaO_7S$	88.67	486.1288	486.1305	97.79	1.78	3.67	$[M_{8ab} + Na]^+$
TRUE	$C_{42}H_{50}N_6NaO_{14}S_2$	81.94	949.2674	949.2719	98.23	4.21	4.44	$[2M_{8ab} + Na]+$

The pyrazolidinol product 8ac was found in excellent yield 99.6 % as a colorless solid characterized by fusion point 83-85 ^{0}C, Table III-4. The ^{1}H NMR spectrum (figure III-17) indicated the low diastereoselectivity explained by the diastereomeric ratio (dr =5:1) calculate at the neighbor proton for hydroxyl group. In ^{1}H NMR spectrum, we can see the heptyl group in vibration region of the aliphatic functions resonate between 1.25-1.32 ppm in total integration 12 protons, the methyl resound at 0.85-0.88 ppm as a multiple peaks with total density integration of three protons. On the ^{1}H-NMR spectrum, an overlap of the peaks relate two stereoisomers was observed we decided to go directly to the oxidation without performing the ^{13}C NMR in order to achieve a perfect spectrum. In HRMS analysis confirmed the appearances of the molecular picks

$[M_{8ac}+ NH_4^+]^+$ and $[2M_{8ac} + Na^+]^+$ accorded to the molecular fragment of 8ac, figure III-18 and table III-7.

- ***Product 8ac***

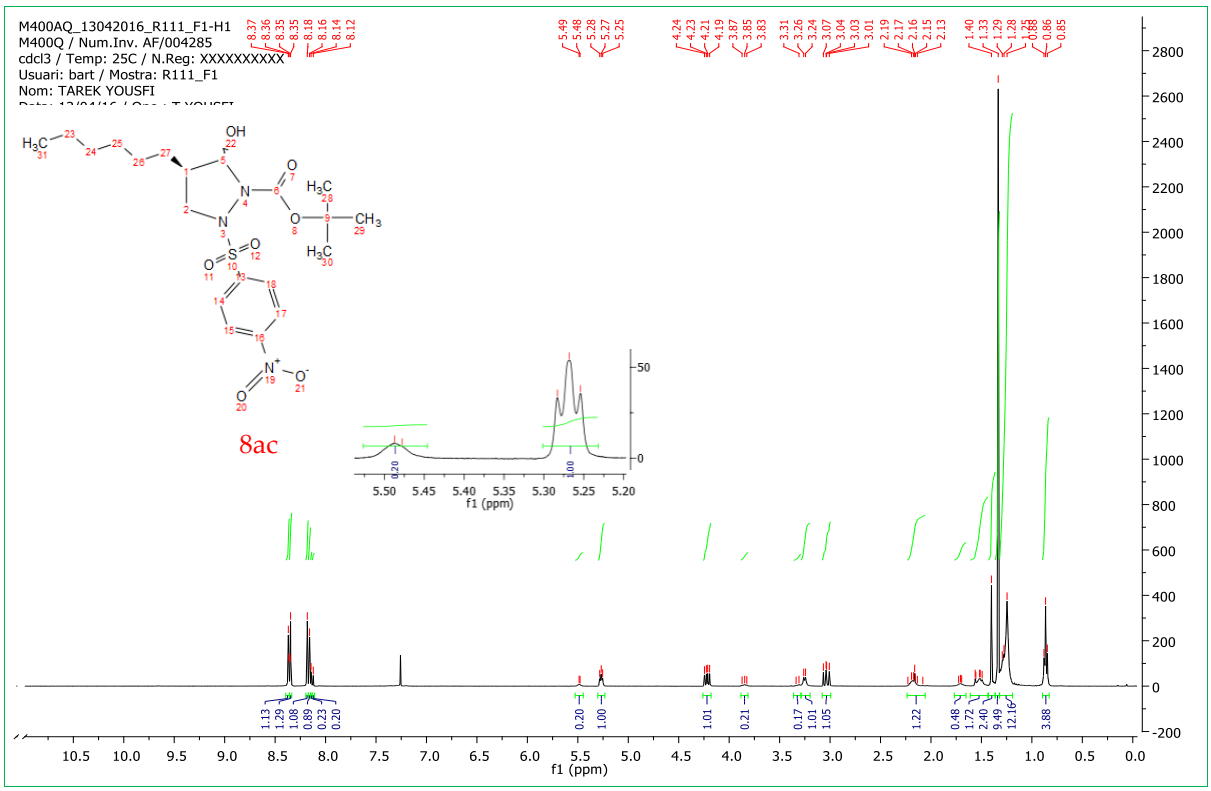


Figure III-17. ^{1}H-NMR (400 MHz) of *tert*-Butyl 4-Hexyl-5-hydroxy-2-((4-nitrophenyl)sulfonyl)-pyrazolidine-1-carboxylate, **8ac**.

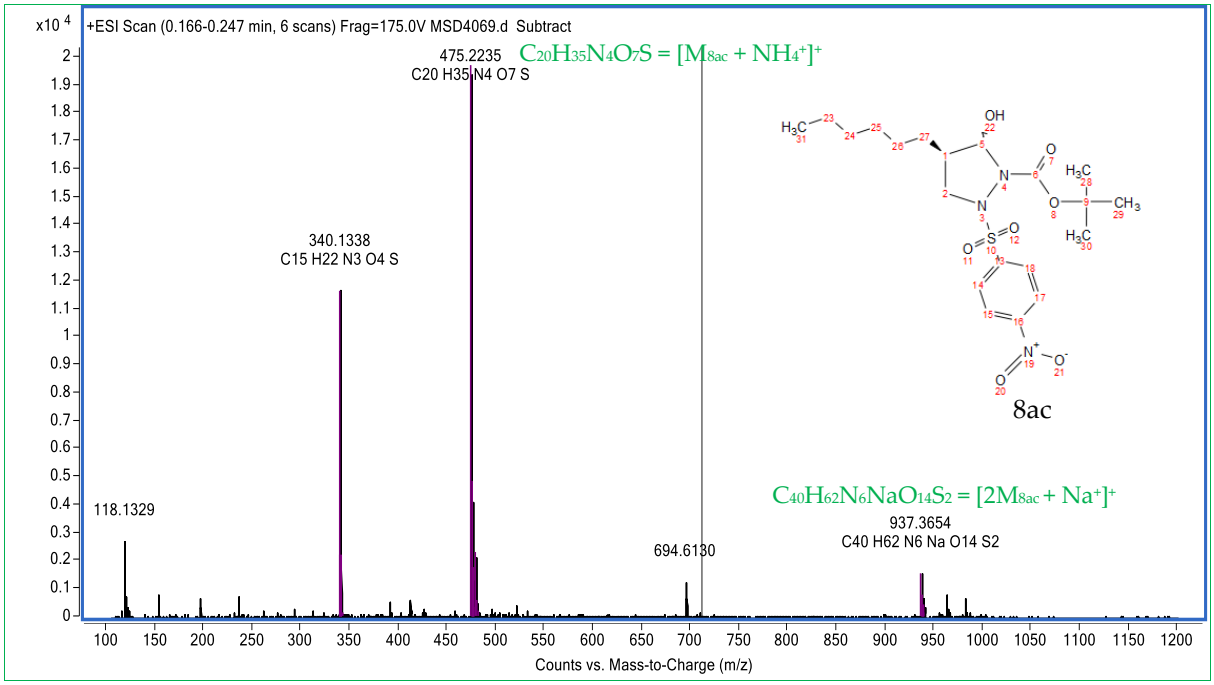


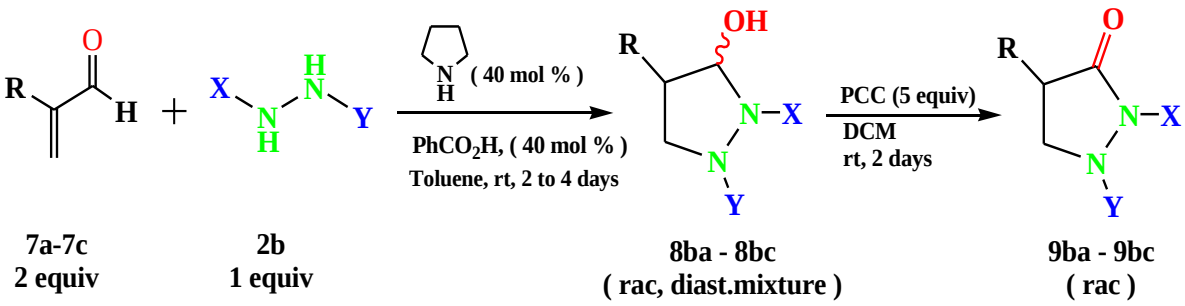
Figure III-18. HRMS analysis of pyrazolidinol, **8ac**.

Table III-7. MS formula results of pyrazolidinol 8ac obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{40}H_{62}N_6NaO_{14}S_2$	97.38	937.3654	937.3658	98.9	0.55	0.59	$[2M + Na]^+$
TRUE	$C_{20}H_{35}N_4O_7S$	93.82	475.2235	475.2221	93.86	-1.45	-3.06	$[Mac + NH_4]^+$

III.1.3.1.2 Racemic 4-substituted pyrazolidin-3-ols from hydrazine 2b

The introduction of the sulfonyl SO_2 group can be carried out by several reactants. Our choice was made for *1*, *2*-bis-(*p*-toluene sulfonyl) hydrazine (2b) for its availability and reactivity in the presence of high acidity of N-H protons favorably supported by the Aza-Michael / cyclization reactions [1a]. We next proceeded to extend the reaction to the use of α-unsaturated aldehydes with different substitution patterns such as methacrolein (7a), 2-benzylpropenal (7b) and 2-(n-hexyl) propenal (7c) in order to survey the scope of the reaction and its performance for the preparation of differently substituted pyrazolidin-3-ols Schema III-6.



Scheme III-6. Organocatalytic synthesis of pyrazolidin-3-ones from hydrazine **2b** and α-substituted enals.

With the same conditions of the last Aza-Michael addition / cyclization system and from the results summarized in table III-8 and figure III-19, we observed that hydrazide (2b) reacts effectively with α-unsaturated aldehydes containing cyclic and a cyclic alkyl chains of different length and size, whilst maintaining both high yields and high levels of the diastereoselectivity. Furthermore, branched and unsaturated α-alkyl substituents were tested with success in the reaction between 2 equivalent of 2-(n-hexyl) propenal (7c) and one equivalent of hydrazine 2b as substrate of nucleophile attack using 40 mol

% of both pyrrolidine and benzoic acid in toluene at room temperature. The final pyrazolidinols 8ba, 8bb and 8bc were obtained in excellent yield (up to 98%) after chromatographic purification and as a diastereomer mixture (dr > 10:1), entries 3, table III-8.

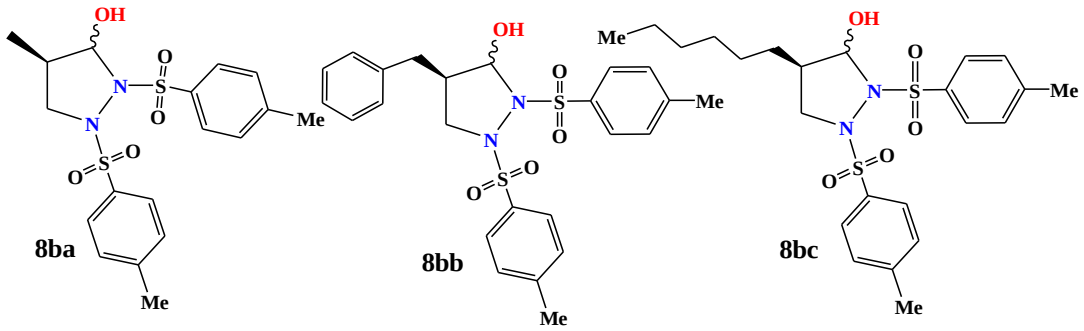


Figure III-19. Pyrazolidin-3-ols (8ba–8bc) from α-substituted enals 7a–7c and hydrazines 2b.

Table III-8. Pyrazolidin-3-ols products **(8ba–8bc)** from α-substituted enals **7a–7c** and hydrazines **2b**.

Pyrazolidinol	Brute formula	M gr.mol^{-1}	Reaction Time (d)	Yield [1]	dr [2]	Fusion point °C
8ba	$C_{18}H_{22}N_2O_5S_2$	410.32	2	88%	**8:1**	131–134 °C
8bb	$C_{28}H_{28}N_2O_5S_2$	536.42	2	85%	**9:1**	110–113 °C
8bc	$C_{23}H_{32}N_2O_5S_2$	480.37	**2**	**98%**	**>10:1**	78–80 °C

[1] Yield of isolated product after chromatographic purification; [2] By 1H-NMR.

The structure of crud products, isolated as yellow solids, was difficult to recrystallize using the ratio of (1:2:7, dichloromethane/chloroform/hexanes) despite several tests. The compounds 8ba, 8bb and 8bc were inferred from the ^{1}H NMR and High-resolution mass (HRMS) spectroscopies.

A about the compound 8ba, we found the presence of a multiple peaks at 5.21–5.22 ppm in the ^{1}H NMR spectrum (figure III-20) , related to proton H_5 of pyrazolidinol 8ba ring proton (as numbered in structure compound) but we didn't identified clearly the significant peak of hydroxyl group due to the overlap peaks . At contrary, it is easy to identify the methyl groups (position 15), the double peaks in pyrazolidinol ring spectrum appear at 0.85 and 0.87 ppm, the tow methyl groups connected to phenyl groups at the positions 26 and 27 resonates at 2.45 ppm and 2.46 as a singlet peak with total density of 6 protons. The ^{1}H NMR spectrum showed the presence of two sets of

signals assigned to two stereoisomers cis and trans which they appeared clearly in the areas of methyl groups, aromatic groups and neighbor proton of hydroxyl group , this presence showed by the diastereomeric ratio (dr = 8:1). In HRMS analysis confirmed the attendances of the molecular pics $[M_{8ba} + NH_4^+]^+$ and $[2M_{8ba} + NH_4^+]^+$ relates to the molecular fragment of 8ba, figure III-21 and table III-9.

In the case of compounds 8bb and 8bc, we can see the two key identifiers of intermediate alcohol are shown in the spectrum data, figure III-22 and III-24. The characteristic peaks in the ^{1}H NMR spectrum included the doublet resonances at 3.45 - 3.45 ppm and 3.35- 3.37 ppm arising from hydroxyl groups , the proton neighboring of the two hydroxyl groups regarded as a multiple peaks vibrate at 5.36-5.41 ppm and 5.28-5.48 ppm separately for the products 8bb and 8bc.

About the specific groups for each compound (8ba, 8bb and 8bc), the ^{1}H NMR spectrum related to 8ba compound, showed the presence of two sets of signals assigned the two stereoisomers cis and trans with a clear distribution of the different orientation in positions 15, 26, 27 and 5 of pyrazolidinol ring corresponds to methyl groups , and adjacent proton of hydroxyl function. The appearance of diastereoisomers compounds coordinated in the aromatic section and hydroxyl group respectively for 8bb and 8bc pyrazolidinol, figures III-22 and III-24. In HRMS analysis established the attendances of the molecular pics $[M_{8ba} + NH_4^+]^+$ and $[2M_{8ba} + NH_4^+]^+$ relates to the molecular fragment through mass identification success greater than 91 % as shown in the figure III-21 and table III-9. The synthetic approach to phyrazolidinol 8bb was similar to that discussed above for the 8ba, the molecular fragments $[M_{8bb} + NH_4^+]^+$ and $[2M_{8bb} + NH_4^+]^+$ exposed the final structure of this compound figure III-23 and table III-10. Similarly, In HRMS analysis confirmed the attendances of the molecular pics $[M_{8bc} + NH_4^{+]+}$ and $[2M_{8bc} + NH_4^+]^+$ relates to the molecular fragment of 8bc, figure III-25 and table III-11.

- ***Product 8ba***

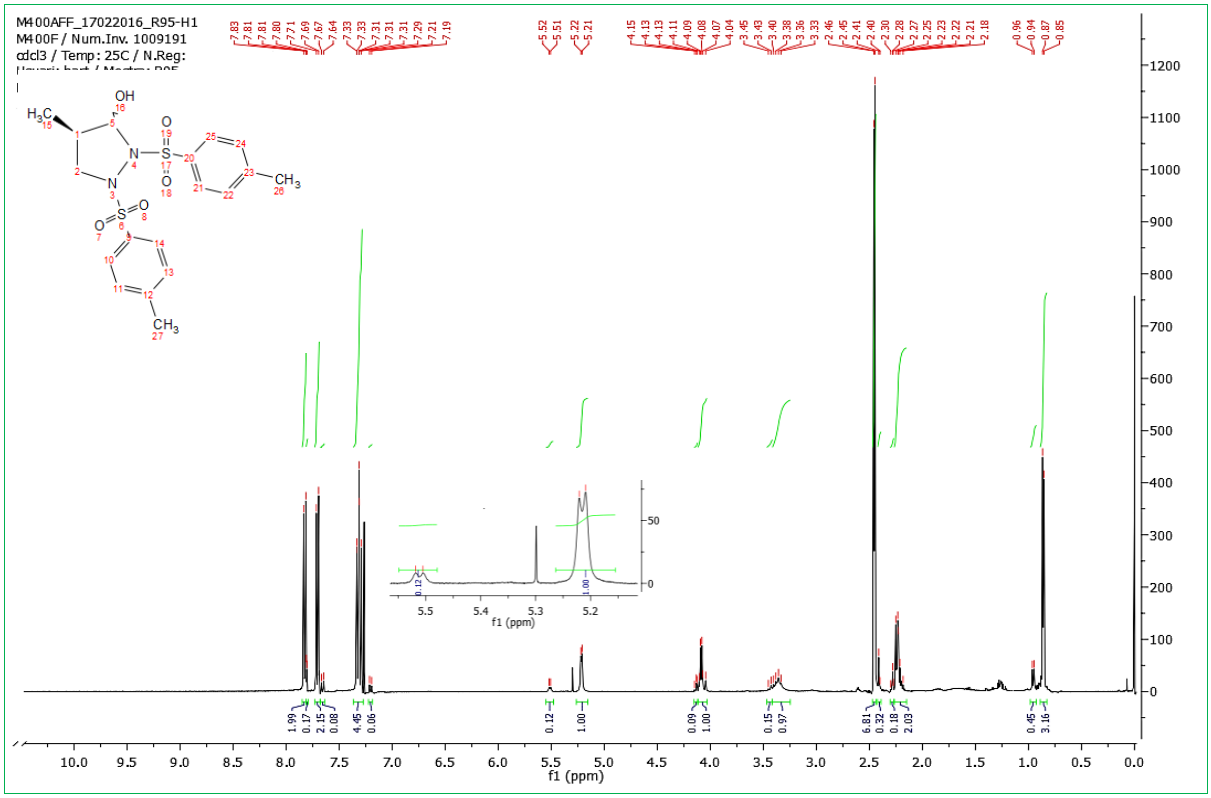


Figure III-20. ^{1}H-NMR (400 MHz) of 4-Methyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-ol, **8ba**.

Table III-9. MS formula results of pyrazolidinol 8ba obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{18}H_{26}N_3O_5S_2$	92.24	428.1323	428.1308	90.9	-1.47	-3.45	$[Mba + NH_4^+]^+$
TRUE	$C_{36}H_{48}N_5O_{10}S_4$	90.83	838.2258	838.2279	84.97	2.01	2.4	$[2Mba + NH_4^+]^+$

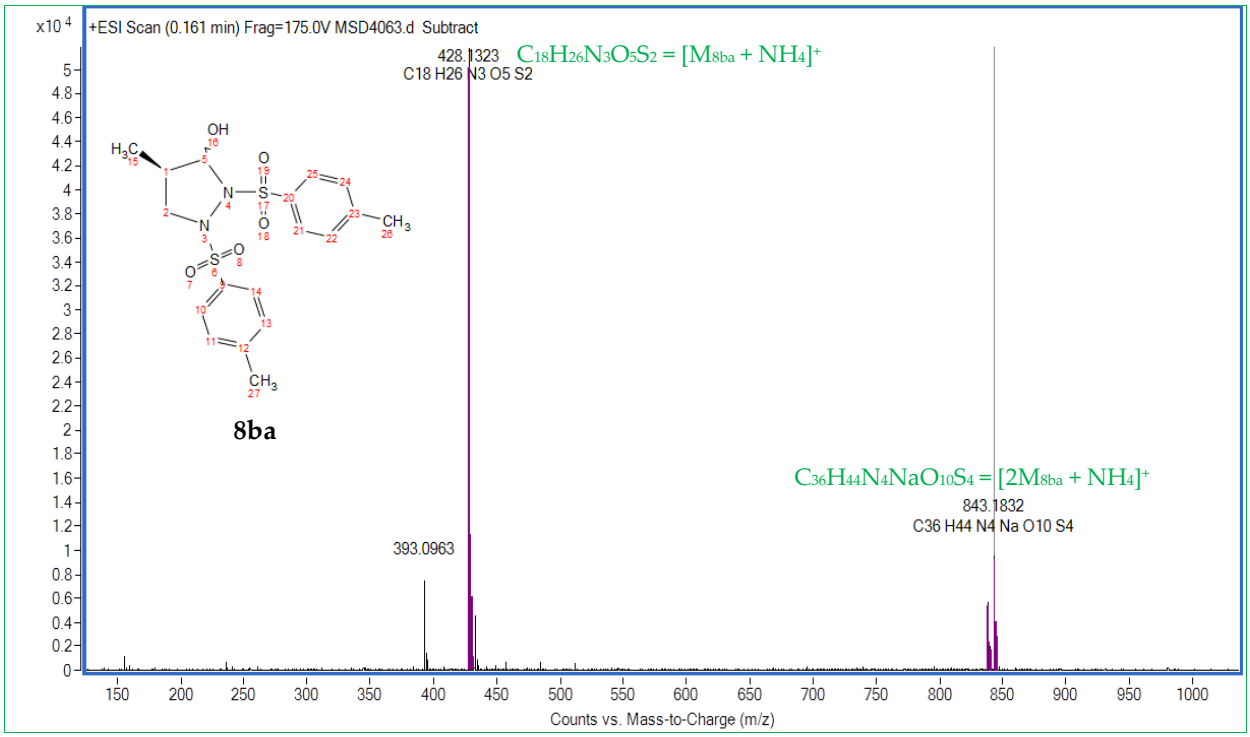


Figure III-21. HRMS analysis of pyrazolidinol , **8ba.**

- ***Product 8bb***

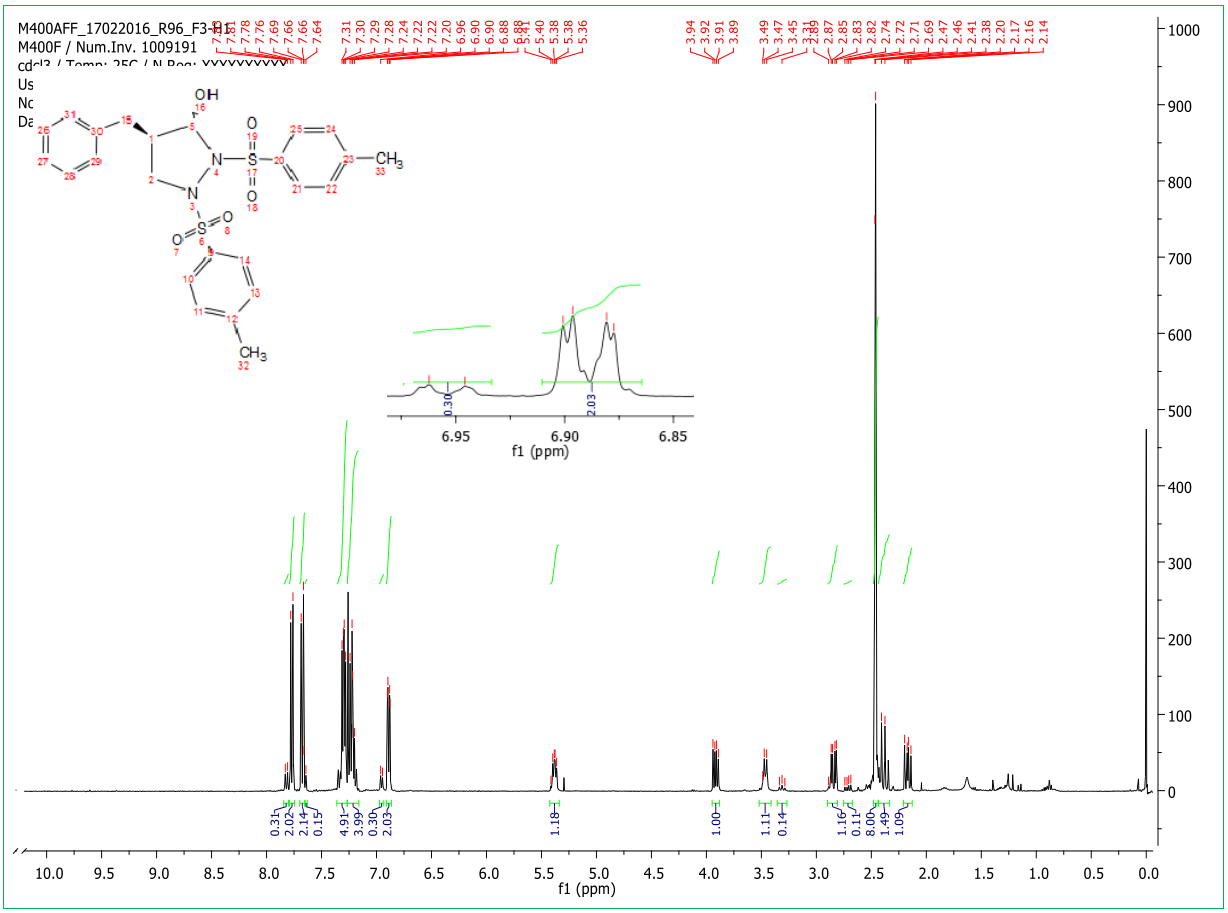


Figure III-22. ^{1}H-NMR (400 MHz) of 4-Benzyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-ol, **8bb**.

Table III-10. MS formula results of pyrazolidinol **8bb** obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{48}H_{56}N_5O_{10}S_4$	96.61	990.2892	990.2905	93.16	1.31	1.32	$[2M_{\mathbf{8bb}} + NH_4^+]^+$
TRUE	$C_{24}H_{30}N_3O_5S_2$	95.43	504.1626	504.1621	85.74	-0.45	-0.9	$[M_{\mathbf{8bb}} + NH_4^+]^+$

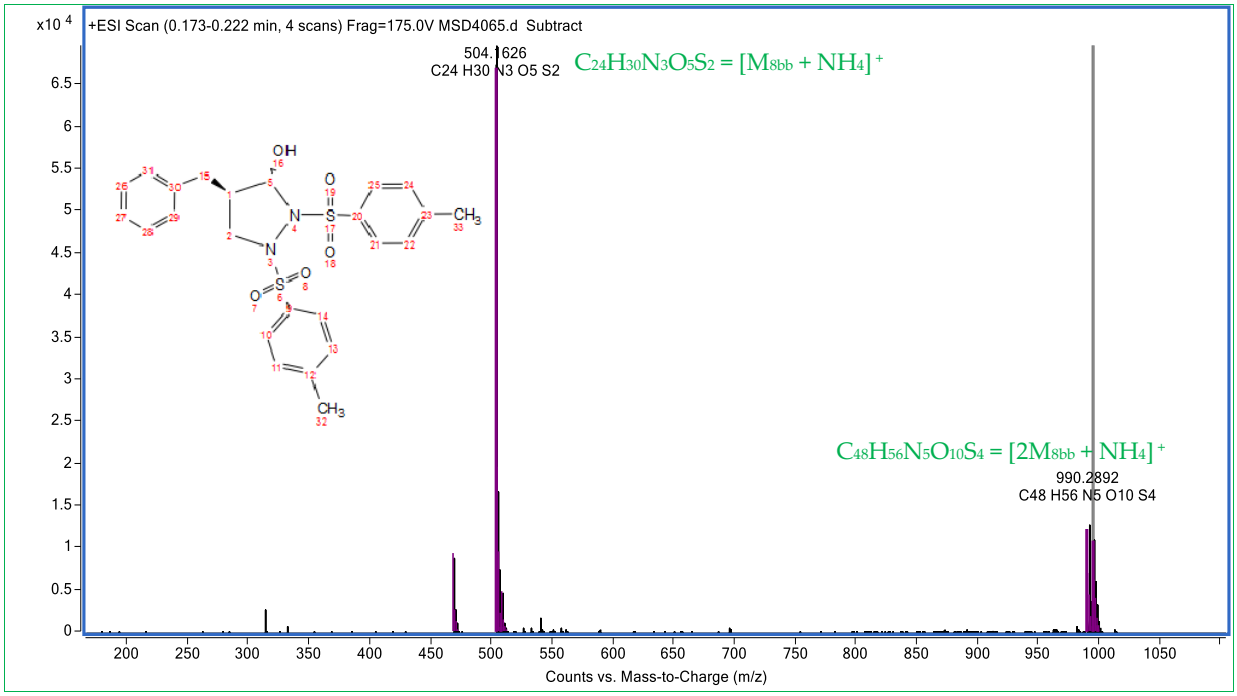


Figure III-23. HRMS analysis of pyrazolidinol, **8bb.**

- ***Product 8bc***

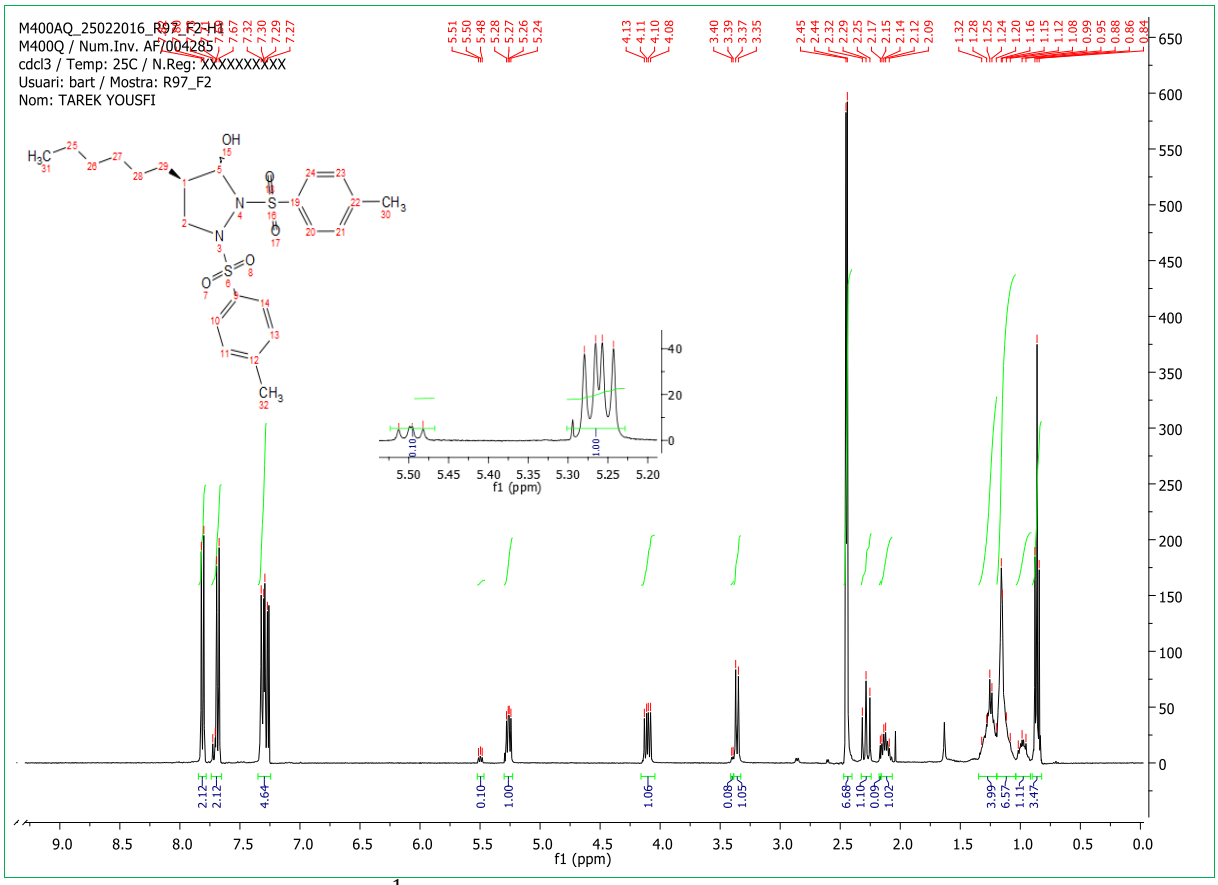


Figure III-24. ^{1}H-NMR (400 MHz) of 4-Hexyl-1,2-bis-(4-toluenesulfonyl)-pyrazolidin-3-ol, 8bc.

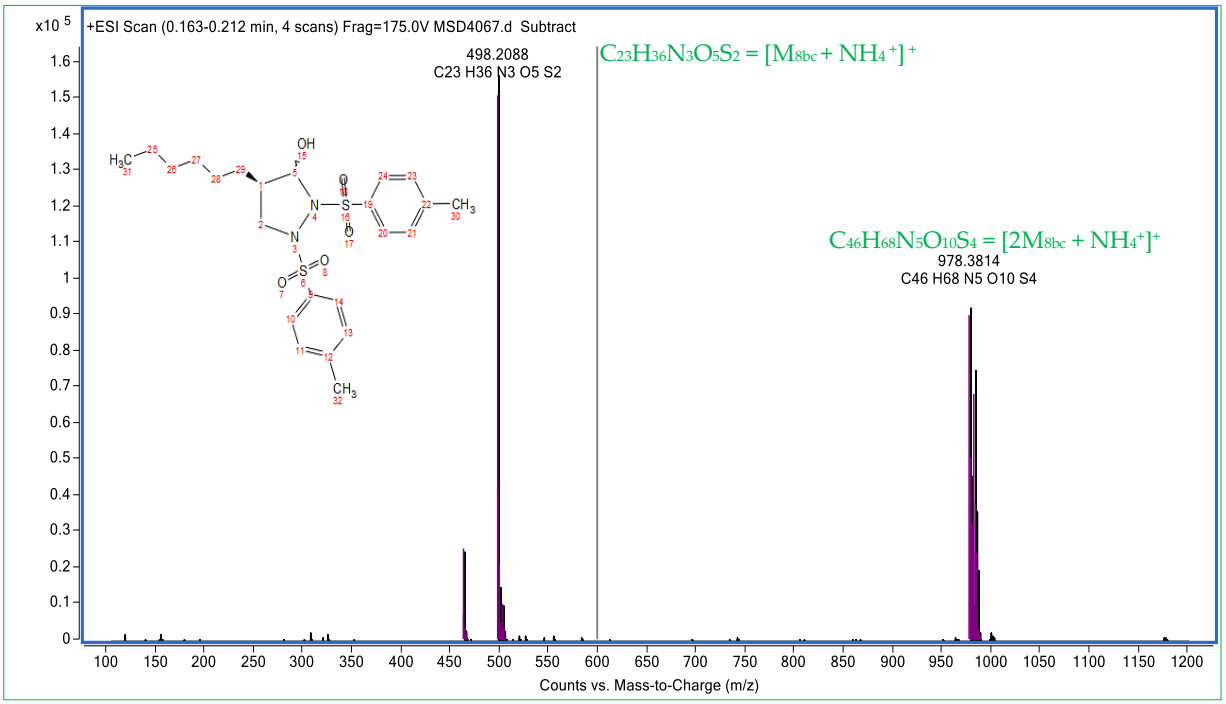


Figure III-25. HRMS analysis of pyrazolidinol, **8bc**.

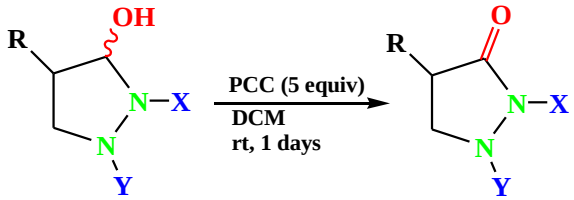
Table III-11. MS formula results of pyrazolidinol **8bc** obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{23}H_{36}N_3O_5S_2$	93.92	498.2088	498.2091	79.81	0.32	0.65	$[M_{8bc} + NH_4^+]^+$
TRUE	$C_{46}H_{68}N_5O_{10}S_4$	90.05	978.3814	978.3844	89.9	2.98	3.04	$[2M_{8bc} + NH_4^+]^+$

III.1.3.2 Oxidation and 4-substituted-3-pyrazolidinones

Derivatives of the 4-substituted-3-pyrazolidinones possess a wide variety of biological and pharmaceutical activities as analgesic, antibiotic, anticonvulsant, and with inhibitory cyclooxygenase, lipoxygenase, and γ-aminobutyrate transferase activity, along with other uses as was mentioned in chapter two. In order to prepare these precursors, we have carried out the oxidation reaction of the pyrazolidinol intermediates, but in the primary results of our work, we have established that pyrazolidinols (3) and (5) synthesized from α, β-unsaturated aldehydes 1 and 4 are resistant the oxidizing agent's such pyridinium dichromate (PDC) and pyridinium chlorochromate (PCC). This step was investigated with particular attention, we have approved out a thorough literature review on the oxidation of pyrazolidinols derivatives and we founded that the reaction route can be approved out by different way [1, 9]. Firstly, we applied the oxidation of the pyrazolidinol 8aa using with sodium chlorite gave unsatisfactory result and no reaction after 3 days of screening in DCM at room temperature . Secondly, the oxidation of this compound did not take place with pyridinium dichromate (PDC) even though that we used an excess of three to five equivalent of oxidizing agent of PDC. However, the transformation could be efficiently brought about using pyridinium chlorochromate (PCC) in the presence of 4 Å molecular sieves, notably that we have repeated the oxidation with three equivalents of PCC but the oxidation reaction not finished after two days of the screening in same conditions. Finally, we concluded that the oxidation reaction is very slow and we decided to increase the molar equivalent to five equivalent of PCC in order to strengthen the operation, the procedure using an excess of five equivalent of PCC as oxidizer agent and one equivalent of the mixture pyrazolidinol 8aa in the presence of 4 Å molecular sieves in CH_2Cl_2 at room temperature afforded corresponding

pyrazolidinon 9aa with excellent yield (up to 94%,) without purification. We are very satisfied with this result and pyrrolidinols 8 are easily converted to pyrazolidinones 9 by oxidation in the presence of PCC (typical reaction time one day), as exposed on Scheme III-7 and table III-12. Lastly, the racemic and enantiomeric purity of the corresponding pyrazolidinones 9 were determined by spectroscopic methods NMR (^{1}H, ^{13}C), HRMS and chiral HPLC analysis, as after.

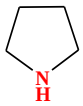
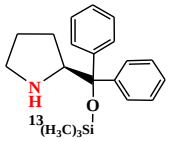
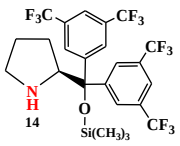


8aa - 8bc
(rac, diast.mixture)

9aa - 9bc
(rac)

Scheme III-7. Oxidation reaction of pyrazolidinols **8** by **PCC**.

Table III-12. Oxidation summary of racemic and asymmetric pyrazolidinols 8.

Entry	Reactants	Catalyst	Pyrazolidinol	Yield [1]	dr [2]	Pyrazolidinone	Yield [1]		Reaction time[6]
1	7a, 2a		**8aa**	93%	4:1	**9aa**	94%	-	18 h
2	7b, 2a		**8ab**	83%	>20:1	**9ab**	98%	-	24 h
3	7c, 2a		**8ac**	99.6%	5:1	**9ac**	99%	-	24 h
4	7a, 2b		**8ba**	88%	8:1	**9ba**	98%	-	18 h
5	7b, 2b	**I**	**8bb**	85%	9:1	**9bb**	97%	-	22 h
6	7c, 2b		**8bc**	98%	10:1	**9bc**	98%	-	24 h
								er [3]	
7	7a, 2a	**13**	**8aa**	82%	4:1	**9aa**	87%	50:50	18 h
8	7b, 2a		**8ab**	77%	>20:1	**9ab**	98%	44:56	24 h
9	7b, 2b		**8bb**	85%	9:1	**9bb**	97%	- [4]	24 h
10	7a, 2b		**8ba**	84%	8:1	**9ba**	98%	96:4	24 h
11	7c, 2b		**8bc**	93%	10:1	**9bc**	98%	78:22	24 h
12	7a, 2a	**14**	**8aa**	99%	3:1	**9aa**	94%	90:10	16 h
13	7b, 2a		**8ab**	98%	>20:1	**9ab**	98%	45:55	18 h
14	7b, 2b		**8bb**	85%	9:1	**9bb**	97%	- [4]	24 h
15	7a, 2b		**8ba**	0% [5]		**9ba**	-	-	24 h
16	7c, 2b		**8bc**	77%	10:1	**9bc**	98%	50:50	24 h

[1] Yield of isolated product after chromatographic purification; [2] By ^{1}H-NMR; [3] By chiral HPLC analysis (See the Supplementary Materials for details); [4] No satisfactory conditions for the HPLC analysis of this compound could be found; [5] No reaction was observed after 7 days; [6] The reaction time controlled by thin-layer chromatography.

With these results in hand summarized in table III-12, we were able to conclude that the oxidation reaction on different enals, with different substituent, using hydrazine 2a as substrates of Aza-Michael system, yielded the corresponding pyrazolidinones (9aa-9ac) with excellent enantioselectivity (up to 96%, column 9) and in good yields (up to 99%) in the majority of cases (column 8). For this part, we will imagine that we have been given a vial containing our dries samples, and that these compounds to our knowledge have never before been synthesized, isolated, or characterized. We are the first to get our hands on it grouped in figure III-26 and table III-13.

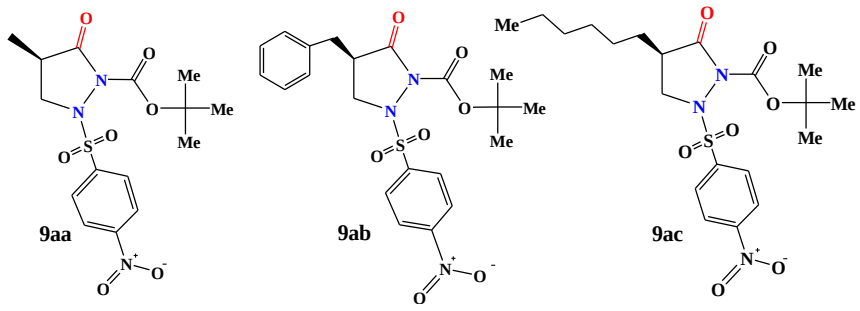


Figure III-26. Pyrazolidin-3-one structures (8aa–8bc) from α-substituted enals 7a–7c and hydrazines **2a.**

Table III-13. Physico-chemical characteristics of Pyrazolidin-3-one products **(9aa–9ac).**

Pyrazolidinon	Brute formula	M gr.mol^{-1}	Fusion point
9aa	$C_{15}H_{19}N_3O_7S$	385.24	131–134 °C
9ab	$C_{21}H_{23}N_3O_7S$	461.3	115–118 °C
9ac	$C_{20}H_{29}N_3O_7S$	455.29	123–126 °C

Now it is finally time to put together all that, we have studied about analysis data NMR (^{1}H and ^{13}C), HRMS and chiral HPLC showed how to really understand the structure of our oxidants products, especially that with rapid verification of the NMR spectrums data confirmed the disappearance of hydroxyl group corresponding to the intermediates alcoholic compounds and the spectrums analysis of NMR ^{1}H and ^{13}C are perfectly in the majority of cases.

The first series reorganized the pyrazolidinols 9aa, 9ab and 9ac that synthesized from hydrazine (2a) and α-enals. We have recrystallized perfectly the pyrazolidinol

9ab in the ratio from (1:2:7, dichloromethane/chloroform/hexanes) and we systematized a white solid for all these products, characterized by fusion points 131–134 °C, 115–118 °C and 123–126 °C correspondingly 9aa , 9ab and 9ac , as show in the table III-13.

Firstly, pyrazolidinone 9aa has a molecular weight of 385.24 $g.mol^{-1}$ corresponding to the brute formula $C_{15}H_{19}N_3O_7S$, we found that the HRMS data (figure III-29 and table III-14) show molecular ionic peaks at m/z = $[M_{9aa} + Na^+]^+$ and $[2M_{9aa} + Na^+]^+$, which gives us a molar mass of 408.0836 and 793.178 with a mass calculation success more then 91.8%. We are off to a good start, so in one mole of our compound there are nineteen hydrogen and fifteen carbon. Now let's look ^1H NMR analysis for confirmation, figure III-27. The intense signal, with a chemical change of 1.47 ppm, incorporates nine hydrogen presented the protecting group. Than is a doublet resonate at 1.15 ppm and 1.17 ppm corresponding to the methyl group and their neighbor proton deliver a multiple signal at 2.54-2.64 ppm.

The middle signal 3.38–3.45 ppm and 4.40–4.45 incorporates two protons separately in the second position of pyrazolidinone ring. We found the accounts for 19 protons with addition of four protons related to aromatic region (8.17-8.42 ppm). In addition, we confirmed the feasibility of oxidation reaction by the total absence of proton neigh boring hydroxyl group in the region of 5.5 ppm. In the ^{13}C-NMR data (figure III-28), we clearly found the carbonyl function at 173.4 ppm and we have 11 signals conforming the number of equivalent carbons in our dry product rac-9aa.

- ***Product 9aa***

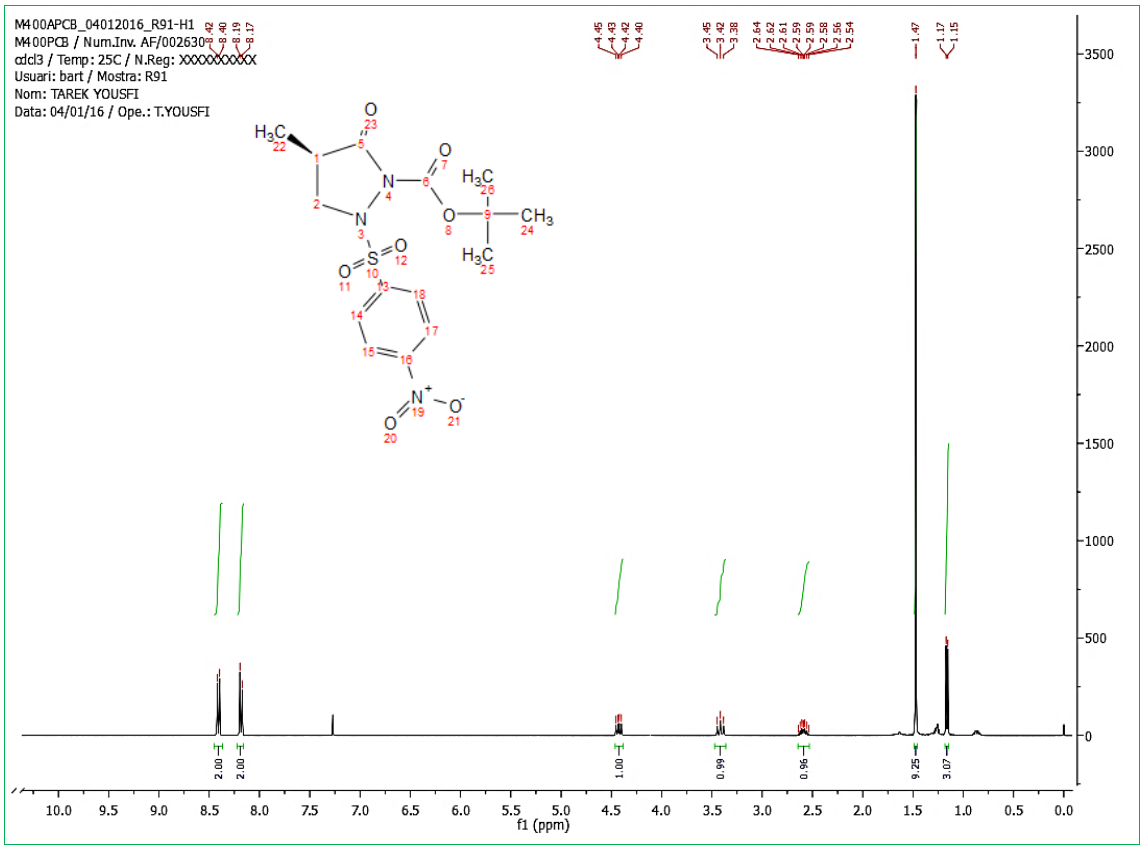


Figure III-27. ^{1}H-NMR (400 MHz) of (−)-*tert*-Butyl 4-Methyl-2-((4-nitrophenyl)sulfonyl)-pyrazolidin-5-one-1-carboxylate, **9aa**.

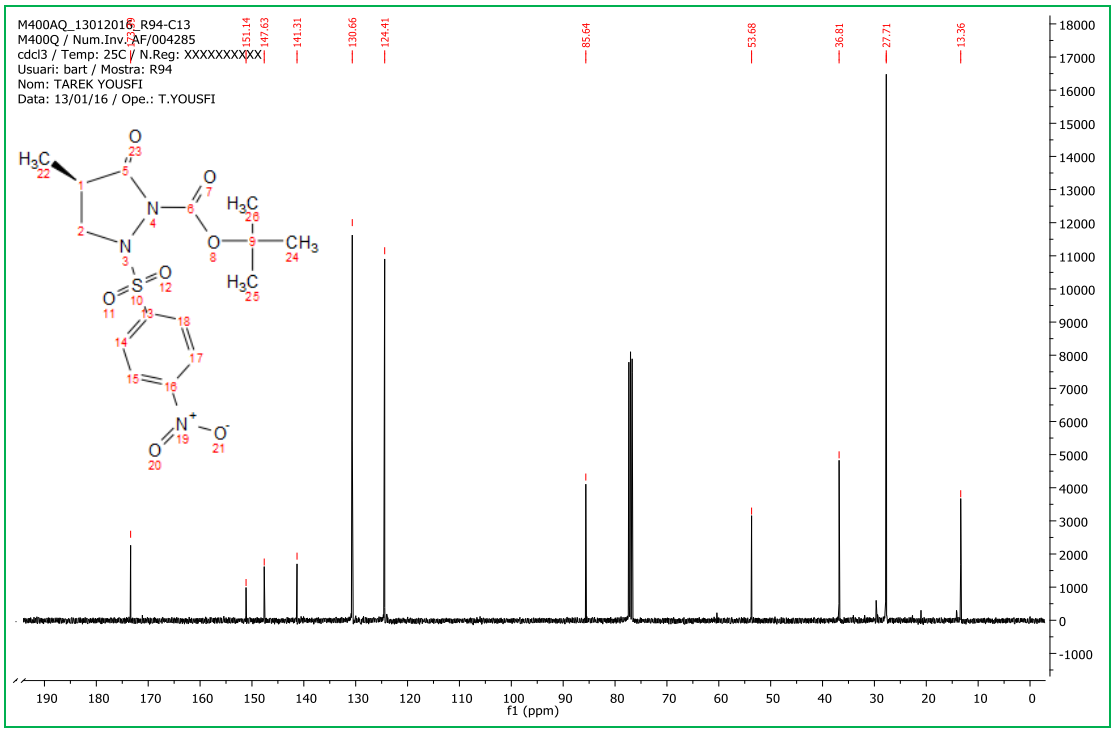


Figure III-28. ^{13}C-NMR (100.6 MHz) of (−)-*tert*-Butyl 4-Methyl-2-((4-nitrophenyl) sulfonyl)-pyrazolidin-5-one-1-carboxylate, **9aa**.

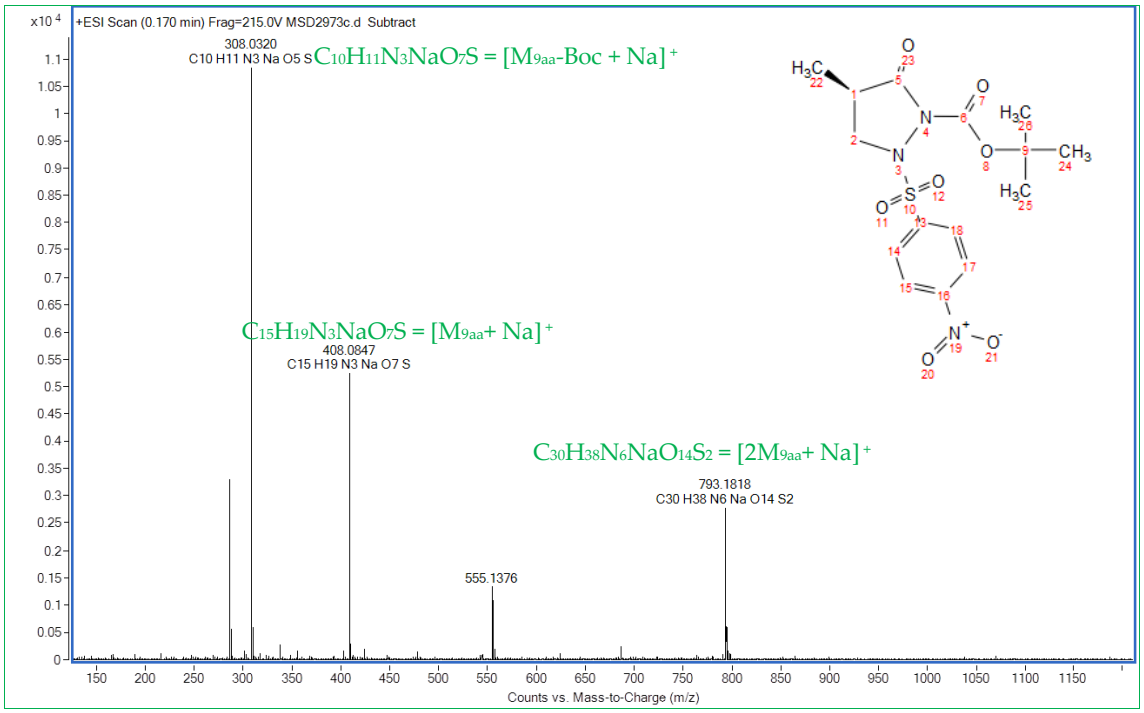


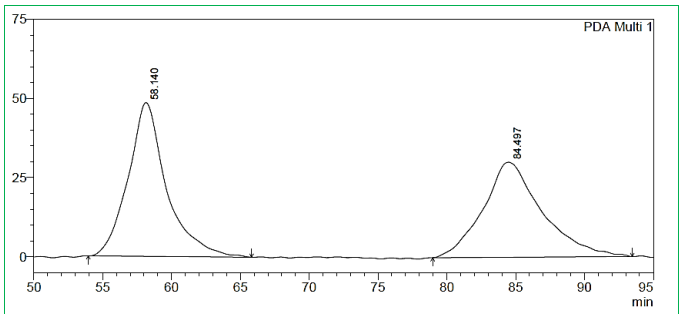
Figure III-29. HRMS analysis of pyrazolidinol, **9aa.**

Table III-14. MS formula results of pyrazolidinol 9aa obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{15}H_{19}N_3NaO_7$ S	91.8	408.0847	408.0836	97.8	-1.17	-2.87	$[M_{9aa}+ Na^+]^+$
TRUE	$C_{30}H_{38}N_6$ $NaO_{14}S_2$	77.8	793.1818	793.178	79.39	-3.8	-4.8	$[2M_{9aa}+ Na^+]^+$

According to Diacel, manufacturer of Chiralpak® IC, hexane, 2-propanol, and ethanol in any compositions are the solvents of choice for use with this column. To perform mobile-phase HPLC analysis hexane and iso-propanol were chosen as solvents. Mobile phase composition was optimised by varying the proportion of the constituents at ambient temperature (25 ^{0}C). The mobile phases finally used were hexane/isopropyl alcohol in 90:10 (v/v) and the spectrophotometric detection was performed at 257 nm. We started the optimization step in order to determine the separation conditions with the racemic compound 9aa. After same experiment, the racemic method is capable of separating the two enantiomers with soft separation due to the low flow rate 1 ml.min^{-1} for HPLC pump but with fast separation factor of 27 min between the appearances of the two enantiomers, typical chromatograms are shown in figure III-30. The enantiomeric separation was performed at the same conditions of asymmetric compound 9aa, synthetised to **8aa** pyrazolidinol en the

presence of asymmetric catalyst 14. So, the mixture of 9aa is actually composed of 90 % of the major enantiomer looked at retention time 57 min and 10 % of the minor enantiomer observed at retention time 84 min, characteristic chromatograms are shown in figures III-30 and III-31. We found that the enantiomeric excess equivalent to 90 %. This result means the performance of our asymmetric model in the presence of asymmetric catalyst 14 and the calculation of the specific rotation of the racemic product 9aa, which has a value of $[\alpha]_D^{25} = -64.7$ (0.67, DCM), we can conclude that the mixture of 9aa contains the major enantiomer (−)-9aa in 90 %. Unfortunately, the HPLC separation of asymmetric compound 9aa obtained for the corresponding alcohol 8aa in the presence of chiral catalyst 13 shows a similar racemic separation, which indicates the non-permanence of asymmetric model with this catalyst.

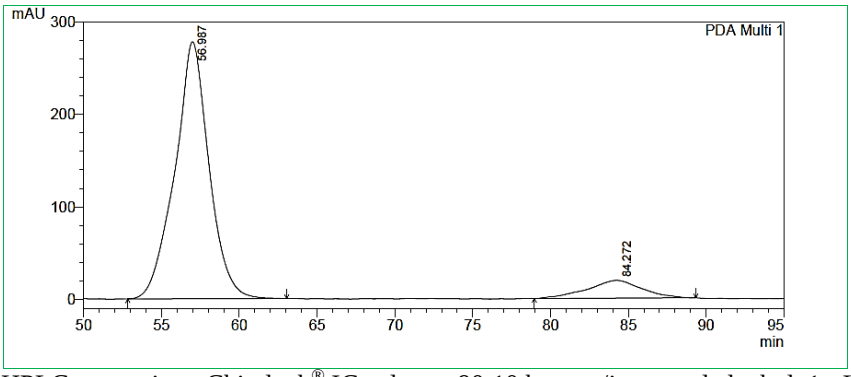


PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	58.140	9422214	48509	51.307	61.789
2	84.497	8942203	29999	48.693	38.211
Total		18364416	78508	100.000	100.000

Conditions of HPLC separation: Chiralpak® IC column, 90:10 hexane/isopropyl alcohol, 1 µL/min, λ = 254 nm, 25 °C.

Figure III-30. HPLC separation of *rac*-**9aa**.



Conditions of HPLC separation: Chiralpak® IC column, 90:10 hexane/isopropyl alcohol, 1 µL/min, λ = 254 nm, 25 °C.

Peak#	Ret. Time	Area	Height	Area %	Height %
1	56.987	42488086	277822	90.079	93.548
2	84.272	4679622	19162	9.921	6.452
Total		47167708	296984	100.000	100.000

Figure III-31. HPLC separation of (−)-**9aa**.

After purification and recrystallization from (1:2:7:dichloromethane /chloroform/ hexanes), pyrazolidinone 9ab was obtained as a white solid in 98% yield. The ^{1}H and ^{13}C NMR spectral data shown in figures III-32 and III-33 support its precise structure. The characteristic peaks in the ^{1}H NMR spectrum include the four peaks resonances in the aromatic region between 7.06-7.32 ppm and 8.12-8.39 ppm, this one indicate that we have two equivalent aromatic groups presented a total integration of nine protons, as shown by the name structure of 9aa. Then, The middle signals at 2.61–2.67 ppm, 2.86–2.92 ppm, 3.17–3.21 and 3.46–3.52 ppm and 4.16–4.21 ppm incorporates five protons , three of them associated to pyrazolidinon ring and the last two neigh boring protons of benzyl group. In the ^{13}C-NMR data, we clearly found the two-carbonyl functions of our dry product rac-9ab resonate at 151.4 (position 6) ppm and 172.1 ppm (position 5). Similarly, In HRMS analysis confirmed the attendances of the molecular pics $[2M_{9ab} + Na^{+}]^{+}$, $[M_{9ab} + Na^{+}]^{+}$ and $[M_{9ab} + NH_4^{+}]^{+}$ correlated to the molecular weight of 385.24 $g.mol^{-1}$ and the crude formula $C_{21}H_{23}N_3O_7S$ of racemic compound 9ab, figure III-34 and table III-15 .

- ***Product 9ab***

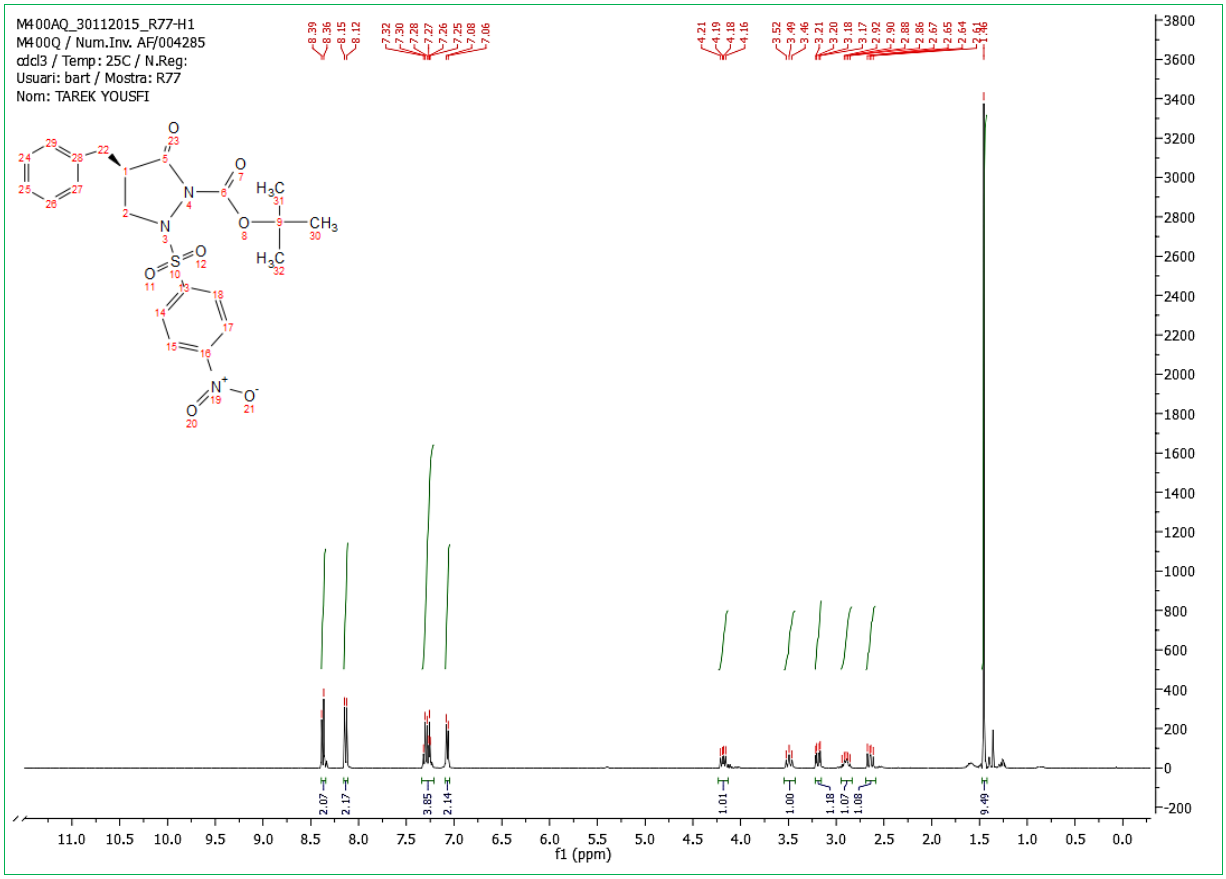


Figure III-32. ^{1}H-NMR (400 MHz) of (−)-*tert*-Butyl 4-Benzyl-2-((4-nitrophenyl) sulfonyl)-pyrazolidin-5-one-1-carboxylate, **9ab**.

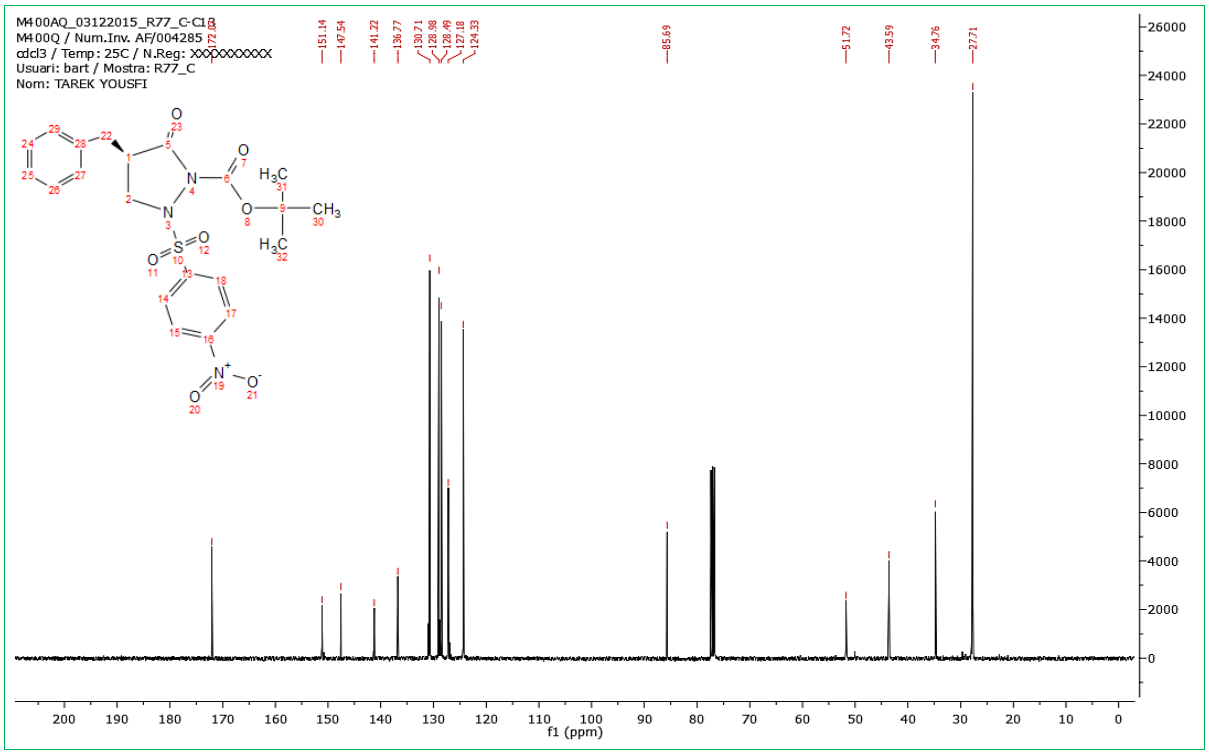


Figure III-33. ^{13}C-NMR (100.6 MHz) of (−)-tert-Butyl 4-Benzyl-2-((4-nitrophenyl) sulfonyl)-pyrazolidin-5-one-1-carboxylate**, 9ab.**

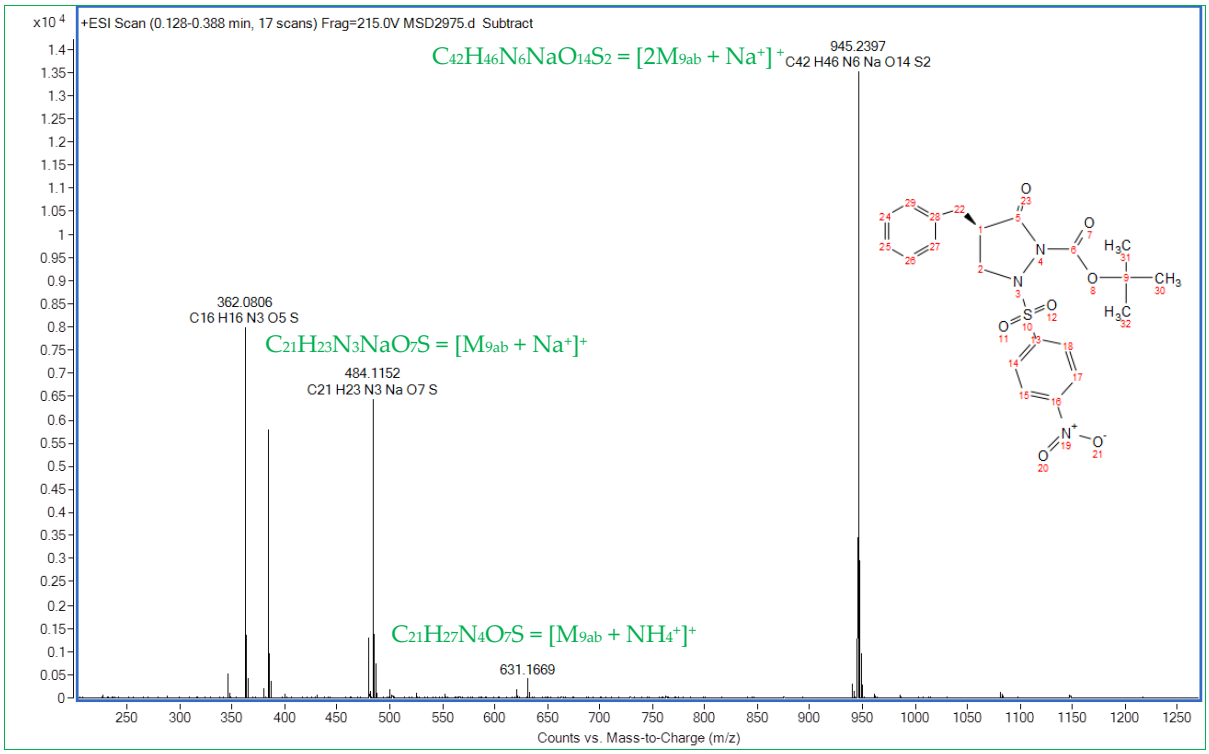
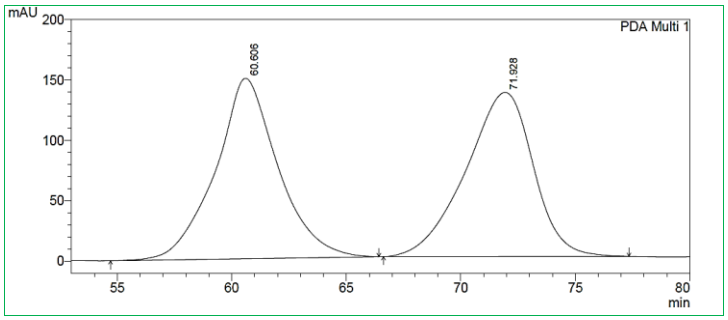


Figure III-34. HRMS analysis of of pyrazolidinol, **9ab.**

Table III-15. MS formula results of pyrazolidinol 9ab obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{42}H_{46}N_6NaO_{14}S_2$	96.31	945.2397	945.2406	91.81	0.85	0.91	$[2M_{9ab} + Na^+]^+$
TRUE	$C_{21}H_{23}N_3NaO_7S$	88.64	484.1152	484.1149	87.34	- 0.32	- 0.66	$[M_{9ab} + Na^+]^+$
TRUE	$C_{21}H_{27}N_4O_7S$	87	479.1588	479.1595	86.97	0.71	1.48	$[M_{9ab} + NH4^+]^+$

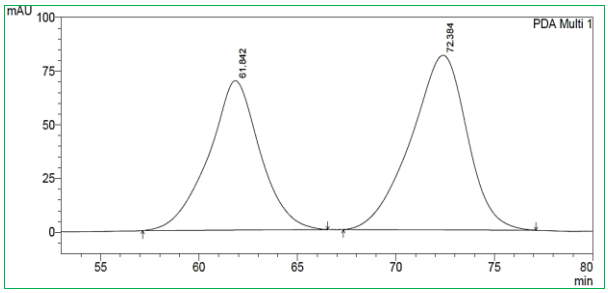
The chiral HPLC separation of racemic and asymmetric compound 9ab were performed at the same conditions as the last similar compound 9aa, so the both mixtures are composed of 50 % of the both enantiomers , looked respectively at retention time 62 min and 73 min. In this case, we can complete that our asymmetric models are not perfect with the asymmetric catalysts, in particular that we found a mixture characterized by the same racemic excess (er =44:56) and $[\alpha]_D^{25}$ = −11.4 (1.19, DCM) for the both mixture compounds 9ab, detailed chromatograms are shown in figure III-35 and III-36.



Peak#	Ret. Time	Area	Height	Area %	Height %
1	60.606	28447344	149356	50.513	52.370
2	71.928	27870083	135839	49.487	47.630
Total		56317428	285195	100.000	100.000

Conditions of HPLC separation: Chiralpak® IC column, 90:10 hexane/isopropyl alcohol, 1 µL/min, λ = 254 nm, 25 °C.

Figure III-35. HPLC separation of *rac*-**9ab**.



Peak#	Ret. Time	Area	Height	Area %	Height %
1	61.842	12677296	69502	43.890	46.085
2	72.384	16207129	81310	56.110	53.915
Total		28884425	150813	100.000	100.000

Conditions of HPLC separation: Chiralpak® IC column, 90:10 hexane/isopropyl alcohol, 1 µL/min, λ = 254 nm, 25 °C.

Figure III-36. HPLC separation of **(−)-9ab.**

After purification, pyrazolidinone 9ac was obtained as a white solid in 99% yield characterised by the crude formula of $C_{20}H_{29}N_3O_7S$. The ^{1}H-NMR spectrum ($CDCl_3$-d_6), figure III-37, showed the presence of aromatic groups integrate four protons, each two protons resonated in double signals at 8.19 ppm and 8.42 ppm. About hepthyl group, we found that the methyl group appeared in aliphatic region at 0.87 ppm with triplet peaks, also we observed the total integration of nine protons formed heptyl alky witch resound between 1.24–1.30 ppm. As previously compounds 9aa and 9ab, the intense signal with a chemical change of 1.47 ppm incorporates the protect group. Then, we observed is a multiple peaks resonates at 1.78–1.83 ppm 2.40–2.47 ppm, 3.42–3.49 and 4.37–4.42 ppm corresponding to the protons of structure ring 9ac. The ^{13}C-NMR spectrum ($CDCl_3$-d_6) specified sixteen carbon signals, among which nine are assigned to aliphatic unit including the carbonyl function of protecting group, three to the pyrazolidinone ring counting the carbonyl function identified at 172.88 ppm (position 5), and the four carbon signals were attributed to aromatic group, figure III-38 . Additionally, in HRMS spectra can be especially to obtain our structure $C_{20}H_{29}N_3O_7S$, HRMS analysis showed the presence of the deprotonated molecule ion at m/z = 473.2072 and m/z = 933.3330 produced respectively the precise fragments $[M_{9ac} + NH_4^+]^+$ and $[2M_{9ac} + Na^+]^+$, table III-16 and figure III-39.

- ***Product 9ac***

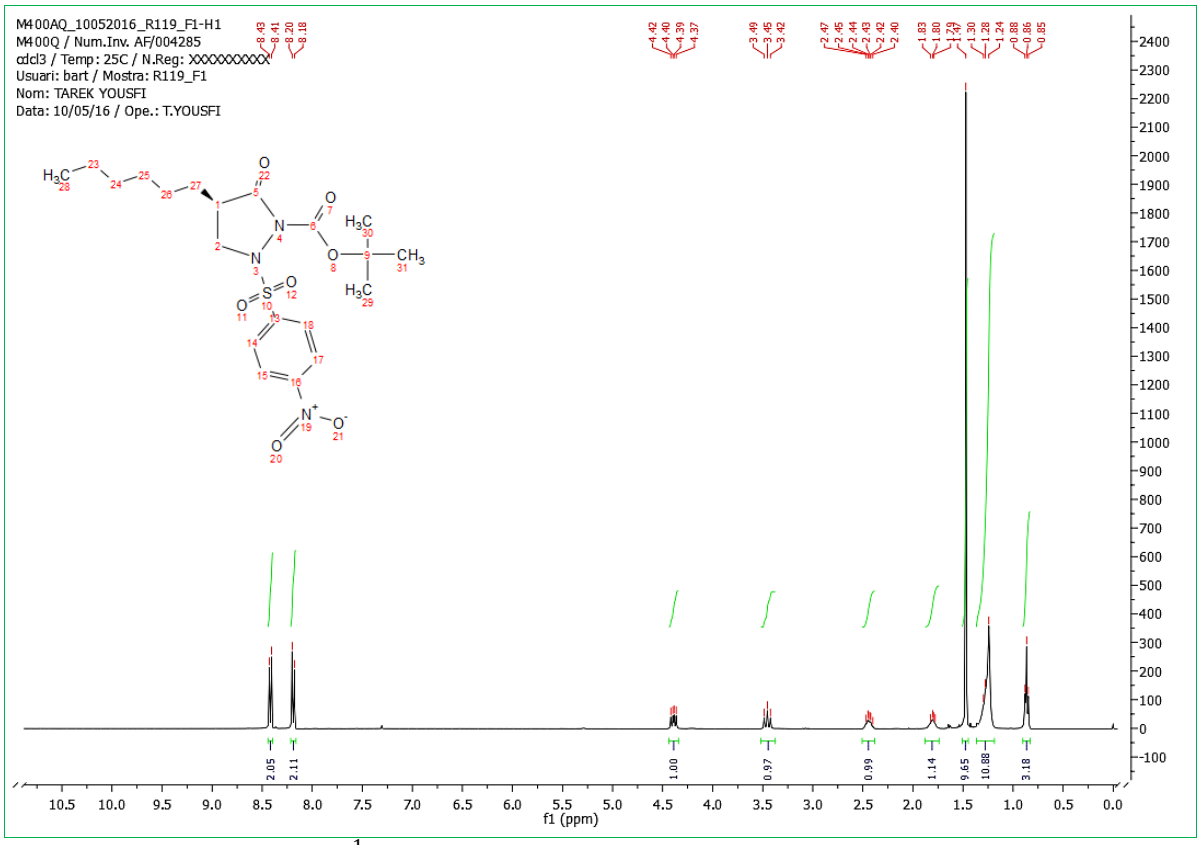


Figure III-37. ^{1}H-NMR (400 MHz) of *tert*-Butyl 4-Hexyl-2-((4-nitrophenyl)sulfonyl)-pyrazolidin-5-one-1-carboxylate, **9ac**.

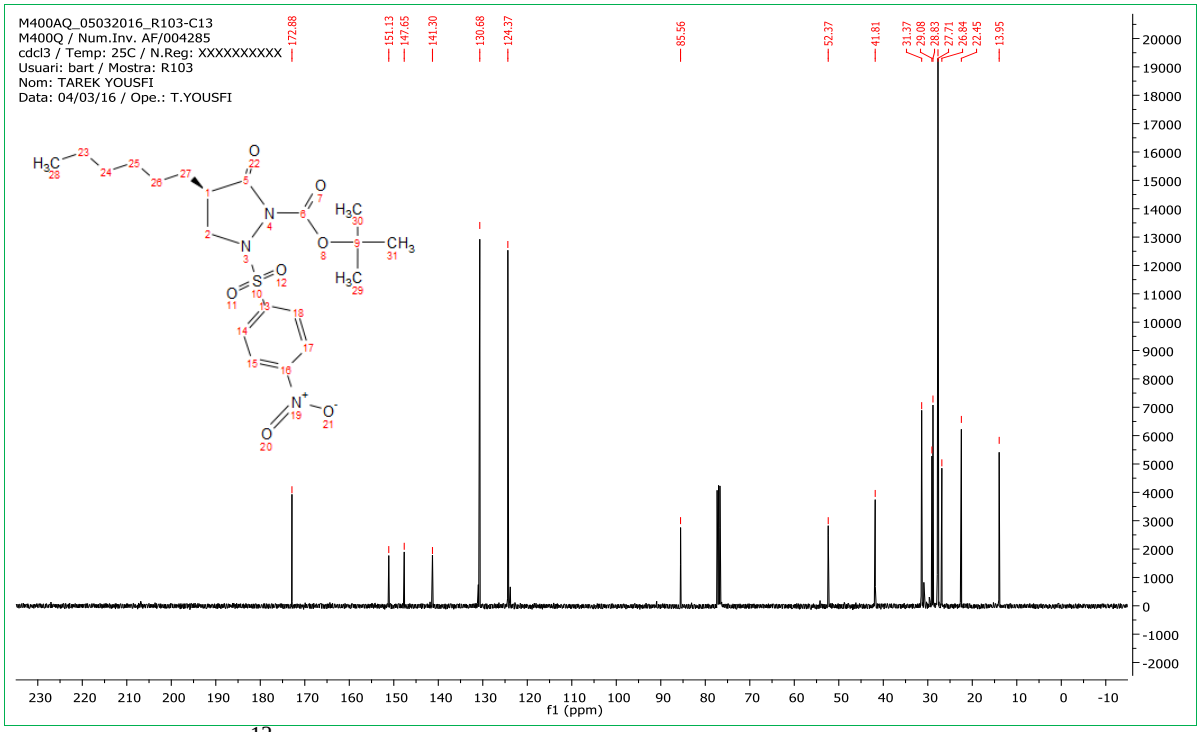


Figure III-38. ^{13}C-NMR (100.6 MHz) of tert-Butyl 4-Hexyl-2-((4-nitrophenyl) sulfonyl)-pyrazolidin-5-one-1-carboxylate**, 9ac.**

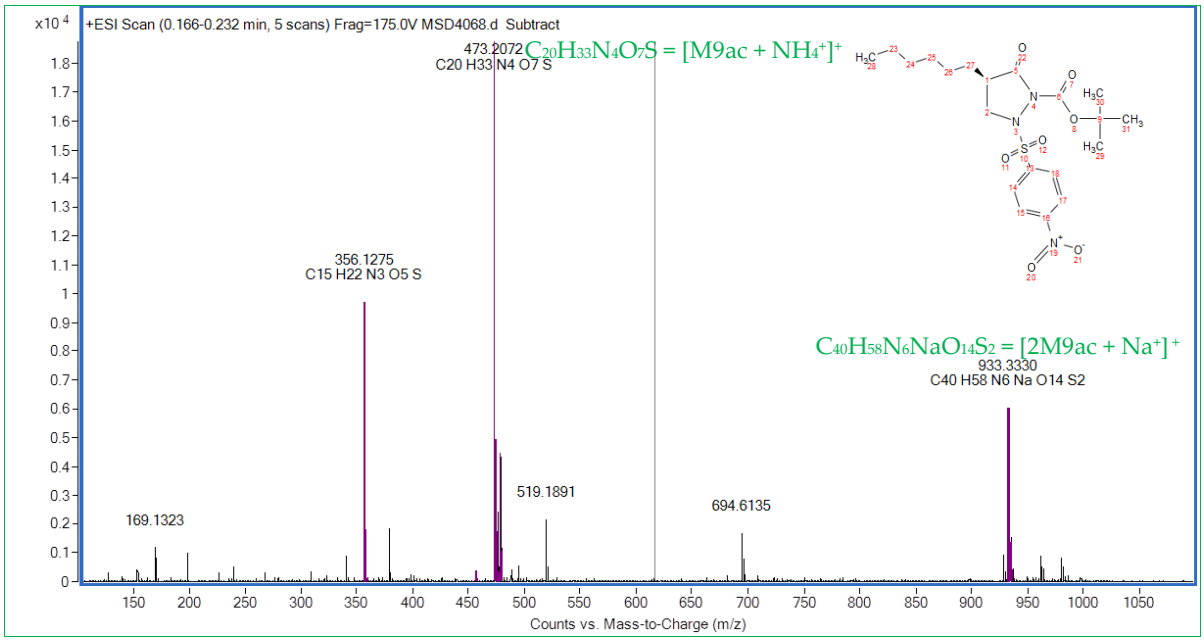
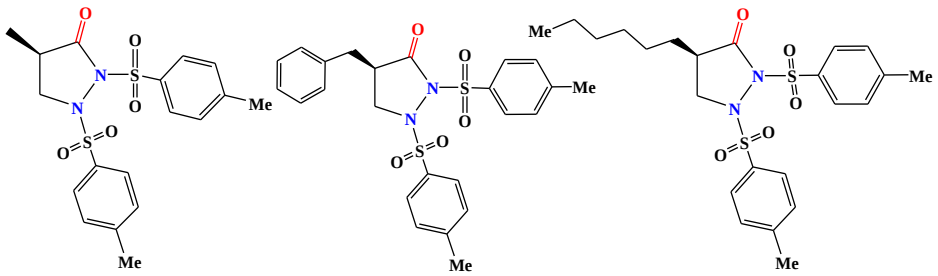


Figure III-39.HRMS analysis of pyrazolidinol, 9ac.

Table III-16. MS formula results of pyrazolidinol 9ac obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{40}H_{58}N_6NaO_{14}S_2$	92.25	933.3333	933.3345	87.16	1.34	0.12	$[2M_{9ac} + Na^+]^+$
TRUE	$C_{20}H_{33}N_4O_7S$	85.98	473.2072	473.2064	84.51	-0.74	-1.56	$[M_{9ac} + NH_4^+]^+$

In order to confirm the performance of the Jørgensen-Hayashi asymmetric catalysts 13 and 14 in the reaction between 1, 2-bis (p-toluene sulfonyl) hydrazine (2b) as a second substrate of Aza-Michael system and the α-aldehydes 7a–7c, using a 20 mol % of the catalyst and 20 mol % of benzoic acid co-catalyst in toluene at r.t. after the correspondences pyrazolidinols (8ba-8ba) were performed by oxidation with five equivalent of PCC. The figure III-40 summarized all the oxidized products 9ba, 9bb and 9bc, we were able to finish that the oxidation reaction using hydrazine 2b substrates of Aza-Michael system, as well yielded the corresponding products with suitable yields (up to 98%, table.12) and in excellent enantioselectivity (up to 98%, table.12) after recrystallization in the ratio from (1:2:7, dichloromethane/chloroform/hexanes) , obtained with pyrazolidinone **9ba** witch synthesized form methacrolein (**7a**) and the nucleophile substrate 1, 2-bis(*p*-toluenesulfonyl)hydrazine (**2b**) en the presence of asymmetric catalyst 13, as shown on the last oxidation summary, table III-17.



9ba **9bb** **9bc**

Figure III-40. Pyrazolidin-3-one structures (9ba–9bc) from α-substituted enals 7a–7c and hydrazines **2b.**

Table III-17. Physico-chemical characteristics of Pyrazolidin-3-one products (**9ba–9bc).**

Pyrazolidinone	Brute formula	M gr.mol^{-1}	Fusion point
9ba	$C_{18}H_{20}N_2O_5S_2$	408.32	156–160 °C
9bb	$C_{24}H_{24}N_2O_5S_2$	484.36	156–160 °C
9bc	$C_{23}H_{30}N_2O_5S_2$	478.35	160–164 °C

Given these previous products, they have never been synthesized, isolated and characterized, all of them characterised by the presence of two sulfonyl groups. After purification in column chromatography, we systematized a colorless solid categorized in the fusion point's 156–160 °C and 160–164 °C respectively for 9ba, 9bb and 9bc. Around the first pyrazolidinone 9ba characterised by the presence of tow sulfonyl (SO_2-C_6H_5-Me) groups, obtained in excellent enantioselectivity (up to 98%) and in respectable yield (up to 98%) with crude formula of $C_{18}H_{20}N_2O_5S_2$. As show in the figure III-41, the ^{1}H-NMR spectrum ($CDCl_3$-d_6) displayed the presence of two aromatic groups integrate eight protons, each four protons resonated at 7.34-7.36 and 7.77-7.78 ppm in double signals. We identified in aliphatic region three methyl groups, tow methyl group appeared to gather in the same position at 2.46 ppm with single peaks take part of six protons corresponding to sulfonyl group, also we observed the total integration of three protons resonated at 0.75–0.77 ppm agreeing the methyl group related to pyrazolidinone ring. The last three protons of the pyrazolidinone 9ba structure distributed by multiples resonate at 4.28-4.33 ppm, 2.83-2.90 ppm and 2.12-2.23 ppm. The ^{13}C-NMR spectrum ($CDCl_3$-d_6), figure III-42, indicated fourteen carbon signals among which three are assigned in the

aliphatic unit including the methyl group, three peaks resemble to the pyrazolidinone ring witch regrouped the carbonyl function at 176.5 ppm, and the nine carbon signals were attributed to aromatic group. Finally, In HRMS spectra can be especially to obtain our structure $C_{18}H_{20}N_2O_5S_2$, HRMS analysis showed the presence of the deprotonated molecule ion at m/z = 834.1963 and m/z = 426.1152 produced respectively the tow fragments $[2M_{9ba} + NH_4{}^+]^+$ and $[M_{9ba} + NH_4{}^+]^+$, as shown in the table III-18 and figure III-43.

- ***Product 9ba***

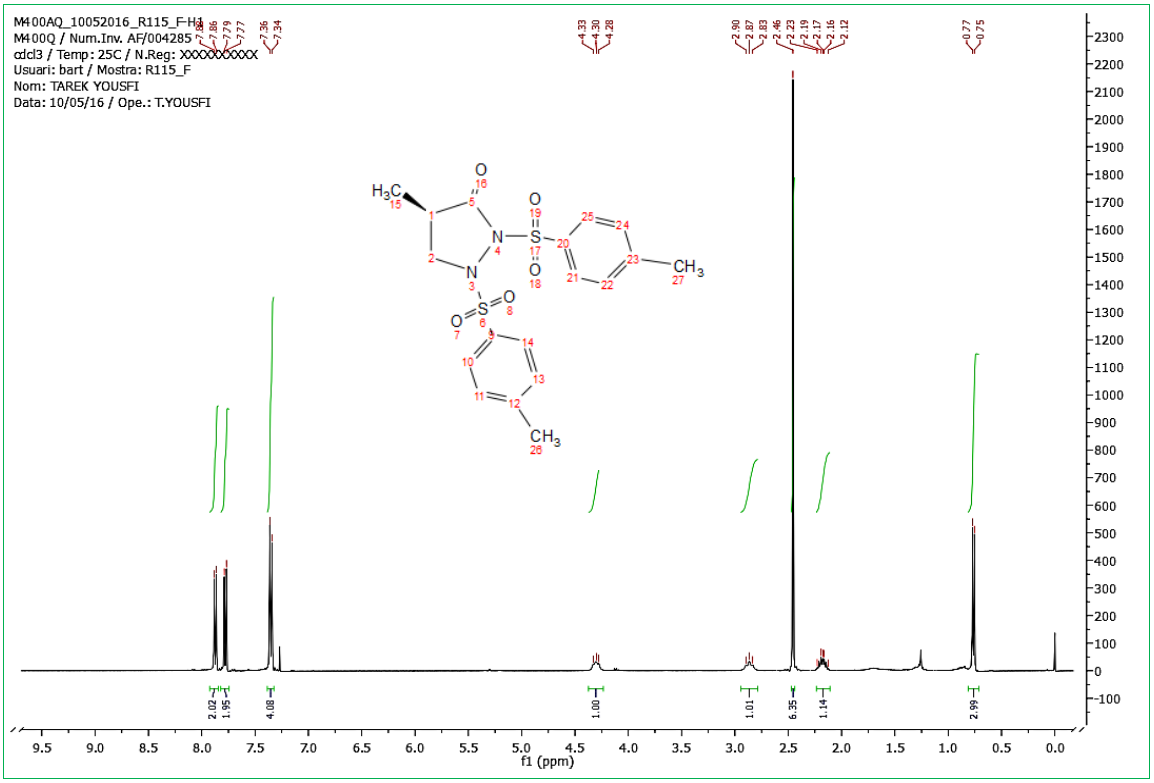


Figure III-41. ^{1}H-NMR (400 MHz) of (−)-4-Methyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one, **9ba**.

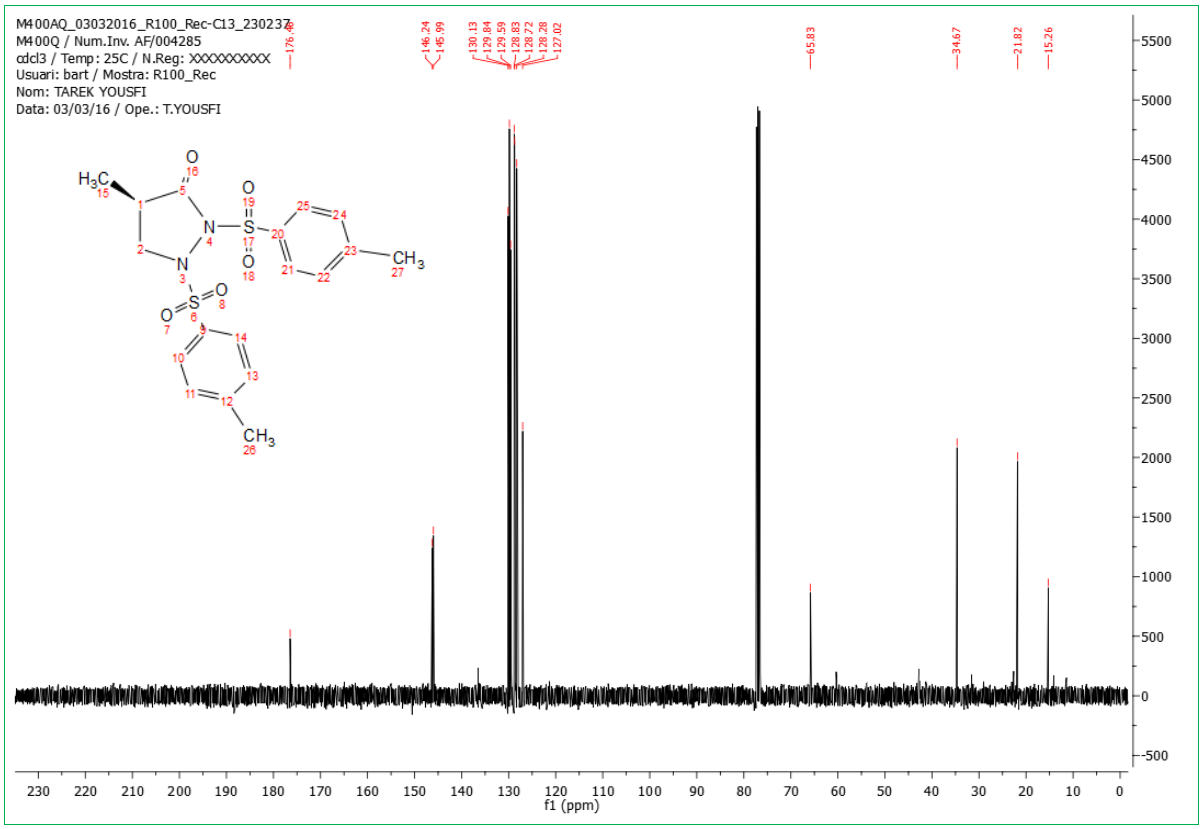


Figure III-42. ^{13}C-NMR (100.6 MHz) of (−)-4-Methyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one, **9ba**.

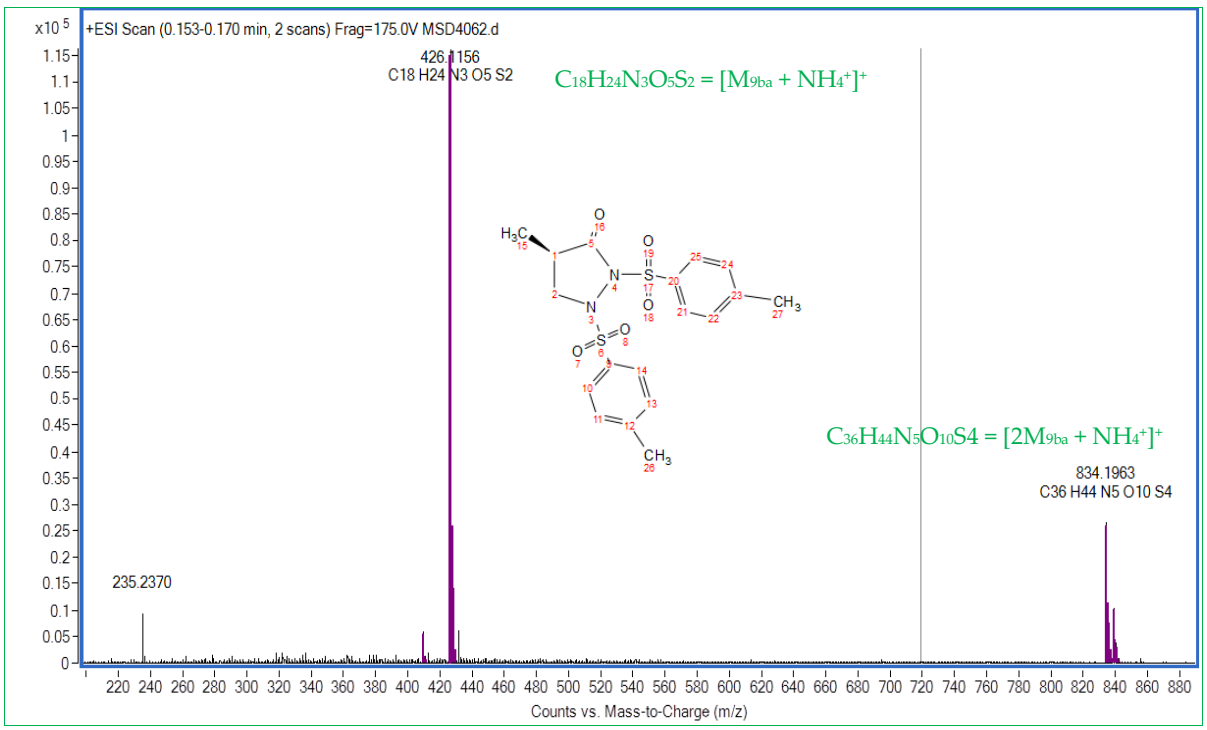


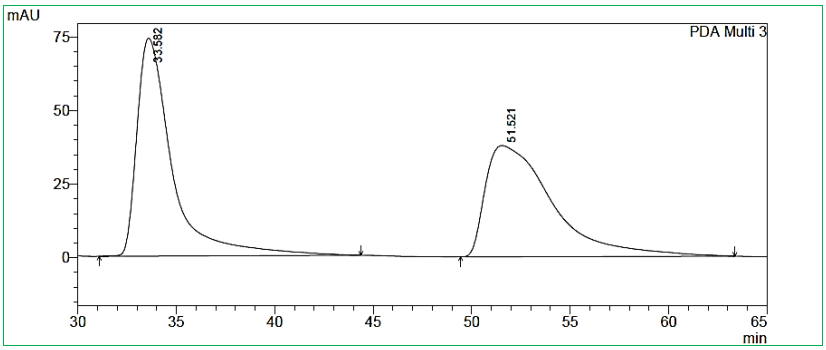
Figure III-43. HRMS analysis of pyrazolidinol, **9ba.**

Table III-18. MS formula results of pyrazolidinol 9ba obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{36}H_{44}N_5O_{10}S_4$	95.93	834.1963	834.1966	86.22	0.19	0.22	$[2M_{9ba} + NH_4^+]^+$
TRUE	$C_{18}H_{24}N_3O_5S_2$	94.72	426.1156	426.1152	84.27	-0.38	-0.9	$[M_{9ba} + NH_4^+]^+$

After same experiment at the same conditions of mobile phase of 90:10 hexane/isopropyl alcohol and IA chiral column, the racemic method is capable to separate the two enantiomers with easy separation due to the low flow rate 1 ml/min for HPLC pump but with fast separation factor of 18 min between the appearances of the two enantiomers. The enantiomeric separation was performed at the same conditions of asymmetric compound 9ba, synthetised from 8ba pyrazolidinol en the presence of asymmetric catalyst 13. Therefore, the mixture of 9ba is actually composed with excellent enantiomeric excess of 96:4.

The major enantiomer looked at retention time 34 min and the minor enantiomer observed at retention time 52 min. This result means the performance of our asymmetric model in the presence of asymmetric catalyst 13 and the calculation of the specific rotation of the enantiomeric product 9ba, which has a value of $[\alpha]_D^{25} = -64.7$ (0.67, DCM). We can conclude that the mixture of 9ba contains the major enantiomer as (−)-9aa structure in 96 %, typical chromatograms are shown in figure III-44 and III-45.

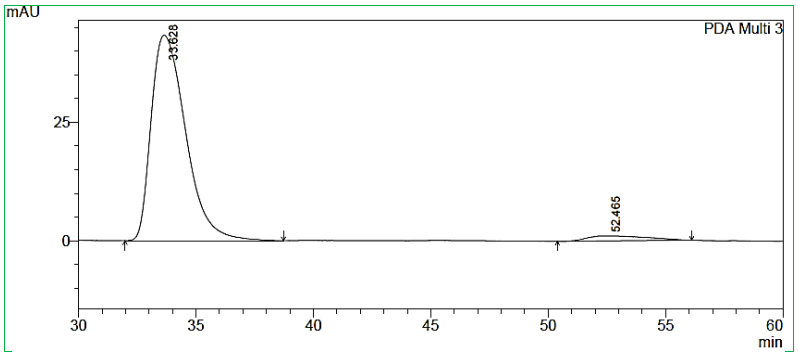


PDA Ch3 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.582	9231871	74031	50.742	66.222
2	51.521	8961982	37761	49.258	33.778
Total		18193854	111792	100.000	100.000

Condition of HPLC separation: (Chiralpak® IA column, 90:10 hexane/isopropyl alcohol, 1 µL/min, λ = 254 nm, 25 °C).

Figure III-44. Racemic compound, ***rac*-9ba.**



PDA Ch3 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.628	4430577	43280	95.943	97.560
2	52.465	187341	1082	4.057	2.440
Total		4617918	44362	100.000	100.000

Condition of HPLC separation: (Chiralpak® IA column, 90:10 hexane/isopropyl alcohol, 1 µL/min, λ = 254 nm, 25 °C).

Figure III-45. Enantiomeric compound, **(−)-9ba.**

The second oxided pyrrolidinone 9bb has a crude formula $C_{24}H_{24}N_2O_5S_2$,was obtained in good yield (up to 97%) after repurification in column chromatography (n-hexane/EtOAc, 65:35) corresponding to racemic and asymmetric pyrazolidinols 8bb. The ^{1}H-NMR spectrum ($CDCl_3$-d_6), (figure III-46), showed the presence of three aromatic groups integrate thirteen total protons, which are resonated between 6.81-7.87 ppm in double signals. We found in aliphatic region binary methyl groups, appeared to gather in the same position at 2.47 ppm and 2.48 ppm as a single peaks regrouped the six protons of sulfonyl section. Additionally at the same position 2.47 ppm, we can see the integration of one proton corresponding to (-CH_2-) function of 4-benzyl group. The last four protons of the pyrazolidinone 9bb ring

dispersed by multiples resonate at 2.01–2.07 ppm, 2.90–2.95 ppm, 2.98–3.01 ppm and 4.05–4.011 ppm. The ^{13}C-NMR spectrum ($CDCl_3$-d_6), figure III-48, designated eighteen carbon signals, among the aromatics signals concentrated between 127.0 ppm and 146.2 ppm in total twelve pics. In the aliphatic area, we found two methyl groups resonated at 21.79 ppm and 21.82 ppm. The pyrazolidinone sphere contained in the first part, the carbonyl group indicted at 176.5 ppm and the three carbon were attributed at 34.7 ppm, 42.7 ppm and 54.0 ppm. Similarly, the HRMS analysis presented the deprotonate molecule ion at m/z = 507.1014, 502.1466 and m/z = 485.1224 produced respectively the three fragments $[M_{9bb} + Na^+]^+$, $[M_{9bb} + NH_3^+]^+$ and $[M_{9bb} + H^+]^+$ related to the molecular weight of 484.36 g.mol^{-1} of the crude formula $C_{24}H_{24}N_2O_5S_2$, table III-19 and figure III-48.

Unfortunately, the chiral HPLC separations of racemic and asymmetric compounds 9bb were performed at the same conditions but we have note satisfactory conditions using the different chiral columns IC, IA and IB.

- ***Product 9bb***

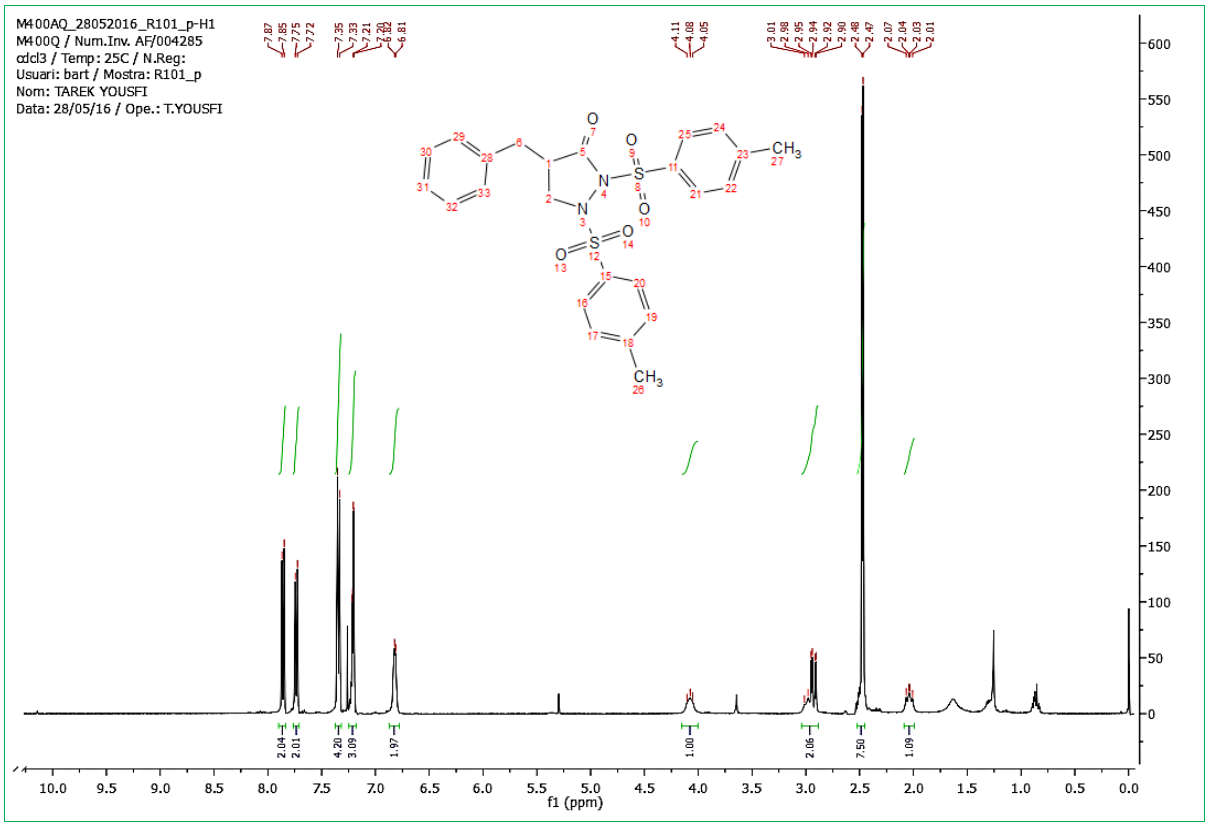


Figure III-46. ^{1}H-NMR (400 MHz) of 4-Benzyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one, **9bb**.

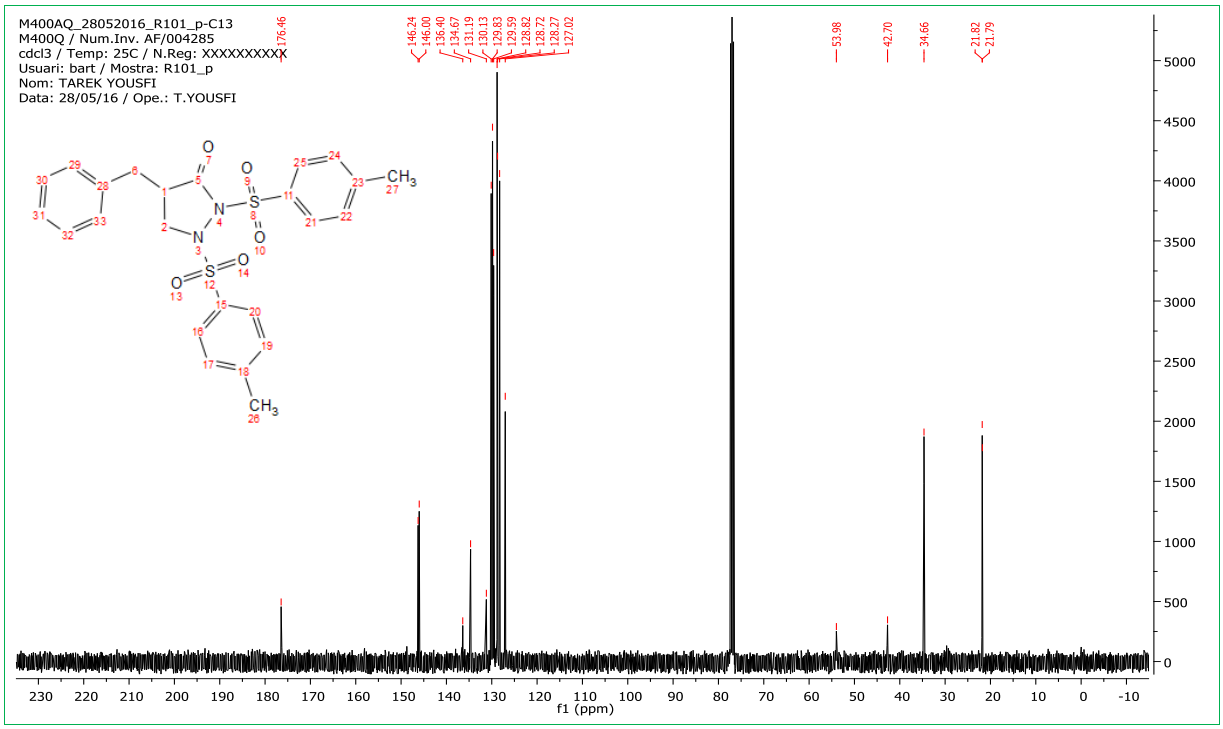


Figure III-47. ^{13}C-NMR (100.6 MHz) of 4-Benzyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one, **9bb**.

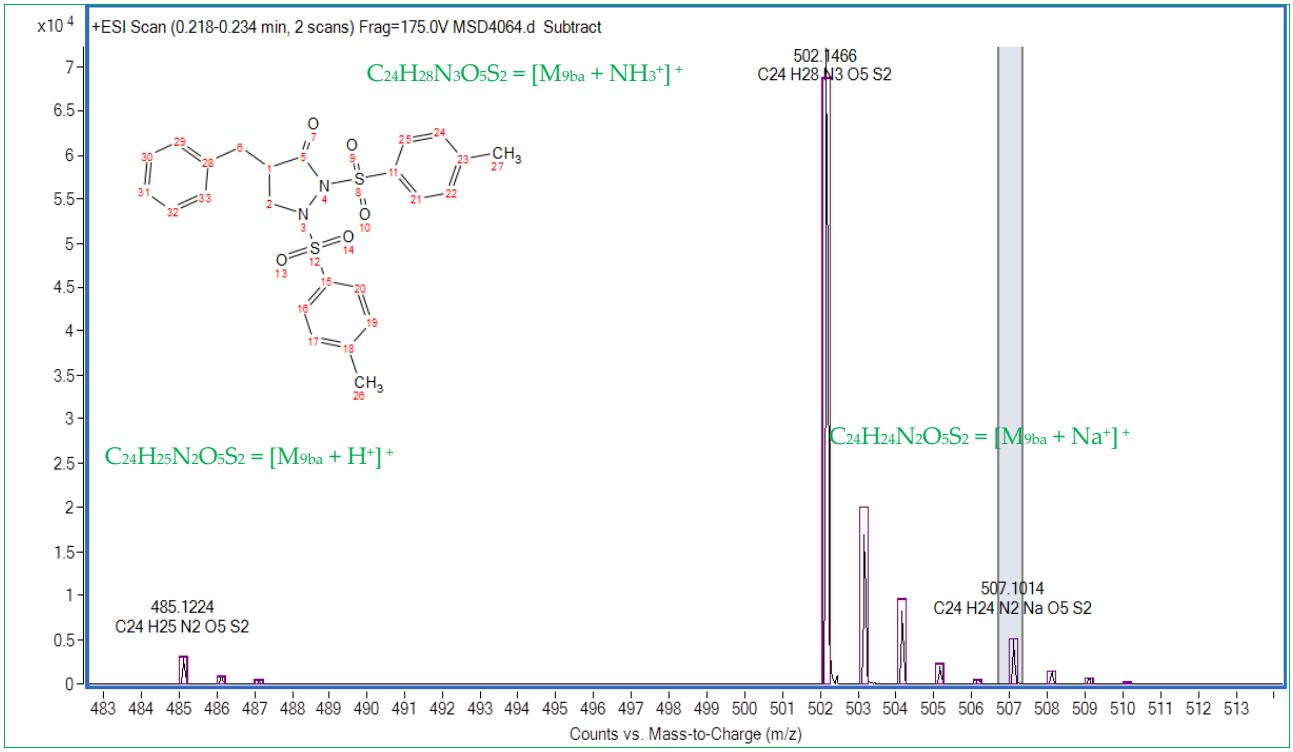


Figure III-48.HRMS analysis of pyrazolidinone, 9bb.

Table III-19. MS formula results of pyrazolidinol 9bb obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{24}H_{24}N_2NaO_5S_2$	94.4	507.1014	507.1019	97.22	0.43	0.86	$[M_{9bb}+ Na]^+$
TRUE	$C_{24}H_{28}N_3O_5S_2$	94.73	502.1466	502.1465	85.7	-0.07	-0.14	$[M_{9bb}+NH_3^+]^+$
TRUE	$C_{24}H_{25}N_2O_5S_2$	82.93	485.1224	485.1199	97.1	-2.38	TRUE	$[M_{9bb} + H^+]^+$

The last oxided product 9bc was isolated as a white solid with fusion point (160–164 °C), characterised by the crude formula of $C_{23}H_{30}N_2O_5S_2$ and molecular weight 478.35 g.mol^{-1}. We have purified by column chromatography (n-hexane/EtOAc, 65:35) in 98 % yield. The ^{1}H-NMR spectrum ($CDCl_3$-d_6) in figure III-49, exposed the appearance of eight protons in the aromatic section each phenyl group appeared at 7.33–7.36 ppm and 7.78 -7.88 ppm. In another part, we established in the aliphatic region a binary methyl group vibrate 2.45 ppm and 2.46 ppm in two superposed peaks regrouped the six protons of sulfonyl alkyls, as has been shown to the above compounds 9aa and 9bb. Also, we found that the hepthyl group contained the methyl group appeared at 0.83-0.86 ppm with triplet signals, we noticed the total integration of ten protons related to the heptyl alkyl witch resonate at between 0.86–1.50 ppm. The three protons of the pyrazolidinone sphere 9bc detached by multiples resonate at 2.04–2.10 ppm, 2.93–3.00 ppm and 4.24–4.29 ppm.The ^{13}C-NMR spectrum ($CDCl_3$-d_6), figure III-50, designated nineteen signals analogous to the number of equivalent carbons where we detect the carbonyl function indicted at 177.5 ppm. Finally, HRMS analysis presented the attendance of the deprotonated molecules ions at m/z = 496.1939 and m/z = 974.351 produced respectively the three fragments $[M_{9bc}+NH_4^+]^+$ and $[2M_{9bc}+NH_4^+]^+$ related to the molecular weight of 484.36 g.mol^{-1} of the crude formula $C_{23}H_{30}N_2O_5S_2$, table III-20 and figure III-51.

- ***Product 9bc***

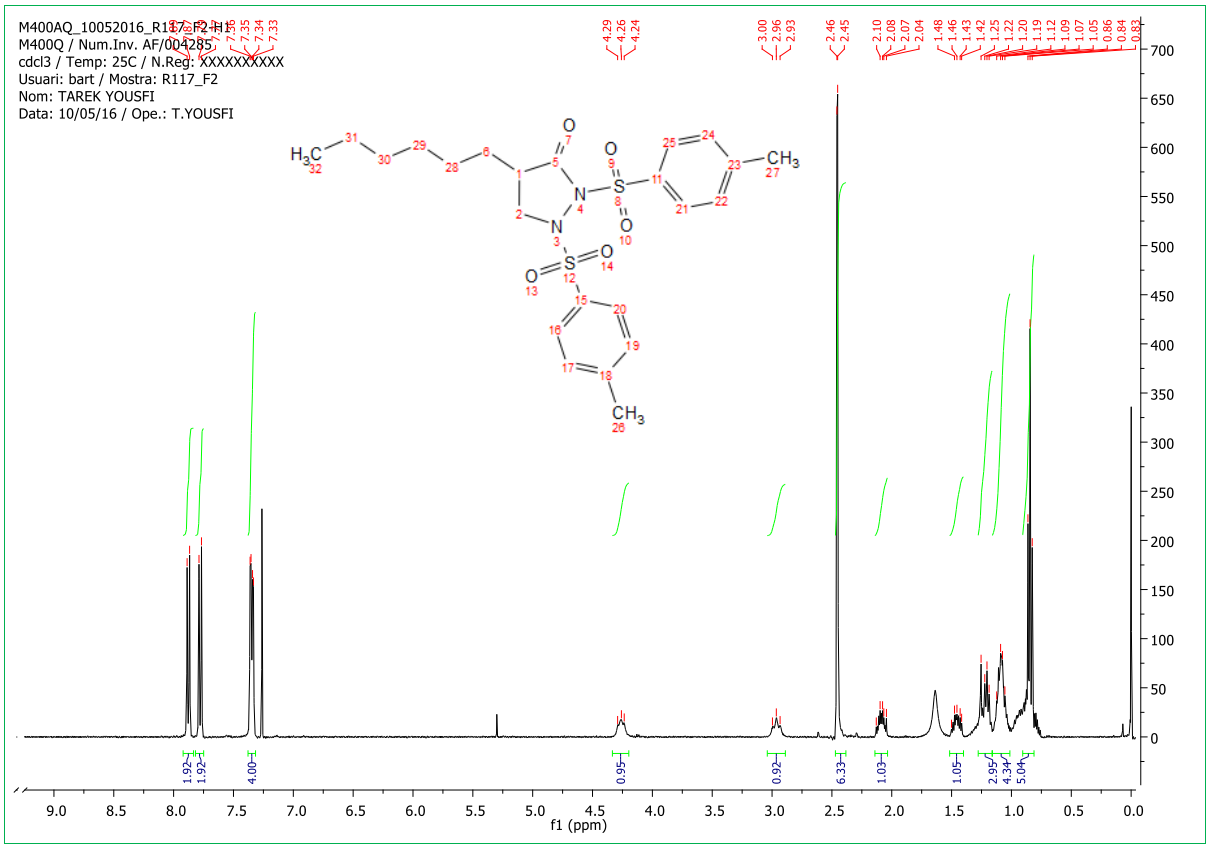


Figure III-49. ^{1}H-NMR (400 MHz) of (−)-4-Hexyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one, **9bc**.

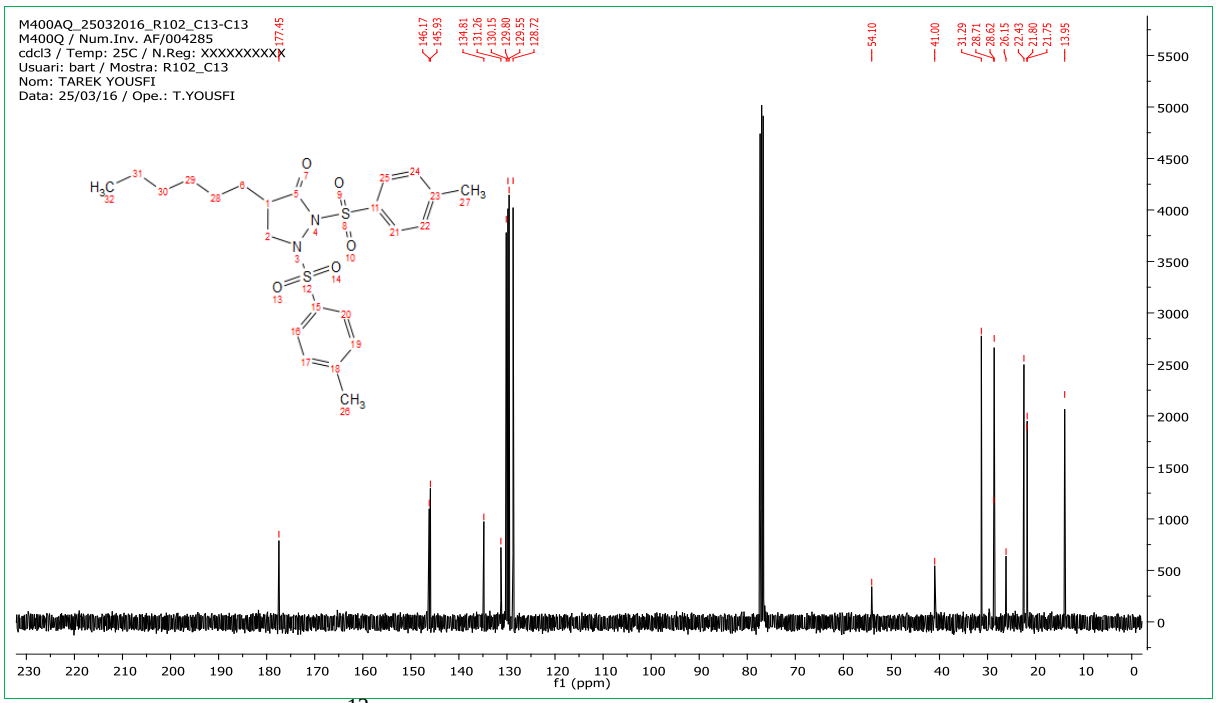


Figure III-50. ^{13}C-NMR (100.6 MHz) of (−)-4-Hexyl-1,2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one, **9bc**.

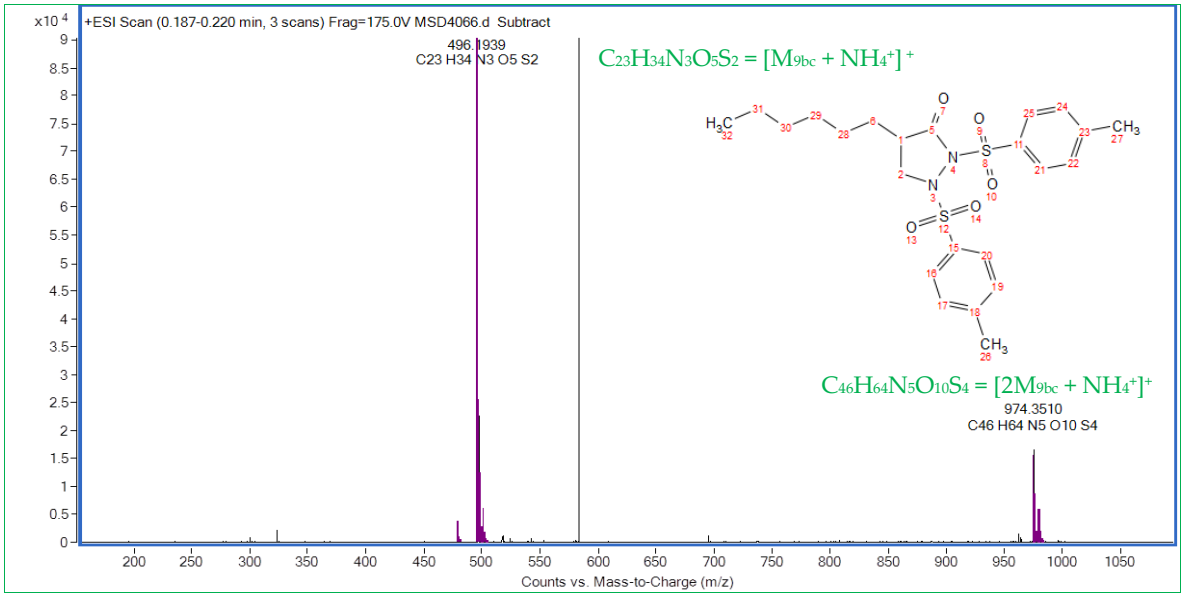


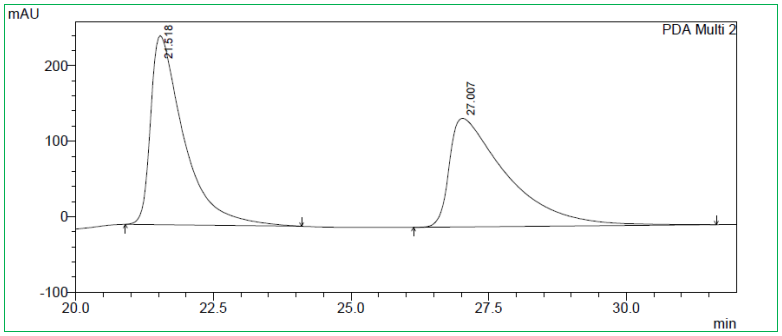
Figure III-51. HRMS analysis of pyrazolidinol, **9bc.**

Table III-20. MS formula results of pyrazolidinol **9bc** obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{23}H_{34}N_3O_5S_2$	95.23	496.1939	496.1934	85.89	-0.46	-0.92	$[M_{9bc} + NH_4]^+$
TRUE	$C_{46}H_{64}N_5O_{10}S_4$	94.64	974.351	974.3531	93.59	1.98	2.04	$[2M_{9bc} + NH_4]^+$

We completed the HPLC separation of 9bc using mobile phase of 93:7 hexane/isopropyl alcohol and IB chiral in λ = 220 nm at room temperature. The racemic method is skillet to separate the two enantiomers with soft separation due to the low flow rate 1 ml/min for HPLC pump with fast separation factor of 26 min between the attendances of the two enantiomers, typical chromatograms are shown in figure III-52 and III-53. The enantiomeric separation was performed of asymmetric compound 9ba, synthetised from pyrazolidinol 8ba in the presence of asymmetric catalyst 13. Therefore, the mixture of 9bc is actually composed with acceptable enantiomeric excess of 78:22. The two enantiomers (major and minor) observed separately at the retention time 22 and 27 min. This result means the performance of the asymmetric model in the presence of asymmetric catalyst 13 and the calculation of the specific rotation has a value of $[\alpha]_D^{25} = -8.0$ (1.01, DCM), we can conclude that the mixture of 9ba contains the major enantiomer as (−)-9ba

structure, typical chromatograms are shown in figure III-52 and III-53. Unfortunately, we not found the performance of asymmetric model in the presence of asymmetric catalyst 14 as show by HPLC separation analogous to racemic parting.

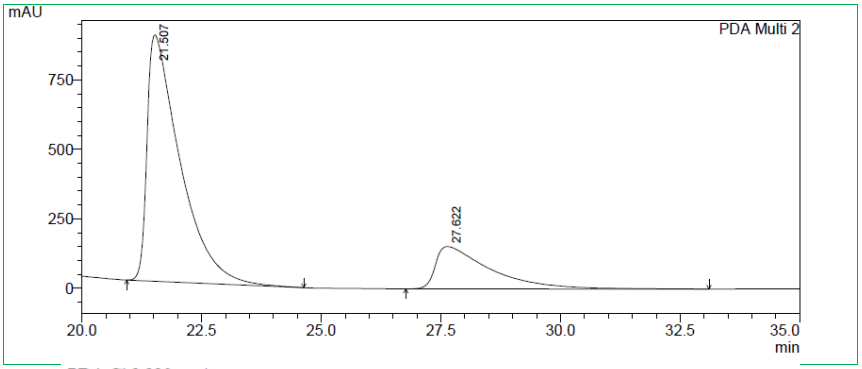


PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.518	10499107	250442	50.153	63.528
2	27.007	10435081	143784	49.847	36.472
Total		20934189	394226	100.000	100.000

Condition of separation HPLC (Chiralpak® IB column, 93:7 hexane/isopropyl alcohol, 1 µL/min, λ = 220 nm, 25 °C).

Figure III-52. Racemic compound, ***rac*-9bc.**



PDA Ch2 220nm 4nm

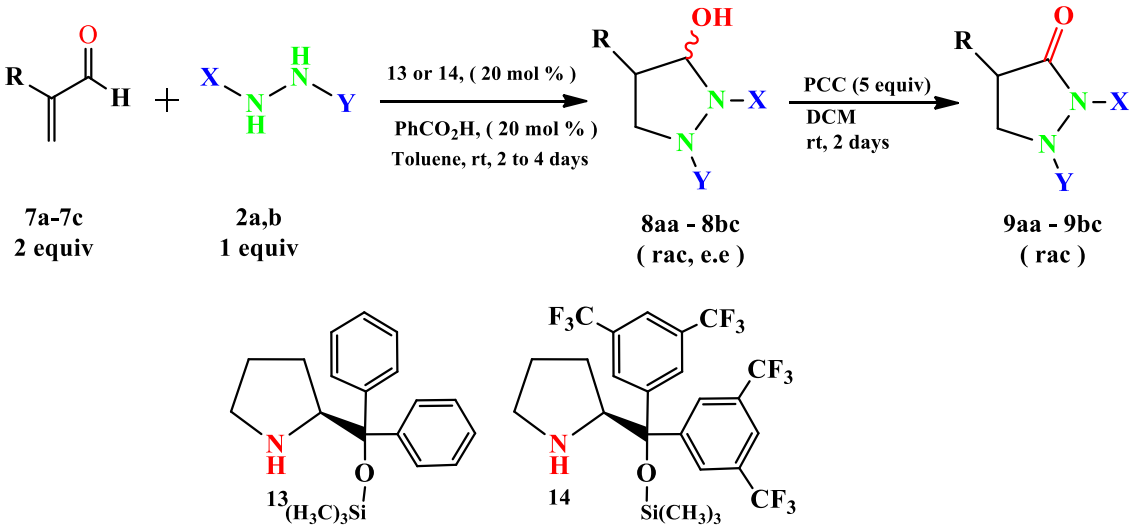
Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.507	42470297	886214	77.915	85.333
2	27.622	12038479	152324	22.085	14.667
Total		54508775	1038538	100.000	100.000

Condition of separation HPLC (Chiralpak® IB column, 93:7 hexane/isopropyl alcohol, 1 µL/min, λ = 220 nm, 25 °C).

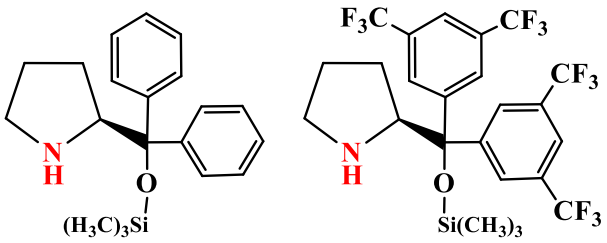
Figure III-53. Asymmetric compound**, (−)-9bc.**

III.1.3.3 Asymmetric synthesis 4-substituted pyrazolidin-3-ols

Previous studies from our research group [1b] and those of Córdova [9a-10] and Vicario [1-2] had shown that the use of chiral diarylprolinol-silyl ethers as catalysts led to high enantioselectivities in the Aza-Michael/cyclization reactions of β-substituted [1a, 9-10] and of α, β-disubstituted enals with hydroxylamines or hydrazines. However, α-branched vinyl carbonyls remain a very challenging substrate for this type of reaction and only one successful example of aminocatalytic asymmetric Aza-Michael addition to α-substituted vinyl ketones has been reported so far [11-12]. Bearing these precedents in mind, we proceeded to examine the performance of the Jørgensen-Hayashi catalysts 13 and 14 (figure III-54) in the reaction between aldehydes 7a–7c and hydrazines 2a and 2b (Table III-21), using a 20 mol % of the catalyst and a 20 mol % of benzoic acid co-catalyst in toluene at r.t. (typical reaction time 3 days), Scheme III-8. After 7 days of stirring at r.t, no product was observed in the attempted reactions of aldehyde 7c with hydrazine 2a, either when using 13 or 14 as catalysts. On the other hand, we could not find satisfactory HPLC conditions for the separation of the enantiomers 9bb, as show before. So, that the enantioselective catalysis for the reaction of aldehyde 7b with hydrazine 2b was not attempted.



Scheme III-8. Asymmetric synthesis of pyrazolidin-3-ones from α-substituted enals.



13 **14**

Figure III-54. Jørgensen-Hayashi catalysts **13** ((*S*)-diphenylprolinol trimethylsilyl ether) and **14** ((*S*)-bis (3, 5-trifluoromethylphenyl) prolinol trimethylsilyl ether) used in the enantioselective synthesis of pyrazolidinones **9**.

Table III-21. Enantioselective synthesis of pyrazolidin-3-ones **9.**

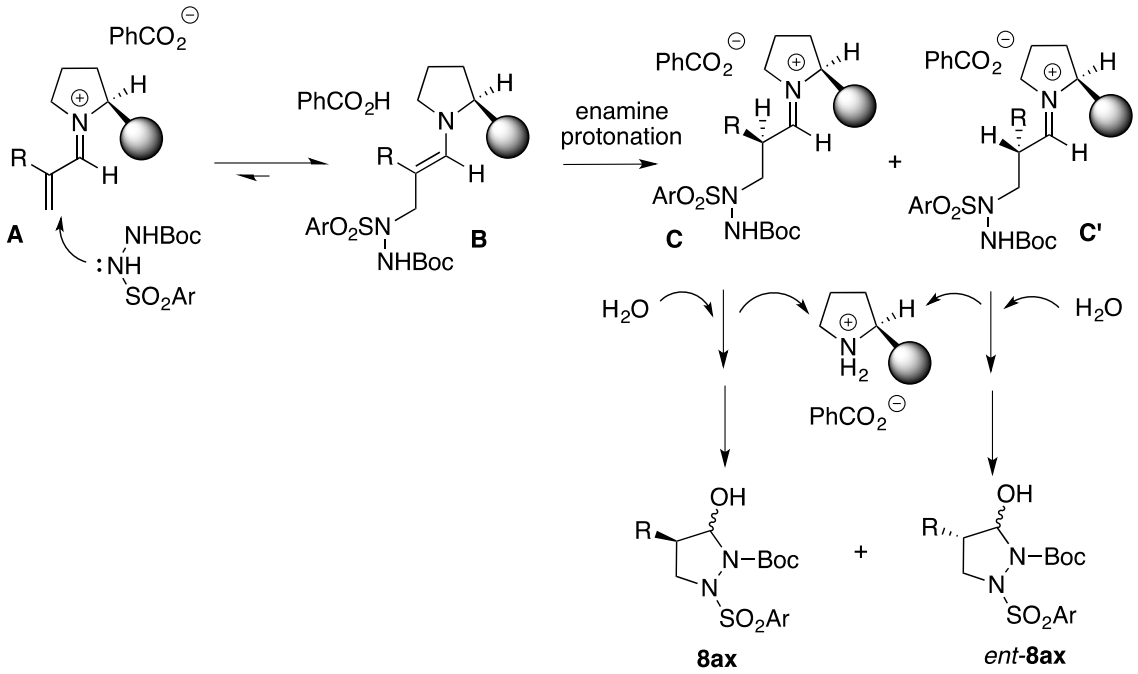
Entry	Reactants	Catalyst	Pyrazolidinol	Yield [1]	dr [2]	Pyrazolidinone	Yield [1]	er [3]
1	**7a**, **2a**	**13**	**8aa**	82%	4:1	**9aa**	87%	50:50
2	**7a**, **2a**	**14**	**8aa**	99%	3:1	**9aa**	94%	90:10
3	**7b**, **2a**	**13**	**8ab**	77%	>20:1	**9ab**	98%	44:56
4	**7b**, **2a**	**14**	**8ab**	98%	>20:1	**9ab**	98%	45:55
5	**7b**, **2b**	**13**	**8bb**	85%	9:1	**9bb**	97%	- [4]
6	**7b**, **2b**	**14**	**8bb**	85%	9:1	**9bb**	97%	- [4]
7	**7a**, **2b**	**13**	**8ba**	84%	8:1	**9ba**	98%	96:4
8	**7a**, **2b**	**14**	**8ba**	0% [5]		**9ba**	-	-
9	**7c**, **2b**	**13**	**8bc**	93%	10:1	**9bc**	98%	78:22
10	**7c**, **2b**	**14**	**8bc**	77%	10:1	**9bc**	98%	50:50

[1] Yield of isolated product after chromatographic purification; [2] By ^{1}H-NMR; [3] By chiral HPLC analysis (See the Supplementary Materials for details); [4] No satisfactory conditions for the HPLC analysis of this compound could be found; [5] No reaction was observed after 7 days.

As it can be seen in Table III-21, the enantioselectivity of the reaction depends strongly both in the nature of the reactants and of the catalyst. The highest enantiomeric purities were obtained for the less hindered methyl-substituted enal 7a, either with hydrazine 2a (entry 2, 90:10 er, catalyst 14) or with hydrazine 2b (entry 7, 96:4 er, catalyst 13) in high isolated yields 94% and 98% respectively. In any case, these preliminary results demonstrate for the first time the feasibility of the asymmetric synthesis of 4-substituted-3-pyrazolidinones by the organocatalytic Aza-Michael/cyclization of activated hydrazines to α-substituted acroleines. It is interesting to note that when hydrazide (2b) and (13) were employed, a very significant dependence of the yield on the length of the α-alkyl substituent was observed, obtaining an excellent yields and high diastereoselectivity when longer substituents were incorporated, although enantioselectivity remained low (entries 5,

7 and 9), contrary to the result obtained by Fernández and Vicario which found an opposite observation with the β-alkyl substituent enals in the presence of the same reagents 2b and 13[1a]. The stereoisomeric mixture of pyrazolidinols 8 was then submitted to oxidation with PCC as before, and the enantiomeric purity of the corresponding pyrazolidinones 9 was determined by chiral HPLC analysis. The NMR analysis (^{1}H and ^{13}C) and HRMS identified all structures of 8 pyrazolidinols and 9 pyrazolidinones, as before.

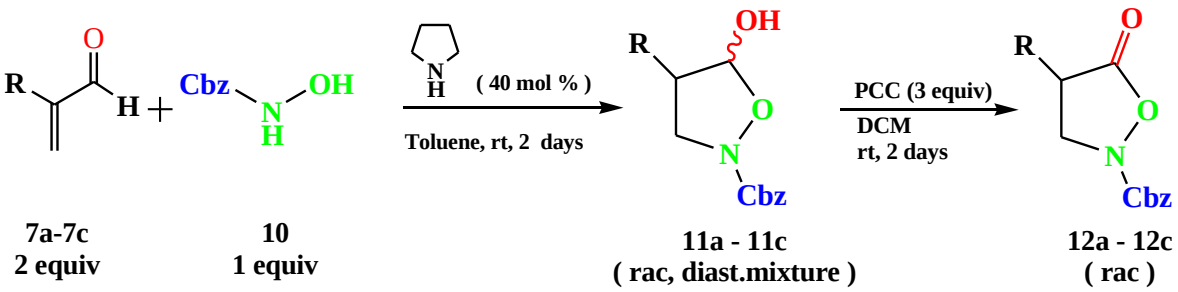
In light of these results, a simplified mechanistic proposal for the formation of enantiomerically enriched 4-substituted pyrazolidinols 8aa–8ac is depicted in Scheme III-9. While in the formation of the first carbon-nitrogen bond by the Aza-Michael reaction of the chiral iminium intermediate (A) (formed from the α-substituted enal 7a–c and the chiral pyrrolidine catalyst 13 or 14) with the hydrazine (2a) no new chiral centre is formed, the protonation of the intermediate enamine (B) can take place on the two diastereotopic faces of the C–C double bond. When using the trifluoromethyl-substituted catalyst 14, we assume (based on our previous studies of Anna and albert Moyano on the asymmetric organocatalytic synthesis of isoxazolidines) **[1b]**. That when R = Me protonation will take place under kinetic control from the face opposite to the bulky pyrrolidine substituent, leading to the second iminium intermediate (C) as the major diastereomer. Fast, irreversible hydrolysis and cyclization of this intermediate would predominantly give the (4R) enantiomer of 8aa. When the steric bulk of the R substituent is increased (7b or 7c), the formation of the diastereomeric iminium ion C' will be relatively favoured (in this intermediate the steric interactions of the α-substituent R with the pyrrolidine substituent are minimized), resulting of the competitive formation of the (4S) enantiomer of the pyrazolidinol 8ab or 8ac.



Scheme III-9. Mechanistic proposal for the Michael addition-cyclization sequence leading to the formation of enantiomerically enriched 4-substituted pyrazolidinols.

III.1.4 Organocatalytic Synthesis of 4-Substituted Isoxazolidines

In the light of these results of the pyrazolidine compounds, we explored the possible use of the α-substituted acroleins **7** as starting materials for the synthesis of 4-substituted isoxazolidin-5-ones, potentially interesting compounds both from the biological point of view and as advanced intermediates towards α-substituted-β-amino acids [1b], by the amine-catalyzed reaction with a suitable protected hydroxylamine. To our satisfaction, we found that in fact α-substituted acroleins **7**, with the sole exception of the isopropyl derivative 3-methyl-2-methylenebutyraldehyde (**7d)**, reacted smoothly with *N*-Cbz-hydroxylamine **10** (Cbz = benzyloxycarbonyl) to afford the isoxazolidinols **11** in good yields (78%–83% isolated yields) as diastereomer mixtures . Subsequent oxidation of these compounds with PCC took place uneventfully, providing the target 4-substituted isoxazolidin-5-ones **12**, scheme III-10 and table III-22.



Scheme III-10. Organocatalytic synthesis of isoxazolidin-5-ones from α-substituted enals.

Table III-22. Pyrrolidine-catalyzed synthesis of isoxazolidin-5-ols 11a–11c from α-substituted enals 7a–7c and N-Cbz-hydroxylamine 10, and oxidation to the corresponding isoxazolidin-5-ones 12a–12c.

Entry	Reactants	R	Isoxazolidinol	Yield [1]	dr [2]	Isoxazolidinone	Yield [1]
1	**7a**, **10**	Me	**11a**	83%	> 2:1	**12a**	98%
2	**7b**, **10**	$PhCH_2$	**11b**	79%	3:1	**12b**	99%
3	**7c**, **10**	*n*-Hexyl	**11c**	78%	3:1	**12c**	87%

[1] Yield of isolated product after chromatographic purification. [2] By ^{1}H-NMR.

Similar to pyrazolidine protocols, we found the perfect conditions for Michael addition/cyclization system, that by using 40 mol % of pyrrolidine catalyst with the presence of a molecular equivalent 2: 1 for (α-aldehydes / hydrazine 2a) in toluene at room temperature for two days, give the excellent yields 83%, 79% and 78% respectively for the isoxazolidinols 11a, 11b and 11c after chromatographic purification by column chromatography (silica gel; hexane/ethyl acetate mixtures of increasing polarity). Unfortunately, we established a low diastereoselectivity as a single isomer (dr = 3:1, entry 2 and 3, table III-22) with isoxazolidine 11b and 11c. As show in the figure III-55 and table III-23, the structures of compounds were controlled by the ^{1}H and ^{13}C NMR analysis.

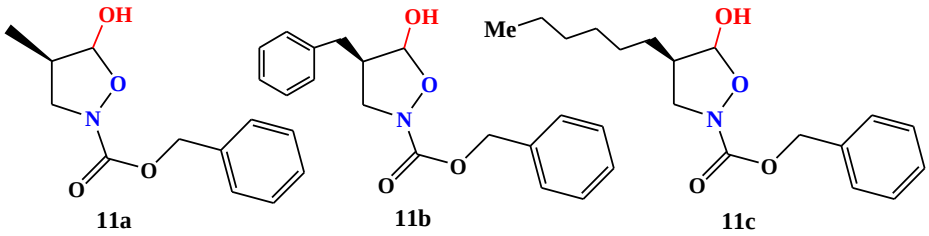


Figure III-55. Isoxazolidin-3-ol structures **(11a–11c)** from α-substituted enals 7**a–7c** and N-Cbz-hydroxylamine **10**.

Table III-23. Physico-chemical characteristics of isoxazolidin-3-ol products (11a–11c).

Isoxazolidinol	Brute formula	M gr.mol^{-1}	Physical appearance
11a	$C_{12}H_{15}NO_4$	237.12	colorless oil
11b	$C_{18}H_{19}NO_4$	313.18	colorless oil
11c	$C_{17}H_{25}NO_4$	307.17	colorless oil

The diastereomeric mixture of 11a was isolated in 83 % yield and dr > 2:1 after purification by column chromatography with (n-hexane/EtOAc to 60:40), it is colorless oil characterised by the crude formula of $C_{12}H_{15}NO_4$ and Molecular weight 237.12 gr.mol^{-1}. The two diastereoisomers of isoxazolidinol 11a appeared clearly in the ^{1}H-NMR spectrum ($CDCl_3$-d_6), figure III-56. Principally, we can identify the carbon neighbour of hydroxyl group to isoxazolidinol ring, resonated at 5.55-5.56 ppm and 5.34-5.36 ppm respectively for the 2 enantiomers. In the case of monomer major, we found that the methyl group, position 6, appeared in aliphatic region at 1.09 ppm as a double peak. In addition, we observed separately three protons vibrate between 2.60–2.67 ppm, 3.61–3.64 and 4.26–4.29 ppm related to the isoxazolidine sphere on positions 1 and 2. The intense signal with a chemical variation of 5.16 ppm incorporates two hydrogen of benzyl group. Then, the multiple signals between 7.32 ppm and 7.39 pp indicate in total integration of 14 protons related to the phenyl group of the two diastereoisomers. In the same way, we have practical different integration of the diverse functions of the minor compound which confirm a diastereomeric ratio (dr > 2:1). The ^{13}C-NMR spectrums ($CDCl_3$-d_6) designated the two diastereomer with twenty signals

corresponding to the number of equivalent carbons for the final structures of each monomer. For example, the methyl group resound at 14.72 ppm and 9.41 ppm separately for the diastereomer major and minor, as show in figure III-57.

- ***Product 11a***

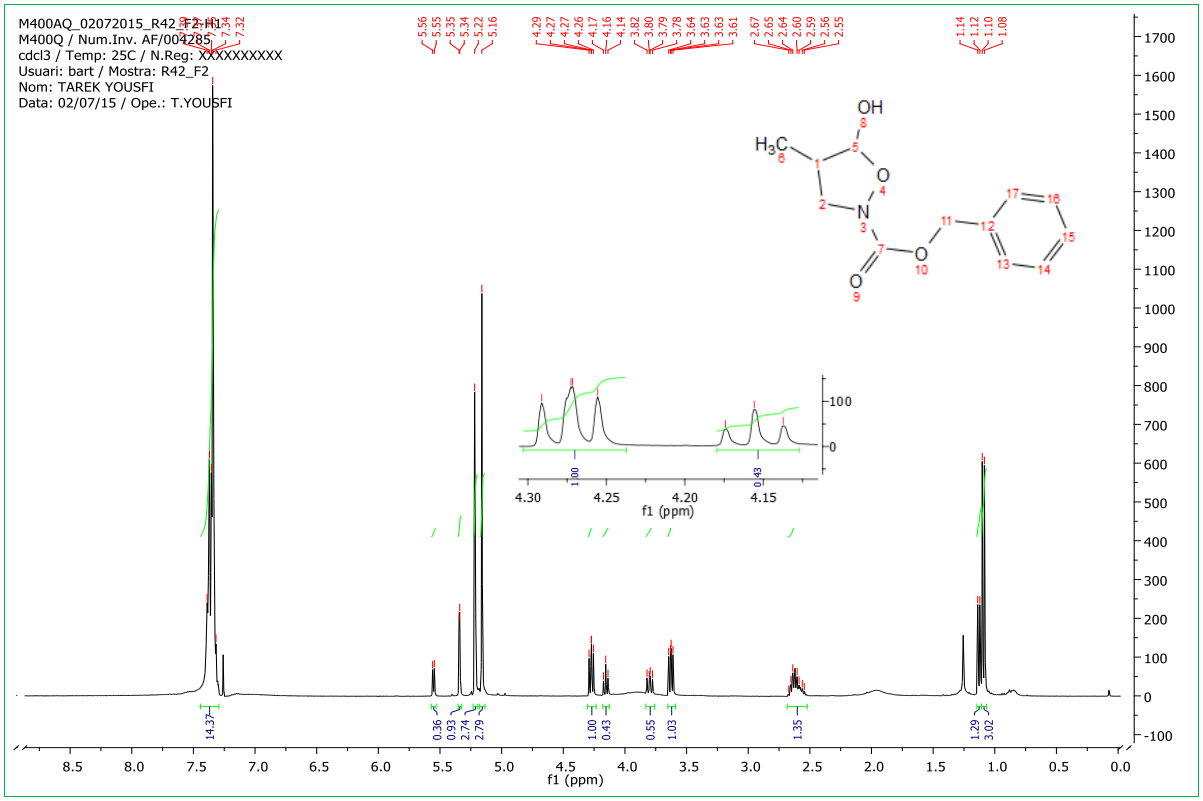


Figure III-56. ^{1}H-NMR (400 MHz) of Benzyl 5-Hydroxy-4-methyl-isoxazolidine-2-carboxylate, **11a**.

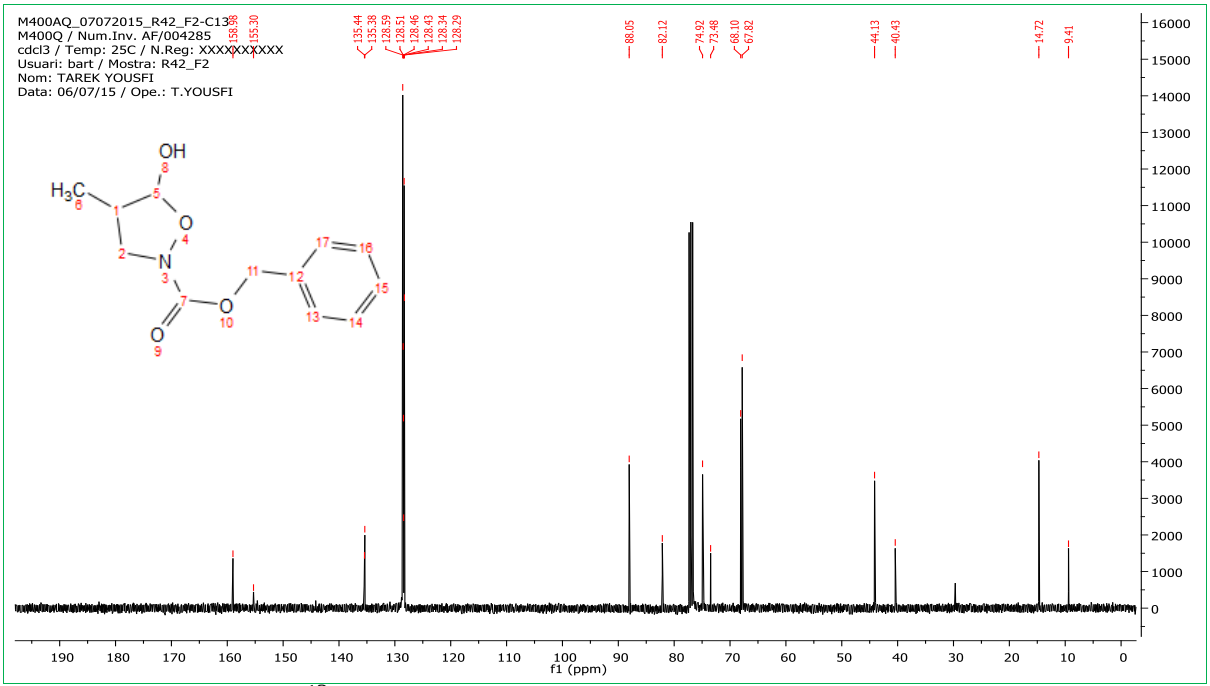


Figure III-57. ^{13}C-NMR (100.6 MHz) of Benzyl 5-Hydroxy-4-methyl-isoxazolidine-2-carboxylate, **11a**.

The diastereomeric mixture of 11b was isolated in 79 % yield with dr = 3:1 after purification by column chromatography with (n-hexane/EtOAc to 65:35), it is a colorless oil characterised by the crude formula of $C_{18}H_{19}NO_4$ and molecular weight 313.18 g.mol^{-1}. In this case, we found difficulties about the separation of final product that present with traces secondary products have the similar polarity. Therefore, the NMR explains the presence of these traces by overlap peaks, as show in figure III-58. The multiple signals between 7.13 ppm and 7.41 ppm show in total integration of 20 protons related to the phenyl group in the diastereoisomers compounds , each ten protons resonates between 7.31–7.41 ppm and 7.13–7.30 ppm. More, the function (-CH_2-) of benzyl alkyl of 11b structure, position 6 and 17, appears respectively at 5.25 and 5.36 ppm.

- ***Product 11b***

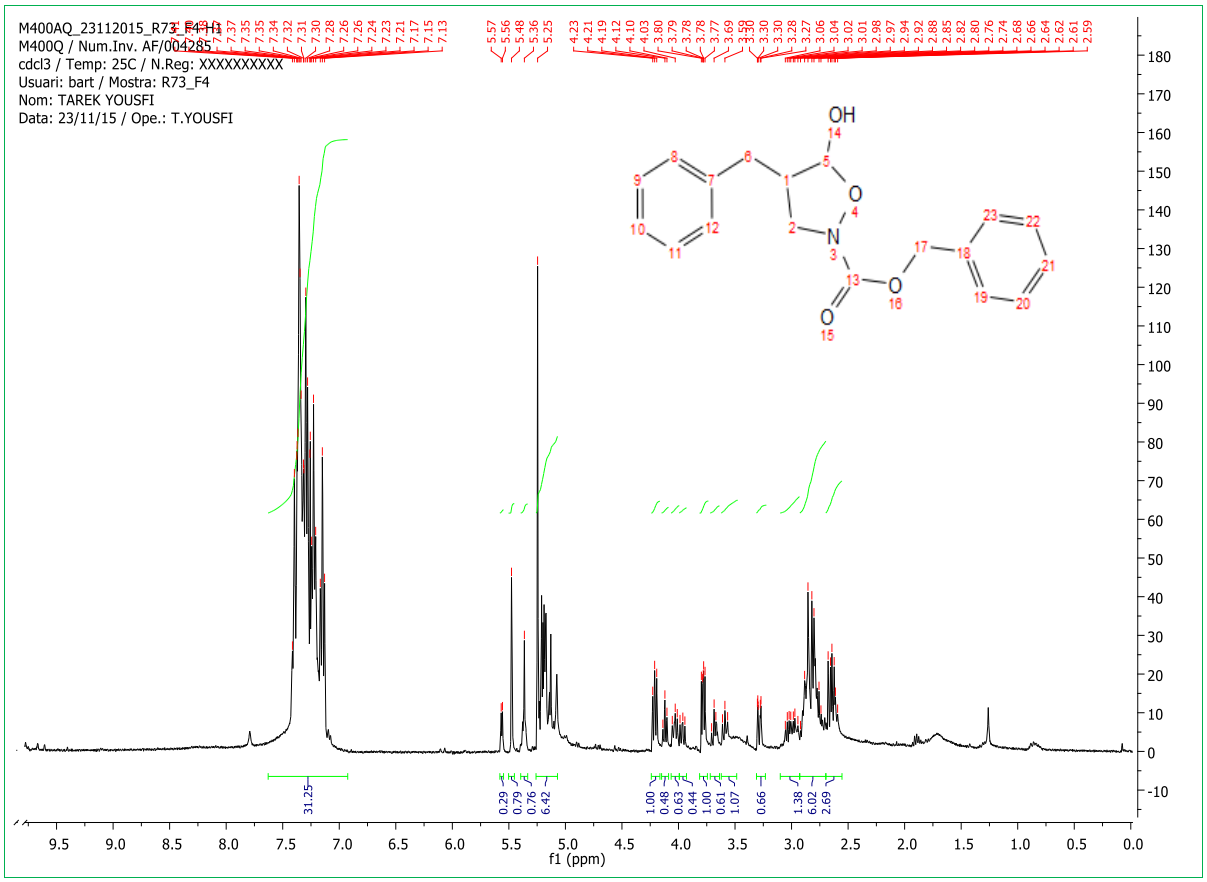


Figure III-58. ^{1}H-NMR (400 MHz) of Benzyl 4-Benzyl-5-Hydroxy-isoxazolidine-2-carboxylate, **11b**.

The racemic compound 11c was found as a 3:1 diastereomer mixture in 78% yield as colorless oil with crude formula of $C_{17}H_{25}NO_4$ and 307.17 gr.mol-1. The ^{1}H-NMR spectrums ($CDCl_3$-d_6), figure III-59, indicated the presence of aromatic groups integrate ten protons relate to diastereomer compounds, they vibrated in multiple signals at 7.32 and 7.40 ppm. About hepthyl alkyl, we found that the methyl group appeared in aliphatic region at 0.87 ppm with triplet peaks, also we observed the total integration of ten protons of heptyl alky between 1.28–1.67 ppm. The intense signals by a chemical change of 5.52 ppm incorporate the two hydrogen of major diastereisomere in the position of (-CH_2-) of benzyl alkyl. Then, we identified in the aliphatic area the different protons of the isoxazolidinol ring resonates at 3.62–3.66 ppm, 4.26–4.28 ppm, 3.81–3.86 and 4.02–4.25 as a multiple signals corresponding to diastereomer mixture of 11c .

- ***Product 11c***

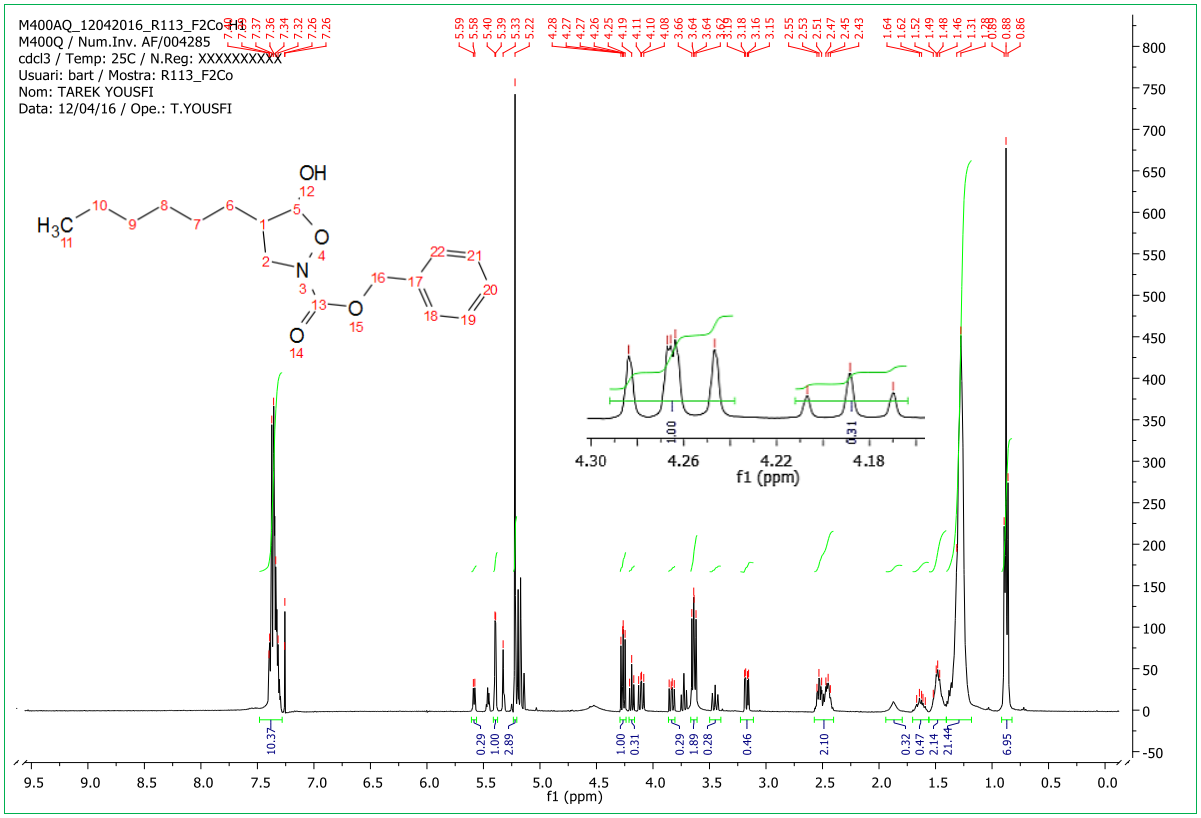


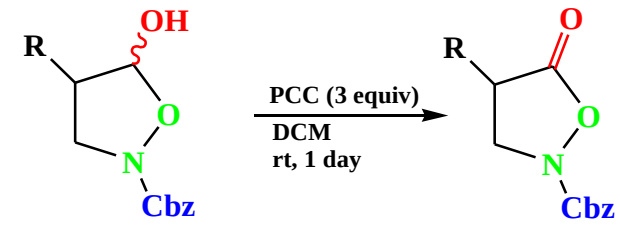
Figure III-59. 1H-NMR (400 MHz) of Benzyl 4-Hexyl-5-hydroxy-isoxazolidine-2-carboxylate, **11c.**

We found complications for the exactly identification about different signals in the last two ^{1}H NMR spectra, figures III-58 and III-59, due to the overlapping of the peaks of 11b and 11c products. We decide to submit the final product **11b** and **11c** to the oxidation reaction without performing the ^{13}C NMR in order to reduce the mixture number (cis and trans monomers) and to achieve a perfect spectrum.

III.1.5 Asymmetric Synthesis of 4-Substituted Isoxazolidines and Oxydation

For the first part , when the asymmetric synthesis of isoxazolidinones 12a–12c was attempted by means of the use of the chiral catalysts 13 and 14 in the reactions between enals 7a–7c and N-Cbz-hydroxylamine 10, the results were much less satisfactory, since after oxidation of the intermediate isoxazolidinols 11a–11c to the corresponding isoxazolidinones 12, we were not able to find suitable HPLC conditions for the determination of the enantiomeric purity of 12a; on the other hand, 12b was obtained in essentially racemic form with both catalysts and 12c

could be prepared but only in low enantiomeric purity (57:43 er) when using 14 as the chiral catalyst, (table III-23, entry 7, column9 , catalyst 14). We have seen that the transformation oxidation of pyrazolidinols 8 take place more efficiently using 5 equivalent of pyridinium chlorochromate (PCC) in the presence of 4 Å molecular sieves in CH_2Cl_2 at room temperature. In our case, the isoxazolidines compounds 11a-11c is characterized by a slight steric hindrance around the hydroxyl group, which facilitates the oxidation transformation. After same experiment, we practiced two-oxidation reaction of 11a composite using one and three equivalents of PCC in the presence of 4 Å molecular sieves and CH_2Cl_2 at room temperature. After 18 hours of screening, we were found that the reactions in the presence of three equivalents of PCC completed in excellent yield 98 % after purification but the second reaction finished in three days in moderate yield 86 %. In light of these results, we decided to put the same amount , three equivalent of oxidizing agent , in oxidation processes for isoxazolidines 11a-11c and we found that the typical reaction time one day, (Scheme III-11 and Table III-24).

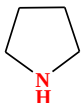
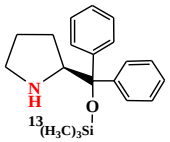
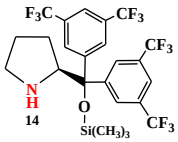


11a - 11c
(rac, diast.mixture)

12a - 12c
(rac)

Scheme III-11. Oxidation reaction of pyrazolidinols **8** by **PCC**.

Table III-24. Oxidation summary of racemic and asymmetric pyrazolidinols **8**.

Entry	Reactants	Catalyst	Isoxazolidinol	Yield [1]	dr [2]	Isoxazolidinone	Yield [1]		Reaction time[5]
1	7a, 10		**11a**	**70 %**	>2:1	**12a**	**93 %**	-	18 h
2	7b, 10		**11b**	**79%**	3:1	**12c**	**99 %**	-	24 h
3	7c, 10		**11c**	**78%**	3:1	**12a**	**80 %**	- **er** [3]	24 h
4	7a, 10	**13**	**11a**	**80%**	>2:1	**12a**	**98%**	- [4]	18 h
5	7c, 10		**11c**	**78 %**	3:1	**12c**	**80%**	51:49	24 h
6	7a, 10	**14**	**11a**	**83%**	>2:1	**12a**	**92%**	- [4]	18 h
7	7b, 10		**11b**	**87%**	3:1	**12b**	**87 %**	57:43	24 h

[1] Yield of isolated product after chromatographic purification; [2] By ^{1}H-NMR; [3] By chiral HPLC analysis (See the Supplementary Materials for details); [4] No satisfactory conditions for the HPLC analysis of this compound could be found; [5] The reaction time controlled by thin-layer chromatography.

These results summarized in table III-24, we were able to conclude that the oxidation reaction on different enals, substitued with different substituent patterns, and N-Cbz-hydroxylamine (10) as substrates of Michael system yielded the corresponding isoxazolidinone 12a-12b in low enantiomeric purity (57:43 er) and excellent yields in the majority of cases (column 8, table III-24). After exposing the stereoisomeric mixture of isoxazolidinol 11 to the PCC oxidation as before, we

engendered a clean NMR (^{1}H and ^{13}C) spectrum and the HRMS revealed all the final isoxazolidinone products 12a-12c, figure III-60 and table III-25.

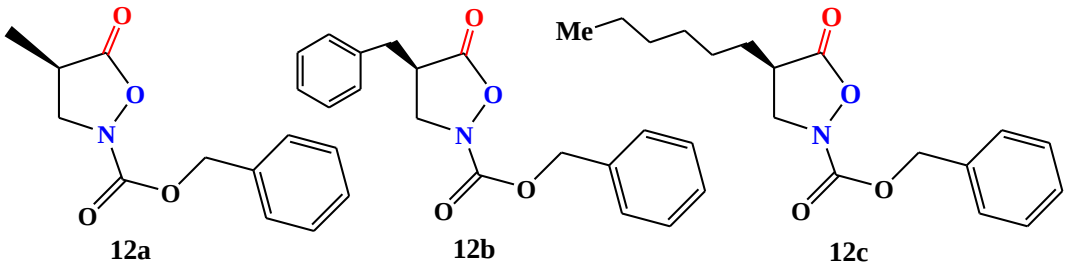


Figure III-60. Isoxazolidinone structures **(12a–12c)** from isoxazolidinol **(11a–11c).**

Table III-25. Physico-chemical characteristics of isoxazolidinone products **(12a–12c).**

Isoxazolidinol	Brute formula	M gr.mol^{-1}	Physical appearance
12a	$C_{12}H_{13}NO_4$	235.12	colorless oil
12b	$C_{18}H_{17}NO_4$	311.18	colorless oil
12c	$C_{17}H_{23}NO_4$	305.17	colorless oil

In every case, we analysed the spectroscopic data in different way about NMR analysis, HRMS and chiral separation HPLC. Oxidizer product isoxazolidinone 12a was obtained as colorless oil in 98% yield after purification in column chromatography. Inopportunely, we have not able to calculate the enantiomeric purity due to no satisfactory conditions could be found for the chiral HPLC analysis. ^{1}H and ^{13}C NMR spectral data showed in figure III-61 and III-62 supports exactly the final structure. The ^{1}H spectrum (Aceton-d_6) contains sixe signals area. The intense signal, with a chemical shift of 5.33 ppm integrates two hydrogens and a multiple signals resonate between 7.33 ppm and 7.45 ppm assimilates five protons, all of them related to benzyl group. In the aliphatic section, we identified the middle multiple signals at 3.01–3.11 ppm, 3.96–4.01 ppm and 4.54–4.58 ppm improved the three protons of the isoxazolidinone ring. Finally, the up field spectrum at 1.29 ppm integrates three hydrogens and is a doublet with J = 6.57 Hz which provided the name structure of 12a, (Benzyl 4-methyl-5-oxo-isoxazolidine-2-carboxylate). On to the ^{13}C-NMR data (Aceton-d6), characteristic peaks in the ^{13}C NMR spectrum (figure III-62) include the two carbonyl groups resonances at 147.7

ppm and 169.9 ppm related to isoxasolidine ring and ester group. More, we see on the other part NMR spectrum eight signals, which tell us that are eight carbons are chemically equivalent. In HRMS analysis presented the appearance of the deprotonated molecules ions at m/z = 488.2022, m/z = 493.1575 and 258.0733 produced respectively the three fragments $[M_{12a} + Na^{+}]^{+}$, $[2M_{12a} + Na^{+}]^{+}$ and $[2M_{12a} + NH_4^{+}]^{+}$ witch calculated the molecular weight of 235.12 $g.mol^{-1}$ of the crude formula $C_{12}H_{13}NO_4$, (table III-26 and figure III-63).

- ***Product 12a***

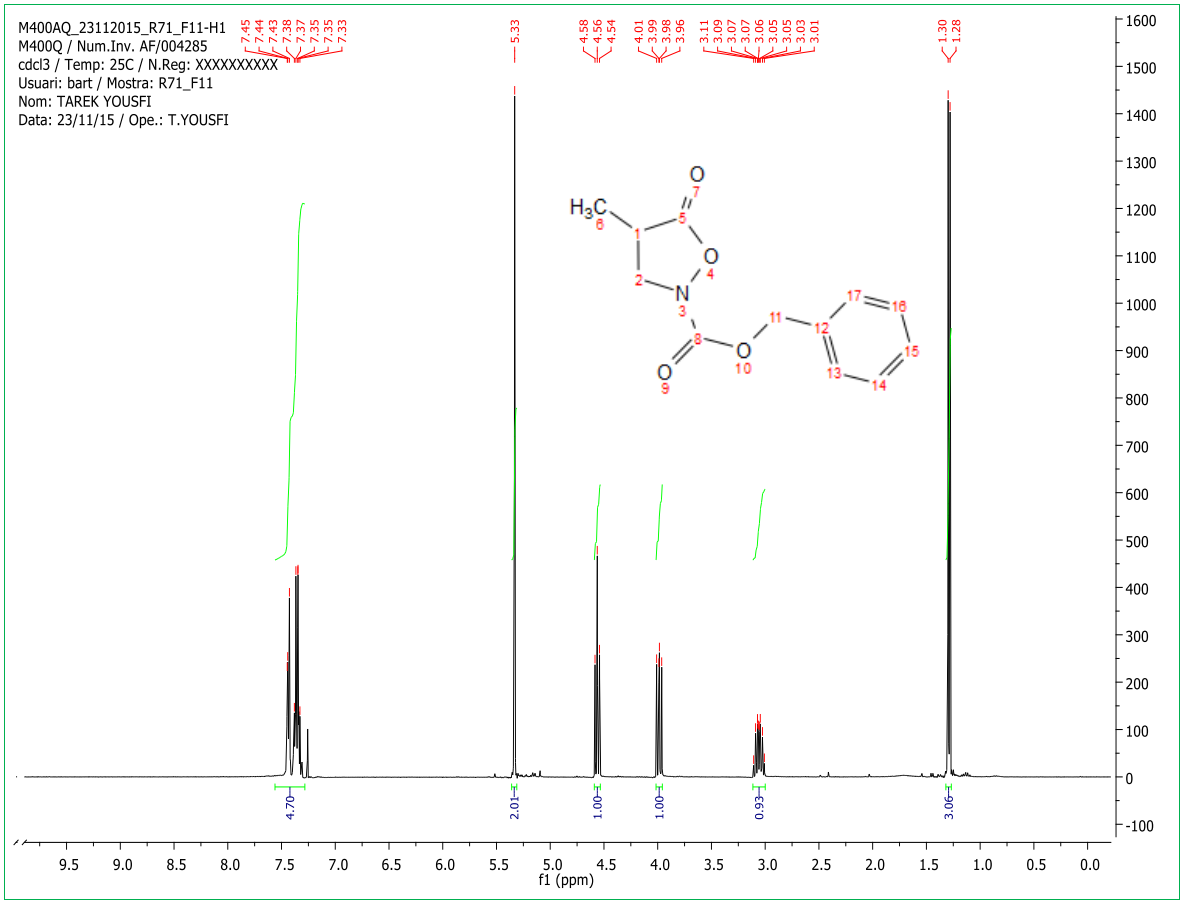


Figure III-61. ^{13}C-NMR (100.6 MHz) of Benzyl 4-Methyl-5-oxo-isoxazolidine-2-carboxylate, **12a**.

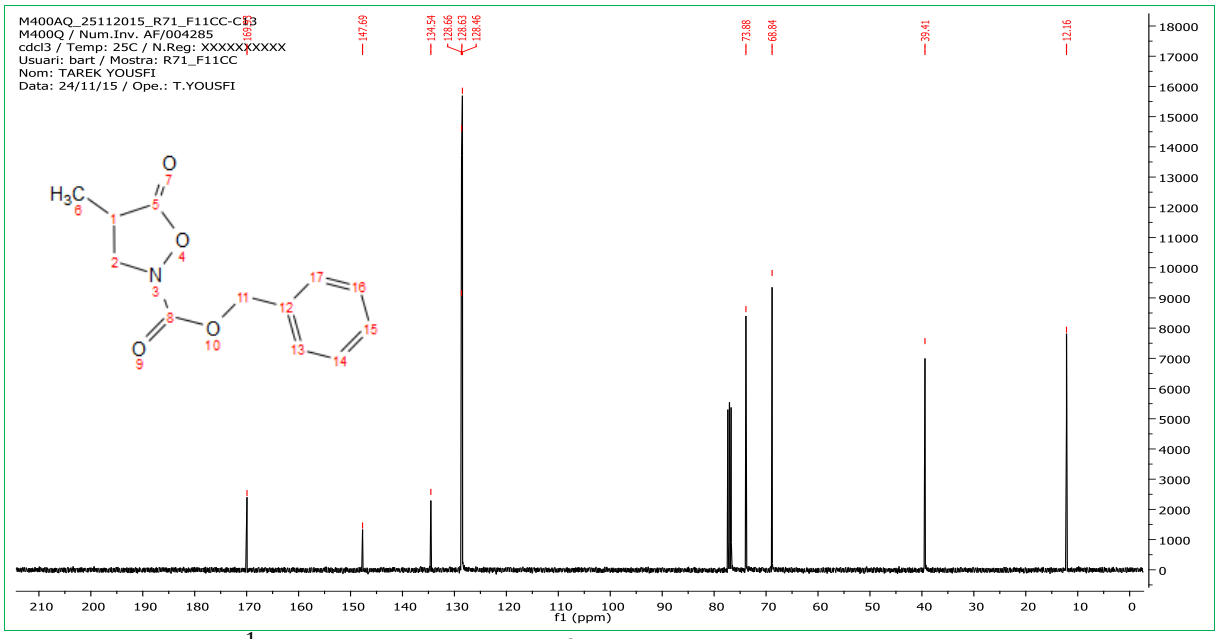


Figure III-62. ^{1}H-NMR (400 MHz) of Benzyl 4-Methyl-5-oxo-isoxazolidine-2-carboxylate, **12a**.

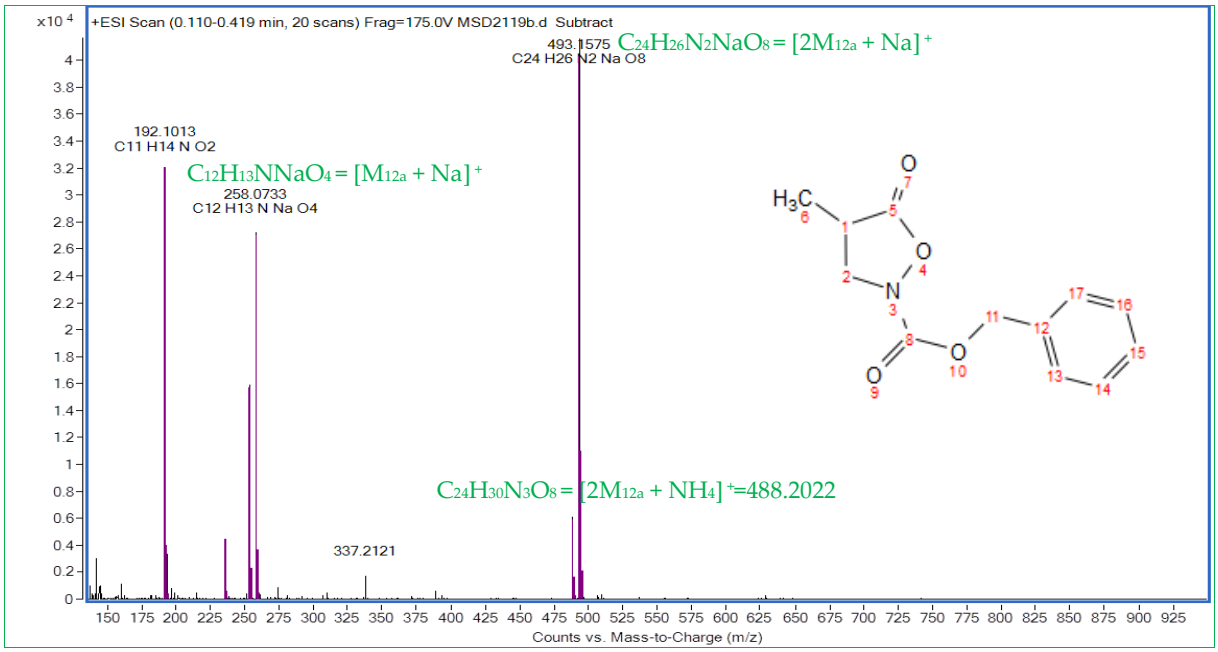


Figure III-63. HRMS analysis of isoxazolidinone, **12a**.

Table III-26. MS formula results of of isoxazolidinone 12a obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{24}H_{30}N_3O_8$	95.35	488.2022	488.2027	86.65	0.54	1.11	$[2M_{12a} + NH_4^+]^+$
TRUE	$C_{24}H_{26}N_2NaO_8$	93.71	493.1575	493.1581	81.42	0.65	1.33	$[2M_{12a} + Na^+]^+$
TRUE	$C_{12}H_{13}NNaO_4$	98.07	258.0733	258.0737	96	0.37	1.44	$[M_{12a} + Na]^+$

In same way, we examined the spectroscopy data of isoxazolidinone compounds **12b** and **12c**. Firstly, the isoxazolidinone 12b was obtained as colorless oil in 99 % yield after purification in column chromatography. In addition, ^{1}H and ^{13}C NMR spectral data (figure III-64 and III-65) supports correctly our configuration. The ^{1}H spectrum (Aceton-d_6) contains sixe signals area, tow benzyl groups disturbed in two aromatic groups resonates a chemical shift between 7.15–7.43 ppm integrate ten hydrogen, a multiple signals vibrate between at 3.24 and 3.28 ppm assimilate two protons (position 11) and we selected the last two protons (position 6) as a single peak at 5.27 ppm. In the aliphatic region, we identified the middle multiples signals at 2.78–2.84 ppm, 4.07–4.11 ppm and 4.35–4.39 ppm enhanced the three protons connect to isoxazolidinon sphere respectively in position 1 and 2. Characteristic peaks in the ^{13}C NMR (aceton-d_6) spectrum (figure III-65) regrouped the two carbonyl groups resonances at 144.4 ppm and 165.4 ppm related to isoxasolidinone sphere and the ester group. In HRMS analysis offered the appearance of the deprotonated molecules ions at m/z = 334.1049, m/z = 329.1494, m/z = 645.2195 and m/z = 640.264 produced respectively the three fragments $[M_{12b}+Na^+]^+$, $[M_{12b}+NH_4^+]^+$, $[2M_{12b}+Na^+]^+$, $[2M_{12b}+NH_4^+]^+$ witch calculated the molecular weight of 311.18 $g.mol^{-1}$ of the crude formula $C_{18}H_{17}NO_4$, as shown in the table III-27 and figure III-66.

- ***Product 12b***

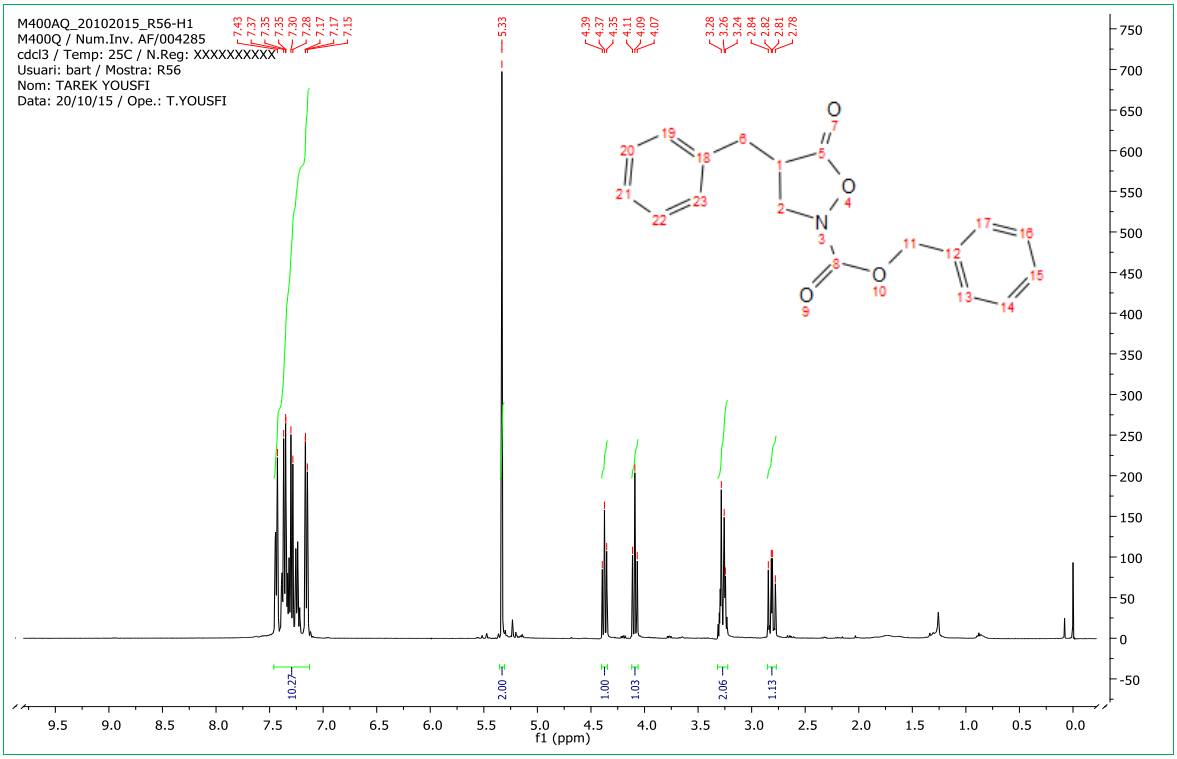


Figure III-64. ^{1}H-NMR (400 MHz) of Benzyl 4-Benzyl-5-oxo-isoxazolidine-2-carboxylate, **12b**.

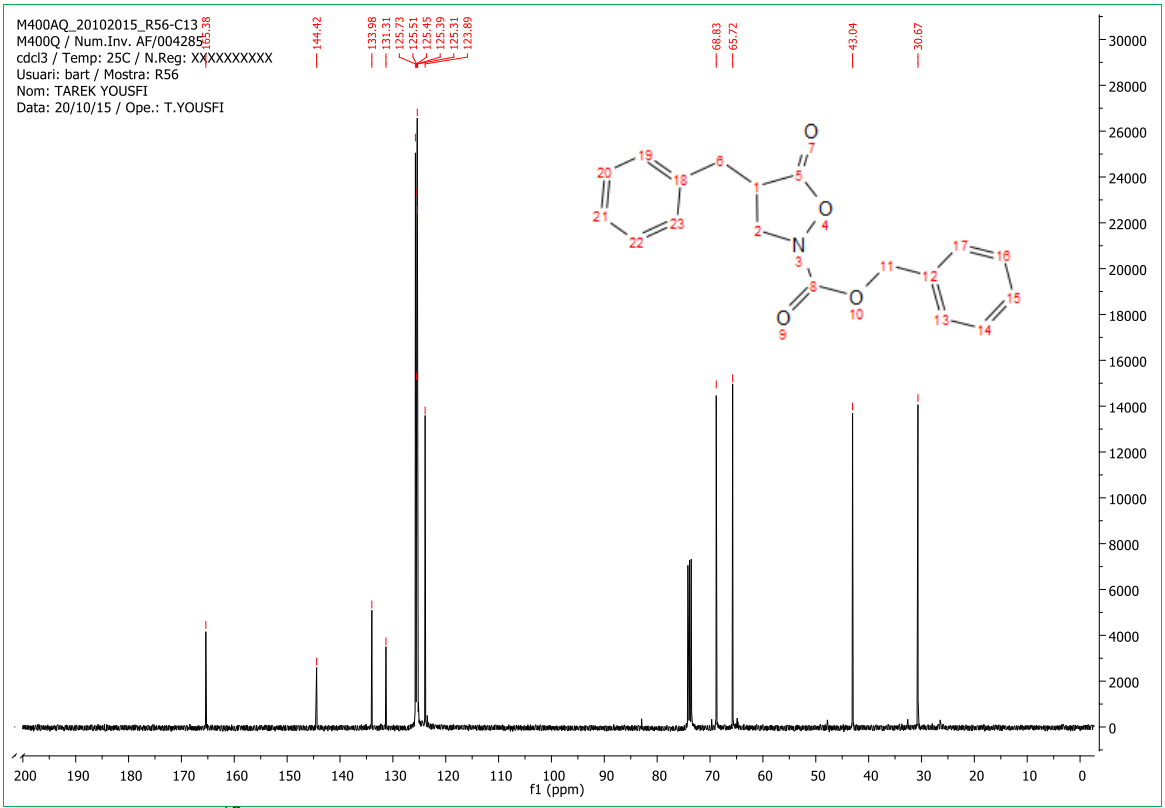


Figure III-65. ^{13}C-NMR (100.6 MHz) of Benzyl 4-Benzyl-5-oxo-isoxazolidine-2-carboxylate, **12b**.

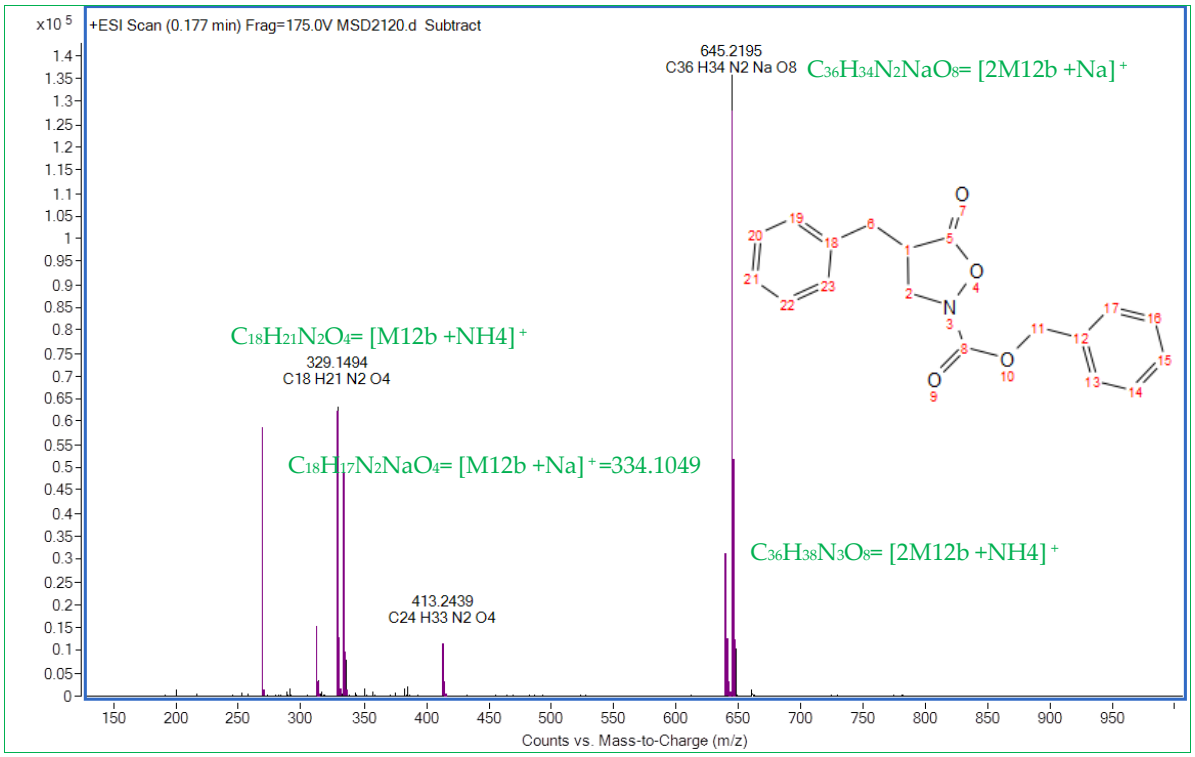


Figure III-66. HRMS analysis of isoxazolidinone, **12b**.

Table III-27. MS formula results of isoxazolidinone, **12b** obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{18}H_{17}NNaO_4$	97.43	334.1049	334.105	92.31	0.11	0.34	$[M_{12b} +Na^+]^+$
TRUE	$C_{18}H_{21}N_2O_4$	98.26	329.1494	329.1496	95.76	0.16	0.5	$[M_{12b} +NH_4^+]^+$
TRUE	$C_{36}H_{34}N_2NaO_8$	92.96	645.2195	645.2207	83.65	1.26	1.95	$[2M_{12b} +Na^+]^+$
TRUE	$C_{36}H_{38}N_3O_8$	95.63	640.264	640.2653	96.63	1.31	2.04	$[2M_{12b} +NH_4^+]^+$

Finally, the isoxazolidinone product 12c was obtained as colorless oil in 87 % yield after purification in column chromatography with low enantioselectivity in er = 57:43. Also, ^{1}H and ^{13}C NMR spectral data showed in figure III-67 and III-68 funds suitably our configuration. The ^{1}H spectrum (aceton-d_6) contains nine signals area, the benzyl group distributed in tow peaks, the first one resonate at chemical shift between 7.33–7.45 ppm integrate five hydrogens and the second one related to tow protons in the position 11 vibrates at 5.33 as a single peak . In the aliphatic region, we calculated a total integration of 13 protons approving to heptyl group witch regrouped three protons of methyl resonated as a multiples at 0.86-0.90 ppm and ten

protons vibrate at 1.28-1.40 ppm, 1.50-1.58 ppm and 1.88-1.94 ppm , separately integrates eight and two separate protons . We identified the intermediate multiples signals at 2.92–2.99 ppm, 4.04–4.08 ppm and 4.52–4.56 ppm enhanced the three protons of the isoxazolidinone sphere. In this part, we turned our attention an rotamer meaning with singularity resonate at 3.36-3.43 and 2.94-2.98 integrate one proton corresponding to 12c ring, position 1, obtained from asymmetric isoxaxolidinol 11c, as show in figure III-68 in the alephatic area . Characteristic peaks in the ^{13}C NMR spectrum (figure III-69) regrouped the carbonyl groups resonances at 147.7 ppm and 169.4 ppm related to isoxasolidine ring and the ester group. More, we see that there are four signals related to aromatic group resonate at 134.6 ppm, 128.6 ppm, 128.6 ppm and 128.46 ppm. In HRMS analysis offered the appearance of the deprotonated molecules ions at m/z = 633.3146 and m/z = 328.1519 produced respectively the three fragments $[2M_{12c} + Na^{+}]^{+}$ and $[M_{12c} + Na]^{+}$ witch calculated the molecular weight of 305.17 $gr.mol^{-1}$ of the crude formula $C_{17}H_{23}NO_4$, table III-28 and figure III-70.

- ***Product12c***

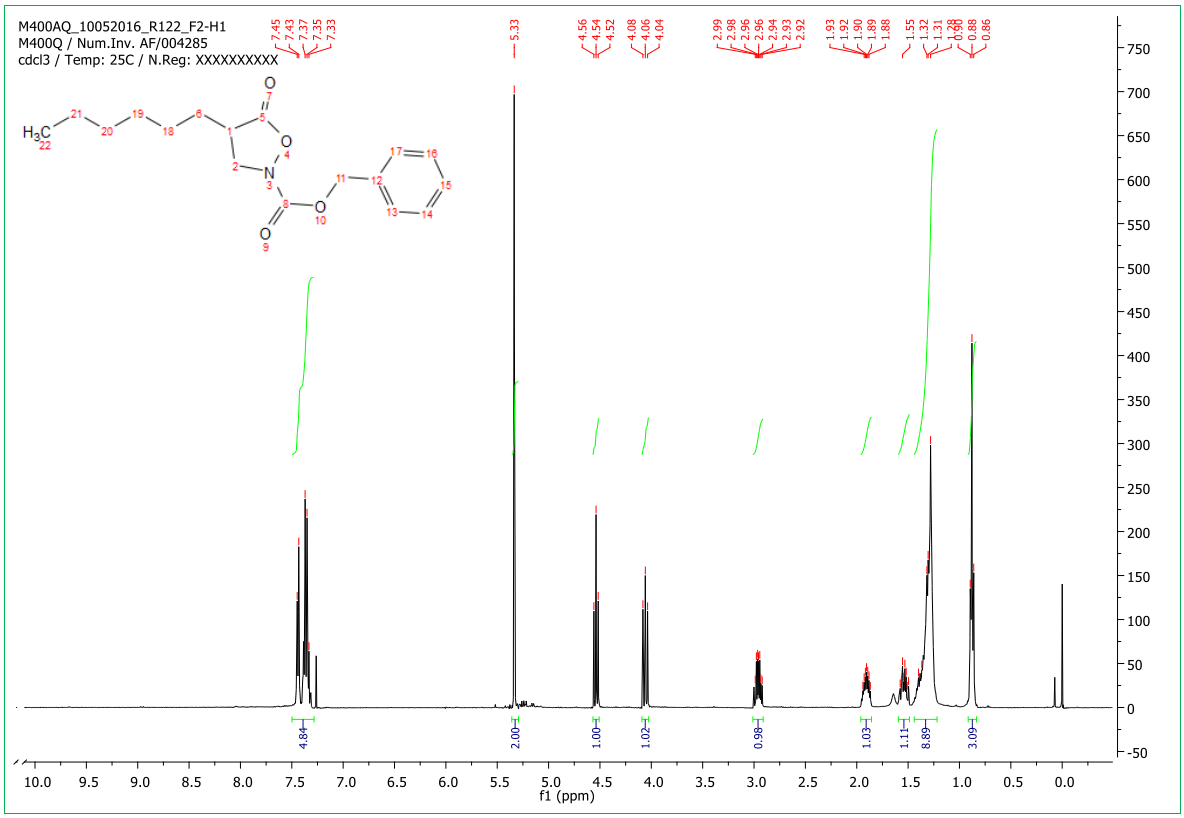


Figure III-67. ^{1}H-NMR (400 MHz) of rac-Benzyl 4-Hexyl-5-oxo-isoxazolidine-2-carboxylate, racemic compound **12c**.

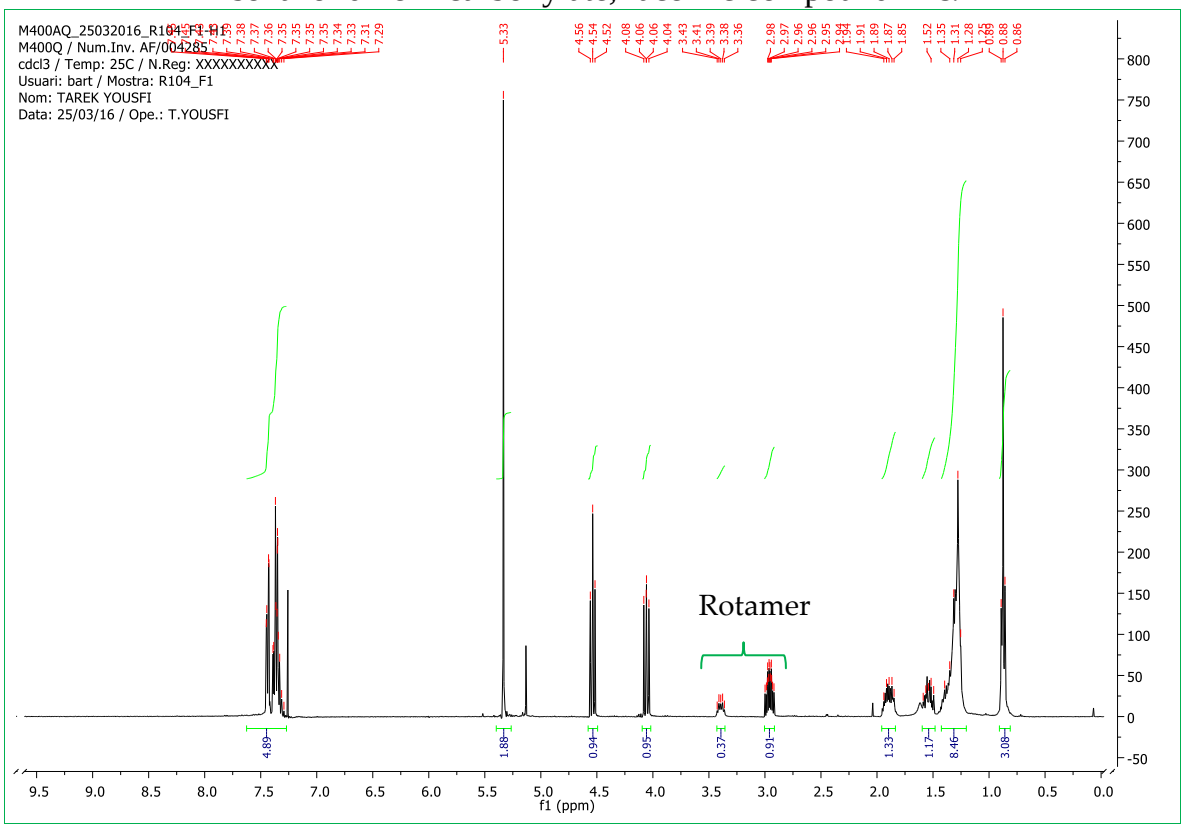


Figure III-68. ^{1}H-NMR (400 MHz) of (−)-Benzyl 4-Hexyl-5-oxo-isoxazolidine-2-carboxylate, asymmetric compound **12c**.

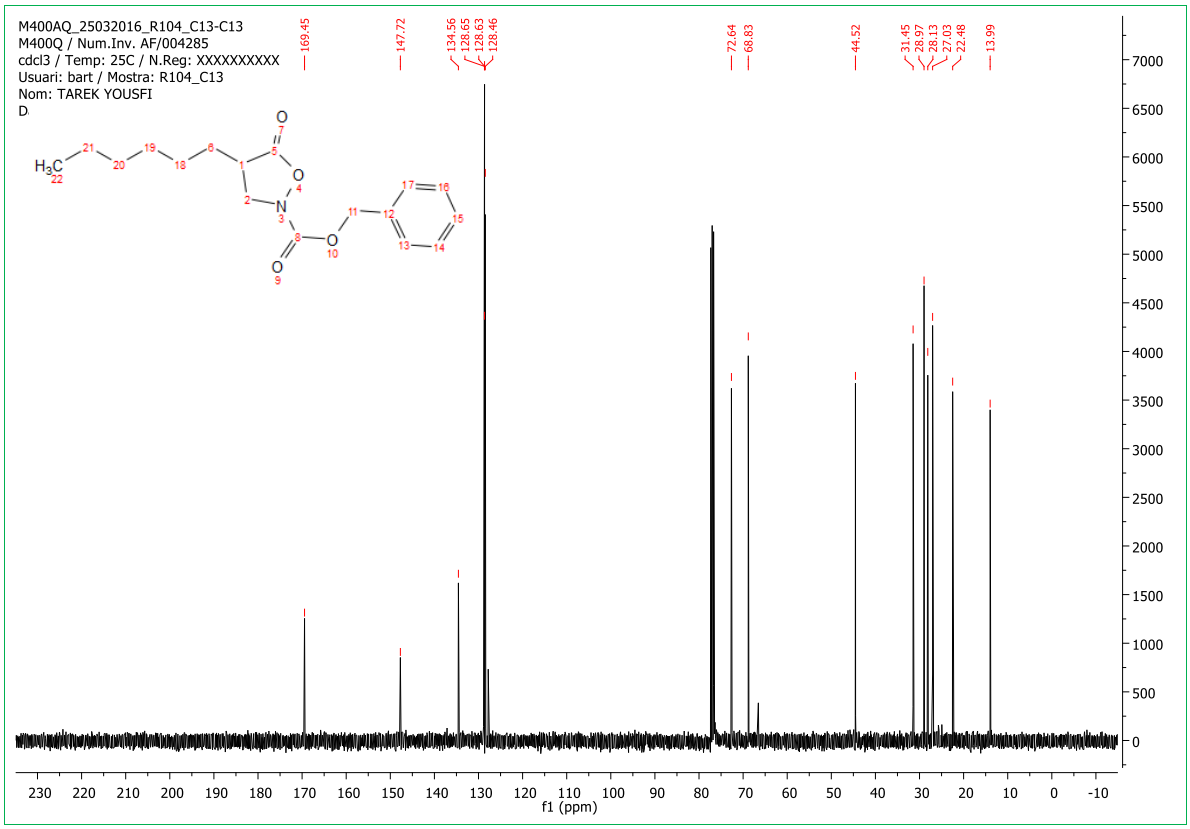


Figure III-69. ^{13}C-NMR (100.6 MHz) of (−)-Benzyl 4-Hexyl-5-oxo-isoxazolidine-2-carboxylate, **12c**.

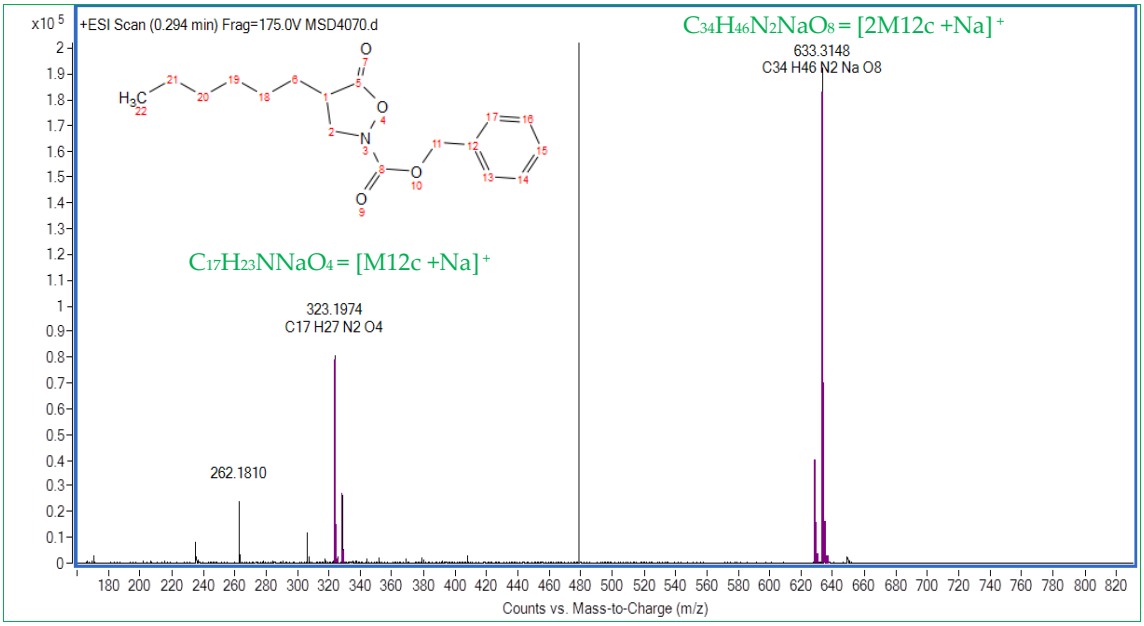
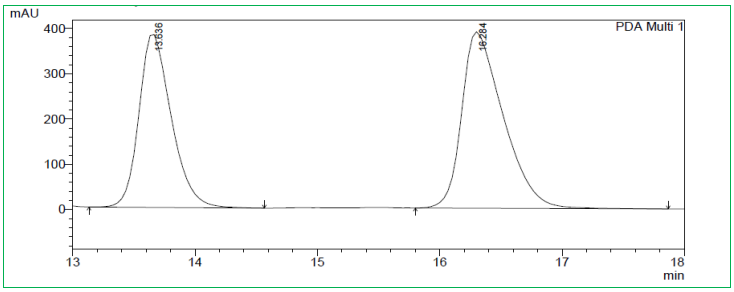


Figure III.70. HRMS analysis of isoxazolidine, **12c.**

Table III-28. MS formula results of isoxazolidine 12c obtained by ESI-TOF.

Best analysis	Ion Formula	Score	m/z	Calc m/z	Abund Match	Diff (mDa)	Diff (ppm)	Molecular Fragment
TRUE	$C_{34}H_{46}N_2NaO_8$	94.88	633.3148	633.3146	84.42	-0.18	-0.29	$[2M_{12c}+Na]^+$
TRUE	$C_{17}H_{23}NNaO_4$	90.06	328.1527	328.1519	92.16	-0.81	-2.47	$[M_{12c}+Na]^+$

After same experiment, we used the mobile phase of 90:10 hexane/isopropyl alcohol and IB chiral column, the racemic method is capable to separate the two enantiomers of 12c isoxazolidinone with soft separation due to the low flow rate 1 ml/min for HPLC pump but with fast separation factor of 3 min between the appearances of the two enantiomers, typical chromatograms are shown in figure III-71. The enantiomeric separation was performed at the same conditions of asymmetric compound 12c, synthetised to 11c pyrazolidinol en the presence of asymmetric catalyst 14. Therefore, the mixture of 12c is actually composed with low enantiomeric excess of er = 57:43. The major enantiomer looked at retention time 13.6 min and the minor enantiomer observed at retention time 16.2 min. This result explain that we have acceptable performance of asymmetric model in the presence of asymmetric catalyst 14 and the calculation of the specific rotation of the enantiomeric product 12c, which has a value of $[\alpha]_D^{25} = -4.1$ (0.41, DCM). We can conclude that the mixture of 12c contain the major enantiomer as (−)-12c structure, typical chromatograms are shown in figure III-72.



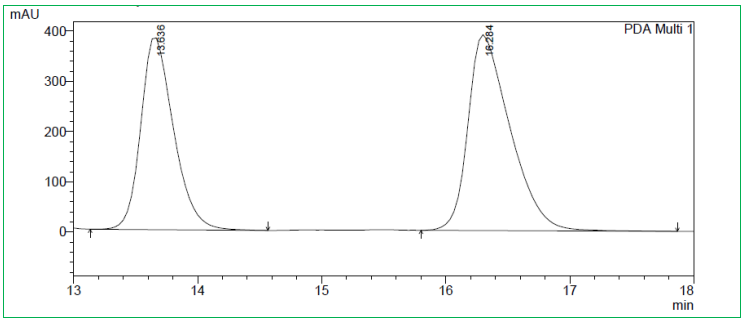
Condition of separation HPLC (Chiralpak® IB column, 90:10 hexane/isopropyl alcohol, 1 µL/min, λ = 254 nm, 25 °C).

Peak Table

PDA Ch3 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.636	1272551	69970	43.403	49.555
2	16.284	1659359	71226	56.597	50.445
Total		2931910	141196	100.000	100.000

Figure III-71. Racemic compound, *rac*-**12c**.



Condition of separation HPLC (Chiralpak® IB column, 90:10 hexane/isopropyl alcohol, 1 µL/min, λ = 254 nm, 25 °C).

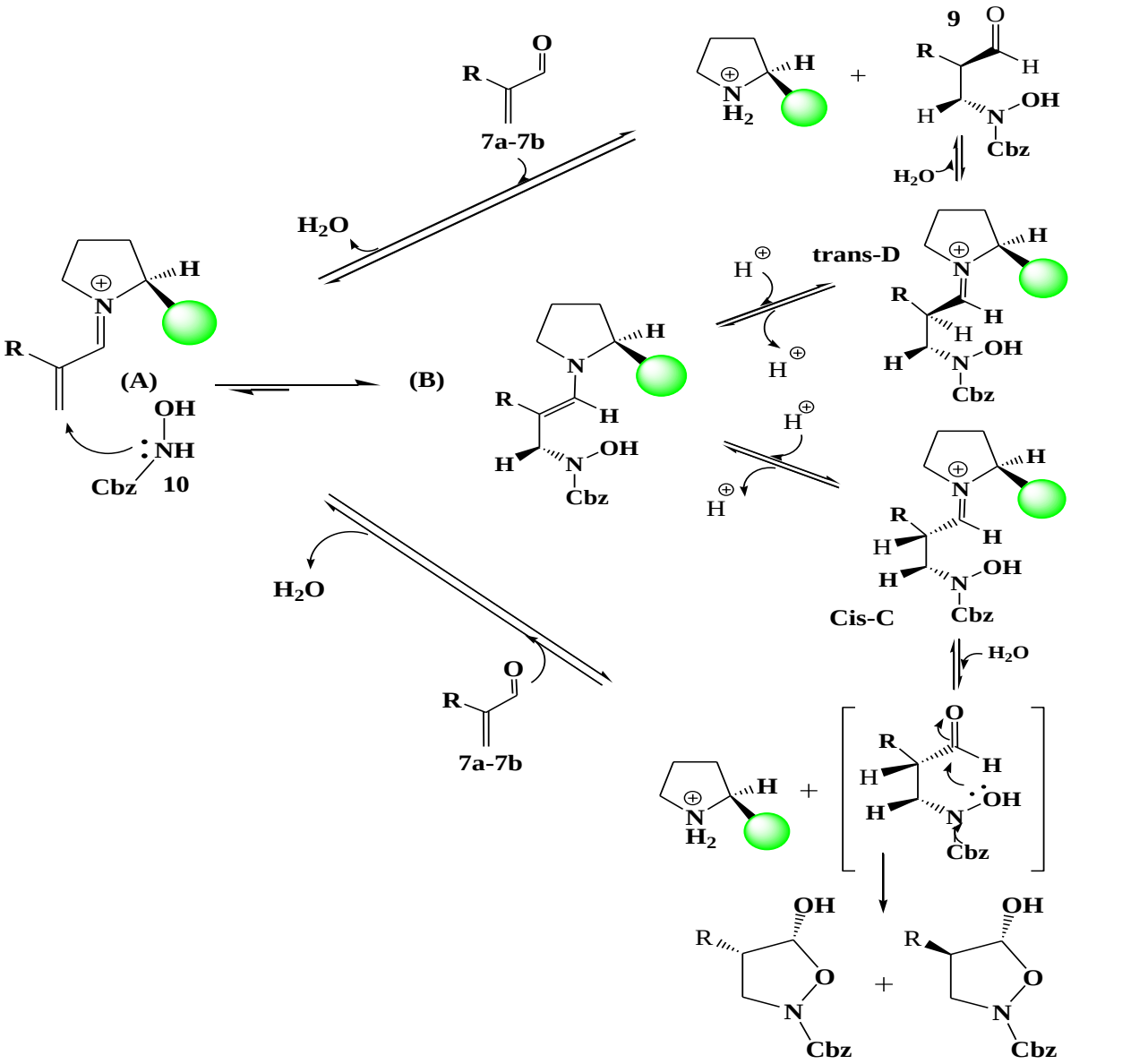
Peak Table

PDA Ch3 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.636	1272551	69970	43.403	49.555
2	16.284	1659359	71226	56.597	50.445
Total		2931910	141196	100.000	100.000

Figure III-72. Asymmetric compound, (−)-**12c**.

A simplified mechanistic proposal for the formation of enantiomerically enriched 4-substituted isoxazolidinols 11a or 11c is depicted in Scheme III-12. This acceptable result clearly shows that the stereochemical outcome of the aza-Michael addition of the α-substituted enals methacrolein (7a), or and 2-(n-hexyl) propenal (7c) and and N-Cbz-hydroxylamine 10, depends on the structure of the secondary amine catalyst. This behaviour can be tentatively rationalized by assuming that in the catalytic cycle, intermediate enamine (B), arising from the nucleophilic attack of N-Cbz-hydroxylamine 10 on unsaturated iminium (A), is protonated to give a mixture of saturated iminium cation *cis-C* and *trans-D*, which are subsequently hydrolysed to give the corresponding aldehydes, Scheme III-12. When using pyrrolidine or diphenylprolinol trimethylsilyl ether (13) as catalysts, intermediates *cis-C* and *trans-D* are in equilibrium through enamine (B), and although presumably *trans-D* is more thermodynamically stable than *cis-C*, its hydrolysis is reversible, so that the subsequent cyclization of the cis aldehyde completely shifts the equilibrium to the formation of isoxazolidine 11a or 11c. On the other hand, when bis-(3, 5-trifluoromethylphenyl)-prolinol trimethylsilyl ether (14) is used as the catalyst, *trans-D* is much more stable thermodynamically than *cis-C*, and its hydrolysis is essentially irreversible. In this way, aldehyde 7a or 7c cannot be equilibrated to 11a and 11c.



Scheme III-12. Rationalization of the stereo chemical outcome of the amine-catalysed aza-Michael addition of N-Cbz-hydroxylamine (10) to α-substituted enals 7a and 7c.

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[13]. Meyers, M.J, Arhancet, G.B., Hockerman, S.L., Chen, X., Long, S.A., Mahoney, M.W., Rico, J.R., Garland, D.J., Blinn, J.R., Collins, J.T., J. Med. Chem., **2010**, 53, 5979-6002.

Chapter IV
Experimental Section

IV.1 Experimental Section

IV.1.1 General Information

IV.1.1.1 Reagents and Reactions

Reactions were generally performed at room temperature, either in round-bottomed flasks or in loosely stoppered glass vials, with magnetic stirring and open to the air. Commercially available reagents, catalysts, and solvents were used as received with the exception of dichloromethane, which was distilled from calcium hydride under nitrogen. Aldehydes cyclopentene-1-carboxaldehyde (**1**) [1], methacrolein (7a), 2-benzylpropenal (7b), 2-(n-hexyl) propenal (7c) [2, 3] were prepared according to literature procedures. Yields refer to products isolated after chromatographic purification. Reactions were monitored both by ^{1}H-NMR and by thin-layer chromatography, carried out on silica gel plates Merck 60 F254 (Sigma-Aldrich Química SL, Madrid, Spain), and compounds were visualized by irradiation with UV light and/or treatment with a solution of $KMnO_4$ as developing agent followed by heating. Flash column chromatography was performed using silica gel Merck 60 (particle size: 0.040–0.063 mm).

IV.1.1.2 Instrumentation

^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded with a Mercury 400 spectrometer (Varian Inc., Palo Alto, CA, USA). Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS), and coupling constants (*J*) are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature. TMS served as an internal standard (δ = 0.00 ppm) for ^{1}H-NMR spectra, and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C-NMR spectra. Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Where appropriate, 2D techniques (COSY, NOESY) were also used to assist in structure elucidation.

High-resolution mass spectra (HRMS) were recorded with a MicrOTOF spectrometer (Bruker, Billerica, MA, USA) by the Unitat d'Espectrometria de Masses, CCiT-UB. Specific rotations were determined at room temperature with a 241 MC polarimeter (Perkin-Elmer, Waltham, MA, USA). Chiral

HPLC analyses were performed with a LC Series 20 apparatus (Shimadzu Corp., Kyoto, Japan) with an M20 diode array UV/Vis detector, using Chiralpak® IC, IA and IB columns (Daicel Corporation, Tokio-Osaka, Japan). The homogeneity of the peaks corresponding to the two enantiomers of the product was thoroughly checked by comparison of the UV spectra. All compounds were named and designed by Chemdraw Pro 12.0.

IV.1.2 General Procedures for the Preparation of Pyrazolidines

IV.1.2.1 Racemic Pyrazolidinols from Enals and Hydrazines

An ordinary glass vial equipped with a magnetic stirring bar was charged with pyrrolidine (1.42 mL, 14 mg, 0.20 mmol, 40 mol %), PhCOOH (24 mg, 0.20 mmol, 40 mol %) and toluene (2 mL). The hydrazine 1-Boc-2-(4-nitrobenzenesulfonyl) hydrazine **2a** or *1, 2*-bis (p-toluene sulfonyl) hydrazine **2b** (0.50 mmol, 1 eq) and the *α*-unsaturated aldehyde (1.0 mmol, 2 eq) were added sequentially. Stirring was maintained at room temperature until the reaction was complete (TLC and or ^{1}H-NMR monitoring, 24 h–4 days) and the crude reaction mixture was diluted with 10 mL of ethyl acetate. The organic phase was washed first with 10% *w*/*w* aqueous sodium bicarbonate solution (10 mL), then with brine (10 mL), and dried over $MgSO_4$. Filtration and evaporation of solvents under reduced pressure afforded the crude reaction product that was purified by column chromatography (silica gel; hexane/ethyl acetate mixtures of increasing polarity) to afford the intermediate pyrazolidinol as a diastereomer mixture.

IV.1.2.2 Asymmetric Synthesis of Pyrazolidinols from Enals and Hydrazines

An ordinary glass vial equipped with a magnetic stirring bar was charged with the chiral prolinol silyl ether **13** or **14** (0.05 mmol, 20 mol %), PhCOOH (6 mg, 0.05 mmol, 20 mol %) and toluene (1 mL). The hydrazine **2a** or **2b** (0.24 mmol, 1 eq) and the *α*-unsaturated aldehyde (0.48 mmol, 2 eq) were added sequentially. The stirring was maintained at room temperature until the reaction was complete (TLC and or ^{1}H-NMR monitoring, 3–6 days) and the crude reaction mixture was diluted with 10 mL of ethyl acetate. The organic

phase was washed first with 10% *w*/*w* aqueous sodium bicarbonate solution (10 mL), then with brine (10 mL), and dried over $MgSO_4$. Filtration and evaporation of solvents under reduced pressure afforded the crude reaction product that was purified by column chromatography (silica gel; hexane/ethyl acetate mixtures of increasing polarity) to afford the intermediate pyrazolidinol as a diastereomer mixture.

IV.1.2.3 Pyrazolidinones by Oxidation of Pyrazolidinols

The pyrazolidinol diastereomer mixture (0.15 mmol) and pyridinium chlorochromate PCC (158 mg, 0.73 mmol, 5 eq) were added sequentially to a stirred suspension of activated 4 Å molecular sieves (300 mg) in anhydrous dichloromethane (2 mL), and the reaction mixture was stirred at room temperature until completion (24–48 h). After the addition of diethyl ether (10 mL) to precipitate the chromium salts, the solution was decanted and filtered through a short pad of Celite® eluting with a 1:10 mixture of ethyl acetate and diethyl ether). After removal of the solvents in vacuo, the reaction product was purified by column chromatography (silica gel, hexane/ethyl acetate mixtures) to give the pyrazolidinones.

IV.1.3 General Procedures for the Preparation of Isoxazolidines

IV.1.3.1 Racemic Isoxazolidinols from Enals and Hydroxylamine 10

Pyrrolidine (from a 10 mg/mL solution in toluene; 1.48 mL, 0.21 mmol, 40 mol %) and *N*-Cbz-hydroxylamine **10** (87 mg, 0.52 mmol, 1 eq) were added sequentially to a magnetically stirred solution of the α-unsaturated aldehyde **7a**, **7b**, or **7c** (1.04 mmol, 2 eq) in toluene (2 mL), and the resulting solution was stirred at room temperature. The progress of the reaction was monitored both by ^{1}H-NMR spectroscopy and by TLC. When the starting hydroxylamine **10** was't detected (2 days), toluene and pyrrolidine were removed in vacuo, and the crude residue was directly purified by column chromatography (silica gel; hexane/ethyl acetate mixtures) to give the corresponding isoxazolidinols as a diastereomer mixture.

IV.1.3.2 Asymmetric Synthesis of Isoxazolidinols from Enals and Hydroxylamine 10

The chiral prolinol silyl ether **13** or **14** (0.104 mmol, 20 mol %) and *N*-Cbz-hydroxylamine **10** (87 mg, 0.52 mmol, 1 eq) were added sequentially to a magnetically stirred solution of the *α, β*-unsaturated aldehyde **7a**, **7b**, or **7c** (1.04 mmol, 2 eq) in toluene (2 mL), and the resulting solution was stirred at room temperature. The progress of the reaction was monitored both by ^{1}H-NMR spectroscopy and by TLC. When the starting hydroxylamine **10** was not detected (3 days), toluene was removed in vacuo, and the crude residue was directly purified by column chromatography (silica gel; hexane/ethyl acetate mixtures) to give the corresponding isoxazolidinols as a diastereomer mixture.

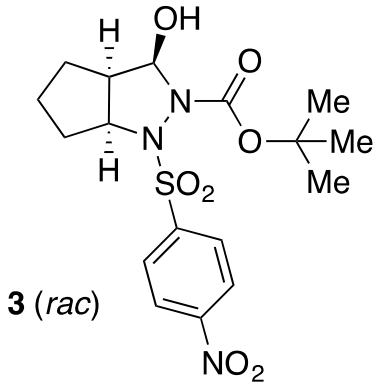
IV.1.3.3 Isoxazolidinones by Oxidation of Isoxazolidinols

The isoxazolidinol diastereomer mixture (0.126 mmol) and pyridinium chlorochromate PCC (82 mg, 0.38 mmol, 5 eq) were added sequentially to a stirred suspension of activated 4Å molecular sieves (150 mg) in anhydrous dichloromethane (2 mL), and the reaction mixture was stirred overnight at room temperature. After the addition of diethyl ether (5 mL) to precipitate the chromium salts, the solution was decanted and filtered through a short pad of Celite® eluting with a 4:1 mixture of hexane and ethyl acetate. After removal of the solvents in vacuo, the reaction product was purified by column chromatography (silica gel, hexane/ethyl acetate mixtures) to give the isoxazolidinones.

IV.1.4 Characterization of the Products

IV.1.4.1 Pyrazolidinols Products from Enals and Hydrazines 2a

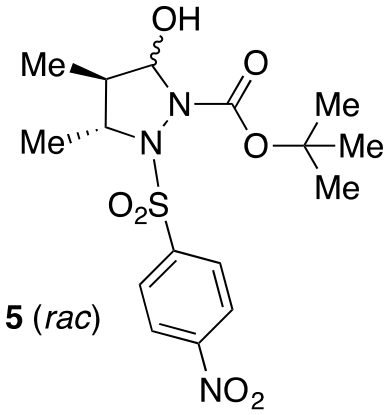
- ***Product 3:*** *tert-Butyl (3RS, 3aRS, 6aSR)-3-hydroxy-1-((4-nitrophenyl) sulfonyl) hexahydro cyclopenta[c]pyrazole-2(1H)-carboxylate*, **3**:



3 (*rac*)

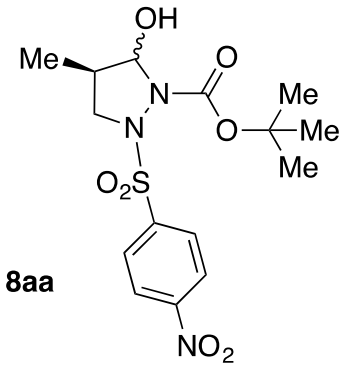
Obtained in 87% yield (450 mg, 1.09 mmol) according to Procedure IV.1.2.1. Colorless solid, m.p. 83–85 °C (from 1:9 chloroform/hexanes). ^{1}H-NMR ($CDCl_3$): δ = 1.24 (s, 9H), 1.47–1.54 (m, 3H), 1.67–1.75 (m, 1H), 1.77–1.83 (m, 1H), 1.86–1.95 (m, 1H), 2.72–2.77 (m, 1H), 3.38 (br d, 1H, OH), 4.73–4.78 (m, 1H), 5.42 (m, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 8.29 (d, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 24.5, 27.8, 30.5, 33.7, 53.6, 62.2, 65.5, 83.0, 91.9, 123.7, 131.1, 141.8, 150.7 ppm. HRMS (ESI): Calculated for $C_{17}H_{27}N_4O_7S$ $[M + NH_4]^+$ = 431.1595; found, 431.1592.

- ***Product 5:*** *tert-Butyl 3,4-trans-5-hydroxy-3,4-dimethyl-2-((4 -nitrophenyl) sulfonyl)-pyrazolidine-1-carboxylate*, **5**:



Obtained as a 6:1 diastereomer mixture in 76% yield (380 mg, 0.95 m mol) according to Procedure IV.1.2.1. Colorless solid, m.p. 71–73 °C (major isomer, 1:9 chloroform/hexanes). ^{1}H-NMR ($CDCl_3$): δ = 1.00 (d, *J* = 7.0 Hz, 3H), 1.24 (s, 9H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.80–1.87 (m, 1H), 2.86 (br d, 1H, OH), 3.72–3.79 (m, 1H), 5.46–5.48 (m, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 8.28 (d, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 11.1, 20.7, 27.81, 27.83, 47.4, 62.2, 83.2, 86.6, 123.6, 130.9, 141.8, 150.6, 154.7 ppm. HRMS (ESI): Calculated for $C_{16}H_{24}N_3O_7S$ $[M + H]^+$ = 402.1337; found, 402.1340.

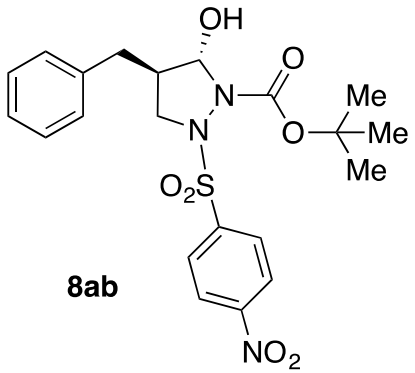
- ***Product 8aa:*** *tert-Butyl 5-hydroxy-4-methyl-2-((4-nitrophenyl)sulfonyl)-pyrazolidine-1-carboxylate,* ***8aa****:*



The racemic compound was obtained as a 4:1 diastereomer mixture in 93% yield (180 mg, 0.47 mmol) according to Procedure IV.1.2.1. Colorless solid, m.p. 111–114 °C (major isomer, 1:9 chloroform/hexanes). ^{1}H-NMR ($CDCl_3$): δ = 1.09 (d, *J* = 7.0 Hz, 3H), 1.35 (s, 9H), 2.25–2.30 (m, 1H), 3.03–3.09 (m,

1H), 3.22 (br d, 1H, OH), 3.29–3.36 (m, 1H), 3.83–3.87 (m, 1H), 5.47 (m, 1H), 8.12 (d, *J* = 8.0 Hz, 2H), 8.34 (d, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 15.0, 27.9, 43.0, 55.3, 83.2, 91.9, 123.9, 131.0, 141.8, 150.8, 154.5 ppm. HRMS (ESI): Calculated for $C_{15}H_{21}N_3NaO_7S$ $[M + Na]^+$ = 410.0992; found, 410.1000. When using **14** as a catalyst and following Procedure IV.1.2.2, scalemic **8aa** was obtained in 98.6% yield (3:1 diastereomer mixture). Colorless solid, m.p. = 135–137 °C (major isomer, 1:9 chloroform/hexanes).

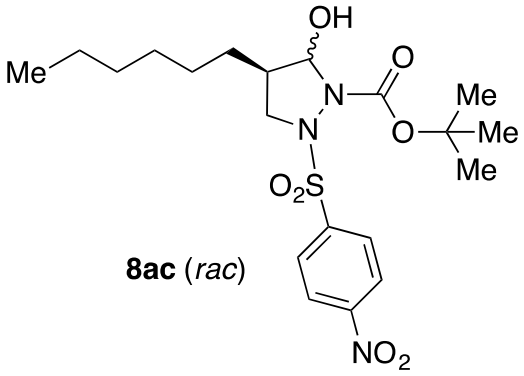
- ***Product 8ab:*** *tert-Butyl 4-benzyl-5-hydroxy-2-((4-nitrophenyl)sulfonyl)-pyrazolidine-1-carboxylate*, **8ab**:



8ab

The racemic compound was obtained in 83% yield (165 mg, 0.36 mmol, >20:1 dr) according to procedure IV.1.2.1. Colorless solid, m.p. 122–126 °C (major isomer, recrystallized from 1:2:7 dichloromethane/chloroform/hexanes). ^{1}H-NMR ($CDCl_3$): δ = 1.36 (s, 9H), 2.53–2.58 (m, 2H), 3.14–3.19 (m, 1H), 3.24 (br d, 1H, OH), 4.01–4.06 (m, 1H), 5.39–5.41 (m, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.20–7.33 (m, 3H), 8.13 (d, *J* = 8.0 Hz, 2H), 8.34 (d, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 27.9, 36.7, 50.1, 53.7, 83.3, 89.9, 123.8, 126.9, 128.4, 128.8, 131.0, 137.8, 141.7, 150.8, 154.3 ppm. HRMS (ESI): Calculated for $C_{21}H_{25}N_3NaO_7S$ $[M + Na]^+$ = 486.1305; found, 486.1298. When using **13** as a catalyst and following Procedure 1.2.2, scalemic **8ab** was obtained in 77% yield. Colorless solid, m.p. = 132–136 °C (major isomer, 1:2:7 dichloromethane/chloroform/hexanes).

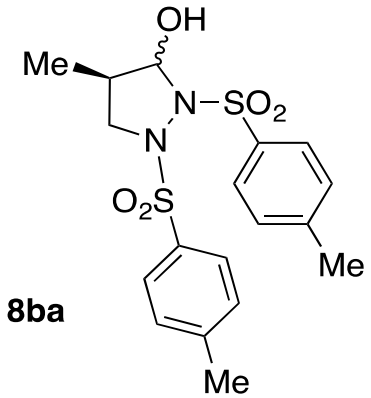
- ***Product 8ac:*** *tert-Butyl 4-hexyl-5-hydroxy-2-((4-nitrophenyl) sulfonyl)-pyrazolidine-1-carboxylate,* **8ac**.



Obtained in 99.6% yield as a diastereoisomer mixture (227 mg, 1.00 mmol, 5:1 dr) according to Procedure IV.1.2.1. Colorless solid, m.p. 83–85 °C. ^{1}H-NMR ($CDCl_3$, major isomer): δ = 0.86 (t, *J* = 7Hz, 3H), 1.25–1.32 (m, 8H), 1.33 (s, 9H), 1.49–1.56 (m, 2H), 2.15–2.19 (m, 1H), 3.01–3.07 (m, 1H), 3.25 (br d, 1H, OH), 4.19–4.24 (m, 1H), 5.25–5.28 (m, 1H), 8.17 (d, *J* = 8.0 Hz, 2H), 8.36 (d, *J* = 8.0 Hz, 2H) ppm. HRMS (ESI): Calculated for $C_{40}H_{62}N_6NaO_{14}S_2$ $[2M + Na]^+$= 937.3658; found, 937.3654.

IV.1.4.2 Pyrazolidinols Products from Enals and Hydrazines 2b

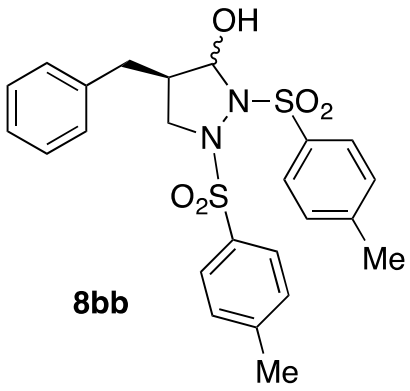
- ***Product 8ba:*** *4-Methyl-1,2-bis-(4-toluenesulfonyl)-pyrazolidin-3-ol,* **8ba***:*



The racemic compound was obtained as an 8:1 diastereomer mixture in 88% yield (75 mg, 0.18 mmol) according to Procedure IV.1.2.1. Yellow solid, m.p. 131–134 °C. ^{1}H-NMR ($CDCl_3$, major isomer): δ = 0.86 (d, *J* = 7.0 Hz, 3H), 2.17–2.25 (m, 2H), 2.45 (s, 3H), 2.46 (s, 3H), 3.33–3.40 (m, 1H), 4.04–4.11 (m, 1H), 5.21–5.22 (m, 1H), 7.29–7.33 (m, 4H), 7.70 (d, *J* = 8.0 Hz, 2 H), 7.82

(d, *J* = 8.0 Hz, 2 H) ppm. HRMS (ESI): Calculated for $C_{36}H_{44}N_4NaO_{10}S_4$ [2M + Na] $^+$ = 843.1832; found, 843.1832. When using **13** as a catalyst and following Procedure 1.2.2, scalemic **8ba** was obtained in 89.4% yield (8:1 diastereomer mixture).

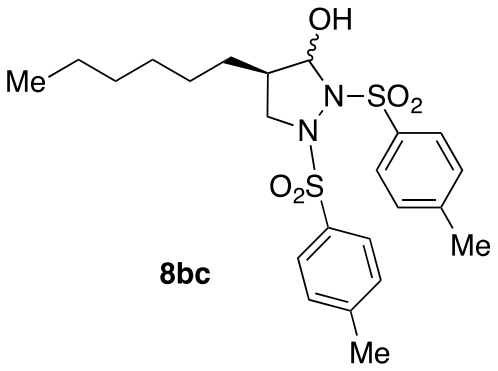
- ***Product 8bb:*** *4-Benzyl-1,2-bis-(4-toluenesulfonyl)-pyrazolidin-3-ol*, **8bb*:***



8bb

The racemic compound was obtained as a diastereomer mixture (>9:1 dr) in 85% yield (85 mg, 0.18 mmol) according to Procedure IV.1.2.1. Yellow solid, m.p. 110–113 °C. ^{1}H-NMR ($CDCl_3$, major isomer): δ = 2.14–2.20 (m, 1H), 2.35–2.42 (m, 2H), 2.46 (s, 3H), 2.47 (s, 3H), 2.82–2.87 (m, 1H), 3.45–3.47 (br d, 1H, OH), 3.89–3.94 (m, 1H), 5.36–5.40 (m, 1H), 7.28–7.31 (m, 5H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H) ppm. HRMS (ESI): Calculated for $C_{48}H_{56}N_5O_{10}S_4$ [2M + NH_4]$^+$ = 990.2805; found, 990.2805. When using **13** or **14** as catalysts and following Procedure 1.2.2, scalemic **8bb** was obtained in the same yield and diastereomeric ratio.

- ***Product 8bc:*** *4-Hexyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-ol*, **8bc**.



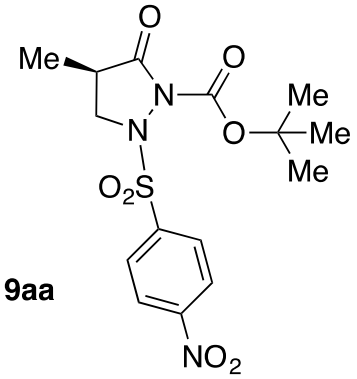
8bc

The racemic compound was obtained as a diastereomer mixture (10:1 dr) in 98% yield (97 mg, 0.20 mmol) according to Procedure IV.1.2.1. Yellow solid, m.p. 78–80 °C. ^{1}H-NMR ($CDCl_3$, major isomer): δ = 0.87 (t, *J* = 7.0 Hz, 3H), 0.95–1.00 (m, 1H), 1.13–1.18 (m, 6H), 1.22–1.27 (m, 3H), 2.01–2.14 (m, 1H), 2.44 (s, 3H), 2.45 (s, 3H), 2.85–2.87 (m, 1H), 3.35–3.37 (br d, 1H, OH), 4.08–4.13 (m, 1H), 5.24–5.28 (m, 1H), 7.27–7.32 (m, 4H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H) ppm. HRMS (ESI): Calculated for $C_{23}H_{32}N_2NaO_5S_2$ $[M + Na]^+$ = 503.1642; found, 503.1645. When using **13** as a catalyst and following Procedure 1.2.2, scalemic **8bc** was obtained in 93% yield (104 mg, 0.23 mmol; 10:1 dr).

IV.1.4.3 Pyrazolidinones products by Oxidation of Pyrazolidinols

IV.1.4.3.1 Original Pyrazolidinols from Enals and Hydrazines 2a

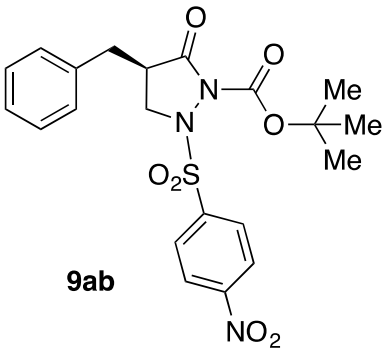
- ***Product 9aa:*** *(−)-tert-Butyl 4-methyl-2-((4-nitrophenyl)sulfonyl)-pyrazolidin-5-one-1-carboxylate*, **9aa**:



9aa

Oxidation of **8aa** obtained by catalyst **14** gave (−)-9aa (90:10 er) in 94% yield (101 mg, 0.26 mmol) according to Procedure IV.1.2.3. Colorless solid, m.p. 131–134 °C (from 1:9 chloroform/hexanes). ^{1}H-NMR ($CDCl_3$): δ = 1.16 (d, *J* = 7.0 Hz, 3H), 1.47 (s, 9H), 2.54–2.64 (m, 1H), 3.38–3.45 (m, 1H), 4.40–4.45 (m, 1H), 8.18 (d, *J* = 8.0 Hz, 2H), 8.41 (d, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 13.4, 27.7, 36.8, 53.7, 85.6, 124.4, 130.7, 141.3, 151.4, 173.4 ppm. HRMS (ESI): Calculated for $C_{15}H_{19}N_3NaO_7S$ $[M + Na]^+$ = 408.0836; found, 408.0847. $[\alpha]_D^{25}$ = −56.0 (1.23, DCM). Conditions for the HPLC analysis: Chiralpak® IC column, 90:10 hexane/2-propanol, 1 µl/min, 25 °C, λ = 254 nm. t_R (major enant.) = 58.1 min, t_R (minor enant.) = 84.4 min.

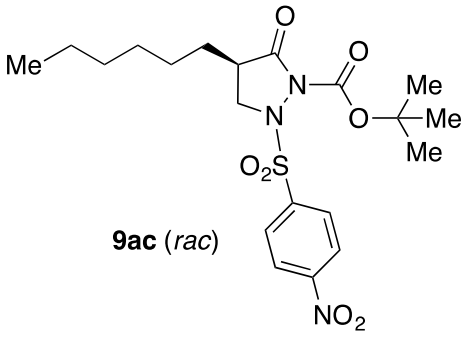
- ***Product 9ab:*** *(−)-tert-Butyl 4-benzyl-2-((4-nitrophenyl)sulfonyl)-pyrazolidin-5-one-1-carboxylate*, **9ab***:*



9ab

Oxidation of 8ab obtained by catalyst 13 gave (−)-9ab (44:56 er) in 98% yield (108 mg, 0.23 mmol) according to Procedure IV.1.2.3. Colorless solid, m.p. 115–118 °C (recrystallized from 1:2:7 dichloromethane/chloroform/hexanes). ^{1}H-NMR ($CDCl_3$): δ = 1.46 (s, 9H), 2.61–2.67 (m, 1H), 2.86–2.92 (m, 1H), 3.17–3.21 (m, 1H), 3.46–3.52 (m, 1H), 4.16–4.21 (m, 1H), 7.07 (d, J = 6.7 Hz, 2H), 7.25–7.32 (m, 3H), 8.13 (d, J = 7.8 Hz, 2H), 8.37 (d, J = 7.8 Hz, 2H) ppm. ^{13}C-NMR (CDCl3): δ = 27.7, 34.8, 43.6, 51.7, 85.7, 124.3, 127.2, 128.5, 130.7, 136.7, 141.2, 147.5, 151.4, 172.1 ppm. HRMS (ESI): Calculated for $C_{42}H_{50}N_7O_{14}S_2$ $[2M + NH_4]^+$ = 940.2852; found, 940.2847. $[\alpha]_D^{25}$ = −11.4 (1.19, DCM). Conditions for the HPLC analysis: Chiralpak® IC column, 90:10 hexane/2-propanol, 1 μL/min, 25 °C, λ = 254 nm. t_R (minor enant.) = 62.4 min, t_R (major enant.) = 73.2 min.

- ***Product 9ac:*** *tert-Butyl 4-hexyl-2-((4-nitrophenyl) sulfonyl)-pyrazolidin-5-one-1-carboxylate*, **9ac**.



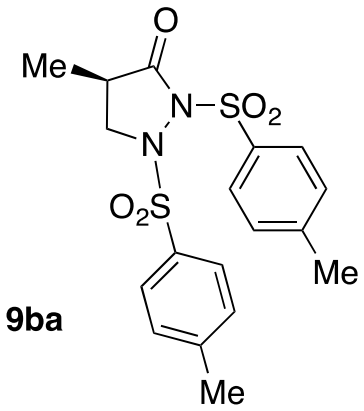
9ac (*rac*)

Obtained in 99% yield (150 mg, 0.33 mmol) according to Procedure IV.1.2.3. Colorless solid, m.p. 123–126 °C. ^{1}H-NMR ($CDCl_3$): δ = 0.87 (t, J = 6.5 Hz, 3H), 1.24–1.30 (m, 9H), 1.47 (s, 9H), 1.78–1.83 (m, 1H), 2.40–2.47 (m, 1H),

3.42–3.49 (m, 1H), 4.37–4.42 (m, 1H), 8.19 (d, J = 7.8 Hz, 2H), 8.42 (d, J = 7.8 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 13.9, 22.5, 26.8, 27.7, 28.8, 29.1, 31.4, 41.8, 52.6, 124.4, 130.7, 141.3, 147.7, 151.3, 172.9 ppm. HRMS (ESI): Calculated for $C_{20}H_{29}N_3NaO_7S$ $[M + Na]^+$ = 478.1618; found, 478.1627.

IV.1.4.3.2 Original Pyrazolidinols from Enals and Hydrazines 2b

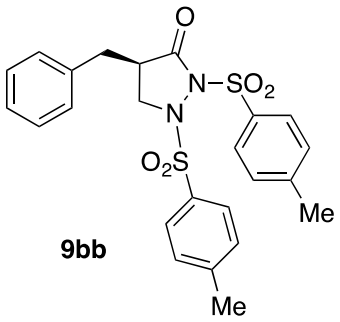
- ***Product* 9ba*:*** *(−)-4-Methyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one*, **9ba**.



9ba

Oxidation of 8ba obtained by catalyst 13 gave (−)-**9ba** (96:4 er) in 98% yield (58 mg, 0.14 mmol) according to Procedure IV.1.2.3. Colorless solid, m.p. 156–160 °C (recrystallized from 1:2:7 dichloromethane/chloroform/hexanes). ^{1}H-NMR ($CDCl_3$): δ = 0.76 (d, J = 7.0 Hz, 3H), 2.12–2.23 (m, 1H), 2.46 (s, 6H), 2.83–2.90 (m, 1H), 4.28–4.33 (m, 1H), 7.34–7.36 (m, 4H), 7.89 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 15.3, 21.8, 34.7, 65.8, 127.0, 128.3, 128.7, 128.8, 129.6, 129.8, 130.1, 146.0, 146.2, 176.5 ppm. HRMS (ESI): Calculated for $C_{36}H_{40}N_4NaO_{10}S_2$ $[2M + Na]^+$ = 839.1519; found, 839.1516. $[\alpha]_D^{25}$ = −64.7 (0.67, DCM). Conditions for the HPLC analysis: Chiralpak® IA column, 90:10 hexane/2-propanol, 1 μL/min, 25 °C, λ = 254 nm. t_R (major enant.) = 33.6 min, t_R (minor enant.) = 51.5 min.

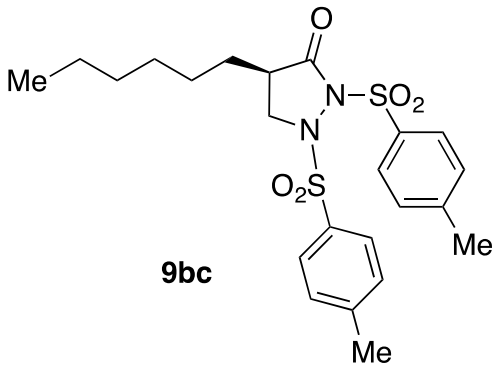
- ***Product 9bb:*** *4-Benzyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one*, **9bb**.



9bb

Oxidation of 8bb according to Procedure IV.1.2.3 gave 9bb in 97% yield (58 mg, 0.12 mmol). Yellow solid, m.p. 156–160 °C. ^{1}H-NMR ($CDCl_3$): δ = 2.01–2.07 (m, 1H), 2.45–2.47 (m, 1H), 2.47 (s, 3H), 2.48 (s, 3H), 2.90–2.95 (m, 1H), 2.98–3.01 (m, 1H), 4.05–4.011 (m, 1H), 6.81 (m, 1H), 7.20 (m, 3H), 7.34 (d, J = 6 Hz, 4H), 7.73 (d, J = 7.6 Hz, 2H), 7.86 (d, J = 7.6 Hz, 2H) ppm. ^{13}C-NMR (CDCl3): δ = 21.79, 21.82, 34.7, 42.7, 54.0, 127.0, 128.3, 128.7, 128.8, 129.6, 129.8, 130.1, 131.2, 134.67, 134.73, 146.0, 146.2, 176.5 ppm. HRMS (ESI): Calculated for $C_{24}H_{28}N_3NaO_5S_2$ $[M + NH_4]^+$ = 502.1465; found, 502.1466. No satisfactory conditions for the chiral HPLC analysis of this compound could be found.

- ***Product 9bc:*** *(−)-4-Hexyl-1, 2-bis-(4-toluenesulfonyl)-pyrazolidin-3-one*, **9bc**.



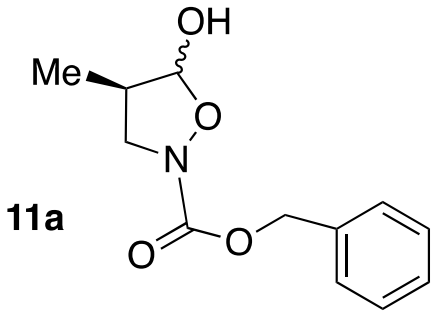
9bc

Oxidation of 8bc (obtained by catalyst 13) according to Procedure IV.1.2.3 gave (−)-9bc (78:22 er) in 98% yield (58 mg, 0.12 mmol). Colorless solid, m.p. 160–164 °C. ^{1}H-NMR (CDCl3): δ = 0.83–0.86 (m, 5H), 1.05–1.12 (m, 4H), 1.19–

1.25 (m, 3H), 1.40–1.52 (m, 1H), 2.08–2.11 (m, 1H), 2.45 (s, 3H), 2.46 (s, 3H), 2.93–3.00 (m, 1H), 4.24–4.29 (m, 1H), 7.33–7.36 (m, 4H), 7.78 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 13.9, 21.7, 21.8, 22.4, 26.2, 28.6, 28.7, 31.3, 41.0, 54.1, 128.7, 129.6, 129.8, 130.1, 131.3, 134.8, 145.9, 146.2, 177.5 ppm. HRMS (ESI): Calculated for $C_{23}H_{30}N_2NaO_5S_2$ [M + Na]$^+$ = 501.1488; found, 501.1491. $[\alpha]_D^{25} = -8.0$ (1.01, DCM). Conditions for the HPLC analysis: Chiralpak® IB column, 93:7 hexane/2-propanol, 1 μL/min, 25 °C, λ = 220 nm. t_R (major enant.) = 21.5 min, t_R (minor enant.) = 27.6 min.

IV.1.4.4. Isoxazolidinols Products from Enals and Hydroxylamine 10

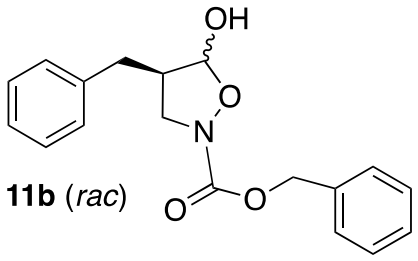
- ***Product* 11a***: Benzyl 5-hydroxy-4-methyl-isoxazolidine-2-carboxylate*, **11a***:*



11a

The racemic compound was obtained as a 2:1 diastereomer mixture in 83% yield (102 mg, 0.43 mmol) according to Procedure IV.1.3.1. Colorless oil. ^{1}H-NMR (CDCl3, major isomer): δ = 1.09 (d, J = 7 Hz, 3H), 2.60–2.67 (m, 1H), 3.61–3.64 (m, 1H), 4.26–4.29 (m, 1H), 5.16 (br s, 2H), 5.34–5.35 (m, 1H), 7.32–7.35 (m, 5H) ppm. ^{1}H-NMR (CDCl3, minor isomer): δ = 1.13 (d, J = 7.0 Hz, 3H), 2.55–2.59 (m, 1H), 3.78–3.82 (m, 1H), 4.14–4.17 (m, 1H), 5.22 (br s, 2H), 5.55–5.56 (m, 1H), 7.37–7.39 (m, 5H) ppm. ^{13}C-NMR (CDCl3): δ = 9.4, 14.7, 40.4, 44.1, 67.8, 68.1, 73.5, 74.9, 82.1, 88.0, 128.29, 128.34, 128.43, 128.46, 128.5, 128.6, 135.38, 135.44, 141.8, 155.3, 159.0 ppm. When using **13** or **14** as catalysts and following Procedure IV.1.3.2, scalemic **11a** was obtained in similar yield and diastereomer ratio.

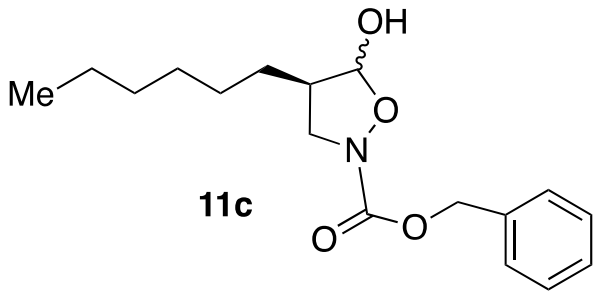
- ***Product 11b:*** *Benzyl 4-benzyl-5-hydroxy-isoxazolidine-2-carboxylate*, **11b**.



11b (*rac*)

The racemic compound was obtained as a 3:1 diastereomer mixture in 79% yield (128 mg, 0.41 mmol) according to Procedure IV.1.3.1. Colorless oil. ^{1}H-NMR ($CDCl_3$, major isomer): δ = 2.74–2.78 (m, 2H), 3.02–3.06 (m, 1H), 3.57–3.61 (m, 1H), 3.77–3.80 (m, 1H), 4.19–4.23 (m, 1H), 5.25 (br s, 2H), 5.47–5.48 (m, 1H), 7.31–7.41 (m, 10H) ppm. ^{1}H-NMR ($CDCl_3$, minor isomer): δ = 2.59–2.68 (m, 2H), 2.94–2.98 (m, 1H), 3.01–3.27 (m, 1H), 3.67–3.71 (m, 1H), 4.01–4.05 (m, 1H), 5.36 (br s, 2H), 5.56–5.57 (m, 1H), 7.13–7.30 (m, 10H) ppm. ^{13}C-NMR ($CDCl^3$): δ = 23.5, 31.2, 35.8, 48.0, 48.8, 51.0, 68.1, 71.9, 72.9, 81.3, 86.1, 97.2, 101.4, 126.5, 126.7, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 135.5, 135.7, 138.2, 138.9, 155.2, 158.8 ppm.

- ***Product 11c:*** *Benzyl 4-hexyl-5-hydroxy-isoxazolidine-2-carboxylate*, **11c**.



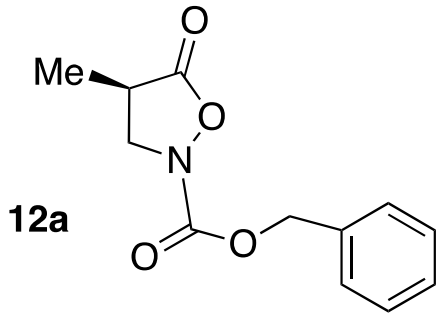
11c

The racemic compound was obtained as a 3:1 diastereomer mixture in 78% yield (120 mg, 0.39 mmol) according to Procedure IV.1.3.1. Colorless oil. ^{1}H-NMR (CDCl3, major isomer): δ = 0.88 (d, J = 7.0 Hz, 3H), 1.28–1.31 (m, 9H), 1.34–1.38 (m, 1H), 2.45–2.55 (m, 2H), 3.62–3.66 (m, 1H), 4.26–4.28 (m, 1H), 5.22 (br s, 2H), 5.39–5.40 (m, 1H), 7.37–7.40 (m, 5H) ppm. ^{1}H-NMR (CDCl3, minor isomer): δ = 0.87 (d, J = 7.0 Hz, 3H), 1.34–1.38 (m, 9H), 3.15–3.19 (m, 2H), 3.81–3.86 (m, 1H), 4.02–4.25 (m, 1H), 5.33 (br s, 2H), 5.39–5.40 (m, 1H),

7.32–7.36 (m, 5H) ppm. When using **14** as a catalyst and following Procedure IV.1.3.2, scalemic **11c** was obtained in 87% yield (201 mg, 0.65 mmol) and in a 3:1 diastereomer ratio.

IV.1.4.5. Isoxazolidinones products by Oxidation of Isoxazolidinols

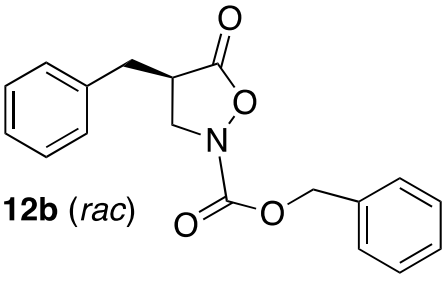
- ***Product* 12a**: *Benzyl 4-methyl-5-oxo-isoxazolidine-2-carboxylate*, **12a**.



12a

Oxidation of 11a gave 12a in 98% yield (50 mg, 0.22 mmol) according to Procedure IV.1.3.3. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 1.29 (d, J = 6.8 Hz, 3H), 3.01–3.11 (m, 1H), 3.96–4.01 (m, 1H), 4.54–4.58 (m, 1H), 5.33 (br s, 2H), 7.33–7.45 (m, 5H) ppm.^{13}C-NMR ($CDCl_3$): δ = 12.2, 39.4, 68.8, 73.9, 98.0, 128.54, 128.6, 134.5, 147.7, 169.9 ppm. HRMS (ESI): Calculated for $C_{12}H_{14}NO_4$ $[M + H]^+$ = 236.0917; found, 236.0916. No satisfactory conditions could be found for the chiral HPLC analysis of this compound.

- ***Product 12b**: Benzyl 4-benzyl-5-oxo-isoxazolidine-2-carboxylate*, **12b**.

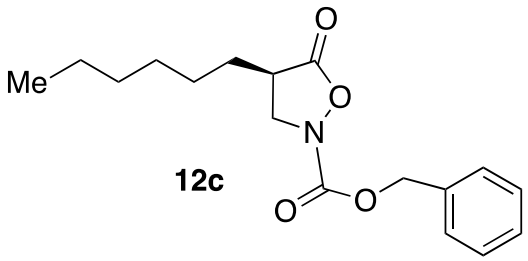


12b (*rac*)

Oxidation of 11b gave 12b in 99% yield (68 mg, 0.22 mmol) according to Procedure IV.1.3.3. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 2.78–2.84 (m, 1H), 3.24–3.28 (m, 2H), 4.07–4.11 (m, 1H), 4.35–4.39 (m, 1H), 5.33 (br s, 2H), 7.15–7.43 (m, 10H) ppm.^{13}C-NMR ($CDCl_3$): δ = 30.7, 43.0, 65.7, 68.8, 123.9,

125.3, 125.4, 125.5, 125.7, 131.3, 134.0, 144.4, 165.4 ppm. HRMS (ESI): Calculated for C18H21N2O4 $[M + NH4]^+$ = 329.1496; found, 329.1494.

- ***Product 12c:*** *(−)-Benzyl 4-hexyl-5-oxo-isoxazolidine-2-carboxylate*, **12c**.



12c

Oxidation of **11c** obtained with catalyst **14** gave (−)-12c (57:43 er) in 87% yield (87 mg, 0.28 mmol) according to Procedure IV.1.3.3. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, J = 7.0 Hz, 3H), 1.28–1.40 (m, 8H), 1.50–1.58 (m, 1H), 1.88–1.93 (m, 1H), 2.92–2.99 (m, 1H), 4.04–4.08 (m, 1H), 4.52–4.56 (m, 1H), 5.33 (br s, 2H), 7.33–7.45 (m, 5H) ppm. ^{13}C-NMR ($CDCl_3$): δ = 14.0, 22.5, 27.0, 28.1, 29.0, 31.5, 44.5, 68.8, 72.6, 128.5, 128.6, 128.7, 134.6, 147.7, 169.5 ppm. HRMS (ESI): Calculated for $C_{34}H_{46}N_2NaO_8$ $[2M + Na]^+$ = 633.3146; found, 633.3148. $[\alpha]_D^{25}$ = −4.1 (0.41, DCM). Conditions for the HPLC analysis: Chiralpak® IB column, 90:10 hexane/2-propanol, 1 μL/min, 25 °C, λ = 254 nm. t_R (minor enant.) = 13.6 min, t_R (major enant.) = 16.3 min.

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[2]. Erkkilä, A., Pihko, P.M., J. Org. Chem., **2006**, 71, 2538-2541.
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Conclusion

Conclusion

The pyrrolidine-catalyzed reaction of the α-substituted enals methacrolein (**7a**), 2-benzylpropenal (**7b**), and 2-(*n*-hexyl)propenal (**7c**) with the activated hydrazines 1-Boc-2-(4-nitrobenzenesulfonyl) hydrazine (**2a**) and 1,2-bis(*p*-toluenesulfonyl)hydrazine (**2b**) takes place in very good yields (83%–99.6%) in toluene at room temperature and in the presence of benzoic acid as a co-catalyst, to afford the 4-substituted pyrazolidin-3-ols **8aa**–**8bc** (generally as diastereomer mixtures); oxidation of these compounds with PCC leads to the corresponding-4-substituted-3-pyrazolidinones **9aa**–**9bc** in essentially quantitative yields. In the same conditions α-substituted acroleins **7a**–**7c** react smoothly with *N*-Cbz-hydroxylamine **10** to afford the isoxazolidinols **11** in good yields (78%–83% isolated yields) as diastereomer mixtures. Subsequent oxidation with PCC gives rise to the 4-substituted isoxazolidin-5-ones **12a**–**12c**. The use of chiral diarylprolinol trimethylsilyl ethers **13** and **14** as catalysts allows the synthesis of several of these compounds in optically active form, in some cases with excellent enantioselectivity (up to 96:4 er). The 4-substituted pyrazolidinols, pyrazolidinones, isoxazolidinols and isoxazolidinones (both in racemic and when possible in enantiomerically enriched form) have been submitted to a primary antimicrobial screening study (antibacterial and antifungal) by whole cell growth inhibition assays in framework of communing for antimicrobial drug discovery at Queensland University , Australia . The primarily Antimicrobial and Antifungal activity has been found for the isoxazolidinones **12a** and **12b**, and for isoxazolidinol **11c**, and the 4-methyl-pyrazolidinol **8aa**, both in racemic and in enantiomerically enriched form, is highly active against *Staphylococcus aureus.*

Publication