TECHNOTRAIN
Enabling *tecnho*logies-driven chemistry: A tailored *train*ing research program for batch and flow synthesis of chiral amino derivatives
H2020-MSCA-ITN-2018, Grant Agreement n. 812944

UNIVERSITÀ DEGLI STUDI DI MILANO

Exploring different organocatalytic strategies for the stereoselective synthesis of chiral nitroesters

Department of Chemistry
PhD in Industrial Chemistry, XXXIV Cycle

PhD candidate
Patricia Camarero González
Matricola R 12467

Doctorate Course in Industrial Chemistry Coordinator
Prof. Dominique Roberto

Tutor
Prof. Maurizio Benaglia

Co-Tutor
Dr. Miguel Sanz

Members of scientific committee
Prof. Alessandra Puglisi, Dr. Sergio Rossi, Dr. David Bevk, Dr. Sumaira Umbreen

Table of Contents

Glossary

1. Glossary

A

AADH. Amino acid dehydrogenases

$AgNO_3$. Silver nitrate

C

CAN. Cerium ammonium nitrate

CPME. Cyclopentyl methyl ether

D

DES. Deep eutectic solvents

DCM. Dichloromethane

DMAP. 4-dimethylamino pyridine

E

ECDI. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

EDC. 1-ethyl-3-cardodiimide hydrochloride

ee. enantiomeric excess

EtOAc. Ethyl acetate

Et_2O. Diethyl ether

G

GC-MS. Gas chromatography-mass spectrometry

H

HCl. Hydrochloric acid

HOBt. 1-hydroxybenzotriazole hydrate

HPLC. High performance liquid chromatography

HWE. Horner Wadsworth Emmons

K

K_2CO_3. Potassium carbonate

L

LR. Less reactive isomer

M

$MgSO_4$. Magnesium sulfate

MR. More reactive isomer

N

$NaBH_4$. Sodium borohydride

NaH. Sodium hydride

$NaHCO_3$. Sodium bicarbonate

NMR. Nuclear magnetic resonance

$NaNO_2$. Sodium nitrate

NaOH. Sodium hydroxide

NR. No reaction

P

PLP. Pyridoxal-5-phosphate

R

RT. Room temperature

T

TA. Transaminases

TBAB. Tetrabutylammonium bromide

TEA. Triethylamine

TEMPO. (2, 2, 6, 6-tetramethylpiperidin-1-1yl)oxyl

tBUOK. Potassium tert-butoxide

TFA. Triluoroacetic acid

THF. Tetrahydrofuran

U

UAAs. Unnatural amino acids

Funding

2. Funding

My PhD research work was funded by the 2018 MSCA project (Marie Sklodowska Curie Actions); the ITN-EID (European Industrial Doctorate) under the research program: TECHNOTRAIN. Enabling TECHNOlogies-driven chemistry: a tailored TRAINing research program for batch and flow synthesis of chiral amino derivatives.

“TECHNOTRAIN” is a 1:1 industrial/academic twinning where three PhD research projects have been carried out in full collaboration between the private and the public research site. As a PhD student, I spent 18 months placed in the University of Milano and 18 months based in Taros Chemicals GmbH & Co. KG, in Dortmund (Germany).

Thesis Summary

3. Thesis Summary

Introduction

Among unnatural α-amino acids, α,α-disubstituted amino acids are key biological scaffolds with many specific roles and properties that have made them increasingly attractive in the fields of organic chemistry, biochemical research and drug discovery.[2,8,10] Structurally, they have unique properties, and this represents an important feature for their use in the design of new pharmaceutically active compounds as well as intermediates for the study of pathological pathways and the role of peptides and their applications in the treatment of the same pathologies they are involved in. Furthermore, their utility as chiral frameworks are critical and so, enantioselectivity plays a key role in their pharmaceutical activity.38 However, there are limited examples in the literature of highly enantioselective synthetic approaches for these compounds or their precursors, that result in sufficient enantioselectivity suitable for their peptidomimetic applications. [9, 12]

Objectives

The global objective of this PhD thesis is to discover unprecedented synthetic strategies for the synthesis of α,α-disubstituted-α-amino acids and/or their precursors, focusing on the stereoselective reactions and employing known and also newly designed organocatalysts, including chiral phase transfer catalysts.

To achieve our goals, two main strategies will be studied:

· The enantioselective conjugate addition of nitroesters to α,β-unsaturated ketones mediated by Cinchona derived thiourea or squaramide catalysts, for the construction of nitroesters bearing a quaternary stereocenter.

· An alternative strategy that started from easily available ketones, converted to tetrasubstituted nitroolefins, which would be organocatalytically reduced to afford enantioeneriched nitroalkanes, featuring two stereocenters, as highly functionalized starting materials for a further alkylation step to generate a quaternary stereocenter.

· Please note that synthetic approaches for di or trisubstituted nitroalkenes are abundant in the literature as intermediates for the synthesis of α,α-disubstituted amino acids[51,52] but, there is very scarce data reporting synthetic routes for tetrasubstituted nitroalkenes. Therefore, new synthetic routes for tetrasubstituted nitroalkenes have been studied and successfully developed in the present research project.

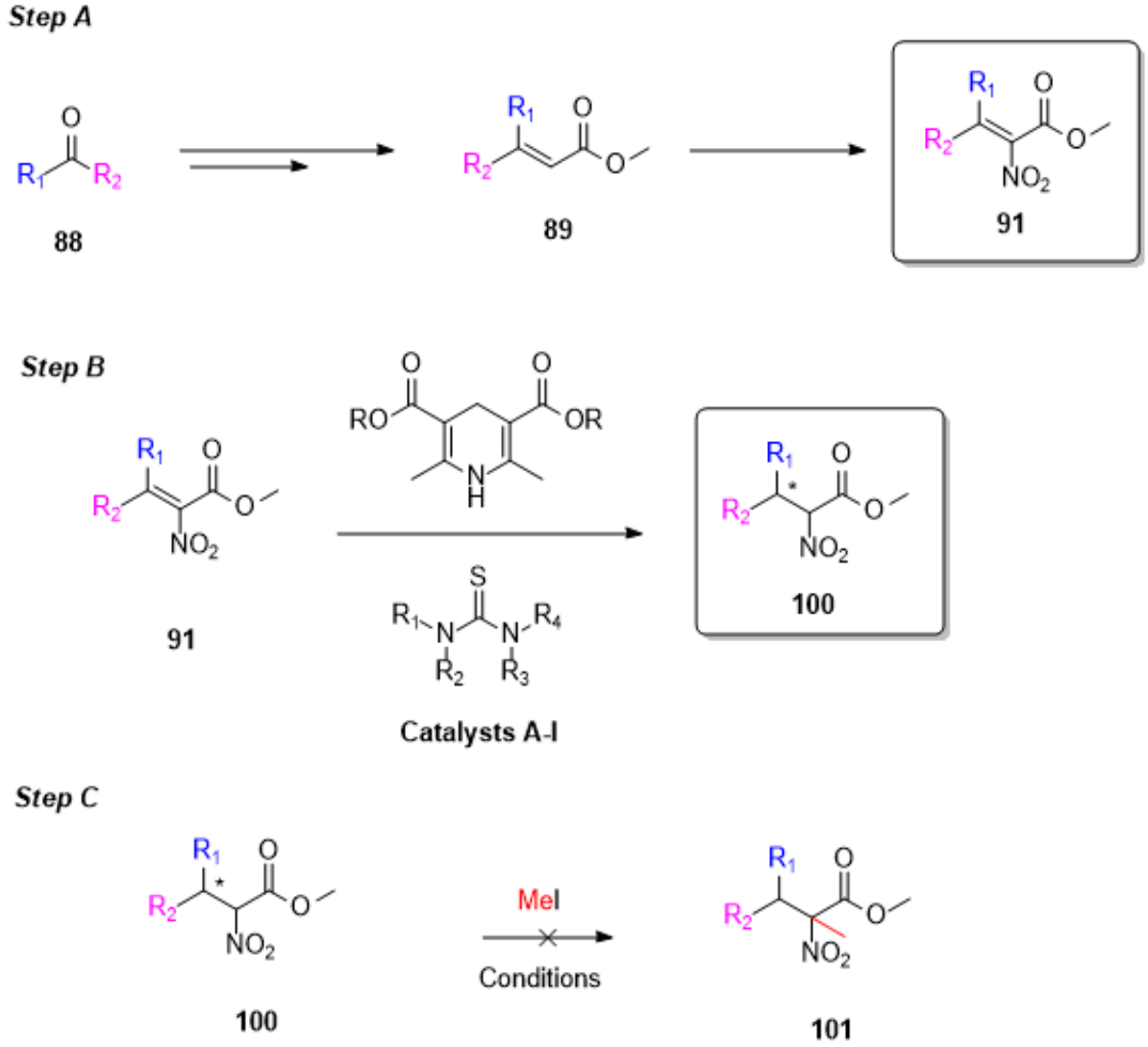
Results and Discussion

The research activity started by using commercially available ketones and transforming them into the corresponding nitroolefins (tetrasubstituted nitroalkenes) using a two-step procedure; firstly the HWE olefination of the ketone to form the corresponding α,β-unsaturated esters **88** was carried out and secondly, they underwent a reaction of nitration with an to introduce the nitro group in the α position of the ester group, in order to afford the desired tetrasubstituted nitroalkenes **91** (Scheme 1, step A).

After that, the enantioselective reduction of these compounds mediates by Hanztsch esters using a thiourea based catalyst followed (Scheme 1, step B). This allowed me to afford the functionalized chiral nitroalkane **100** featuring two stereocenters. The alkylation step (Scheme 1, step C), to generate a quaternary stereocenter in alfa position to the nitro group was further investigated using different alkylation conditions and also phase transfer catalysis conditions. Unfortunately, I encountered several difficulties during the alkylation process including the formulation of undesired products and unsuccessful isolation of my target alkylated compound **101**.

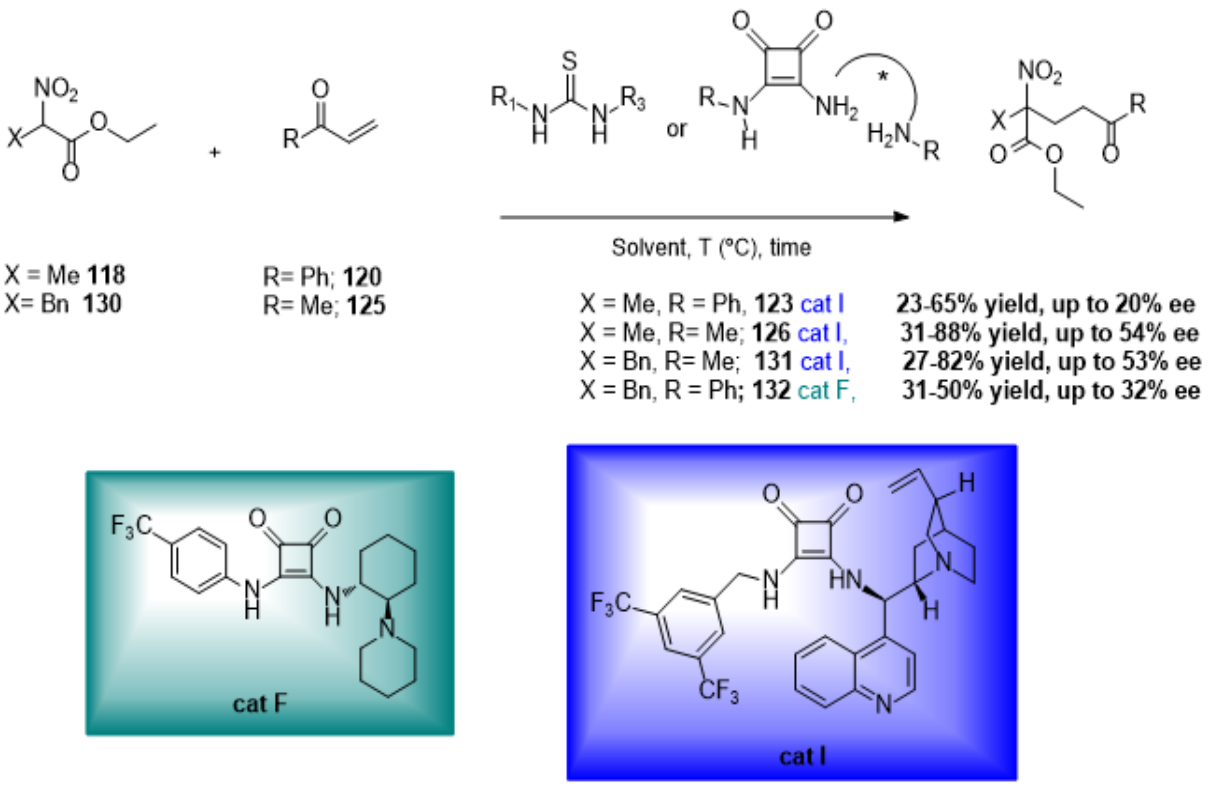
However, in order to establish the absolute stereochemistry of the stereocenter in beta position to the nitro group, generated in the organocatalyzed reduction of the nitroalkene, a decarboxylation of the ester moiety was accomplished, to afford the corresponding trisubs-

tituted nitroalkane, precursor of a known amino derivative. The experimental optical rotation of the corresponding trisubstituted nitroalkane was measured using a polarimeter and the result obtained was compared with the published rotation values for this compound confirming that the synthetized trisubstituted nitroalkane was preferentially obtained with R-configuration at carbon **3** of the molecule. This result agreed with the DFT calculations performed for this reaction.



Scheme 1: Proposed synthetic route for the synthesis of tetrasubstituted nitroalkenes 89, their enantioselective reduction and alkylation step of nitroalkane 100

Furthermore, a detailed, although explorative study was performed to investigate the organocatalyzed conjugate addition of nitroesters **118**, **130** to unsaturated ketones **120**, **125** to get enantiopure nitroesters **123**, **126**, **131**, **132** bearing a quaternary stereocenter, which were obtained with good to moderate yields (Scheme 2)



Scheme 2: Organocatalyzed conjugate addition of nitroesters using thiourea or squaramide derived catalysts

These compounds are not extensively reported in literature, in some cases they are only reported as a racemic mixture, so to the best of our knowledge, for the first time it was demonstrated that it is possible to do this transformation in an enantioselective manner.

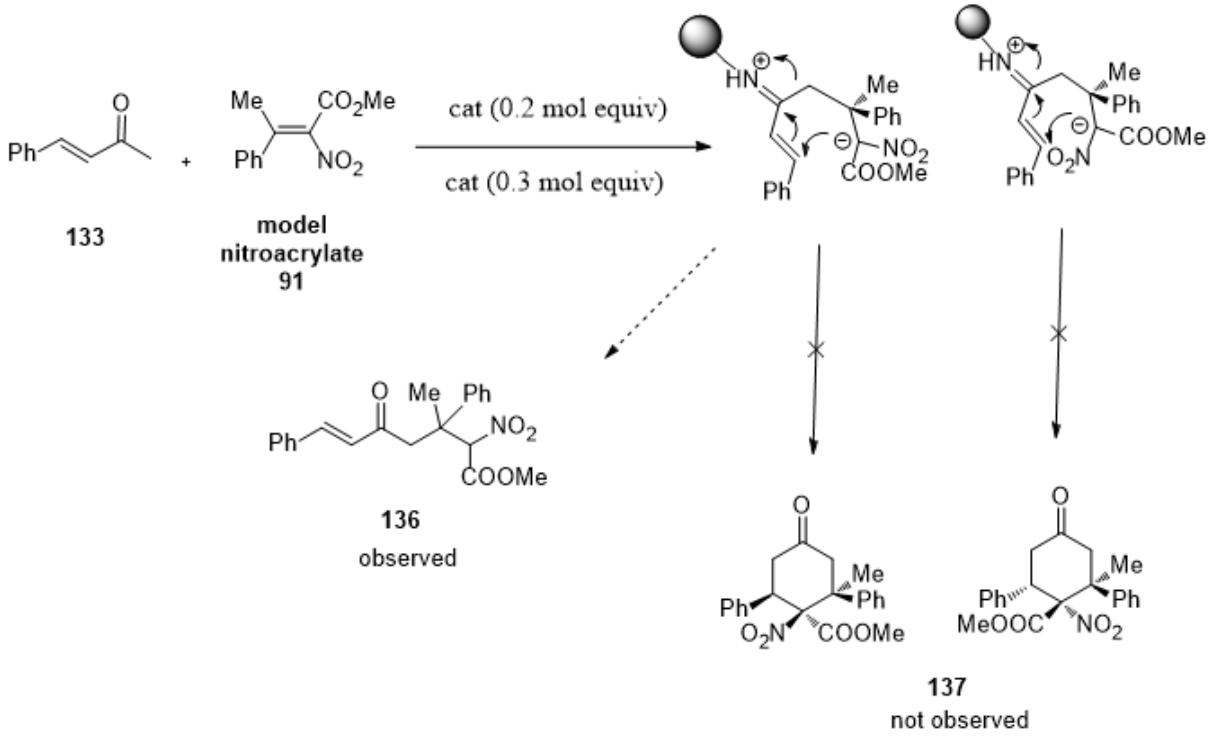
The best enantioselectivities were obtained using a squaramide derived catalyst **F** or **I**. However, the values observed, were not very high so, I searched for another type of activation for this transformation which could produce better enantioselectivity results and decided to try aminocatalysis conditions **79** and phase transfer catalysis. Unfortunately, neither of these two modes of activation afforded satisfactory results.

Conclusions

In summary, new synthetic approaches for the generation of α,α disubstituted α amino acids, using organocatalysis were studied. A reproducible strategy for the synthesis of tetrasubstituted nitroalkenes was successfully developed, and enantioselective organocatalyzed reductions performed, to afford the functionalized nitroalkanes. However, several

challenges were found in the further alkylation step, and despite trying different variations to the process, the synthesis of a α,α disubstituted α amino acid derivative was not accomplished, following this route.

Based on preliminary studies of the reactivity of trisubstituted nitroacrylates in Michael addition reactions followed by cyclisation, involving dienamine formation and reaction with nitroacrylates, **58** the reactivity of the new synthetized tetrasubstituted nitroalkenes was also studied (Scheme 3).



Scheme 3: Reactivity experiments of tetrasubstituted nitroalkenes **91**

Unfortunately, it was only possible to obtain the Michael adduct **136**, after long reaction times in comparison with their trisubstituted analogues. Increasing the temperature of the reaction did not overcome this problem as the stability of the starting material **91** was compromised. Therefore, further optimization of the reaction is needed in future to overcome these issues.

Regarding the organocatalyzed conjugate addition of nitroesters **118** and **130** to unsaturated ketones **120** and **125** to get enantiopure nitroesters **123**, **126**, **131** and **132** bearing a quaternary stereocenter (Scheme 2), the best yields (good to moderate) were obtained

with squaramide derived catalyst **I**. The best enantioselectivity results achieved were moderate (54% ee and 53% ee for compounds **123** and **131**). To the best of our knowledge only two out of the four compounds synthetized had been reported in literature before this work and only as a racemic mixture (compounds **123** and **126**) and the other two synthetized products **131** and **132** were novel compounds, synthetized for the first time in an enantiomeric manner, being this an important achievement.

These Michael adducts **123**, **126**, **131** and **132** have great potential as precursors of several bioactive pharmaceutical products, playing an important role in emerging therapeutic drugs for the treatment of inflammation and cancer.[73]

Aim and Ojectives of PhD thesis

4. Aim and ojectives of PhD thesis

The global aim of this thesis is to develop general, reproducible, and profitable, stereoselective, catalytic synthetic methods applicable for industrial production of enantiomerically pure, functionalized amino derivatives featuring a quaternary stereocenter. Particularly, the main focus was on the development of **stereoselective reactions** of **nitroesters** promoted by different organocatalysts.

Two main general objectives stem from the main aim:

· Synthesis of target molecules, which will be chiral pharmaceutically active ingredients, or immediate precursors, including non-proteogenic α-disubstituted-amino acids.

· To develop highly efficient, technology-driven methodologies that are safe and respect the principles of sustainable chemistry.

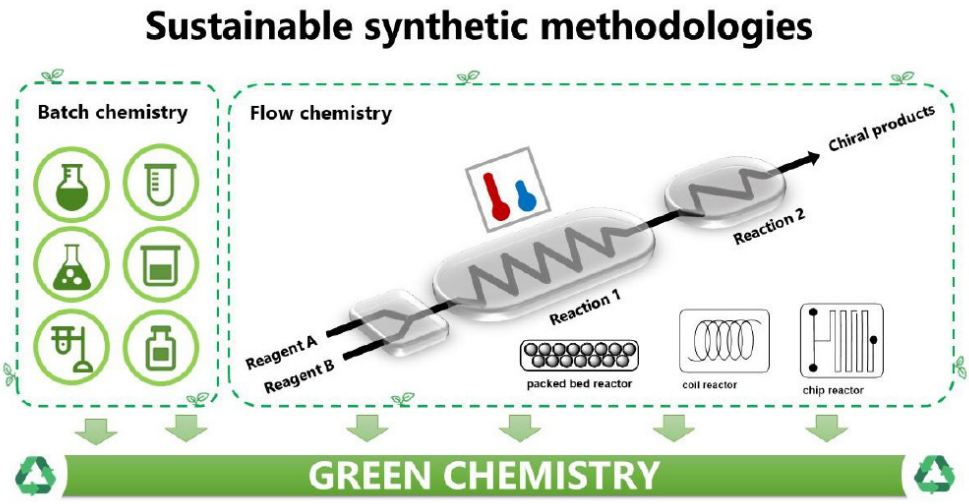


Figure 1: Aim of Technotrain European Program

The PhD objectives are embedded within the larger research program, TECHNOTRAIN, which has a broader aim to employ modern enabling technologies (flow chemistry, microwave irradiation, photocatalysis, deep eutectic solvents, DES, as alternative reaction media), in the development of general, reproducible and profitable stereoselective, catalytic methods applicable for industrial production of enantiomerically pure, functionalized amino derivatives featuring quaternary stereocenters (Figure 1).

Specific objectives:

· Study a strategy which starts from easily available ketones, converted to nitroolefins which will be reduced to afford enantiopure nitroalkanes using organocatalysis, as highly functionalized starting materials for further derivatization (Figure 2, Approach A).

· Study unprecedented synthetic strategies for the synthesis of α,α -disubstituted amino acids employing known or newly designed organocatalysts, including chiral phase transfer catalysts (Figure 2, Approach B).

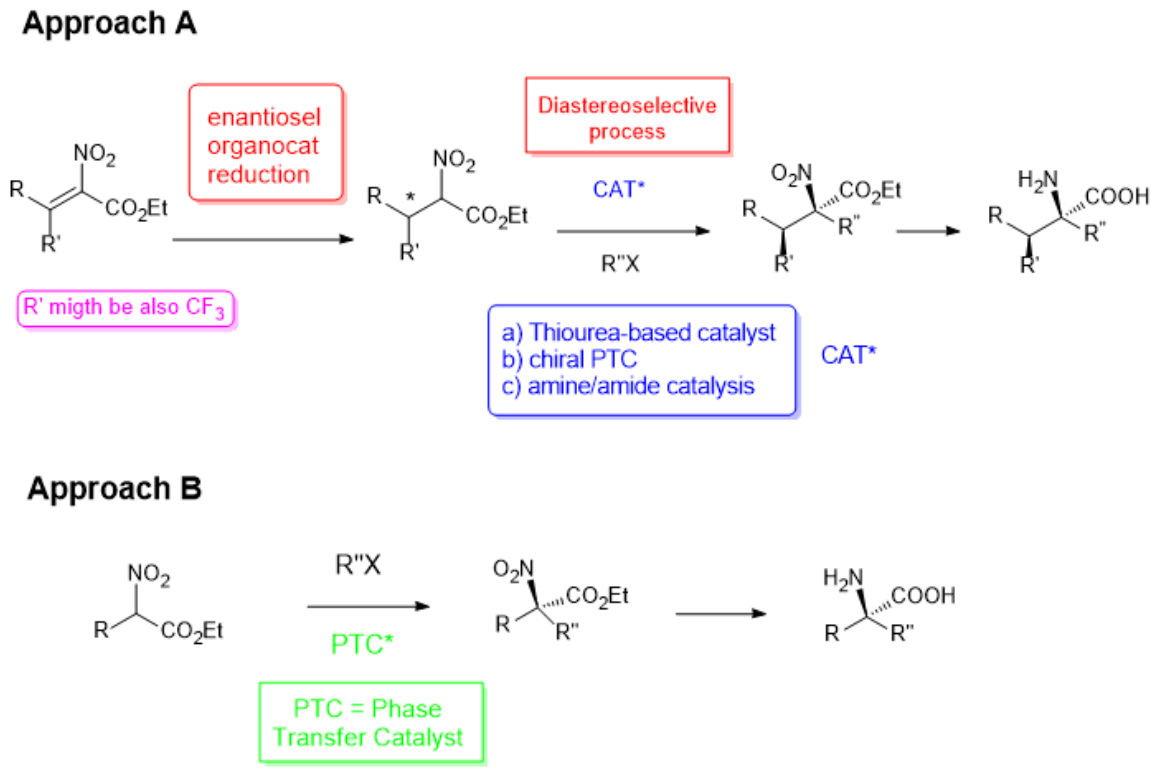


Figure 2: Specific objectives of ESR research project: Exploring different organocatalytic strategies for the stereoselective synthesis of chiral nitroesters

Introduction

5. Introduction

5.1 Non proteinogenic α-amino acids: natural origin and biological functions

Proteins are biochemical compounds formed by building blocks called amino acids that play many important roles in biological reactions such as acting as biocatalysts or regulating gene expression. In addition, amino acid-based chains, called peptides and proteins are also extensively used in tissue engineering and regenerative medicine applications.[1]

There are alpha, beta and gamma amino acids. In an alpha amino acid (α-amino acids) the amino group is attached to the carbon adjacent to the carboxyl group (also called carbon alpha).[1] In the beta amino acids (β-amino acids), the amino group is bound to the second carbon from the carboxylic group (also called carbon beta) and the gamma amino acids (γ-amino acids), have the amine group attached to the third carbon from the carboxylic group (also called carbon gamma). Most proteins found in living organisms are α-amino acids.

Amino acids can be divided into two groups: natural amino acids and unnatural amino acids (UAAs). Amino acids that are naturally incorporated into polypeptides creating proteins are called natural or proteinogenic amino acids.[1] On the other hand, UAAs are not present in natural polypeptides, hence they are also called non proteinogenic. There are twenty-two natural amino acids, the replacement of one by another of the twenty-one natural amino acids has allowed to gathered solid data about protein structure, functions, interactions, and stability.

In addition, UUAs can be incorporated into proteins unfolding a wide variety of new functions. For example, incorporating UUAs that carry novel side chains will result in multiple possibilities to change or adapt the biological and biochemical properties of the proteins we want to obtain or study. This versability creates a vast number of possibilities with clear interesting applications in drug discovery.

UAAs can be naturally found in plants or microorganism extracts (e.g., produced by fungi, bacteria, or marine organisms) or be synthetically obtained using biocatalytic and chemical routes (Figure 3).[2] The enzyme catalyzed synthesis of UAAs is a useful methodology which requires only a few reaction steps. It employs mostly water media and protecting groups is not necessary. However, the dependence on a cofactor means a synthetic inconvenient for this route, due to the high recycling/elimination cost of it.

The chemical synthetic routes are quite complex and produce low yields of the final compounds. Moreover, the lack of enantioselectivity and poor stereoselectivity together with the difficulties to protect the amino and carboxylic acid groups, are also key problems with regards to these methods.

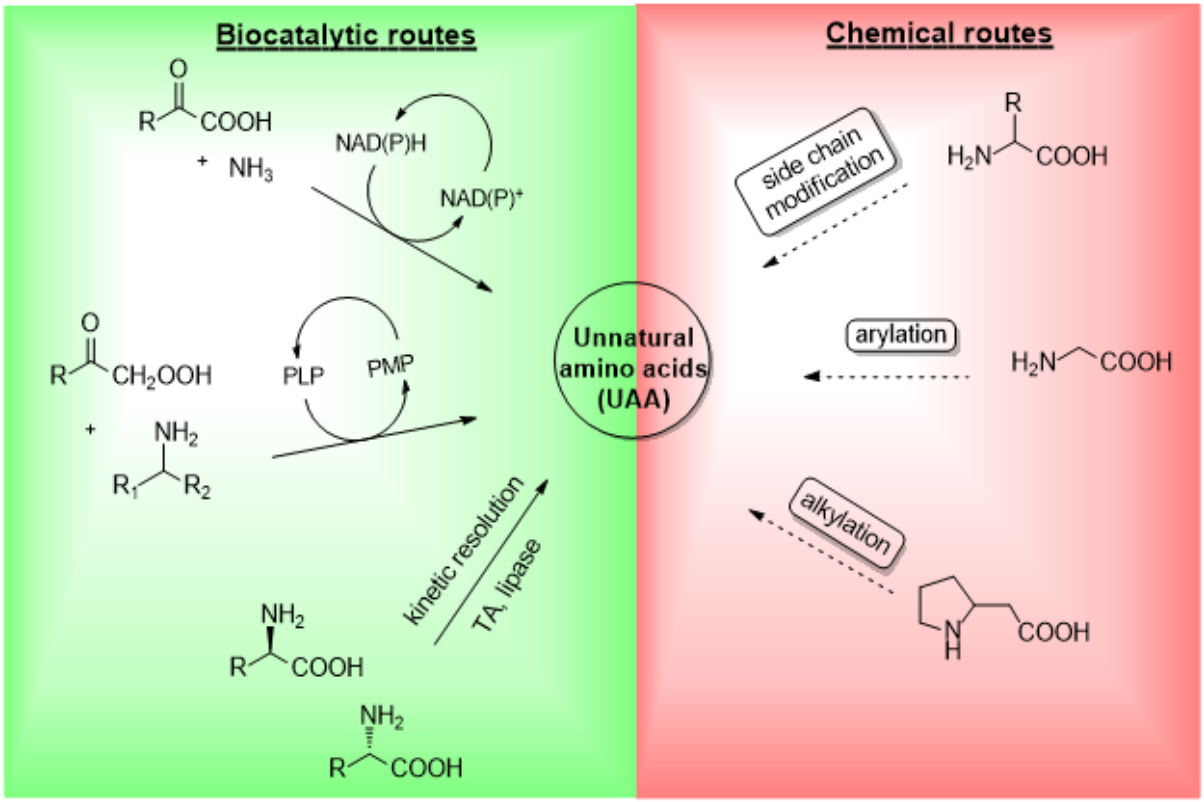


Figure 3: Synthetic routes for the synthesis of UAA

Two of the most widely used methods of biocatalytic synthesis of unnatural amino acids are kinetic resolution and asymmetric synthesis. These routes lead to high yields and in the case of asymmetric synthesis, new natural molecules can be successfully synthetized.[2] However, as previously mentioned, the use of cofactors in these processes can be problematic, due to difficulties to achieve the cofactor recycling, which can significantly impact the cost and length of these reactions. On the other hand, protein and metabolic enginee-

ring are powerful synthetic biology tools for the design of new biocatalysts. For example, amino acid dehydrogenases (AADHs) are largely employed as biocatalysts in the synthesis of amino acids by reductive amination of ketoacids.[2,3]

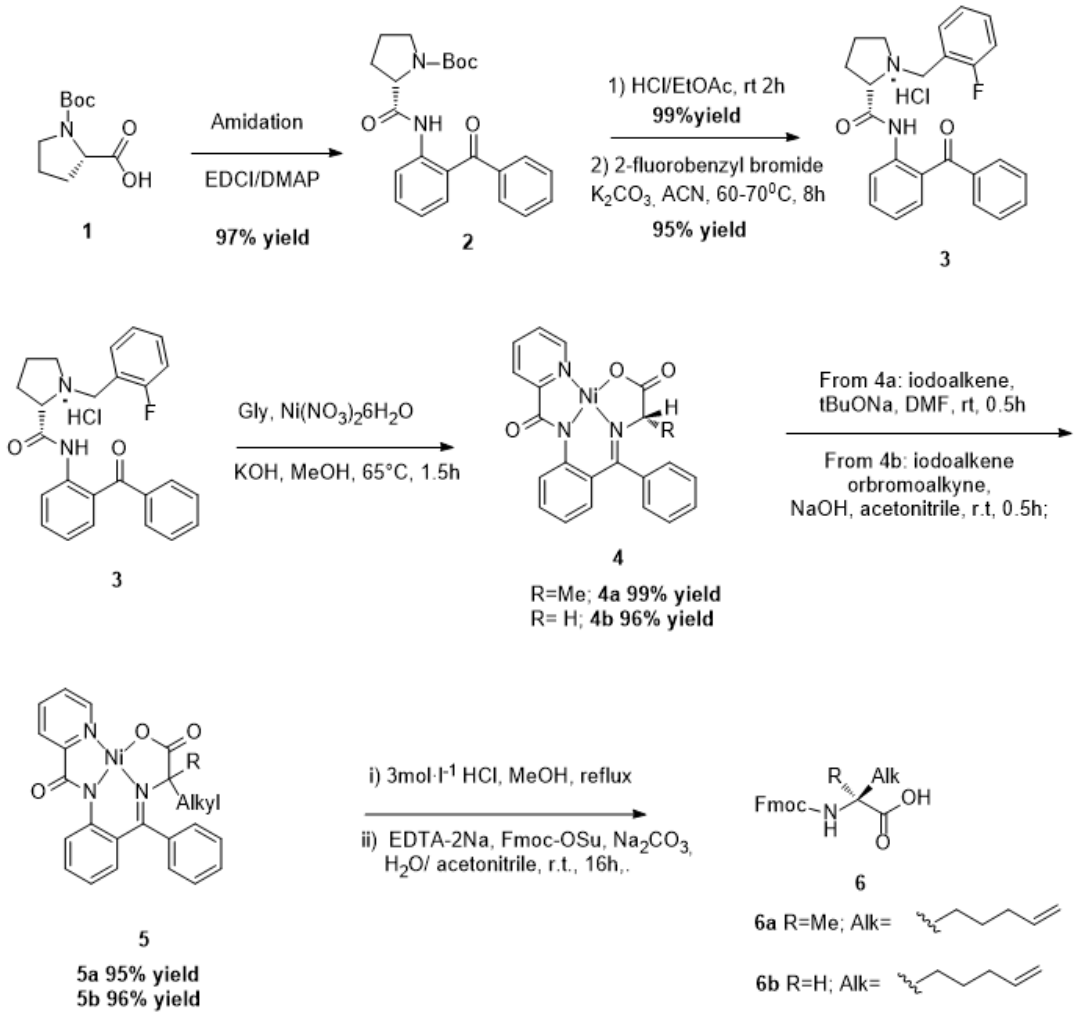
Since AADHs are NAD(P)H dependent, the cofactor also needs to be recycled during the process but, there are plenty of synthetic routes described in literature using these enzymes to products UAAs and efficient ways of cofactor recycling have also been developed to improve the performance of these reactions.[2] In contrast, Transaminases (TAs) are ubiquitous types of enzymes, which are naturally involved in nitrogen metabolism, can aminate a wide range of substrates included aldehydes and ketones.

These enzymes are also cofactor dependent, but external recycling process is not needed, due to the presence of PLP (pyridoxal-5-phospate) an amino group intermediate that is recycled during the process.

Unnatural L-amino acids such us L-*tert*-leucine, a precursor of protease inhibitors, were obtained using this strategy. L-homoalanine, or 2-aminobutyric acid, which is a precursor of the antiepileptic drug *Levetiracetam*, and the antituberculosis drug *ethambutol*, can be obtained using bacterial catalysts easily obtained with metabolic engineering techniques.[4,5]

Regarding the chemical synthesis of UUAs, alkylation of glycine, catalytic asymmetric amination and derivatization of natural amino acids are the most common synthetic strategies.[6,7,8] It is worth noting that the use of toxic reagents such us methylsulfonyl chloride, necessary for having high chemical yields and the moderate enantioselectivities observed with its use, can cause problems for the alkylation strategy. Nevertheless, one study showed the combination of proline **1** and ECDI/DMAP to form a chiral intermediate **3** followed by alkylation with sodium *tert*-butoxide lead to the formation of the corresponding amino acids **6** with 60-70% yield range and >99% ee (Scheme 4).[9]

The catalytic asymmetric amination which directly leads to the formation of C-N bonds is a very simple route to derivatize α-amino acids however, it normally requires the use of lower temperatures to get high enantioselectivities.[7] Lastly, the derivatization of typical natural amino acids such us serine, threonine or tyrosine can originate several UAAs but, it has only been possible to synthetize a limited number of UAAs with it.[2]



Scheme 4: Synthesis of unnatural amino acids employing ECDI/DMAP followed by alkylation with tBuONa

These count with a clear advantage to form three-dimensional compounds capable of stereospecific catalysis due to their potential chiral center (carbon alpha) between the planar peptide bonds. In particular, unnatural α,α-disubstituted α-amino acids have been of great interest for the pharmaceutical industry in recent years.[10] This is due to several special properties such as significant helix-inducing potential when present in peptides.

Many important proteins involved in pathways that cause or lead to human diseases are found to use this peptide α-helix configuration when engaging in plenty of biochemical events at an intermolecular level. This ability is responsible for the use of unnatural α,α-disubstituted α-amino acids to destabilize and damage lipid membranes which grants them with antibiotic activity in compounds such as peptaboils. [11]

In addition, the possibility of adopting a peptide α-helix configuration also allows for multiple research pathways when using these compounds to mimic and study functional domains of similar families of proteins involved in disease, in order to understand better the pathology and changes that occur in these proteins and discover new ways and drugs to treat a wide range of diseases.[11,12]

Furthermore, another advantage of peptides that contain α,α-disubstituted α-amino acids is that they often show enhanced resistance to enzymatic degradation.[12,13]

Besides this, some α,α-disubstituted α-amino acids also have the potential to act as enzyme inhibitors, which is a very important property of these compounds with significant implications not only in medicine but, also in agriculture.[14] It should also be noted that most pharmaceutically active compounds and natural compounds contain this type of building blocks (Figure 4).[15,16]

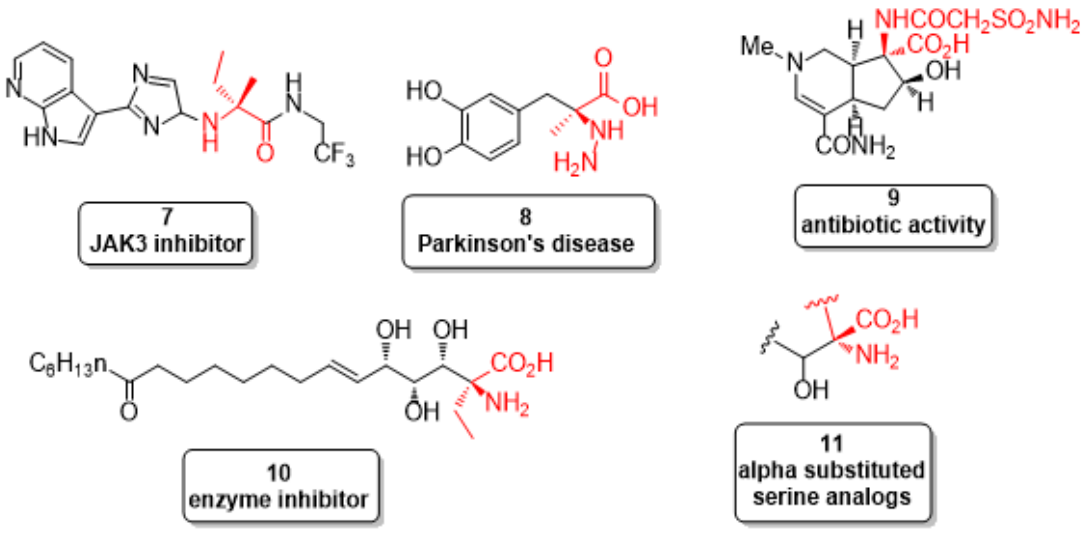


Figure 4: α,α-disubstituted-α-amino acids containing drugs and natural compounds

All of the special properties mentioned make α,α-disubstituted α-amino acids highly desirable in biochemical, genetic, plant health research and drug discovery[13, 14, 15] and so, extensive research into the discovery of new and more efficient synthetic routes has been carried out over the past two decades.[17] However; obtaining fully substituted stereocenters in α,α-disubstituted α-amino acids still proves challenging to this date so, it is important to keep researching new ways of achieving this goal.

Investigating and discovering unprecedented stereoselective reactions of nitroesters, precursors of α,α-disubstituted α-amino acids, promoted by different organocatalysts is the main objective of this thesis which I will further explain in the next chapter. Before this, I will proceed to review the most relevant modern synthetic approaches for the synthesis of α,α-disubstituted α-amino acids.

5.2 Methodologies for the synthesis of α,α-disubstituted amino acids

α,α-disubstituted-α-amino acids are structurally very important due to the presence of an additional substituent in the α-position of the amino acid that limits the free rotation of its side chain or fixes the conformation by forming heterocyclic compounds. [15]

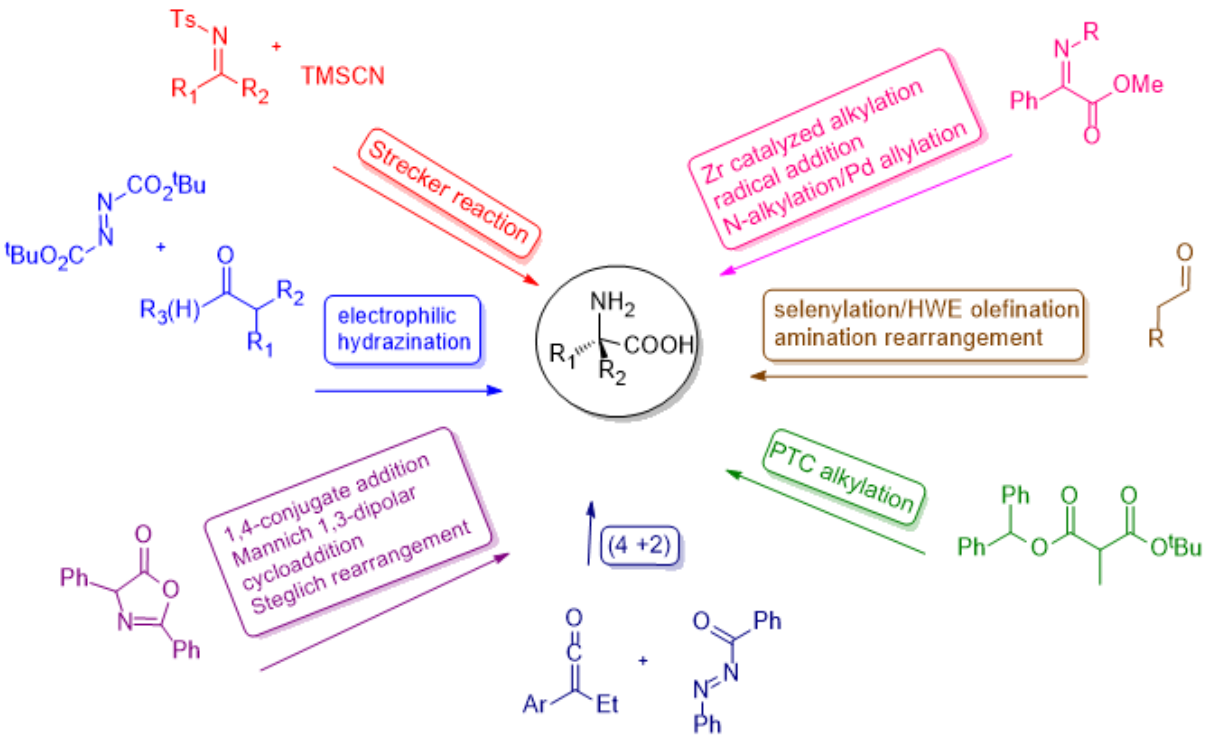


Figure 5: Approaches for the synthesis of α,α-disubstituted amino acids

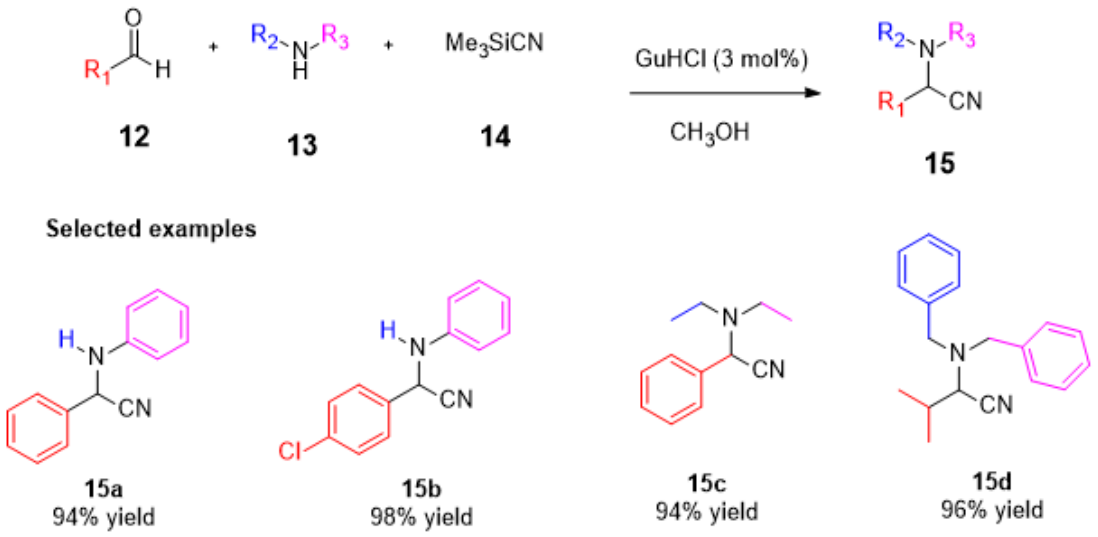
The synthesis of complex peptide biomolecules using enantiomerically pure α,α-disubstituted-α-amino acids is still a big challenge for the scientific community. Up to date, the most common methodologies used for the synthesis of these compounds involve allylations, alkylation of Shift bases, conjugate additions, rearrangements, and ring openings.[18]

The asymmetric Strecker reaction[19] has also demonstrated to be useful for the introduction of the chiral center. Overall, different approaches for the synthesis of these compounds have been reported (Figure 5).[15]

5.2.1 Strecker synthesis

This synthetic approach consists of generating amino acids from aldehydes and ketones (via imines). This procedure enables to synthetize a wide range of amino acids by changing the group *"R"* of the imine. The multicomponent reaction between an aldehyde, an amine and an alkaline metal cyanide or hydrogen cyanide followed by the hydrolysis of the resulting alpha aminonitrile is the most common reaction used for the synthesis of α,α-disubstituted-α-amino acids using this method.[19]

A great number of cyaniding agents have been successfully used, but this reaction has two clear synthetic downsides: it normally requires the use of very expensive reagents, and it involves a tedious work-up that generate considerable amounts of toxic waste, making it costly and harmful for the environment.

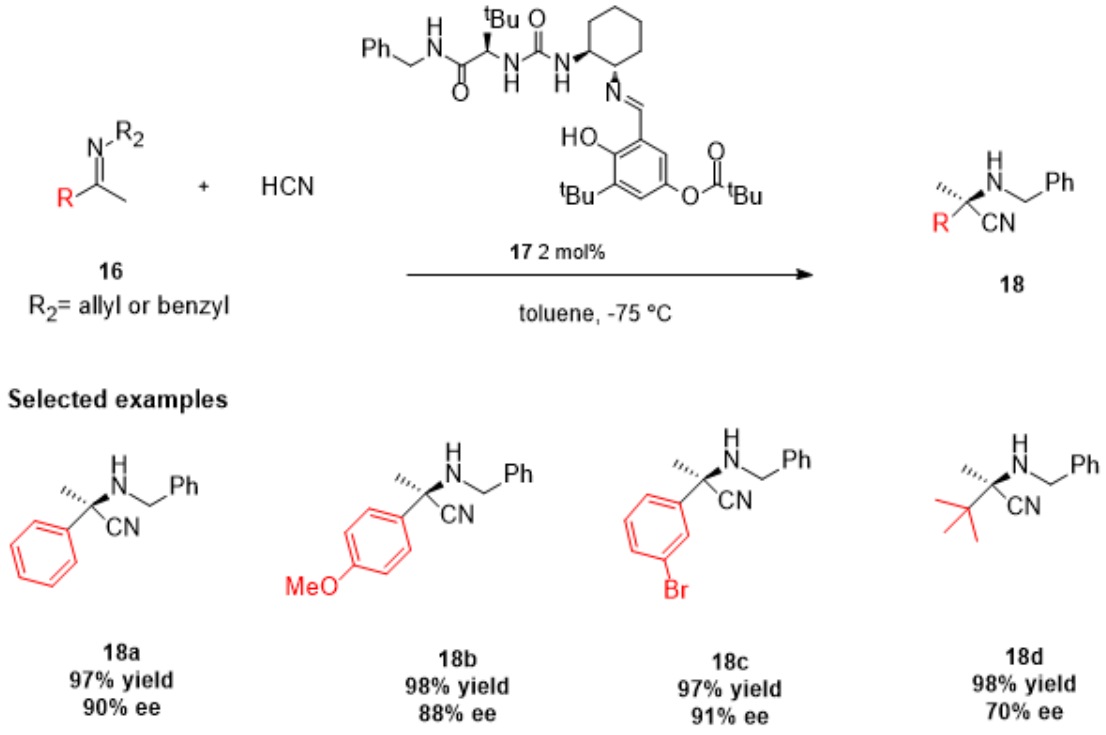


Scheme 5: Guanidine hydrochloride as efficient catalyst for Strecker reaction

Heydari and co-workers[20] have reported the use of guanidine hydrochloride (GuHCl), a commercially available, stable, and white solid, as an effective and water-soluble catalyst

for the Strecker synthesis of α-amino nitriles **15** (Scheme 5) which are used as precursors in the synthesis of natural and unnatural α-amino acids.

This environmentally friendly and inexpensive catalyst was able to promote the multi-component reaction with only 3% loading obtaining the best results when non-enolizable aldehydes **12** were used but using aliphatic, heterocyclic, and conjugated aldehydes also worked efficiently. Primary and secondary amines **13** act as very good activators, and no formation of non-desired products was observed. In addition, purification in some cases was not necessary. In 2000, Jacobsen and Vachal **21** reported the first enantioselective synthesis of α-disubstituted amino acids **18** and their derivatives using N-protected ketoimines **16** and recyclable Shift bases **17** as catalysts (Scheme 6). Thiourea based catalysts were also tried but were found less reactive than urea catalyst **17.**

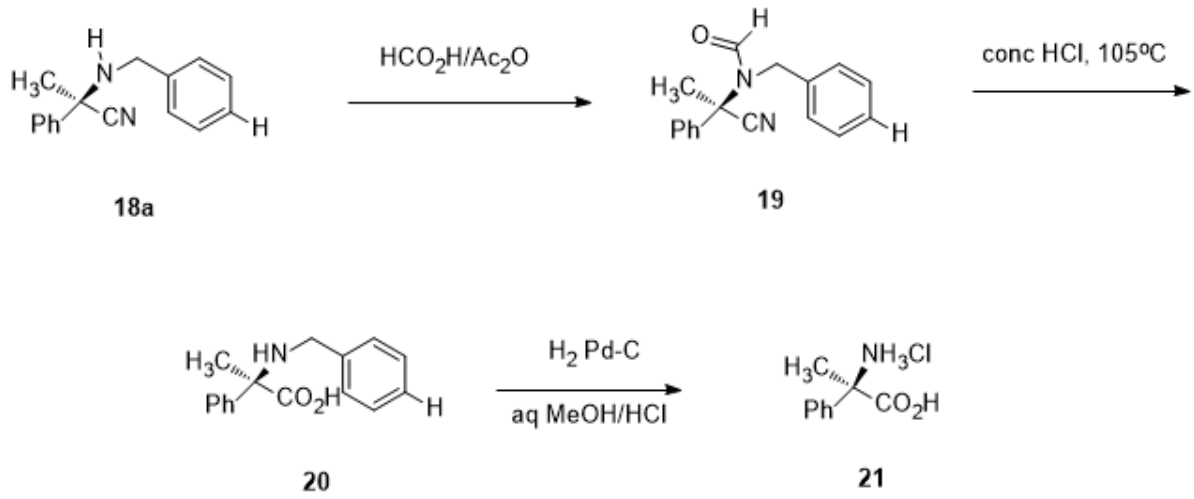


Scheme 6: Enantioselective catalytic addition of HCN to ketoimines. Catalytic synthesis of quaternary amino acids

The reaction was initially tested with N-allyl protected ketoimines **16**, yielding the corresponding Strecker adducts with excellent yields and enantioselectivities demonstrating to be stable under neutral conditions, however, a competitive retro-Strecker reaction might occur when acidic or basic conditions are applied. In order to avoid this, N-benzyl ketoimines **16** were used and a notable improvement of stability for the Strecker adducts was

observed. Nevertheless, the hydrolyzation of the nitrile group under acidic or basic conditions was a difficult challenge.

Thus, compound **18a** was transformed into their formic analogue **19** by reaction with formic anhydride under solvent free conditions. The N-benzyl protection group was successfully eliminated by selective debenzylation confirming that the generated stereocenter was stable under strong acid conditions and the corresponding quaternary amino acid **21** was obtained in quantitative yield (Scheme 7).

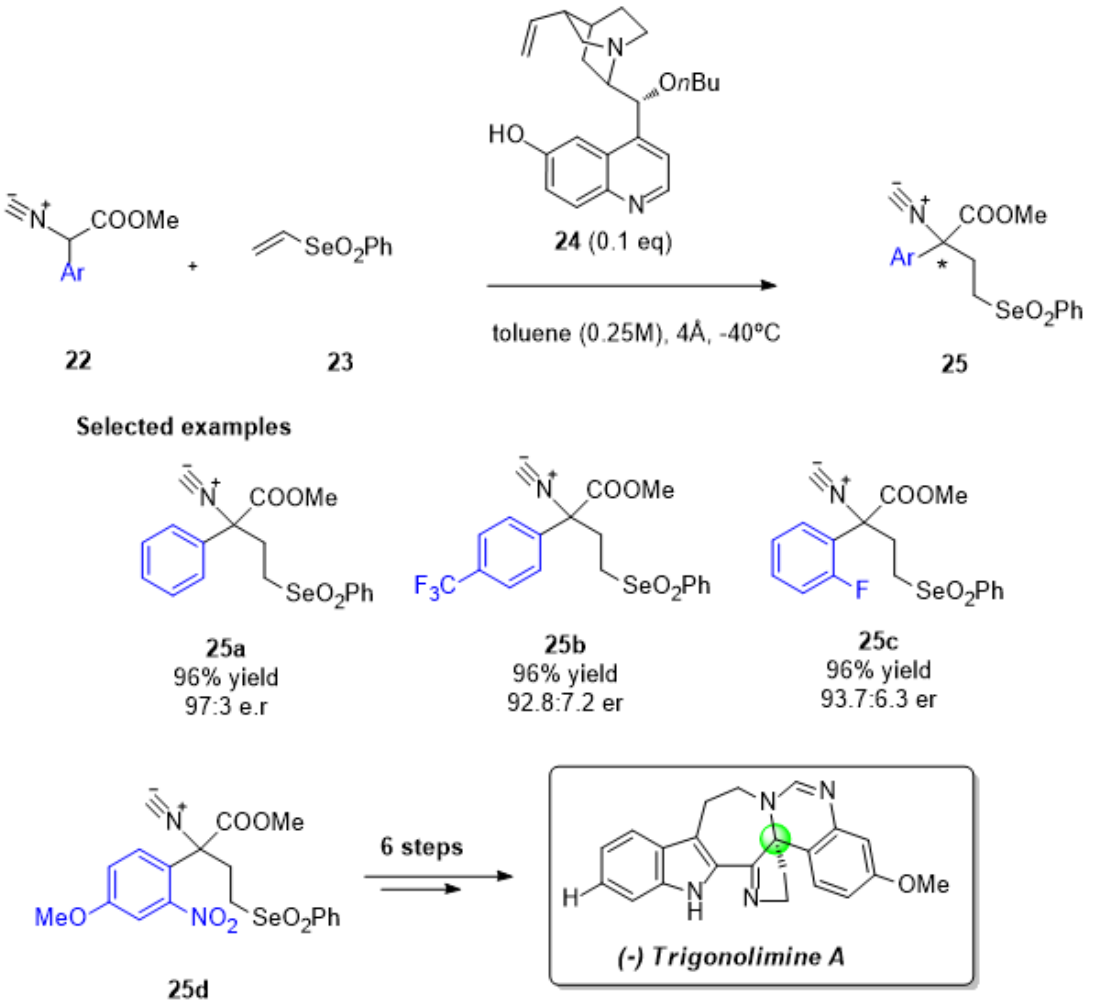


Scheme 7: Conversion of **18a** into α,α-disubstituted amino acid **21**

Furthermore, optimization of reaction conditions showed that when the temperature was increased up to +5°C degrees, the reaction time was also improved to only 8 min and the final product was obtained with moderate yield and ee. The replacement of the phenyl group of the amide group of the catalyst **17** by a resin bound, involved less reactivity, but it was easier to remove by filtration and this avoided a negative impact on the enantioselectivity. This synthetic strategy was demonstrated to be effective and lead to the formation of a broad range of enantiopure α-quaternary amine derivatives.

5.2.2 Asymmetric synthesis of α,α-disubstituted-α-amino acids

There are limited examples of organocatalyzed approaches for the synthesis of enantiomerically pure α,α-disubstituted-α-amino acids in the scientific literature.

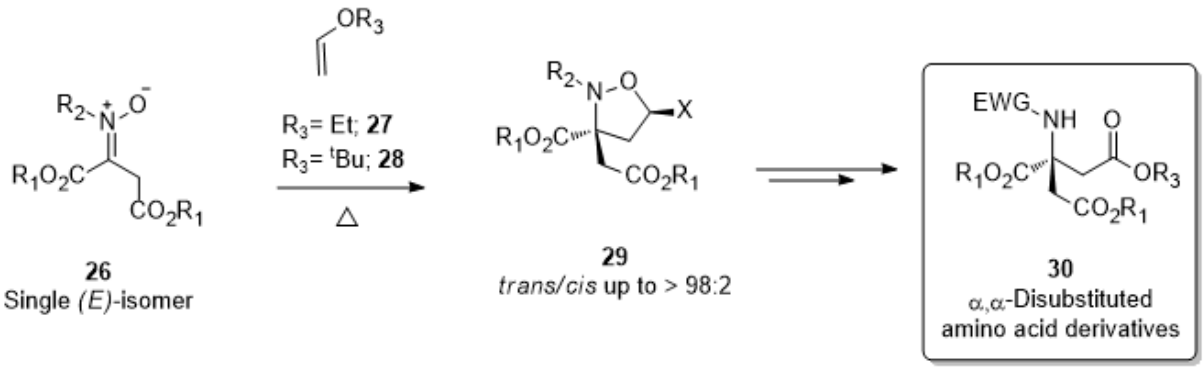


Scheme 8: Enantioselective Michael addition of α-aryl-α-isocyanoacetate to vinyl phenylselenone

Buyck, et al,[22] reported an catalytic enantioselective Michael addition of α-aryl-α-isocyanates **22** to vinyl selenone **23** for the synthesis of α,α-disubstituted-α-amino acids **25** and the natural product *Trigonolimine* A (Scheme 8). The reaction was tested using both electron-withdrawing and electron donating groups in the *ortho meta* and *para* position of the aromatic ring of **22** finding higher e.r in the electron donating groups sample. It was also reported that the Michael adducts **25** were obtained with excellent yields and enantioselectivities. However, this strategy used a selenium-based reagent which is highly toxic for

the human body and the environment and so, should be discarded and has no role in any attempt to develop new strategies that aim to be respectful with the environment, specially in medicinal chemistry.

Another chemical strategy worth mentioning is the 1,3-dipolar cycloaddition of ketonitrones **26** using several dipolarophiles **27**, **28** for the synthesis of isoxazolidines **29** which are precursors of α,α-disubstituted-α-amino acids **30**. Py and their co-workers,[23] have developed an asymmetric synthesis of α,α-disubstituted amino acids by cycloaddition of *(E)*-ketonitrones **26** with vinyl ethers **27**, **28** (Scheme 9).

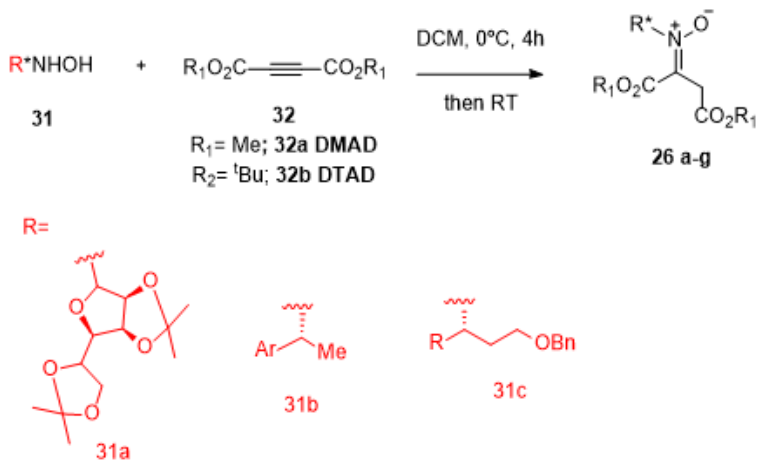


Scheme 9: Synthesis of α,α-disubstituted-α-amino acids by 1,3-cycloaddition of ketonitrones

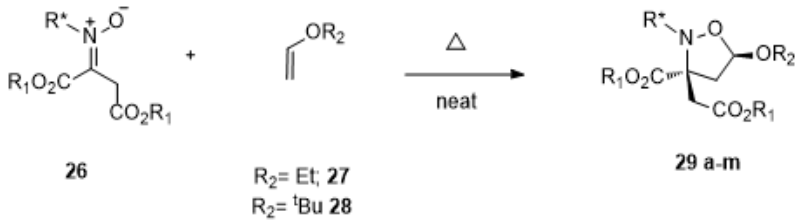
Furthermore, Chiral nitrones **26** are also useful α,α-disubstituted amino acid precursors (Scheme 10). They were synthesized by reaction of dialkyl acetylene dicarboxylates **32** with chiral N-hydroxylamines **31** (Scheme 10a) and obtained as crystalline solids with *E*-configuration confirmed by X-ray analysis. Then, the 1,3-cycloaddition reaction of nitrones **26a-g** with vinyl ethers **27** and **28** was investigated (Scheme 10b).

Compounds **29a-m** were obtained with *trans* configuration as majors as well as excellent stereoselectivities and regiocontrol. Nitrones containing a valinol-derived chiral auxiliary were found less reactive, and large reaction times (7 days) together with high temperatures were needed to get a full conversion. However, the use of Vasella's chiral auxiliary **31a** provided the best results and the reaction time was successfully decreased by employing MW conditions without losing stereoselectivity. Synthetizing isoxazolidines **29**, furnished access to enantiopure tetrafunctional disubstituted amino acid derivatives and were also transformed into beta peptides **38** by regioselective transformations of the isolated α,α-disubstituted amino acids **29** (Scheme 11).[10]

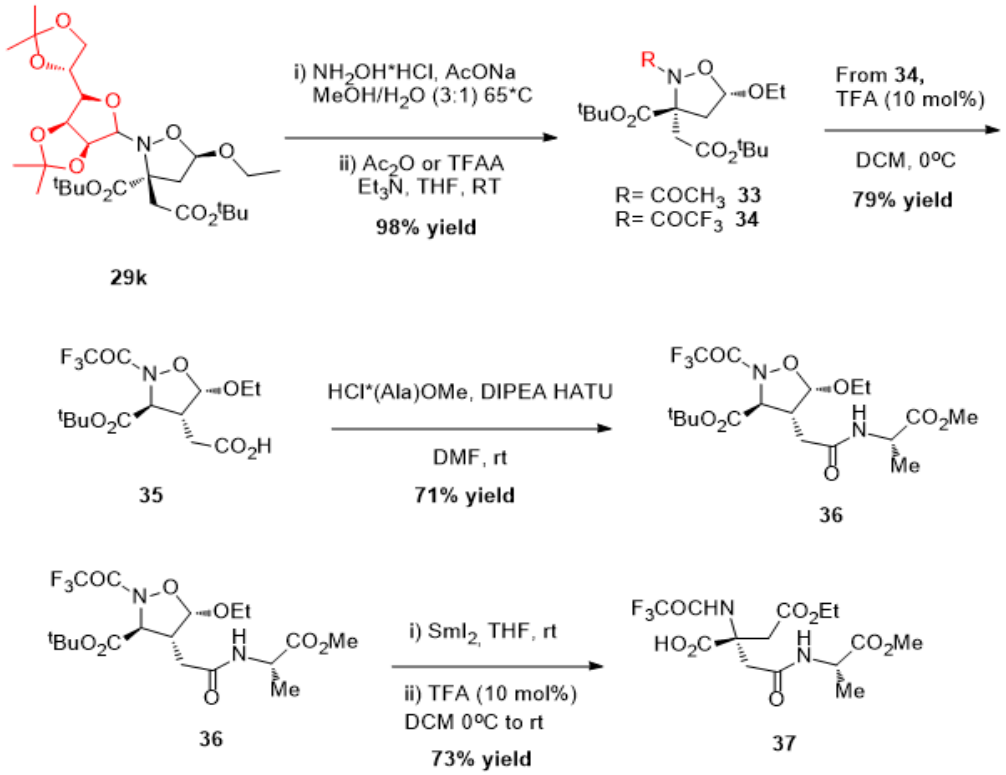
Scheme 10a: Synthesis of chiral Nitrones 26 a-g



Scheme 10b: Diastereoselective Cycloadition of Nitrones 26 with Vinyl Ethers 27 and 28



Scheme 10: Synthesis of chiral nitrones **26** and their reaction of cycloaddition with vinyl ethers and **29**

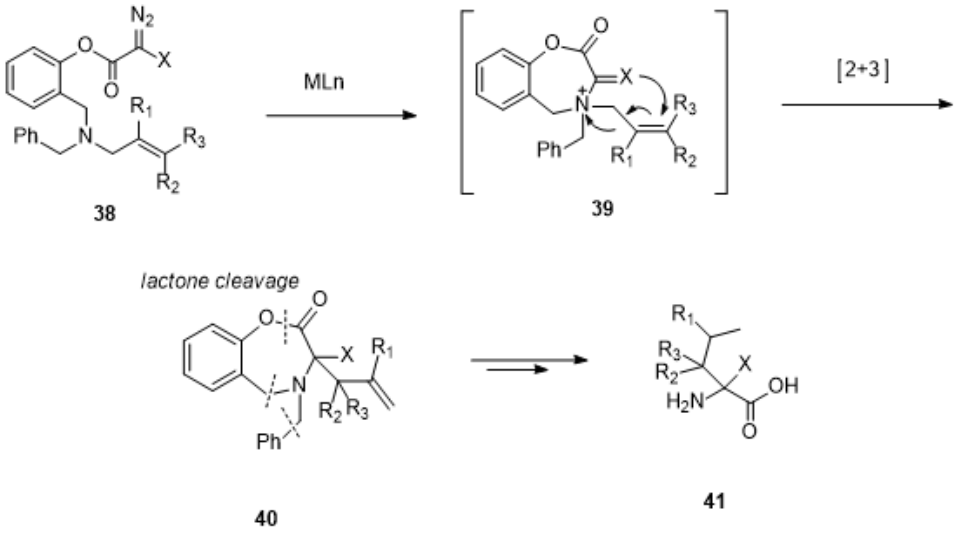


Scheme 11: Transformation of ketonitrone **29k** into beta peptide **37**

Starting from ketonitrone **29k**, the valinol chiral auxiliary was removed yielding the enantiopure isoxazolidine as an intermediate, which was then treated with N-acetyl or N-trifluoromethyl reagents to get the corresponding N-acetylation or N-trifluoromethylation compounds **33** and **34** in 98% yield. Following this, compound **34** was easily converted into compound **35** by regioselective cleavage of the *tert* butyl ester moiety. Peptide coupling between **35** and alanine methyl ester followed by SmI2 reduction and acidic cleavage, lead to the formation of dipeptide **37** with 73% yield.

5.2.3 Rearrangements

Synthetic approaches based on rearrangements or [2,3] sigmatropic rearrangements are also suitable routes for the synthesis of α,α-disubstituted-α-amino acids. Using this economic strategy, high levels of stereocontrol and stereospecificity have been shown due to the reaction proceeding through well-defined transition states. The sigmatropic [3,2] rearrangement[24] or [1,2] Steven's rearrangement[25] are commonly used for the synthesis of heterocycles containing nitrogen atoms. Nevertheless, the synthetized amino acids, were not susceptible for the union of additional amino acids.[26]



Scheme 12: Novel α-substituted and α,α-disubstituted amino acid synthesis by rearrangement of ammonium ylides **39** generated from metal carbenoid

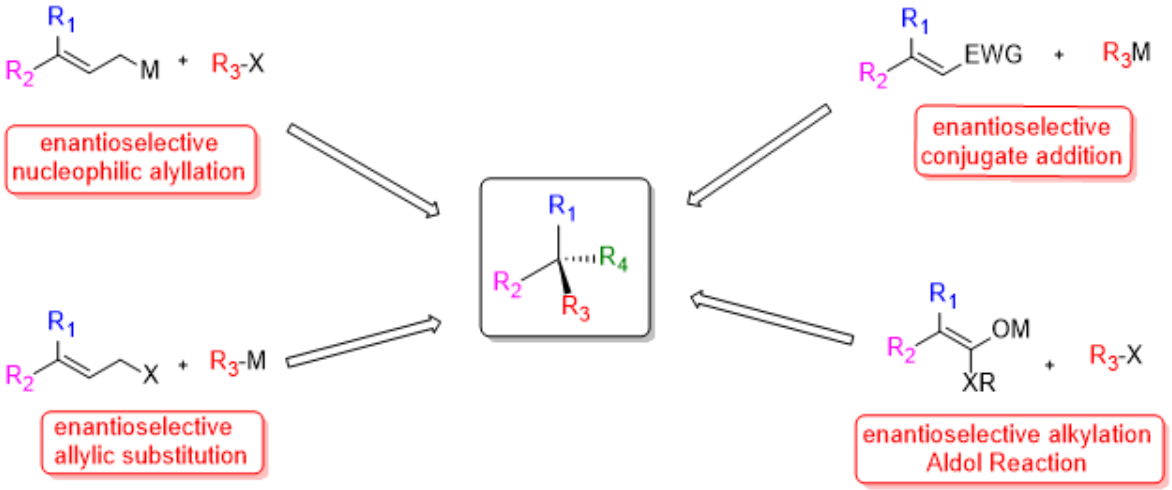
Clark and Middleton[26], developed a few years ago a novel α-substituted and α,α-disubstituted amino acid synthesis by rearrangement of ammonium ylides **39** generated from me-

tal carbenoids (Scheme 12). This synthetic route involves the formation of the ammonium ylide by reaction of metal carbenoid and an allylic amine **38** followed by the rearrangement which produces an azalactone **40**.

Importantly, it is possible to obtain a variety of amino acids **41** bearing unusual groups at the α-position using this strategy. In addition, β-substitution was also possible when an allylic substituted amine was used, making this approach very versatile.

5.3 Enantioselective construction of quaternary stereocenters

The synthesis of compounds bearing a quaternary stereocenter is another synthetic challenge. Although different improvements on this field have been recently done, the development of new synthetic methodologies is highly desirable. The utilized routes used for the synthesis of acyclic compounds bearing a quaternary stereocenter are summarized in Scheme 13. [27]

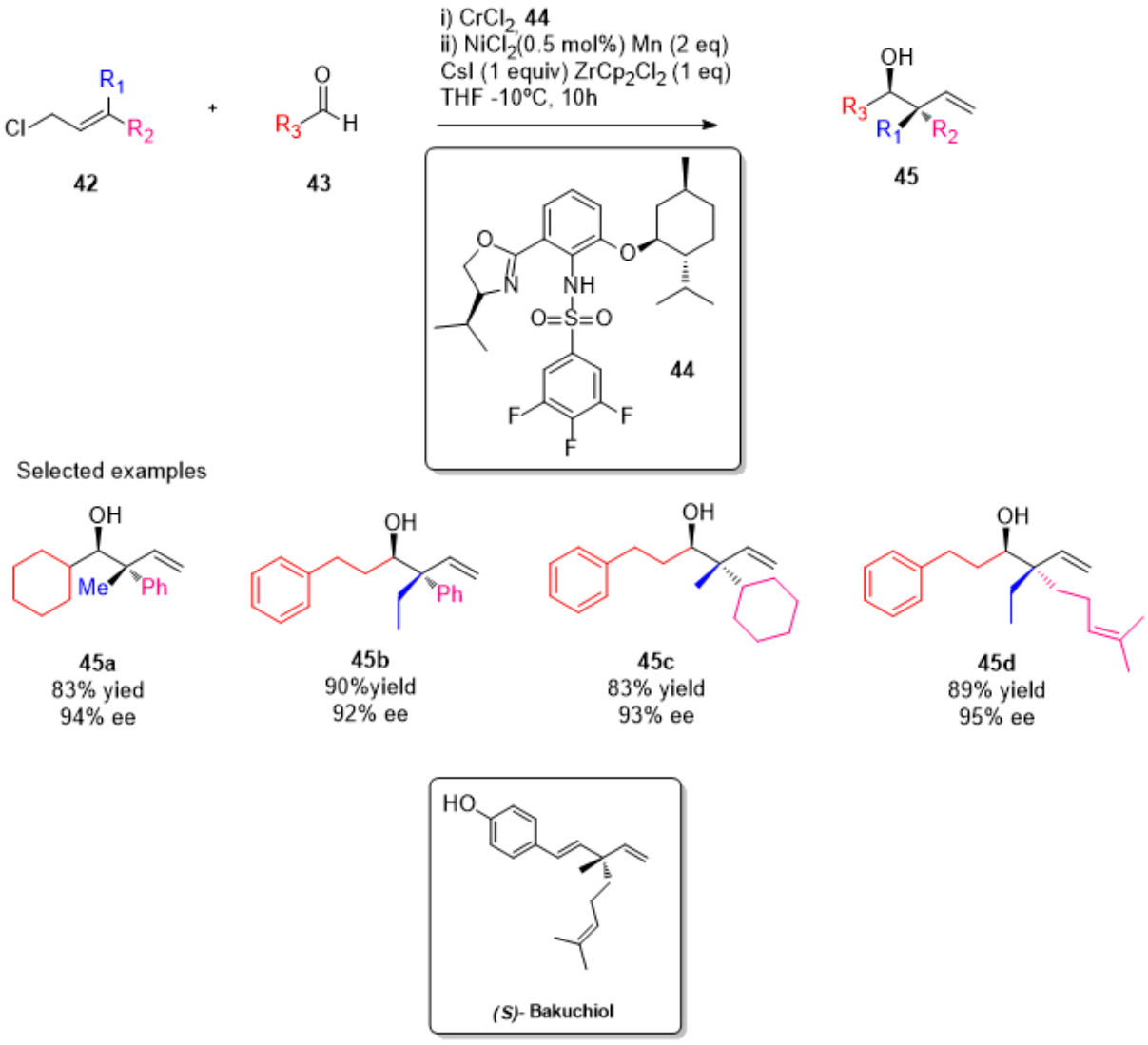


Scheme 13: Synthetic approaches for the synthesis of acyclic compounds bearing quaternary stereocenters

The enantioselective allylic substitution is an important reaction for the synthesis of optically active molecules which have decisive applications like drug scaffolds in the synthesis of pharmaceutical compounds and act as intermediates in the synthesis of natural compounds.[28]

Zhang and Xiong[29] have reported an enantioselective synthesis of quaternary stereocenter by asymmetric allylation of aldehydes **43** with γ-disubstituted allyl halides **42** catalyzed by a sulfonamide/oxazoline chromium complex **44** (Scheme 14).

The reaction worked well employing different types of aldehydes **43**. Moreover, when bulky substituents were used in the allylic chloride **42**, very good yields and more than 90% ee was observed. The substitution on the aromatic ring of the aldehyde was also tried providing the corresponding products with a 90-95 range of ee. Other substrates like geranyl bromide were successfully employed leading to the formation of compound **45d** with excellent yield and enantioselectivity.



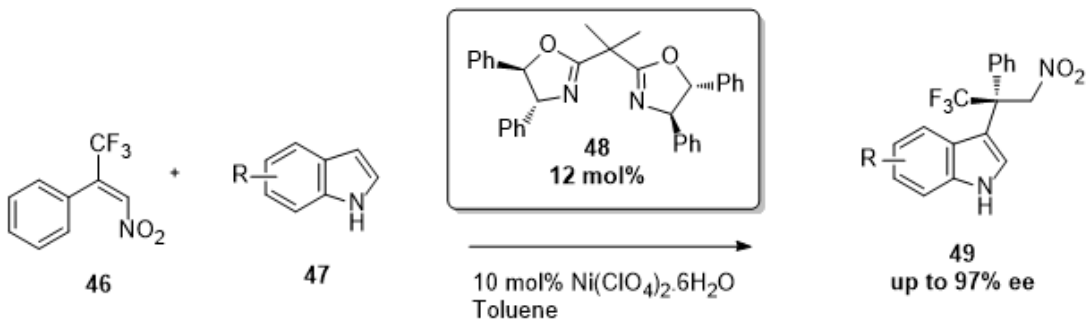
Scheme 14: Asymmetric allylation of aldehydes with γ-disubstituted allyl halides

Further derivatization of these compounds gives access to pharmaceutical intermediates such us (S)- bakuchiol, a monoterpene phenol with anti-bacterial and anticancer properties.[30, 31] A broad substrate scope, mild reaction conditions, high diastereoselectivity and enantioselectivity makes this approach very interesting for its application in the synthesis of complex molecules and pharmaceutical potent inhibitors.

The construction of molecules bearing a CF_3 moiety also represents an important challenge due to the capability of this functional group to modify the activity of pharmaceutically active compounds. To date, different approaches for the synthesis of these compounds have been focused on the use of trifluoromethylation agents (nucleophilic, radical and electrophilic) in the direct asymmetric trifluoromethylation reaction or the enantioselective transformation of prochiral trifluoromethylated substrates.[29]

Friedel-Crafts alkylation employing electron poor olefins is one of the most utilized methods in the creation of chiral benzylic stereocenters, even if these compounds are poorly reactive which limits the reactivity. However, monosubstituted nitroalkenes were found to be suitable substrates for the alkylation of indoles although their potential in this reaction has not been extensively studied yet.

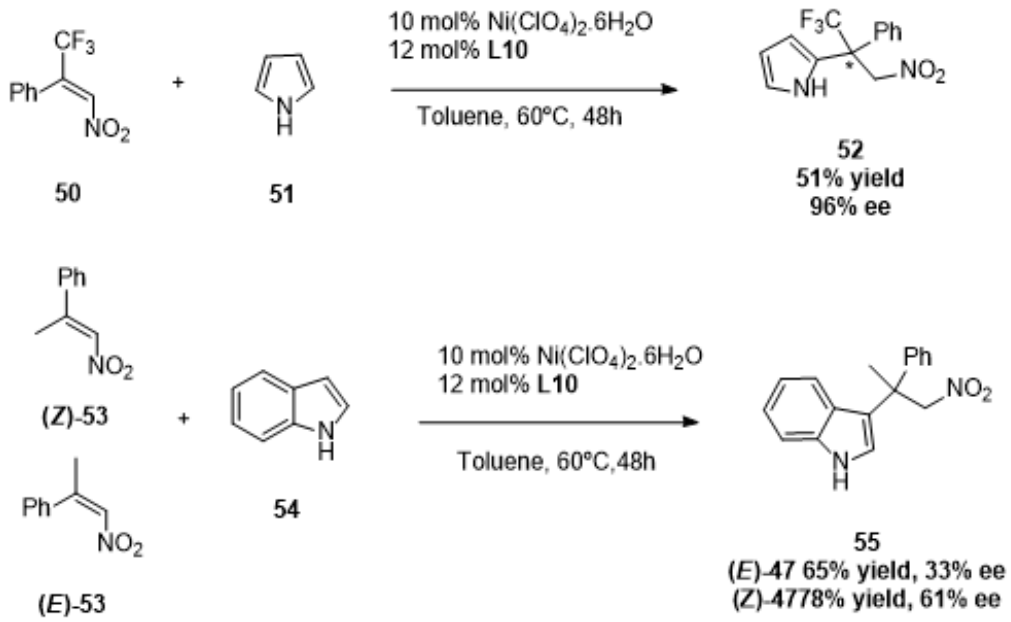
Jia and their co-workers[32] have reported the use of β,β-disubstituted nitroalkenes **46** as effective alkylation reagents for the enantioselective construction of trifluoromethylated all-carbon quaternary stereocenters **49** by Nickel catalyzed Friedel-Crafts alkylation (Scheme 15).



Scheme 15: Friedel-Crafts alkylation of indoles with β,β-disubstituted nitroalkenes

Bisoxazoline derived ligand **48** which contains additional phenyl groups in the oxazoline rings, was the best catalyst giving the highest values of enantioselectivity. The *para* and *meta* substitution of the nitroalkene derivative, was well-tolerated leading to the corresponding compounds with excellent enantioselectivities whereas when electron withdrawing groups were used in para position, the yield was decreased most likely due to the steric effect of the substrate. Heteroaromatic substitution of the aromatic also demonstrated to be effective, obtaining the compounds with excellent yields and enantioselectivities.

A wide range of indoles **49** containing both electron withdrawing and donating groups in C4-C7 positions were also tested providing the best results with 5-metoxi, 5-methyl, 7-methyl substitutions. The reaction with bromo derivative proceeds slowly at 60ºC obtaining the compound with low yield, but it was successfully improved when it was heated at 80ºC. Pyrrol was also used instead of indol, however the yield observed was significantly less than with indol (Scheme 16).

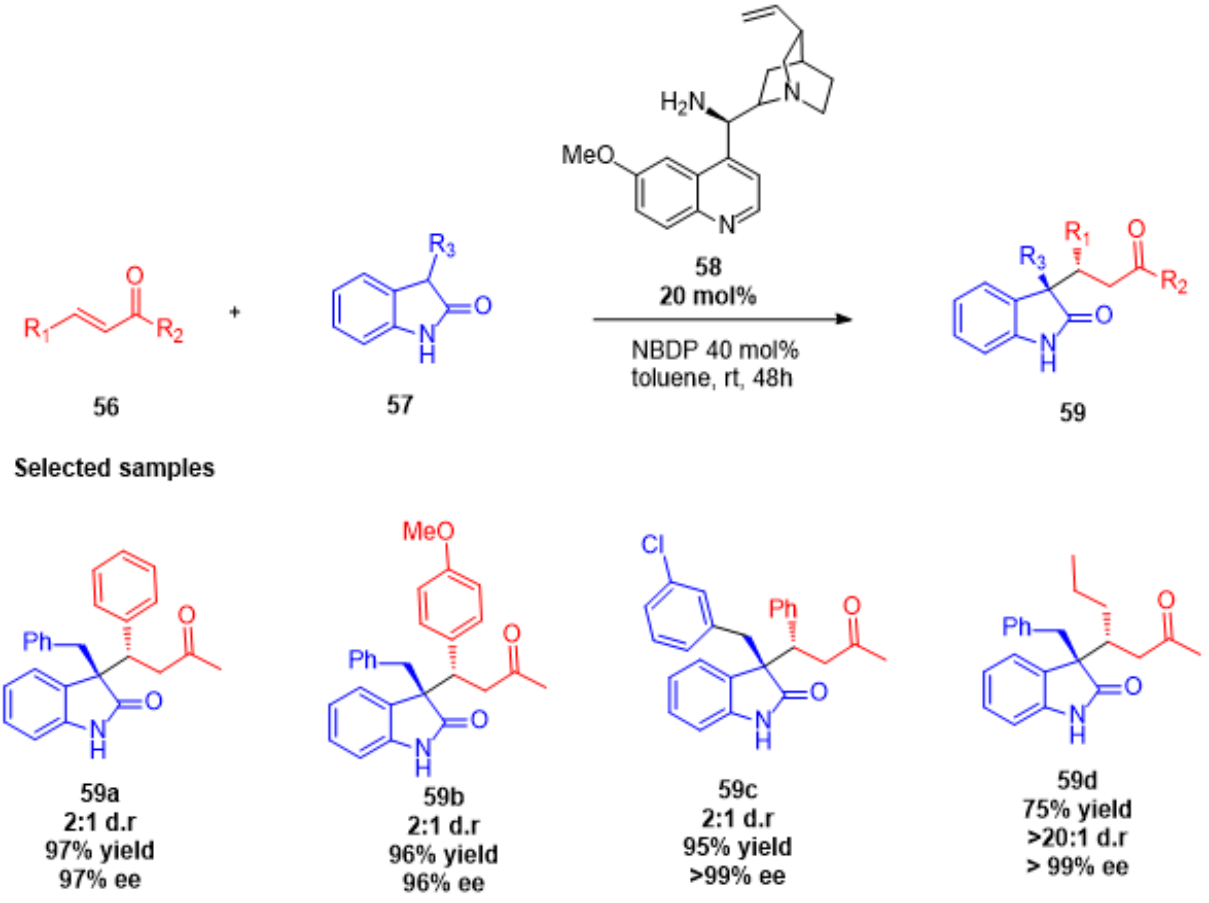


Scheme 16: Pyrrole vs Indole experiments

The synthesis of chiral trifluoromethyl benzyl compounds has been achieved by Friedel-Crafts alkylation of indoles using nitroalkenes as effective substrates for this transformation yielding the compounds with excellent yields and enantioselectivity. This is the first enantioselective example of this transformation.

Compounds containing the oxindol moiety are considered to have great potential as pharmaceutically active compounds as well as intermediates for the synthesis of natural compounds, and for that reason their synthesis has attracted more attention over the last few years.[33] The synthetic strategies applied until now involve chiral resolution or diastereoselective reactions using mostly chiral auxiliaries and stoichiometric amounts of starting materials.

Organocatlytic Michael addition using enals or nitroolefins has been also tested to afford enantioenriched 3,3-disubstituted oxindoles, however, the employment of enones as Michael acceptors, still remains unexplored most likely due to their inability to form stable intermediates with secondary amines.



Scheme 17: Enantioselective conjugate addition of oxindoles **57** to enones **56**

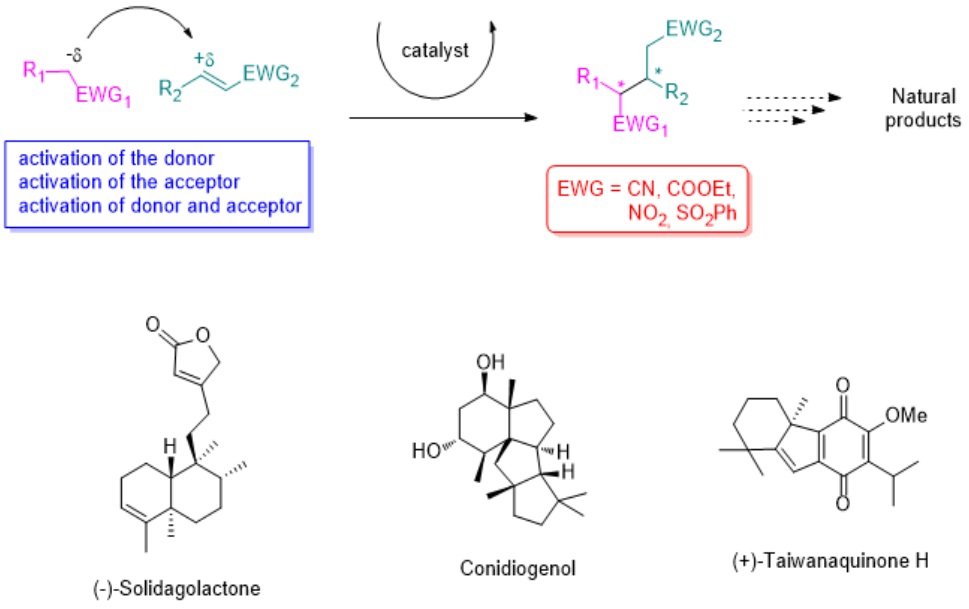
In 2010 Wang *et al*[34] reported an asymmetric construction of quaternary stereocenters by direct conjugate addition of oxindole **57** to enone **56** (Scheme 17) using a chiral cinchona based primary amine **58** to afford 3,3-disubstituted oxindoles **59** in good yields, moderate to high diastereoselectivities and excellent enantioselectivities were reported.

The conjugate addition of different substituted oxindoles **57** and enones **56** catalyzed by cinchona derived primary amine **58** leads to the formation of the corresponding compounds **59** in excellent yields and enantioselectivities. Aromatic substituents in the enone give less diastereoselectivity but high enantioselectivity compared to alkyl substituents which were found to be slightly less reactive, however, a considerable improvement of diastereoselectivity was observed.

The substitution in the oxindol moiety was also well-tolerated, yielding the corresponding compounds **59** with excellent enantioselectivity, however, when 3-phenyloxindol was tested, no enantioselectivity was observed. This synthetic procedure for the synthesis of chiral quaternary oxindoles derivatives which also play an important role like building blocks in the synthesis of pharmaceutically active compounds was demonstrated to be an effective protocol allowing the tolerance of a broad range of substrates.

5.4 Organocatalytic conjugated addition in stereoselective synthesis

The formation of C-C bonds in organic synthesis represents a very helpful tool to achieve successful synthesis of complex molecules. The most popular and widely used conjugate addition is the organocatalyzed Michael addition (Scheme 18), which counts with many synthetic advantages including the presence of functional groups easily derivatized, mild reaction conditions and easily scalable conditions.[35]



Scheme 18: Organocatalytic Michael addition reaction and their application in natural products synthesis

In this type of reaction, the nucleophile or electrophile is activated by the catalyst leading to the formation of the corresponding Michael adduct which contains at least two functional groups which can be transformed in further reactions for the synthesis of complex chemical compounds with biological functions as well as natural compounds catalyzed by metal complexes.[36]

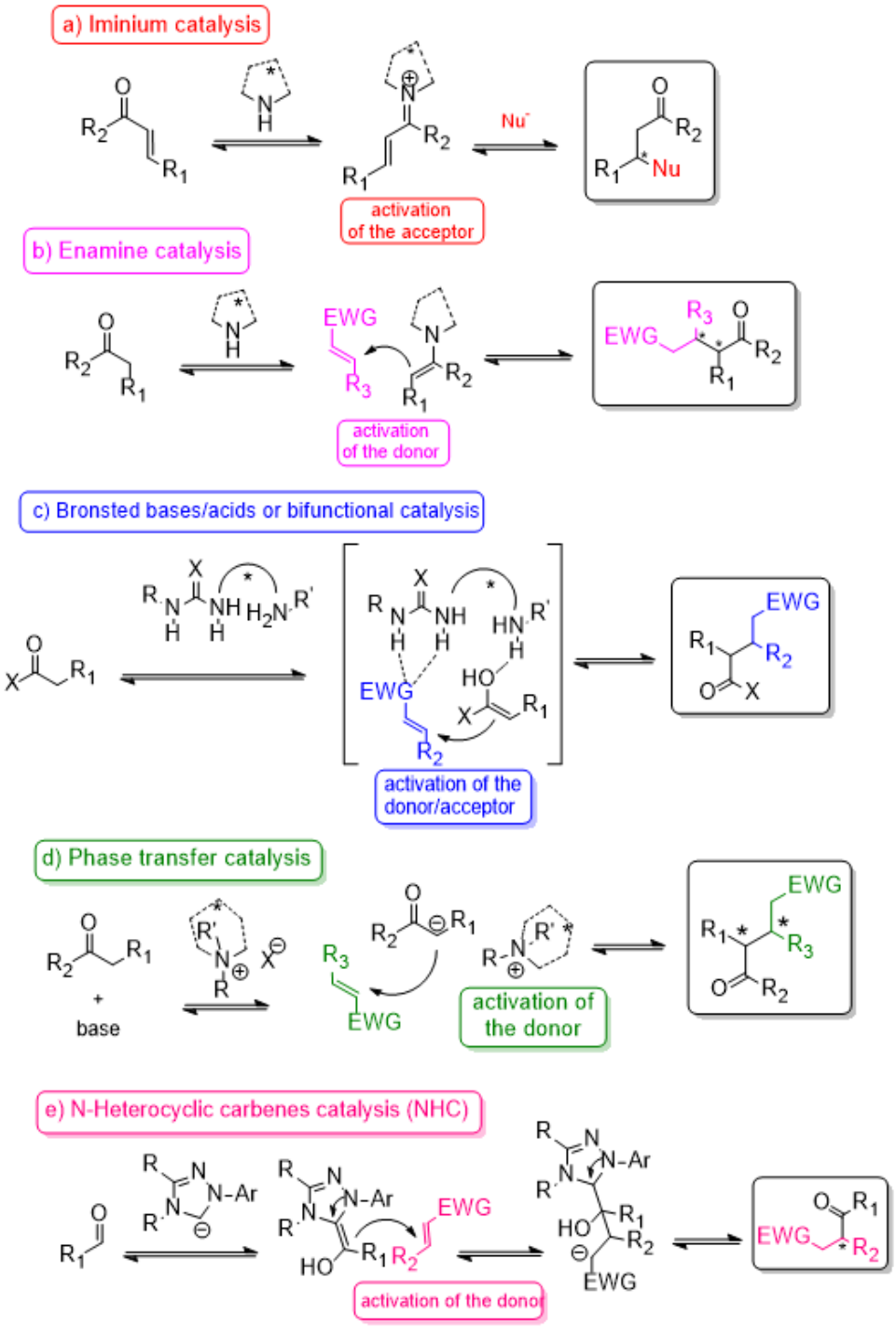
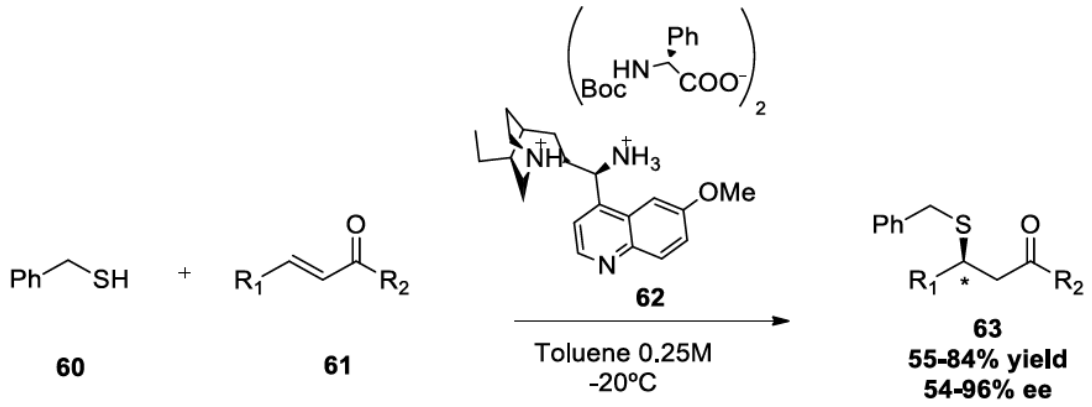


Figure 6: Organocatalytic Modes of action in Stereoselective reactions

Based on the type of interaction between the species, different reactions can occur and are represented in Figure 6.[35] There are plenty of variations of this reaction, in this section, examples of iminium and enamine catalysis as well as hydrogen-bond bronsted acid catalyzed Michael addition and phase transfer catalysis will be discussed.

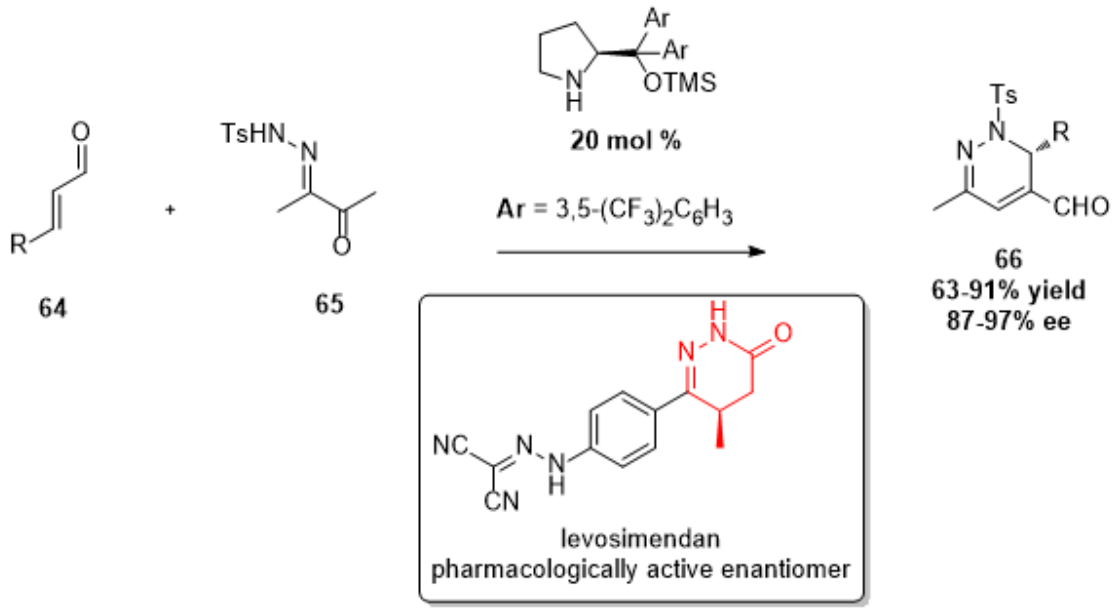
5.4.1 Iminium catalysis

The iminium catalysis (Figure 6a) involves the formation of the imine intermediate by reaction of a primary/secondary amine with an α,β-unsaturated carbonyl compound followed by the attack of a nucleophile which leads to the formation of the corresponding enantioenriched Michael adduct. In 2008, Melchiorre and co-workers[37] reported an organocatalyzed asymmetric sulfa-Michael addition to α,β-unsaturated ketones **61** using the catalytic salt **62** as an effective iminium activator for simple ketones (Scheme 19). The corresponding Michael adducts **63** were obtained sometime with excellent yields and enantioselectivities.



Scheme 19: Organocatalytic asymmetric sulfa-Michael addition to α,β-unsaturated ketones

In 2012, Vicario and co-workers[38] demonstrated the use of hydrazones **64** as effective nucleophiles for the organocatalytic enantioselective synthesis of 2,3-dihydropyridazines **65** (Scheme20) which are important building blocks for the synthesis of antibacterial, antihypertensive and antihistaminic agents.[39, 40, 41]



Scheme 20: Organocatalytic enantioselective synthesis of 2,3-dihydropyridazines

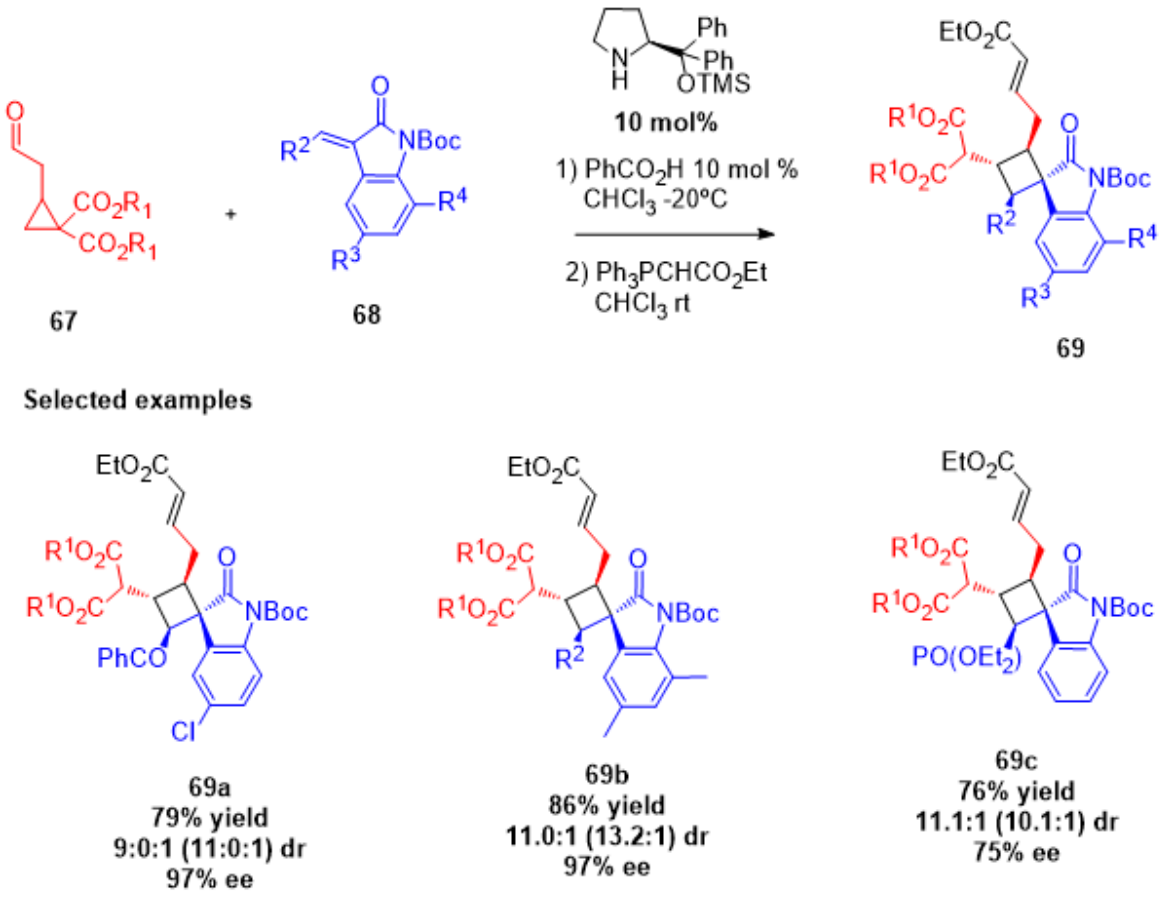
Chirality also plays an important role in the synthesis of pyridazines. An example of this is *levosimendan*, used for the treatment of chronic heart failure, in which only the *R*-enantiomer has pharmaceutical activity.

5.4.2 Enamine catalysis

Carbonyl compounds can be also activated by enamine catalysis (Figure 6b) through reaction of primary and secondary amines to form the corresponding enamine which is able to react with electrophiles or electrophilic radicals.[35] The employment of chiral amines as catalyst, represents an advantage for the enantiocontrol of the reaction. In addition, the α-carbonyl stereocenters will maintain their stereochemical configuration, due to the kinetical stability of the products formed.

Jørgensen and co-workers[42] have reported the organocatalytic enamine activation of cyclopropanes **59** for highly stereoselective formation of cyclobutanes **69** (Scheme 21). These compounds are normally activated by or employing N-heretocyclic carbenes as well as boronate urea catalysts mediating the activation of the acceptor or aminocatalyst. Therefore, the new methodology proposed by Jørgensen and co-workers[42] involved the formation of

the donor-acceptor cyclopropane by condensation of an aminocatalyst which meant the first LUMO-lowering mode of activation for this class of molecules. Indeed, the participation of these species in stereoselective cycloaddition reactions to synthetize cyclobutane structures makes this approach very attractive.

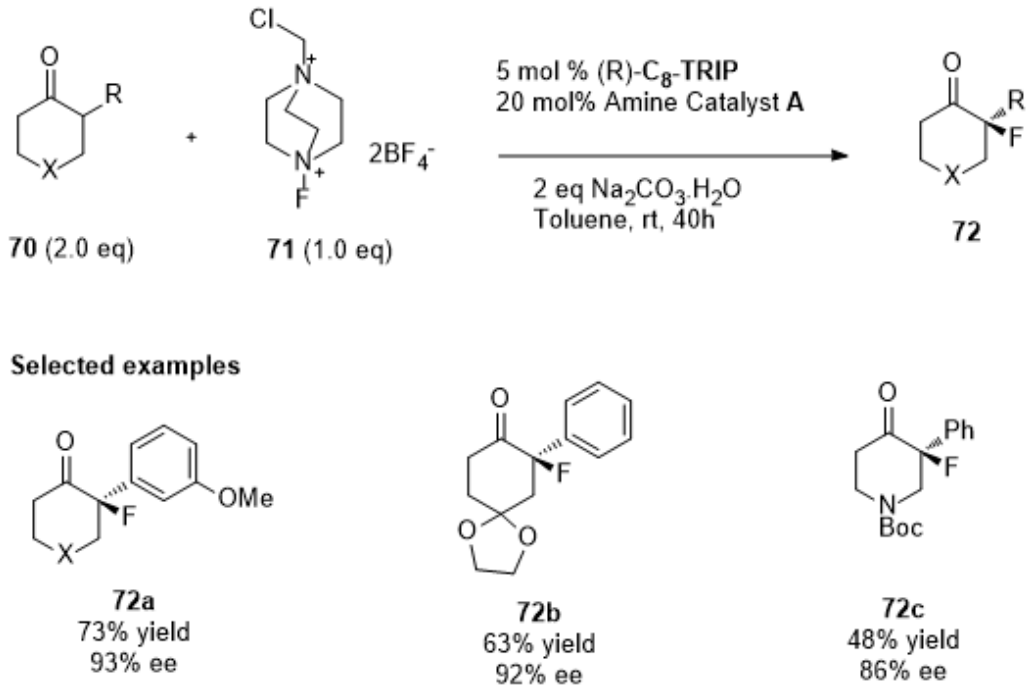


Scheme 21: Organocatalytic enamine-activation of cyclopropanes for highly stereoselective formation of cyclobutanes

Chiral cyclobutanes bearing a quaternary stereocenter are a privileged scaffold commonly found in bioactive natural products.[43] Their structural rigidity and well-defined arrangements of substituents makes them extremely appealing in drug discovery chemistry.[44] Furthermore, the possibility to perform ring-cleavage or ring-expansion reactions is a significant advantage too.

Another interesting approach in which enamine activation is involved in the generation of compounds bearing a quaternary stereocenter is the one reported by Toste et al in 2014 .[45] In their publication, they reported the asymmetric fluorination of α-branched cyclohexa-

nones **70** by dual activation of the chiral anion by phase transfer catalysis and, enamine catalyzed activation of the ketone employing protected amino acids (Scheme 22).



Scheme 22: Asymmetric fluorination of α-branched cyclohexanones

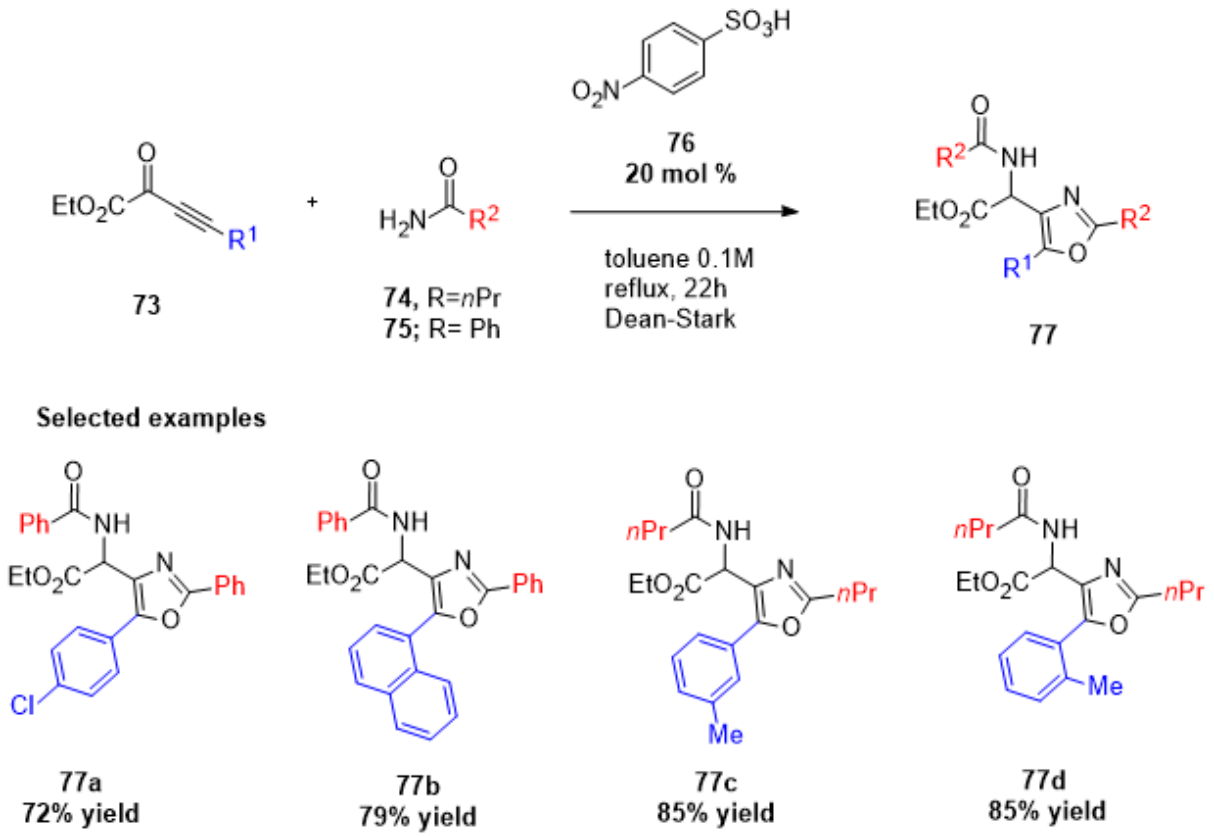
5.4.3 Brønsted bases/acids or bifunctional catalysis

Hydrogen bond activation is one of the most powerful and utilized methods in asymmetric catalysis due to the capability of thioureas or phosphoric acids, which are typical catalysts employed in this catalysis, to activate a wide range of electrophiles by asymmetric nucleophilic attack (Figure 6c).[35] Moreover, Brønsted bases such as tertiary amines for example, could also activate carbonyl compounds by deprotonation resulting in chiral ion pairs.

The α-amino acids containing oxazole rings, have been used in different drug molecules which show very high potency as oxytocin receptor antagonists (used in preterm labour) or non-peptide galanin receptor agonists (reduce exhibitory signals in the central and peripheral neurons).[46] However, current synthetic strategies for the synthesis of these com-

pounds involves multistep reactions in which is necessary to pre-introduce the amino acid functionality as well as the oxazole moiety.

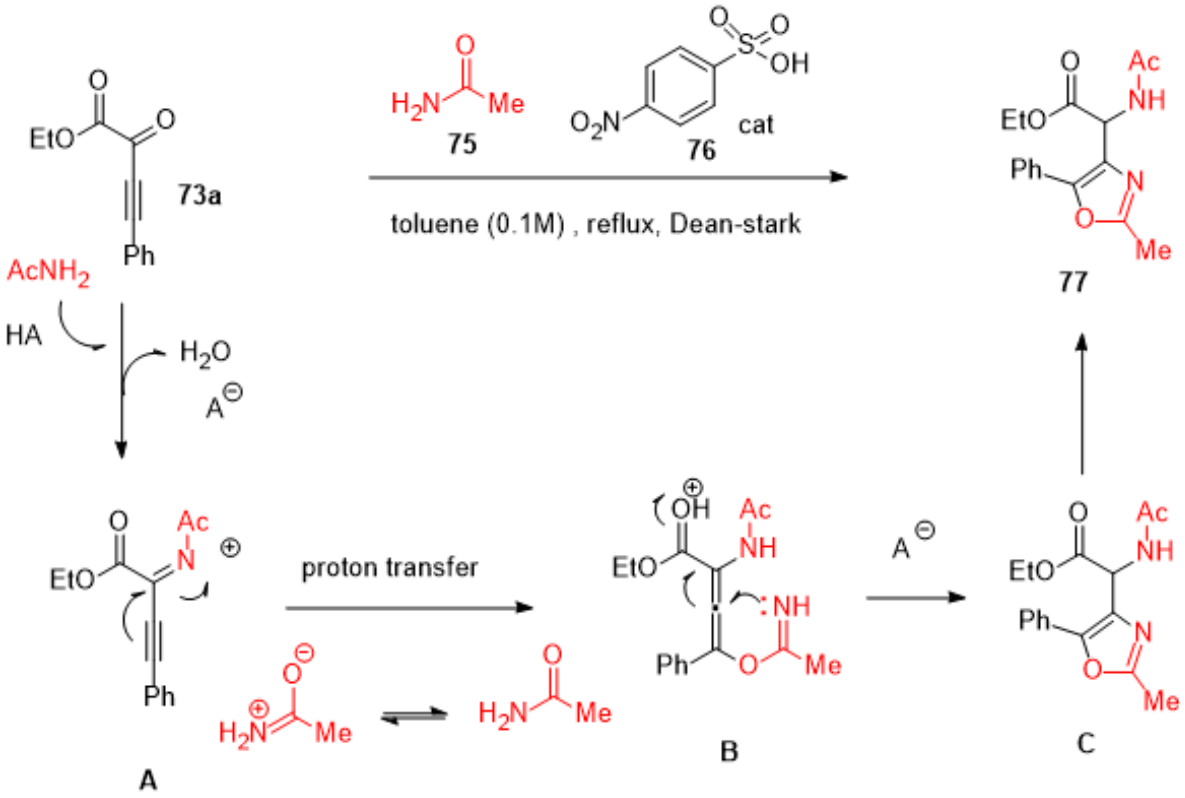
Kim and co-workers[47] reported in 2018 a one pot synthetic strategy for the synthesis of α-(4-oxazolyl) amino esters **77** catalyzed by 4-nitrobenzene sulfonic acid **76** by bond-forming reactions including imine formation and Michael addition both intramolecular and intermolecular to introduce both functionalities (Scheme 23).



Scheme 23: Synthesis of α-(4-oxazolyl) amino esters via Brønsted acid catalyzed Tandem reaction

Previous studies using **73** as the electrophile agent suggest that it can participate in 1,2-addition reactions with nucleophiles and forming the corresponding imino ester. Nevertheless, the compounds obtained by Kim and co-workers[47] have shown two acetamide moieties, which can be an indication that another additional reaction is occurring. Indeed, in their proposed mechanism (Scheme 24), after the formation of the imine **A** by reaction of ethyl 2-oxobut-3-ynoate **73a** and an amide **75**, an intermolecular Michael addition of the formed intermediate with an amide is produced to generate the oxazole ring followed by an intramolecular Michael addition to generate the corresponding compounds **77**. This one

pot efficient synthetic strategy allows getting these important bioactive scaffolds in a single reaction step.

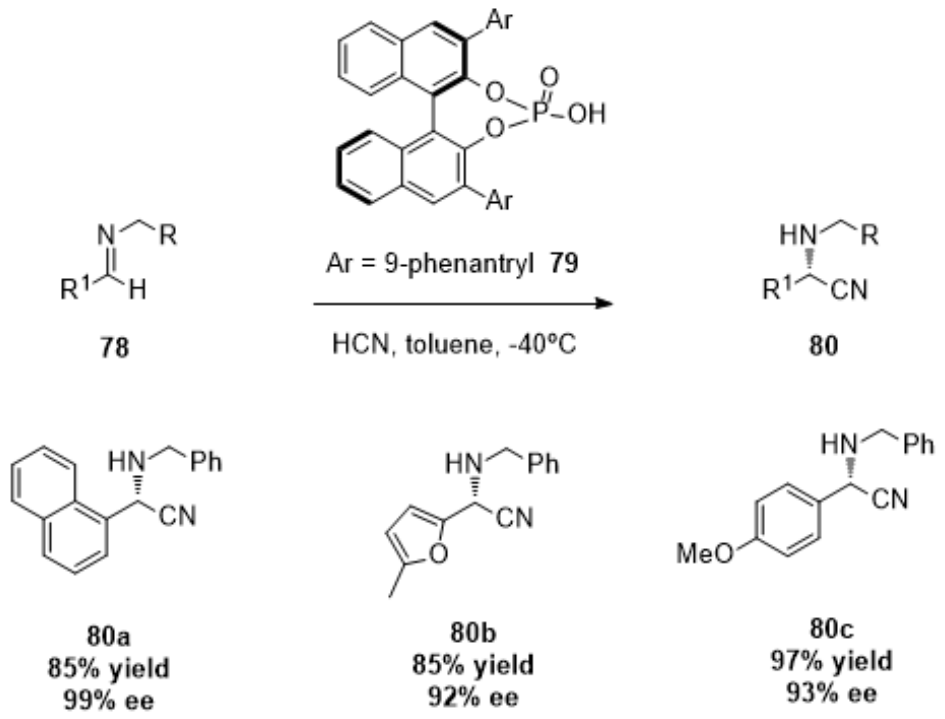


Scheme 24: Mechanism for the synthesis of compound 3aa as suggested by Kim and co-workers

Binol phosphonates **79** have also been demonstrated to be effective bronsted acid catalysts for asymmetric catalysis (i.e enantioselective transfer hydrogenation reactions). Rueping *et al*[48] reported in 2006 the use of this type of catalyst in the enantioselective Strecker reaction (Scheme 25), one of the most common synthetic strategies to access α-amino acids.

The corresponding amino protected nitriles **80** were obtained with excellent yields and enantioselectivities. Further transformation into the final amino acid and diamines by reduction and hydrolysis of the amino nitriles was also performed to evaluate the stereochemistry of the reaction.

The S-configuration observed for the unprotected amino acid, indicates that the attack of cyanide nucleophile is produced by the most favored re-face instead of the *si*-face which is very likely obstructed by the large size groups of the catalyst.



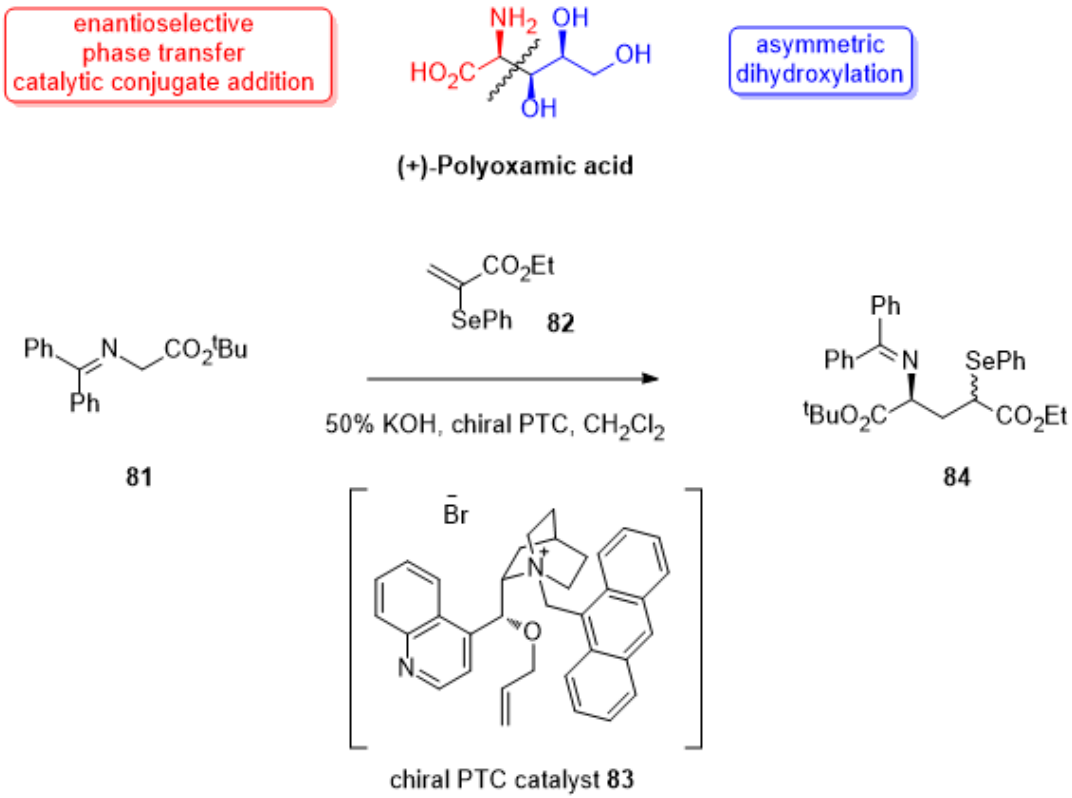
Scheme 25: Highly enantioselective Bronsted acid catalyst for the Strecker reaction

5.4.4 Phase transfer catalysis

Phase transfer catalysis (Figure 6d) has been largely studied and employed as activation mode in asymmetric catalysis most likely due to the numerous synthetic advantages such us excellent group tolerance and mild reaction conditions.[35] Polyoxamic acid is an amino acid containing three hydroxi contiguous groups (two of them are part of stereogenic centers) which is the central core of polyoxins, which are antibiotics and antifungal agents. In 2011, Park and their co-workers[48] reported an enantioselective synthesis of (+) polyoxamic acid via phase transfer catalytic conjugate addition and asymmetric dihydroxylation (Scheme 26).

The use of methylacrylate as Michael acceptor to introduce the α-carbomethoxyethyl moiety did not give satisfactory results because of the moderate enantioselectivity observed but also the racemization that can occur during the α-phenylselenylation process. Thus, the starting cyclohexanone was modified by the introduction of an α-phenylselenylacrylate **82** moiety which was found an effective Michael acceptor for this transformation.

The cinchona-based phase transfer catalyst **83** was able to promote the reaction with excellent conversion and 90% ee when the reaction was performed at RT, and the enantioselectivity improved up to 96% when performing the reaction at -20°C. The synthesis of the corresponding (+) Polyoxamic acid was further complete with 6 more steps and overall yield of 46%.



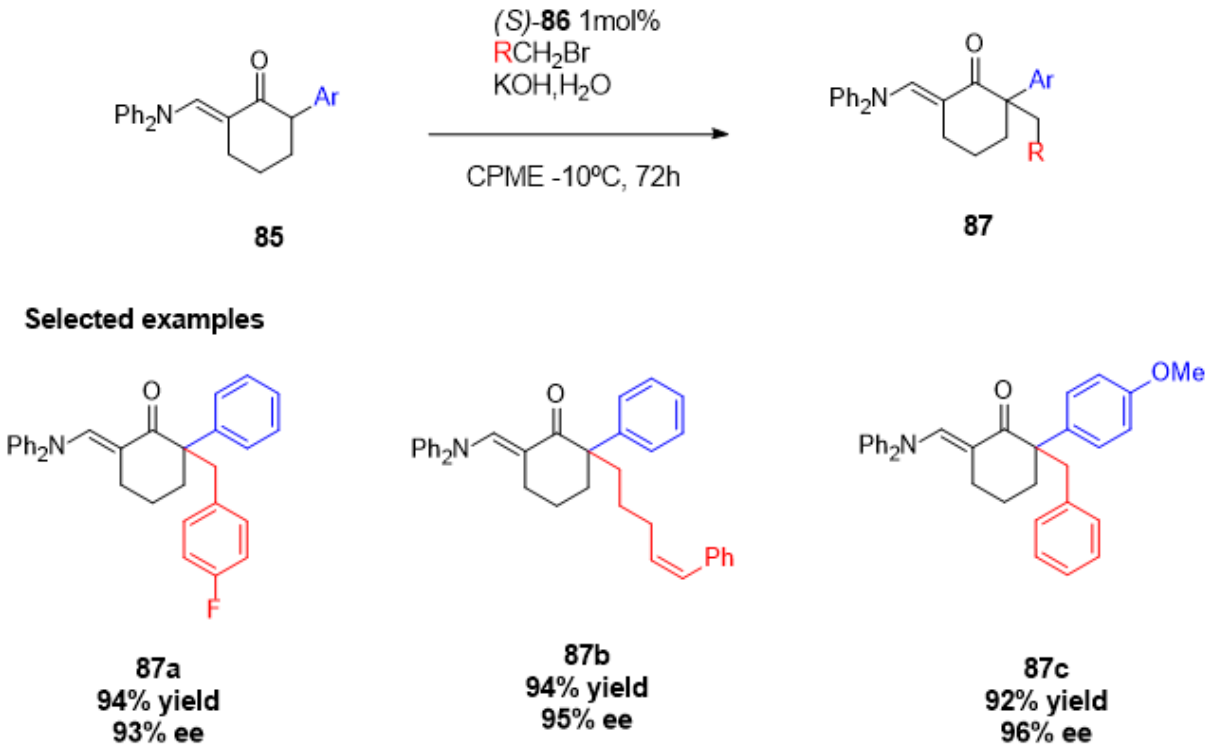
Scheme 26: Enantioselective Phase-Transfer Catalytic Conjugate addition of **81**

Phase transfer catalysis is also a very useful chemical reaction for the asymmetric alkylation of several substrates and indeed, is employed for the enantioselective construction of quaternary stereocenters.

Maruoka *et al*[50] reported an asymmetric alkylation of 2-arylcyclohexanones **85** under phase transfer conditions, using cyclopentyl methyl ether (CPME) as a solvent, for the generation of a chiral quaternary center **87** (Scheme 27).

One of the main problems in the asymmetric alkylation of cyclohexanones is the low enantioselectivity observed with phase transfer catalysis, it could be due to the difficulties to determine which si/re face will be most suitable for the corresponding transfer process

(the catalyst employed in this experiment is also very bulky). To avoid this, the starting cyclohexanone was modified by the introduction of an *N,N*-diphenylaminomethylene group which can perform and enantioface control giving to higher enantioselectivities



Scheme 27: Asymmetric alkylation of 2-arylrcyclohexanone

Indeed, a notably improvement of ee was found in the experiments containing the cyclohexanone modification meaning. In contrast, when modified cyclopentanone was used as ketone, a significant decrease of ee was observed. In summary, the synthetic methodology proposed by Maruoka *et al*[50] has been demonstrated to be effective for the enantioselective construction of quaternary carbons expanding the use of phase transfer catalysis in asymmetric synthesis.

5.4.5 N-Heterocyclic carbenes catalysis (NHC)

Lastly, N-heterocyclic carbenes (Figure 6e) are also another type of organocatalysts that are often employed in umpolung catalysis, where they are involved in the inversion of the innate polarity of a functional group. For example, in the Stetter reaction they are

used for the umpolung of aldehydes, they are also largely employed in the umpolung of Michael Acceptors or the hydroacylation of electron-neutral olefins.[51] The origin of umpolung catalysis is partly linked to the discovery of thiazolium salts, analogues of the vitamin thiamine, reacting in an unexpected way compared to their innate polarity.[52] Nowadays, thiamine pyrophosphate derived enzymes are commonly used as catalysts for umpolung cellular reactions such us the decarboxylation of pyruvic acid to acetaldehyde or the decarboxylation of pyruvic acid to active acetate.[52]

During this section, different examples have been commented to explain the most widely used organocatalyzed methods of activation in asymmetric catalysis. As previously mentioned, the C-C bond formation is an essential and useful chemical reaction for the synthesis of complex molecules and natural compounds with pharmacological activity and the enantioselective construction of quaternary carbons can be made using imine or enamine catalysis but also using Bronsted acid catalysis and phase transfer catalyzed Michael addition. However, as it will be described in more detail in the next chapter, for the purpose of my research work I focused on using organocatalysis, mostly organocatalyzed enantioselective conjugate addition reactions and transfer catalysis.

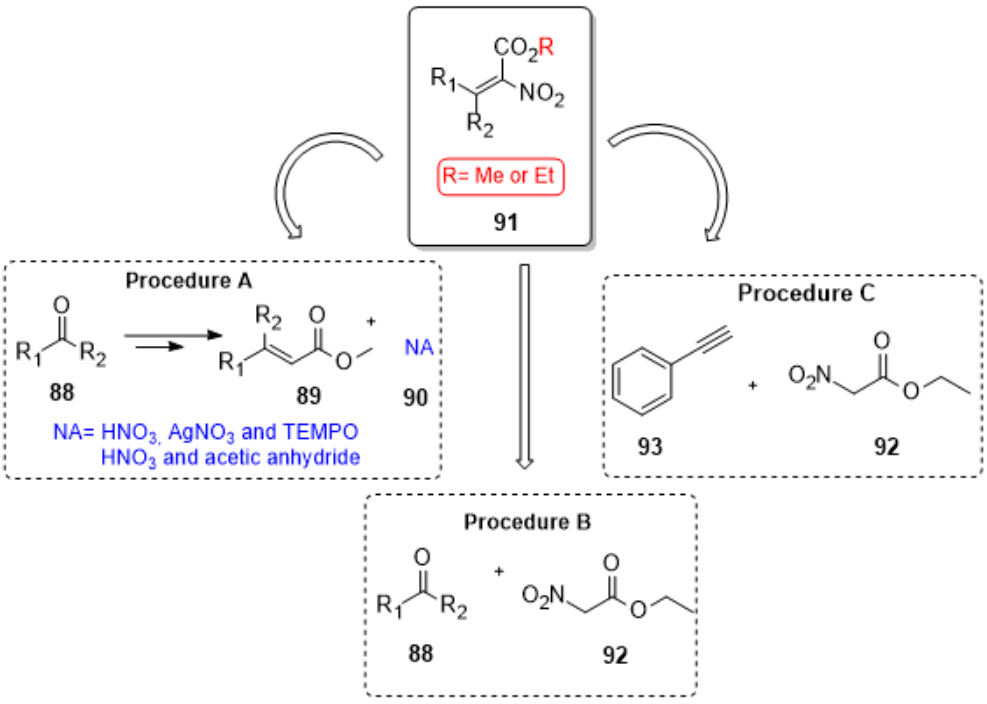
Discussion of Phd ressults

6. Discussion of PhD results

6.1 Synthesis and enantioselective reduction of tetrasubstituted nitroalkenes

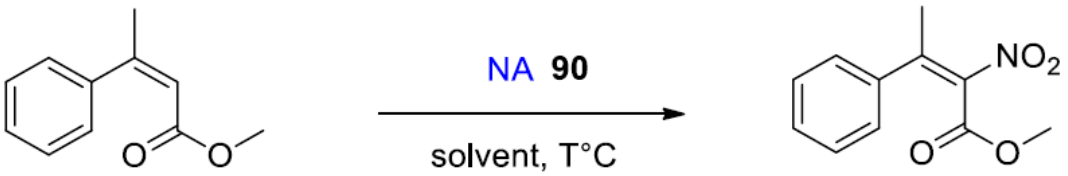
6.1.1 Preparation of tetrasubstituted nitroalkenes

At first, work on this PhD project focused on the synthesis of tetrasubstituted nitroalkenes, key starter products of the Approach A discussed earlier. There are very limited papers available on the preparation of these compounds[53, 54] so, we could only concentrate on very scarce data to base different synthetic access for the synthesis of these compounds as shown in Scheme 28.



Scheme 28: Proposed synthetic strategies for the synthesis of tetrasubstituted nitroalkenes **91**

The first strategy suggested was **Procedure A** (Scheme 29), which involves the reaction of an acrylate **89**, (previously synthetized from a commercially available ketone **88** using a HWE reaction[55] and an appropriate nitration reagent **90** (nitric acid, AgNO3 and TEMPO as well as acetic anhydride in combination with nitric acid were used).[56, 57]



89a **91a**

Entry	NA	solvent	T°C	yield
1	HNO_3 fuming	H_2O	0°C→RT	<10%
2	HNO_3 fuming	H_2O	0°C	13%
3	$AgNO_2$, TEMPO	DCE	70°C	No reaction
4	HNO_3, acetic anhydride	TEA, $CHCl_3$	- 10°C→0°C	No reaction

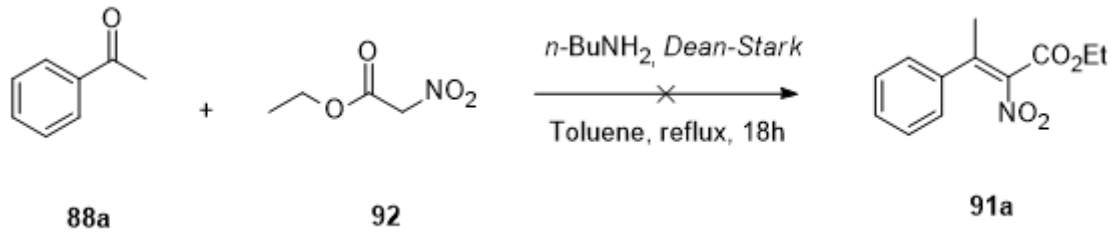
Scheme 29: Reaction of nitration of compound **91** using approach A

Starting from Acetophenone **88a** as readily available ketone, the formation of the corresponding α,β-unsaturated ester **89a** using conditions reported in literature[55], worked well obtaining the product with good yield (50-80%) and diastereoselectivity (< 4:1 E/Z ratio) after purification.

Then, the reaction of nitration with the nitration reagents **90** previously commented was performed.[56, 57] The use of nitric acid (Scheme 29, entries 1,2), led to the formation of the product mainly with the nitro group in the aromatic ring and several byproducts were also detected in the NMR crude.[56] Furthermore, the yields after purification were very low (<10%). In order to reduce the nitration in the aromatic ring, selective nitration conditions for double bonds (Scheme 29, entry 3) were also tried, but no signals of desired product were observed.[57]

The presence of an aromatic ring in the starting ketone and the use of nitric acid or nitric salts as nitration reagents increased the possibility to carry out the reaction in the aromatic ring. In addition, the methyl group of the acetophenone made the aromatic substitution in the aromatic ring easier due to their ortho/para activation. In view of this, other conditions to synthetize the desired compound were tested.

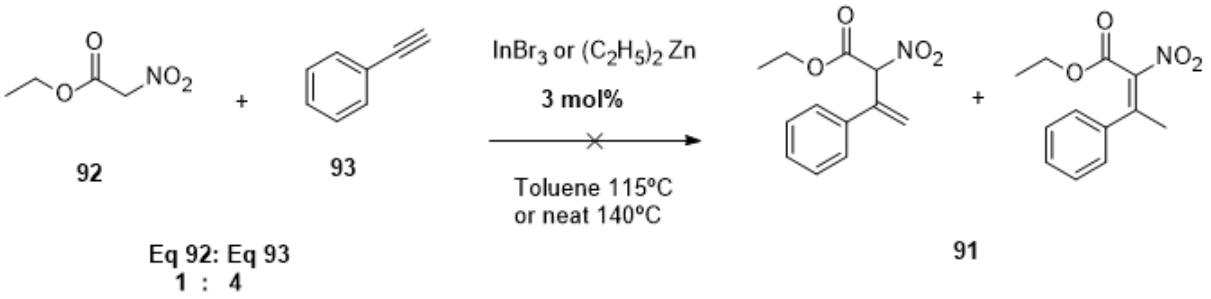
Procedure B[58, 5t9] was then suggested as an alternative synthetic procedure for the synthesis of tetrasubstituted nitroalkenes **91**.The condensation between acetophenone **88a** and ethyl nitroacetate **92** was tested and did not lead to the formation of the corresponding nitroolefin **91a** (Scheme 30) and only signals of starting materials were found in the NMR crude.[58] In an attempt to check if by collecting the water produced during the reaction the product yields improved, a Dean-Stark apparatus was used but, no significant changes were observed.[59]



Scheme 30: Synthesis of tetrasubstituted nitroalkene **91** by condensation of ethyl nitroacetate **92** and acetophenone **88**

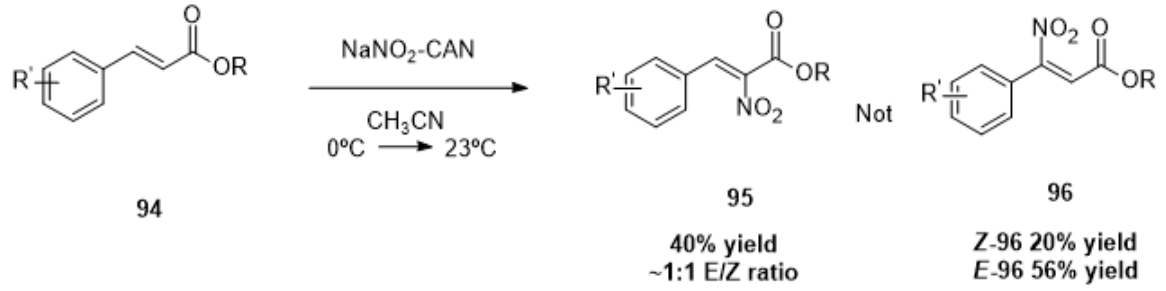
As I struggled to find published examples of less hindered ketones used in this reaction, I abandoned this approach and as advised by my supervisor, I tried the replacement of the ketone for a terminal alkyne as an alternative strategy to achieve our first synthetic goal.

Procedure C was tested using phenylacetylene **93** and ethyl nitroacetate **92** catalyzed by indium salts (Scheme 31), which were found effective mediators for the addition of methylene active compounds to terminal alkynes to form Markovnikov addition products in good yields.[60] Although these conditions were promising, again, in this case the reaction did not work as expected, and no product **91** was found. The use of diethylzinc (in catalytic or stoichiometric amount) as catalyst which was also a good promotor for Knoevenagel condensation products, did not allow me to synthetize the target tetrasubstituted nitroalkenes.[61]



Scheme 31: Synthesis of tetrasubstituted nitroalkene **82** employing alkynes as substrates

Overall, the initial synthetic procedures proposed for the synthesis of tetrasubstituted nitroalkenes **91** represented in Scheme 28, did not work as expected.[55-61] Among them, the results obtained with **Procedure A** (Scheme 29) were the best ones, however, several problems in the nitration step such us low yield, poor reproducibility, and difficult separation, were difficult to solve.[56-58] Further optimization of the nitration step was then performed, by searching for another possible nitration reagents. It is well-known that nucleophilic addition in the α-position of an α,β-unsaturated carbonyl compound is not common, but Buevich and co-workers reported the first example of a contra-Michael addition to a cinammic ester **94** by utilizing CAN-NaNO2 system (Scheme 32).[62]

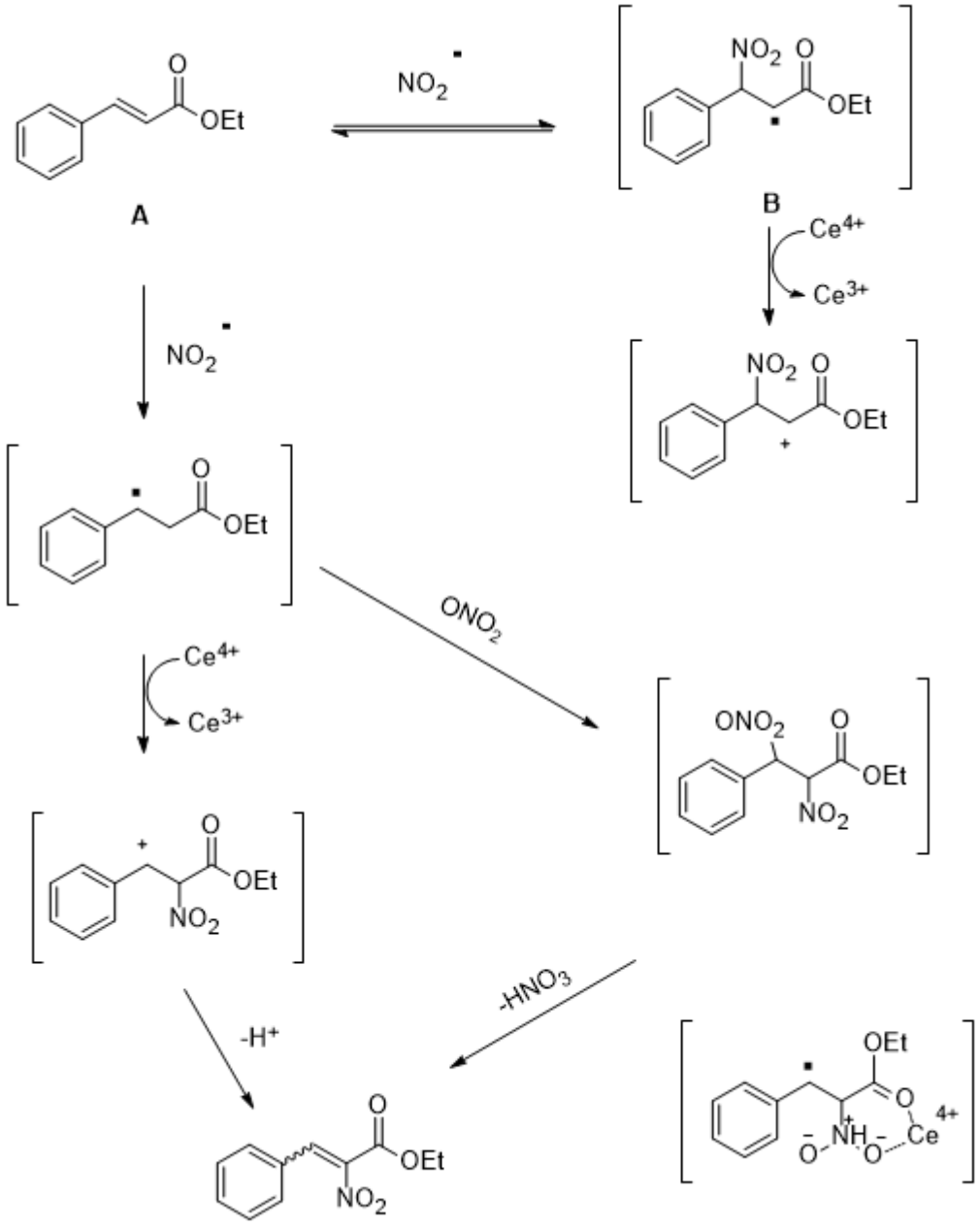


Scheme 32: unusual contra Michael addition of $NaNO_2$-CAN to acrylic esters **94**

The suggested mechanism for the nitration of Buevich and co-workers is represented in Scheme 33. Among the two possible routes, the route A is predominant in comparison with route B, due to several factors:

· In the first step of route A, the phenyl group of the intermediate, stabilizes the newly formed radical and also the formed carbocation resulting from the oxidation of Ce4+ with intermediate (the generated intermediate carbocation of route B, is less favored from an energetic perspective).

· The resulting cerium complex with the nitro and ester groups in route A, leads to the formation of a six-member ring intermediate, whereas the route B intermediate is a seven member ring, which is less stable than the one formed in route A and this makes approach B unsuitable for this reaction.

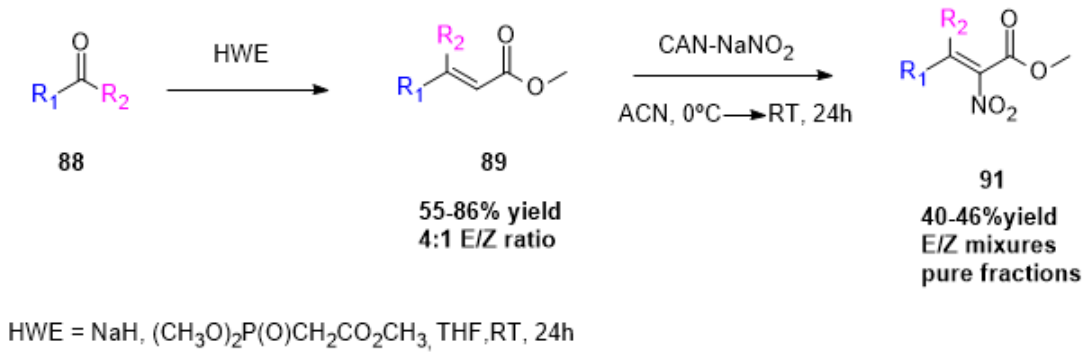


Scheme 33: Suggested Mechanism for the unusual contra-Michael addition of CAN to acrylic esters

The good results obtained with this interesting system from Buevich and co-workers[62] suggested me to apply this combination of reagents for the synthesis of the target tetrasubstituted nitroalkene **91**. The results obtained were successful and the desired tetrasubstituted

nitroalkenes **91** of interest were finally synthetized with moderate yields (40-48%) but in a reproducible manner. In addition, the purification using a Biotage system, allowed to isolate the product as an enriched mixture of isomers and to separate fractions of isomers.

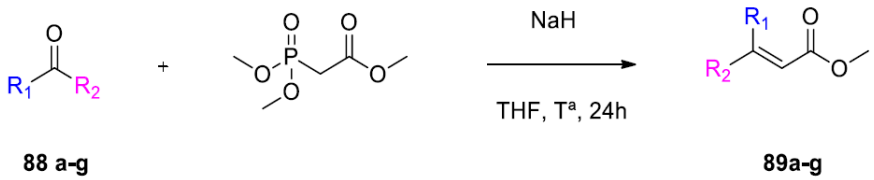
The optimization of the nitration step using CAN-NaNO2 as an effective nitration reagent enabled me to develop **a reproducible synthetic strategy for the synthesis of tetrasubstituted nitroalkenes 91 starting from commercially available ketones 88** (Scheme 34).[55,62] To the best of our knowledge, the developed strategy represents the first synthetic route for the access of tetrasubstituted nitroalkenes.



Scheme 34: First synthetic strategy for the synthesis of tetrasubstituted nitroalkenes

After discovering a successful methodology for the preparation of α-nitroacrylates, the next step was to study the scope of the reaction by the synthesis of a variety of compounds. The scope was investigated by synthetizing a wide variety of α,β-unsaturated esters **89a**-g starting from their corresponding commercially available ketones **88a-g** using the conditions reported in literature as shown in Scheme 35.[55] The results are summarized in Table 1.

Compounds **89 a-g** were obtained after reaction of the corresponding commercially available ketones **88 a-g** with trimethylphosphonoacetate in THF for 24h with good to moderate yields after purification with column chromatography. Reactions were performed at RT, but with compounds **89c** and **89e** (Table 1, entries 3, 5) it was necessary to employ high heat (at 66°C). Their E/Z ratio was checked by NMR of reaction crude. No formation of product **89d** (Table 1, entry 4) was observed after 24h at RT. The low yield observed for the isolation of pure product **89c** (Table 1, entry 3) can be explained by its high volatility.



88 a-g 89a-g

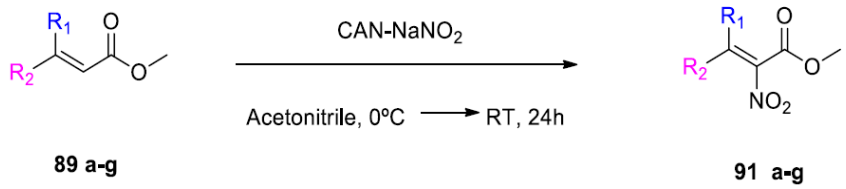
Scheme 35: Synthesis of α,β-unsaturated esters 89 a-g

Table 1: Synthesis of α,β-unsaturated esters 89 a-g

Entry	R_1	R_2	T[a] °C	Product	E/Z ratio[a]	Yield[b] %
1	Me	Ph	RT	89a	4:1	52
2	CF_3	Ph	RT	89b	3:1	79
3	Me	^{t}Bu	66	89c	9:1	4
4	Me	2,4,6-trimethylphenyl	RT	89d	---	NR
5	^{i}Pr	Me	66	89e	2:1	33
6	Me	4-Brphenyl	RT	89f	2:1	76
7	Me	4-methylphenyl	66	89g	3:1	86

a= obtained in the NMR crude; b= after purification with column chromatography; NR = no reaction

The acrylate intermediates **89** were directly used in the next step which involved the reaction of nitration. The α,β-unsaturated esters **89a-g** were treated with CAN-$NaNO_2$ in Acetonitrile to afford the corresponding tetrasubstituted nitroalkenes **91a-g** as shown in Scheme 36. The results are summarized in Table 2.



89 a-g 91 a-g

Scheme 36: Synthesis of tetrasubstituted nitroalkenes 91 a-g

Table 2: Synthesis of tetrasubstituted nitroalkenes 91 a-g

Entry	R_1	R_2	Acrylate	Nitroacrylate	Yield[a] %
1	Me	Ph	81a	82a	46
2	CF_3	Ph	81b	82b	76[b]
3	Me	^{t}Bu	81c	82c	NR
4	^{i}Pr	Ph	81e	82e	25
5	Me	4-Br-phenyl	81f	82f	47
6	Me	4-Me-phenyl	81g	82g	48

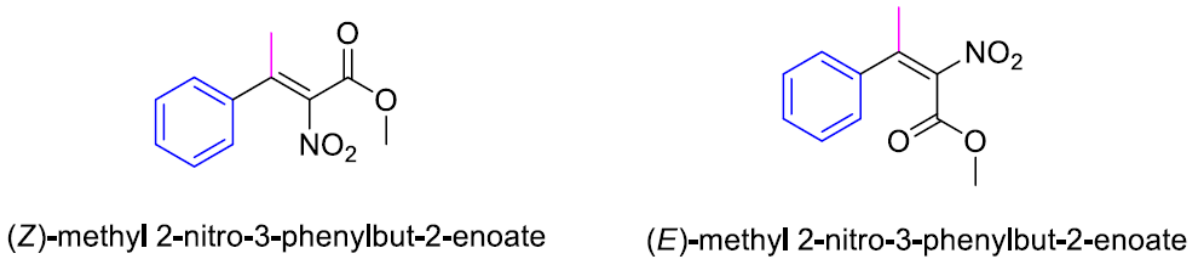
a= after purification with column chromatography; b= yield of the corresponding p-nitroacrylate

The reaction of nitration of acrylates **89a**, **89b**, **89c**, **89e**, **89f** and **89g** was performed with CAN-$NaNO_2$ as the nitration reagent and the corresponding nitroacrylates **91a**, **91b**, **91c**, **91e**, **91f**, **91g** were obtained with low yield after purification. In case of nitroacrylates **91a** and **91f**, two different fractions which might correspond with both isomers of the product were obtained after purification (different chemical shift for the OMe and Me proton signals was detected by NMR), however in case of nitroacrylates **91e** and **91g** only one fraction corresponding with one isomer (by comparison of the septuplet signal of the starting acrylate and the corresponding septuplet of the nitroacrylate, the *E* isomer of the nitroacrylate was possible to isolate) and a mixture fraction containing both isomers was obtained after purification (second purification was required in case of nitroacrylate **91e**).

The nitration of acrylate **89b**, did not lead to the formation of their corresponding nitroacrylate **91b** with the nitro group in the α-position, but the corresponding (Z)-methyl 4, 4, 4-trifluoro-3-(4-nitrophenyl)but-2-enoate analogue was observed as major compound in this reaction, most likely due to the presence of the CF_3 moiety which is a strong electroatractor group and that makes the aromatic ring even more accessible for the nitration. The nitration of acrylate **89c** did not lead to the formation of compound **91c**.

As previously mentioned, in the reaction of nitration of acrylates **89a** and **89f**, it was possible to obtain separate fraction of the corresponding isomers of the nitroacrylate as confirmed by different chemical shift of the proton signal of OMe and Me groups in H-NMR. However, we could not confirm which isomer is Z and which one is E with only ^{1}HNMR. To clarify this, it was necessary to perform further NMR experiments in collaboration with Prof Francesca Vasile.

A chemical shift study on the methoxy group signal of both Z/E forms of the tetrasubstituted nitroalkene **89a** (Figure 7) has been performed, using a NOESY experiment.



(*Z*)-methyl 2-nitro-3-phenylbut-2-enoate (*E*)-methyl 2-nitro-3-phenylbut-2-enoate

Figure 7: E/Z isomers of compound 89a

As shown in Figure 8, the OMe group is more shielded (3.55 ppm, Figure 8) in the more abundant form, suggesting that it can be near to the shielding cone of the aromatic ring (corresponding to *(E)* isomer), while it resonates at 3.8 ppm in the less abundant isomer of Figure 8.

NOESY experiment, showing through-space correlation within the molecule, was also acquired to understand if the more abundant form of the tetrasubstituted nitroalkene corresponds to *(E)* or *(Z)*, considering that the NOE contact between methoxy group and phenyl ring can only be observed in the *(E)* isomer. The analysis of NOE contacts suggested that the significant cross peak between OMe group and Phenyl ring (Figure 9) is present only in the more abundant form that can be assigned to *(E)* configuration.

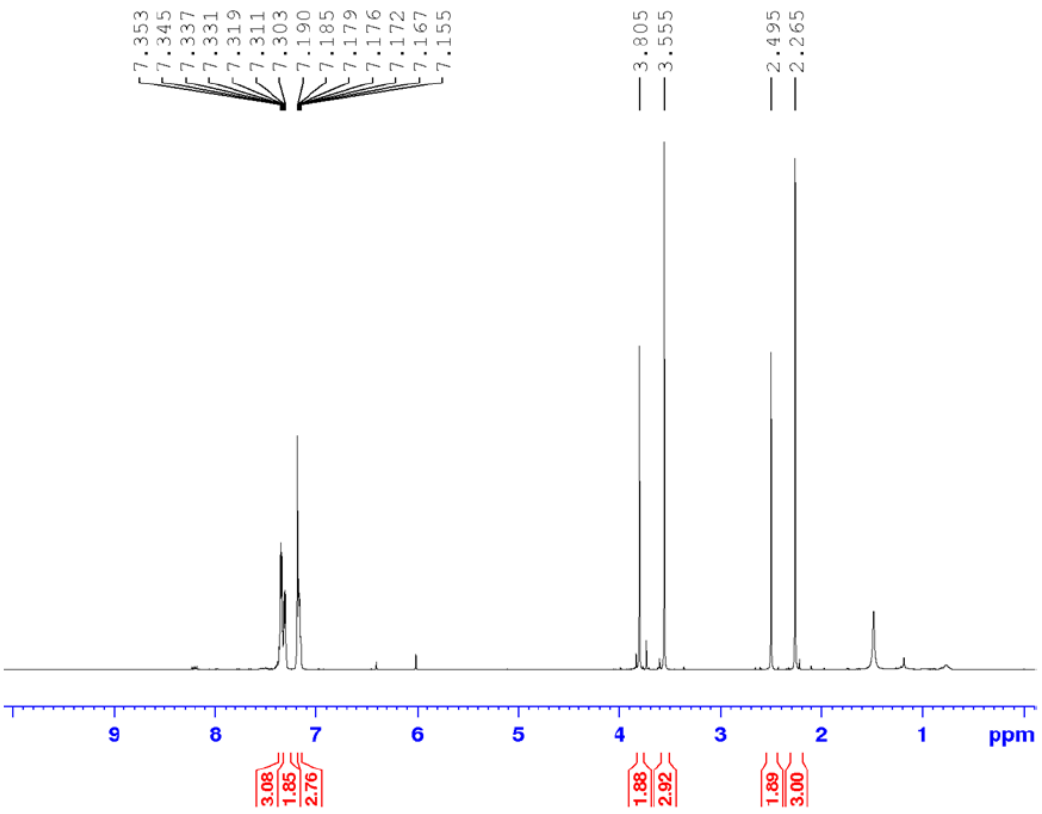


Figure 8: NMR spectra of both isomers of tetrasubstituted nitroalkene **82a**

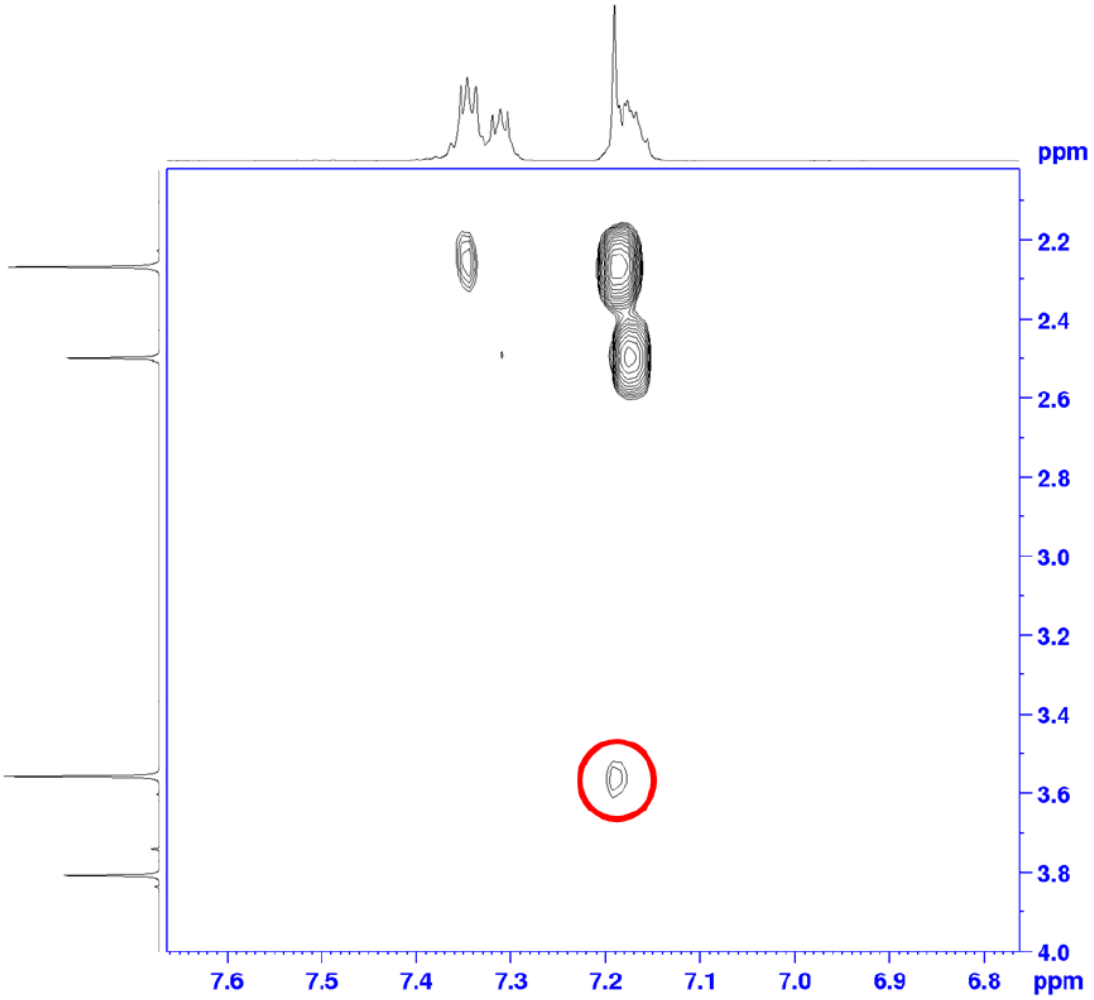


Figure 9: NOE contact observed between OMe and Ph groups in the more abundant form of the tetrasubstituted nitroalkene **82a**

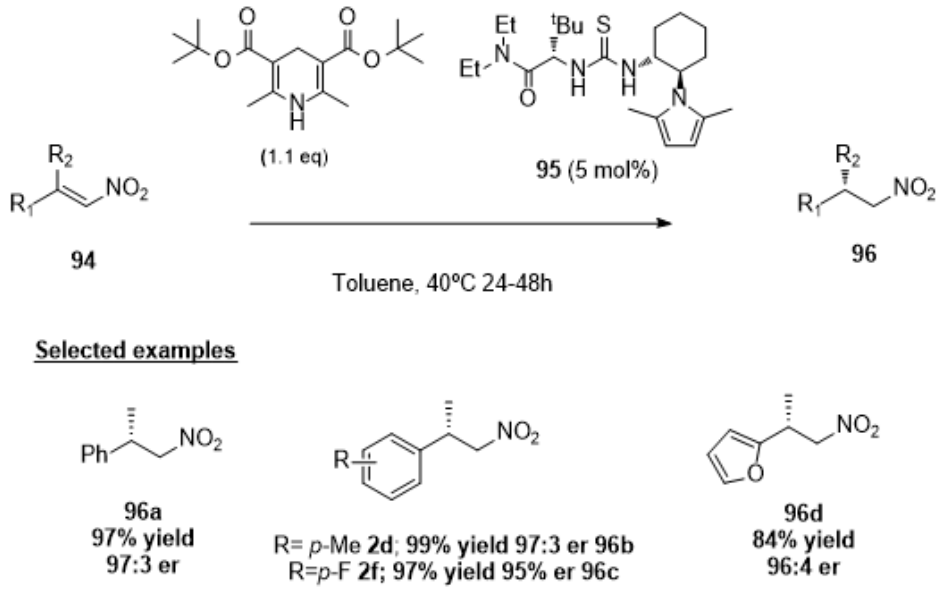
6.1.2 Enantioselective reduction of tetrasubstituted nitroalkenes

In the previous section, an important goal of the aim of this PhD project was fortunately solved by developing an efficient synthetic strategy for the synthesis of tetrasubstituted nitroalkenes **91**, key compounds of our innovative approach to achieve the synthesis of α,α-disubstituted amino acids derivatives.

Then, the enantioselective reduction of these compounds was studied to obtain the corresponding functionalized nitroalkanes as starting material for the alkylation step.

In 2007, List and their co-workers[63] have reported a highly enantioselective organocatalytic transfer hydrogenation of β,β-disubstituted nitroolefins **94** mediated by Hantzsch ester using a Jacobsen type thiourea catalyst **95** as shown in Scheme 37:

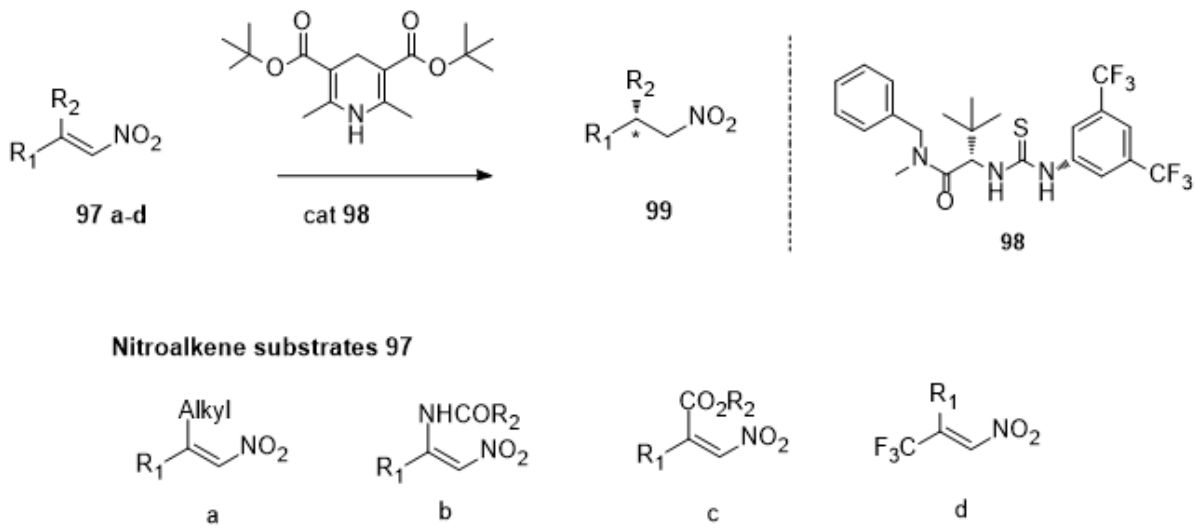
This hydrogen-bonding activation mediates for Hantzsch esters, is a suitable methodology for the reduction of this type of compounds. Furthermore, is also well tolerated for a wide range of substrates such us aldehydes, ketones, ketimines and ketoesters. In addition, Hantzsch esters are easily synthetized and available, making this an advantage to use them in the organocatalyzed reduction reactions.



Scheme 37: Organocatalytic transfer hydrogenation of β,β-disubstituted nitroolefins **88** using a Jacobsen type thiourea catalyst

In 2016, Bernardi and Fochi[64] reported a general enantioselective transfer hydrogenation reaction of β,β-disubstituted nitroalkenes **97** with *tert*-butyl Hantzsch ester catalyzed by a simple and thiourea-based catalyst **98** (Scheme 38) applicable to all nitroalkene classes a-d.

A mechanism of the transfer hydrogenation of this catalyst **98** was also suggested (Figure 6),assuming the coordination of the NO2 by the NH atoms of the thiourea whereas the NH atom of the Hanztsch ester is involved in a H-bonding interaction with the carboxamide group of the catalyst, which allowed the proton transfer between the Hantzsch ester and the nitroolefin **99**.[65,66] The *tert*-butyl moiety is responsible of the 3D conformation of the catalyst and dictates the enantioselectivity of the reaction, whereas the substituents of the nitroalkene did not have a significant role in this model.



Scheme 38: General enantioselective transfer hydrogenation of β,β-disubstituted nitroalkenes with *tert*-butyl Hantzsch ester catalyzed by a simple Jacobsen thourea

The enantioselectivity of the final products **99** (Figure 10) will be determined by the geometric arrangement of the polar groups of the catalyst and in the transition state, leading to the *R* ensntiomer, the repulsive interactions between the substrate and the catalyst are minimized. Only the *R*-enantiomers of the final compounds were obtained, as the transition state TSs which led to the S-enantiomers of these compounds are at higher energy levels.

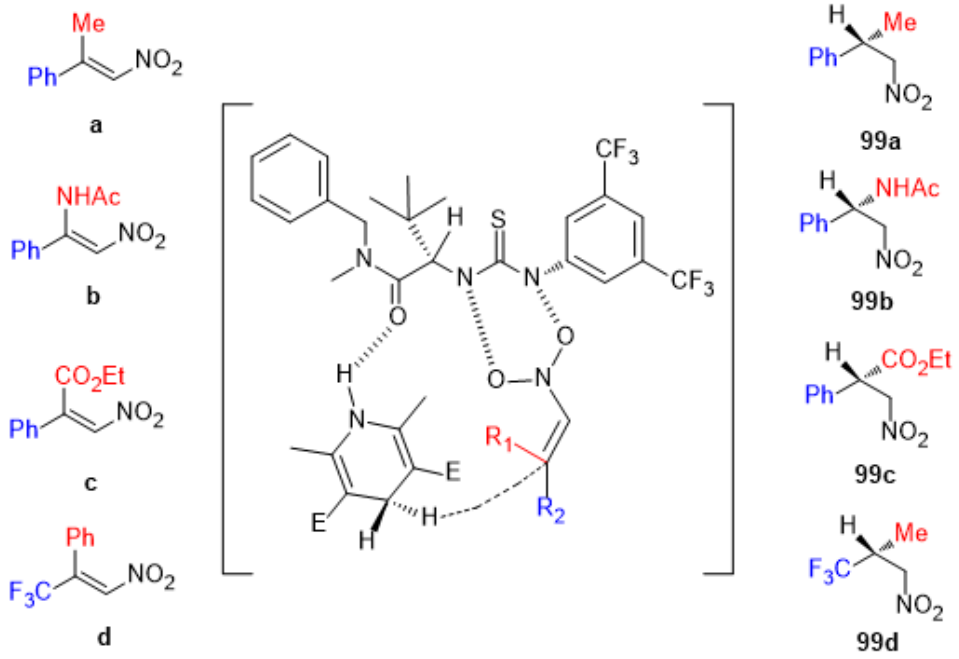
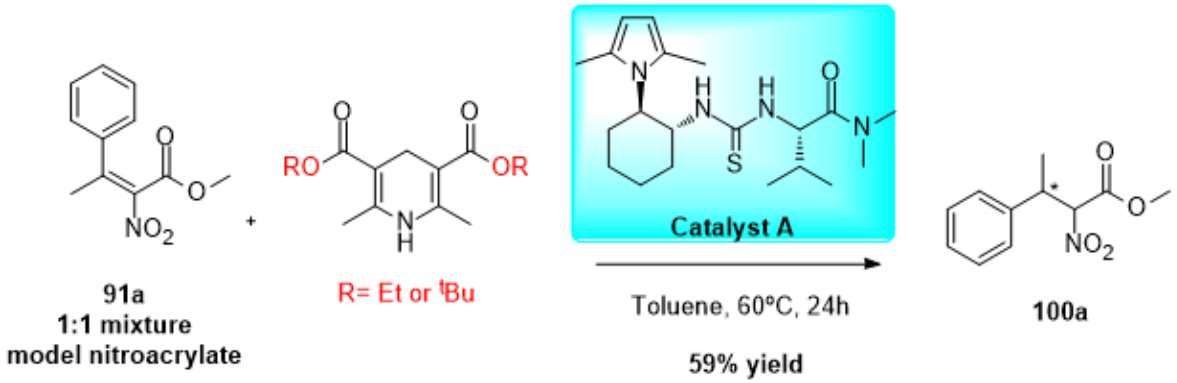


Figure 10: Attack of the hydride to the same pro-chiral face of a-d according to the TS model

These two reports, attracted our attention due to the excellent results obtained in terms of enantioselectivity and diastereoselective ratio for List and co-workers[63] and the application to a broad of different classes of nitroalkenes in the case of Bernardi and Fochi.[64]

Therefore, we decided to apply this organocatalyzed transfer hydrogenation to our tetra-substituted nitroalkenes **91** and specifically, concentrate on the enantioselective reduction of nitroacrylate **91a** employing Hantzsch ester as a reductive agent and the thiourea **Catalyst A** for the synthesis of compound **100a** (Scheme 39).

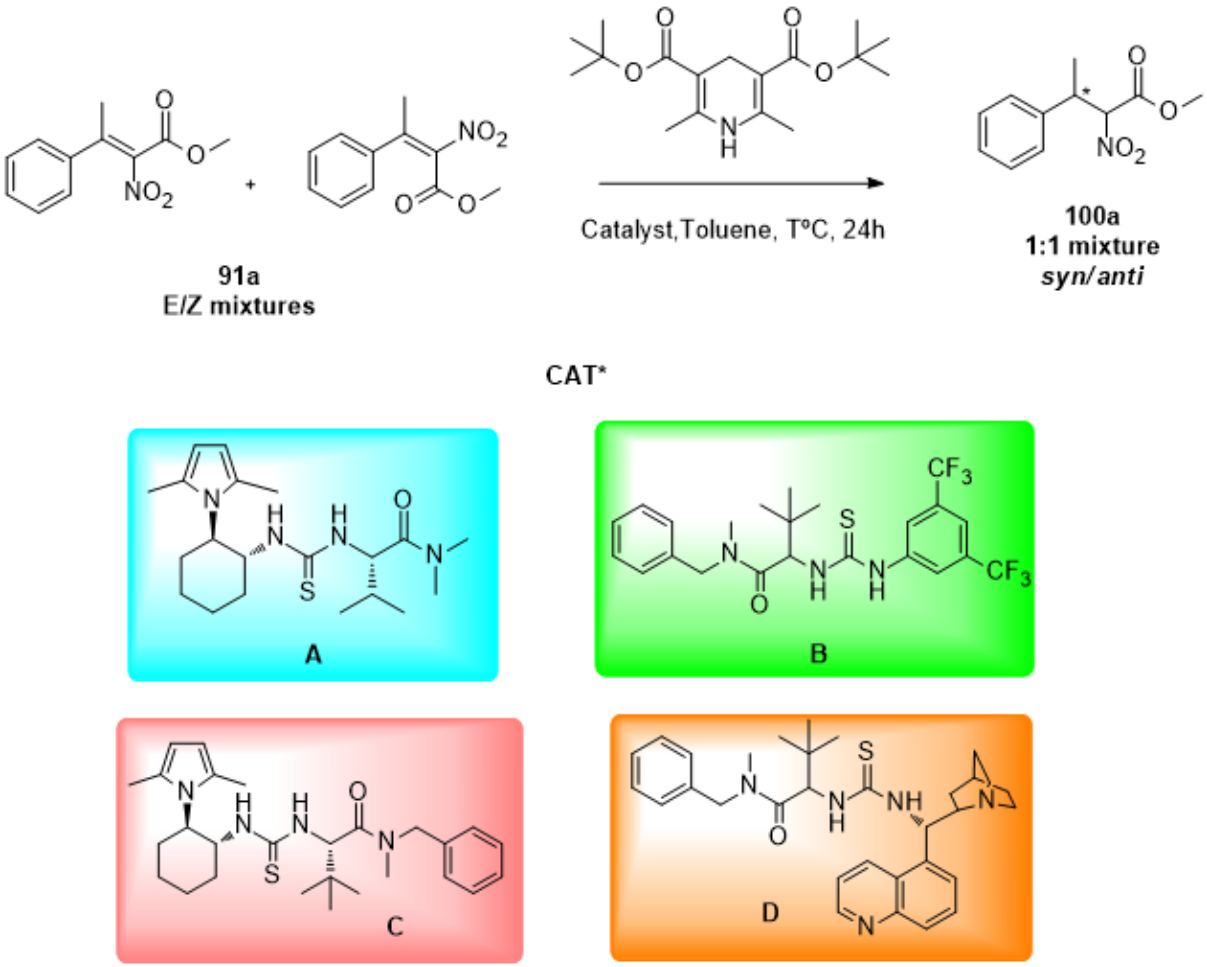


Scheme 39: Preliminary studies of the enantioselective reduction of tetrasubstituted nitroalkenes **91**

The reaction was initially performed with a 1:1 mixture of nitroacrylate **91a** *E* and *Z* (which was used as model substrate), using diethyl Hanztsch ester as reductive agent and thiourea **catalyst A** , which had to be synthetized before running the experiments, using the conditions reported in the literature.[67] After 24h heating at 60°C, a 4:1 ratio between compounds **91a** and **100a** was observed by NMR check and a 2:1 ratio for the isomers of the starting material was detected. This surprising fact gave us an initial idea about the reactivity of these compounds in the reaction.

After achieving good results with diethyl Hanztsch ester, *tert*-butyl Hantzsch ester was synthetized and tested, according to literature procedure.[68] In this case, after 24h at 60°C, a 1:1 ratio between compounds **91a** and **100a** was observed and only one isomer of the starting product was present, confirming that this isomer was less reactive.

However, the reaction required additional optimization studies. Therefore, several experiments starting from different fractions of starting compound **91a** using Hanztsch ester and thiourea catalysts **A-D** were conducted (Scheme 40). The results are summarized in Table 3.



Scheme 40: Enantioselective reduction of nitroacrylate **91a**

Table 3: Enantioselective reduction of nitroacrylate **91a**

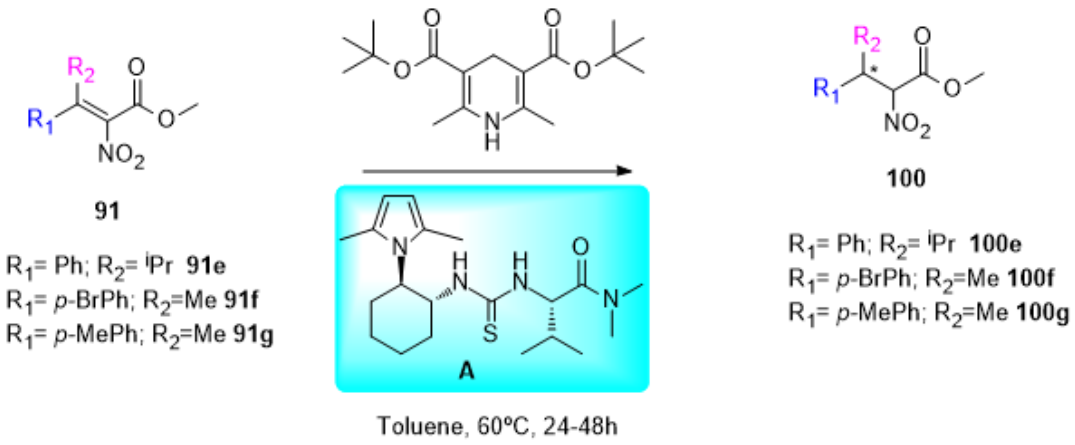
Entry	T °C	Isomer Ratio 91a (MR-*E* - LR-*Z*)	Catalyst	Yield[a] (%)	ee(dr)[b] (%)
1	100	80-20	**A**	37	19-20
2	60	4-96	**A**	trace	ND
3	60	90-10	**A**	44	63-61
4	60	61-39	**B**	69	33-32
5	RT	40-60	**C**	15	ND
6[c]	RT→60	92-8	**C**	19	ND
7[c]	RT→60	76-24	**D**	<10	ND

a= after column chromatography; b= using chiral HPLC column Phenomenex-Lux-Cellulose 5, Hexane/IPA 98:2 c= after 48h of reaction time; MR =more reactive isomer of starting material; LR= less reactive isomer of starting material; ND= not determinated

In general, compound **100a** was obtained in a 1:1 mixture of *syn/anti* products after 24h of reaction time. The reactions performed with enriched mixtures of the more reactive isomer *(E)* of starting product (Table 3, entries 1,3,6,7) lead to the formation of the product with higher yields in comparison with the reactions starting from enriched mixtures with the less reactive isomer of starting product (Table 3 entries 2,5). Indeed, when the reaction was tested with a pure fraction of the less reactive isomer, *(Z)*, only traces of the desired nitroalkane **100a** was observed (Table 3, entry 2) meaning that this was the less reactive isomer of the starting product.

The enantioselectivity of these compounds was measured by HPLC analysis of the pure samples on chiral stationary phase, and two pairs of enantiomers corresponding with *syn/anti* products were found (see experimental section). Thiourea **catalyst A** was synthetized immediately before running the experiments, whereas **catalysts B**, **C** and **D** were available in the group laboratory. When thiourea **catalyst B** was used (Table 3, entry 4), the corresponding nitroalkane **100a** was obtained with good yield, but the enantioselectivity observed was lower than with the **catalyst A** (Table 3, entries 1,2,3), which was the best catalyst for this transformation. However, when the thiourea **catalysts C and D** were tested (Table 3, entries 5, 6, 7), the yield was drastically reduced obtaining a very low quantity of product after purification and enantioselectivity was not measured.

With all this information, the enantioselective reduction of the tetrasubstituted nitroalkenes **91d**, **91f** and **91h** synthetized in the previous section was carried out using Hanztsch ester and thiourea **catalyst A** (Scheme 41). The results are summarized in Table 4.



Scheme 41: Enantioselective reduction of nitroalkenes **91e**, **91f**, **91g**

Table 4: Enantioselective reduction of nitroacrylates **91e**, **91f** and **91h**

Entry	R_1	R_2	nitroacrylate	nitroalkane	Yield[a] racemic %	Yield[a] chiral %	eeA-eeB[b]
1	^{i}Pr	Ph	91e	100e	3	32	12-13
2	Me	4-bromophenyl	91f	100f	53	59	24-4
3	Me	4-methylphenyl	91g	100g	20	51	46-42

a= after purification by preparative HPLC purification; b= using chiral HPLC column Cellulose 5, Hexane/IPA 95:5

The enantioselective reduction of nitroacrylates **91e**, **91f** and **91g** worked well obtaining their corresponding nitroalkanes **100e**, **100f** and **100g** with good to moderate yields after purification. The racemic compounds **100e** and **100g** (Table 4, entries 1, 3) required 48h of reaction time at RT. Furthermore, the yield of the racemic compound **100e** (Table 4, entry 1) was very low due to starting material being recovered after purification and because it was isolated using preparative HPLC.

Also, in the case of racemic compound **100g** (Table 4, entry 3) a small amount of starting material was recovered in the purification. The enantiomeric excess of the compounds was measured using chiral HPLC column (see experimental section), obtaining the highest value of enantioselectivity with the nitroalkane **100g**.

DFT computational studies[69] on the enantioselective reduction of tetrasubstituted nitroalkanes **100** were performed in order to rationalize the stereochemical outcome of the reaction. Computational studies were performed using Gaussian g16 package by Dr Sergio Rossi and Prof. Laura Raimondi, using **Catalyst A** as model catalyst.[69] All geometries of reactants and products (ground states and transition states) were located at a B3LYP/6-31G (d,p) level of theory and finer electronic energies were successively obtained, increasing the basis set up to 6/311+(2df,2pd) with B3LYP functional.

In Figure 11, are represented all four possible geometries of the TS leading to the formation of the corresponding nitroalkanes **100**.

Transition states responsible of the hydride transfer were located assuming the coordination of the nitro group of compound **91a** to the thiourea moiety and of the Hantzsch ester NH group with the catalyst carboxyamide group, according to the so-called Takemoto model (Figure 12). The energy profile is reported in Figure 12.

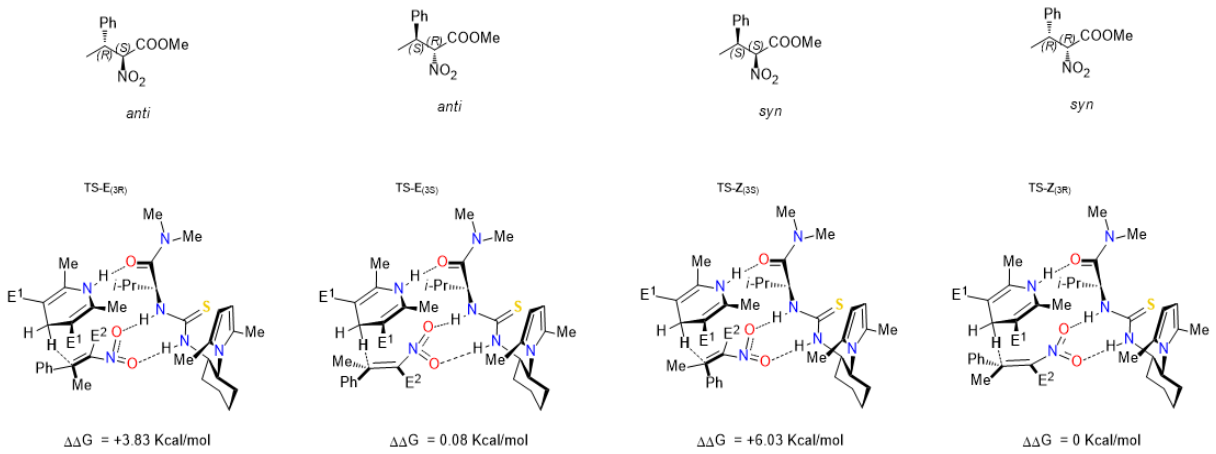


Figure 11: possible TS geometries to afford compound **100**

DFT computational studies revealed that the transition state TS-Z-*(3S)* originated from *(Z)*-olefin is higher in energy compared to TS-Z-*(3R)* and to those obtained from *(E)*-olefin.[69] However, as established in NMR analysis, the more reactive isomer is the *(E)*-nitroacrylate which seems to be more reactive, as demonstrated by NOESY experiment performed for this compound by Prof. Vasile. Here below (Figure 13a and 13b) the geometries of the transition states originated by *E*-isomer of compound **91a** are shown.

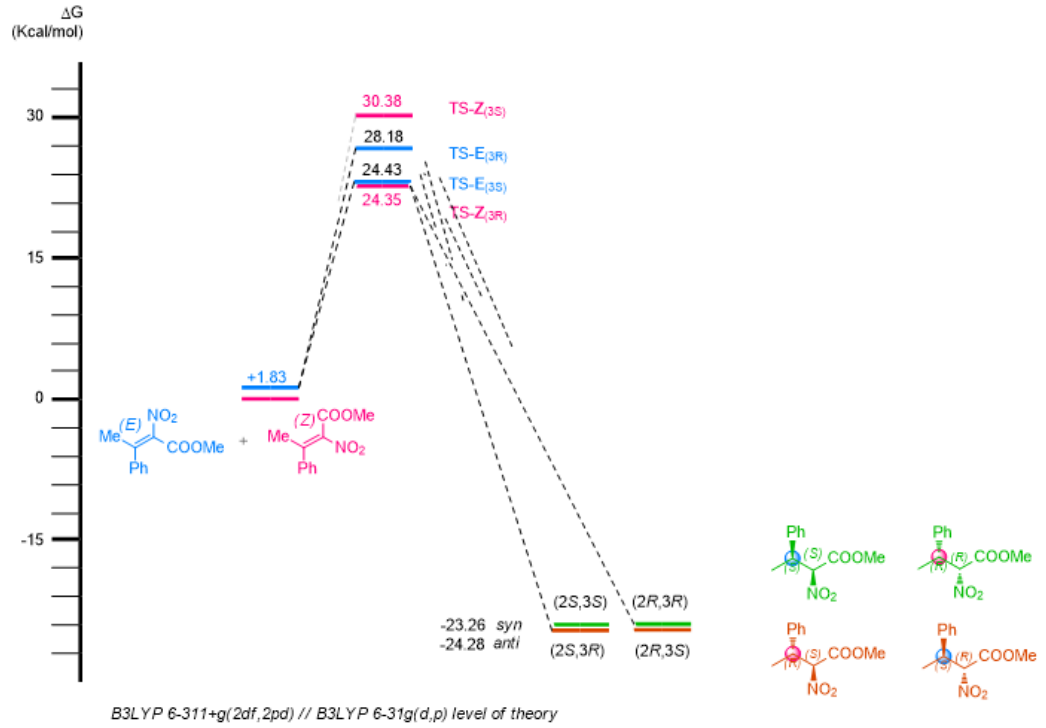


Figure 12: DFT calculations performed for the enantioselective reduction of tetrasubstituted nitroalkene **91a**

The blue spheres represent the nitrogen atom of the nitro group of 91a, and of the thiourea catalyst A. The yellow sphere represents the sulfur atom of the thiourea moiety. The red spheres represented the oxygen atoms corresponding with nitro and ester groups of compound **91a**, and of the carboxyamide group of the catalyst. The pink sphere represents the *tert*-butyl groups of the Hantzsch ester. The grey spheres represent carbon atoms and white spheres are those of hydrogen atoms. The broken lines showed the H-bonding interaction between the nitro group of compound **91a** and the thiourea moiety of the catalyst and the transfer hydride between Hantzsch ester and carbon C_3 of the nitroolefin.

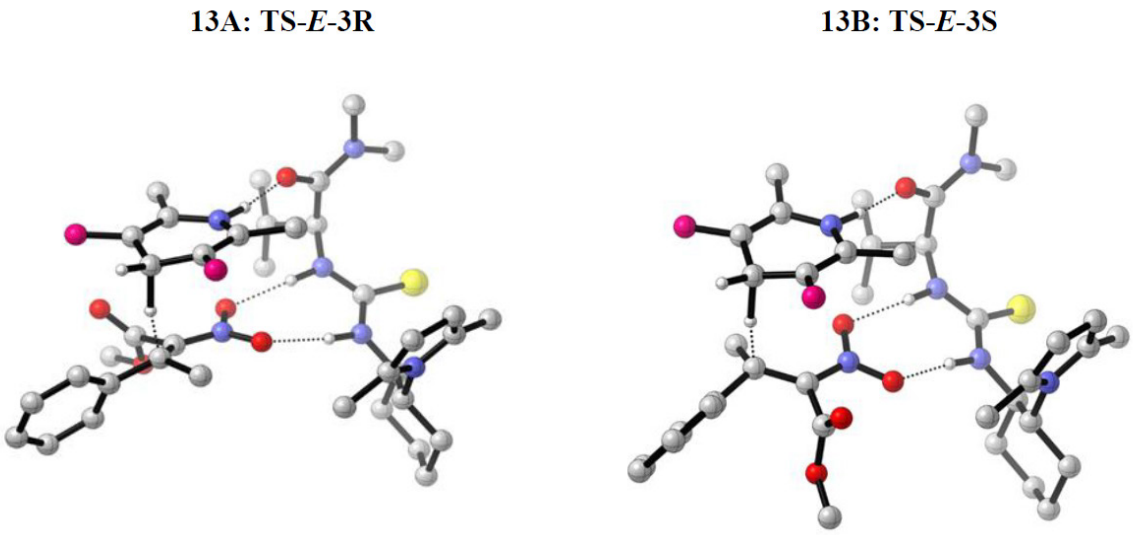


Figure 13: Transition states formed by E- isomer of nitroacrylate **82a**

According to the calculations, among the two transition states originated from Z-olefin, TS-Z-*(3R)* was responsible for the formation of the final product with R-configuration at the C3 carbon, as it is the lowest in energy. However, it is (Z) isomer, which was experimentally, demonstrated to be very poorly reactive, while the reactive isomer is the *E* olefin, which, according to the calculations, should preferably afford the (S) enantiomer at C_3 carbon of **100a**.

This prediction by the calculations is in contrast with the absolute configuration of the product that was experimentally determined to be *(R)*, as demonstrated below (see Section 6.1.3, pag.62).

Therefore, we can conclude that at the moment, the prediction (with high levels of accuracy) of the absolute configuration is not possible. The proposed TS according to the Takemoto model, is not able to explain why the *E* isomer should be more reactive than the *Z* isomer, and, furthermore, cannot predict the correct configuration at C_3 of the nitroalkane.

Those results are probably an indication that other coordination modes are active in the TS of the reactions, and other models need to be taken under consideration to rationalize the stereochemical outcome of the reaction. For example, at the moment further computational studies are underway considering the coordination of the thiourea group to the ester moiety, instead of the nitro group, as viable alternative.

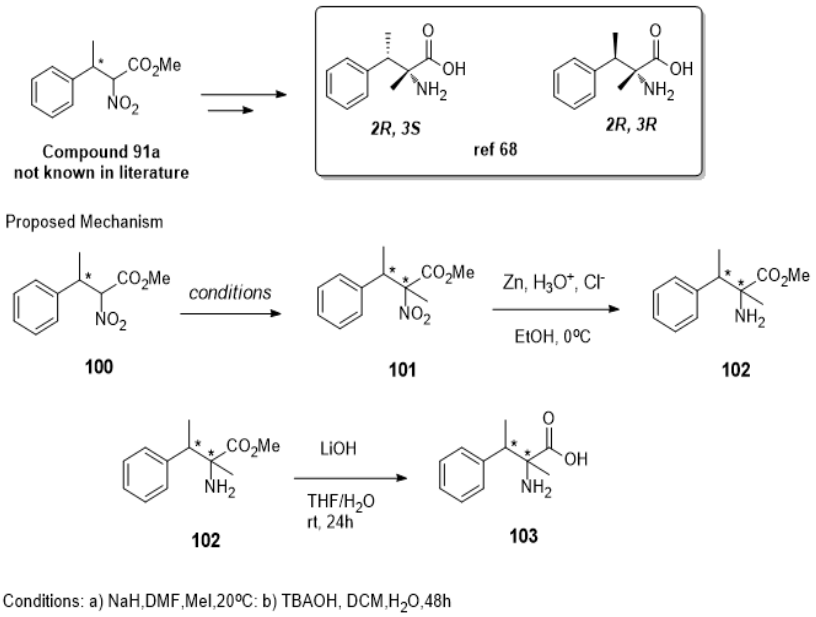
6.1.3 Determination of the absolute configuration of tetrasubstituted nitroalkanes

In previous sections, the synthesis of tetrasubstituted nitroalkenes **91** and their enantioselective reduction was successfully developed getting the corresponding functionalized nitroalkanes **100** with good to moderate yields. DFT computational studies of the enantioselective reduction also demonstrated that transition state TS-*Z-3R* of starting material was responsible of the formation of the product with *R* configuration at C_3 of the compound.[69] Nevertheless, in order to validate the predictions obtained with the DFT calculations, it was necessary to determine experimentally the absolute configuration of the generated stereocenter.

To achieve this goal, we choose to convert our target nitroalkane **91a**, which was not published in literature before, into a published known compound **103** to compare the experimental value with the value offered by the published one. A literature search was then performed to find a suitable strategy for the transformation of our molecule in a published compound.[70] In Scheme 42, the proposed synthetic procedure for the synthesis of the corresponding amino acid **103** is represented.

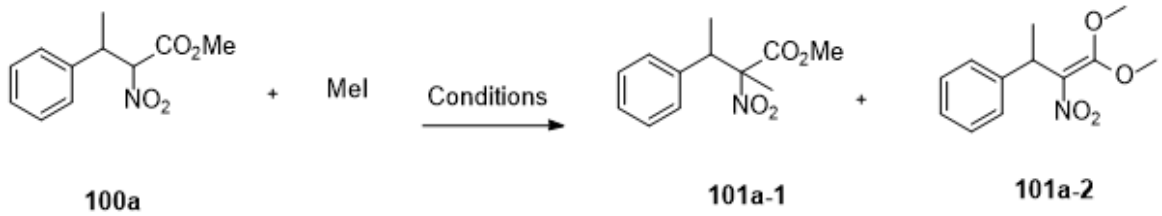
A shown in Scheme 42, compound **91a** was transformed into already published amino acid **103** by initial formation of the corresponding alkylation intermediate **101** followed by the reduction of the nitro group to obtain the amino ester **102** and finally, hydrolyzation of the

ester group, which led to the formation of the desired amino acid **103**.



Scheme 42: Proposed synthetic strategy for the experimental determination of the absolute configuration

The alkylation step was firstly investigated. [71,72] In particular, the reaction between compound **100a** using methyl iodide as the alkylation agent and different reaction conditions were tested (Scheme 43). The results are summarized in Table 5.



Scheme 43: Alkylation of compound 100a

Table 5: Alkylation of compound 100a

Entry	Conditions	Compound 101a-1	Compound 101a-2	Presence of compound 100a in the NMR crude
1	NaH, DMF, 18h, 20ºC	Observed	Observed	No
2	TBAOH*30H_2O DCM/H_2O 48h, RT	traces	Observed	No
3	CsOH*H_2O, O-Allyl-N-(9-anthracenylmethyl)-cinchonidinium-bromid , Toluene/$CHCl_3$, RT, 48h	traces	Observed	Yes
4	TEA, 4d,RT	Not observed	Not observed	Yes
5	K_2CO_3, Acetone, 4d, RT	Not observed	Observed	No
6	TBAB, tBUOK, Toluene, 48h RT	Not observed	Traces	Yes

The alkylation of compound **100a** with methyl iodide was very challenging. Despite many different conditions tested, it was not possible to isolate the target compound **101a-1**, which was the *C*-alkylation compound, obtaining the corresponding *O*-methylation compound **101a-2** as the major one in most of the reactions carried out (Table 5, entries 1, 2, 3 and 5). This compound was isolated after column chromatography and identify as the O-methylation due to the presence of an additional OMe group signal in the ^{1}HNMR spectra (Figure 14).

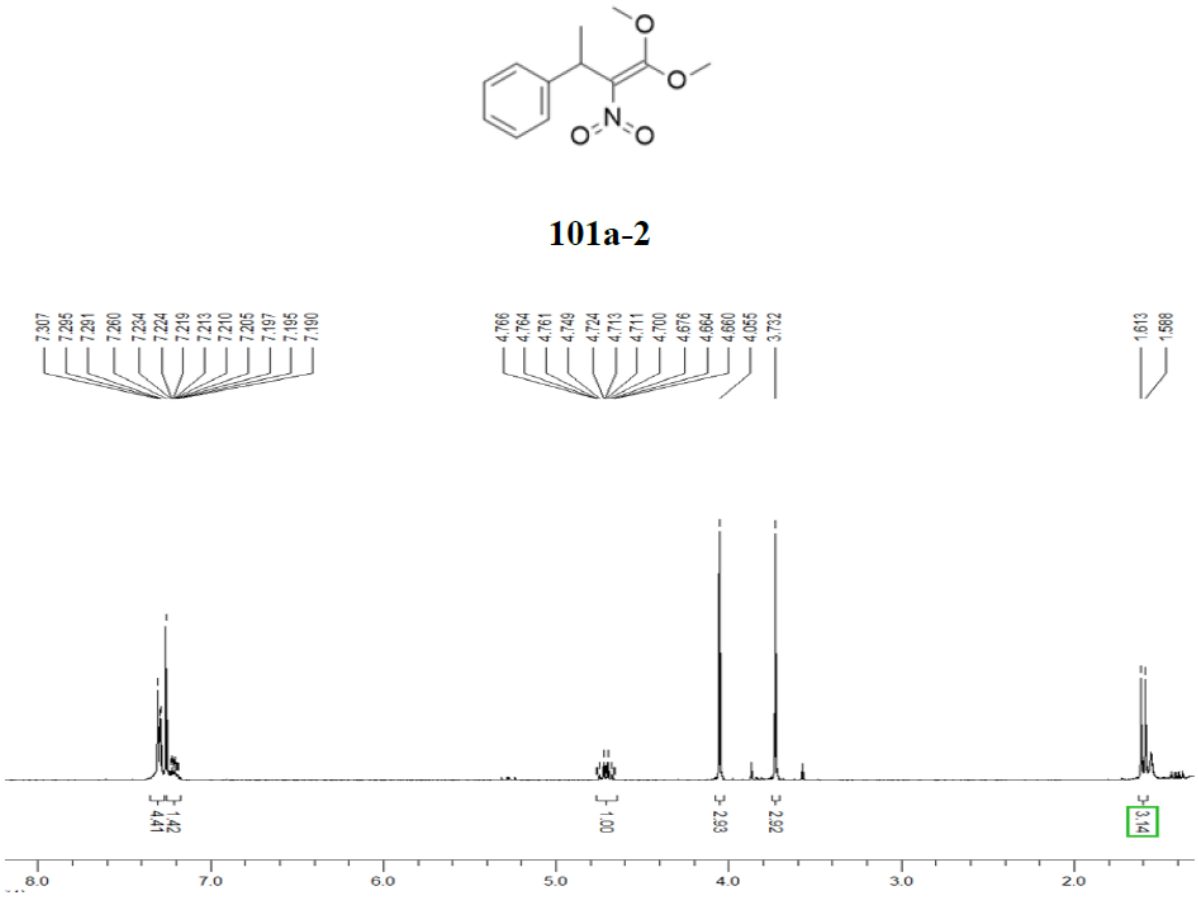


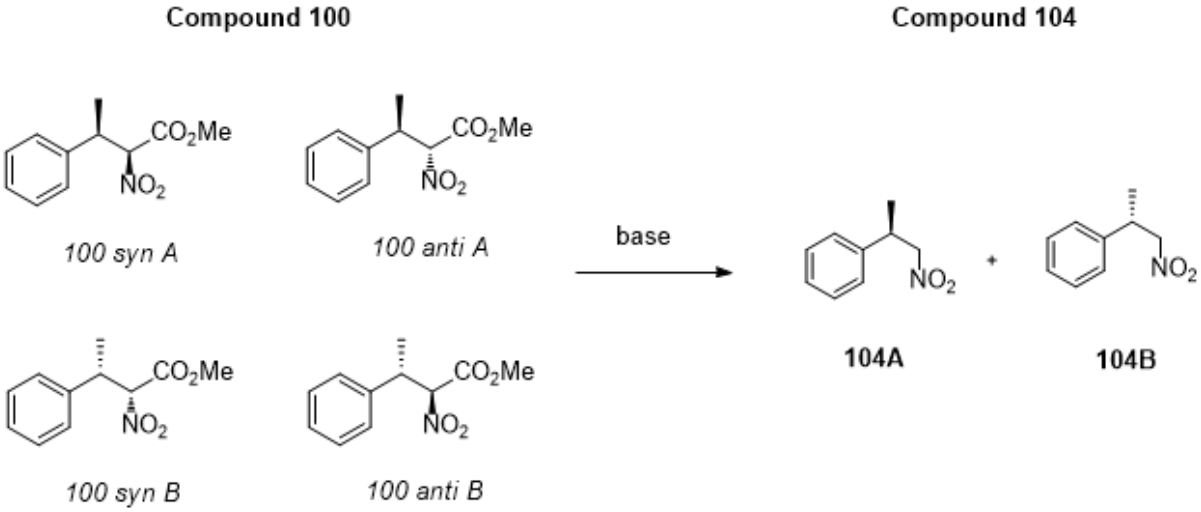
Figure 14: NMR obtained for compound O-methylation compound **101a-2**

Using sodium hydride conditions (Table 5, entry 1) and 1.5 equivalents of methyl iodide, compound **101a-1** was observed, but unfortunately, could not be isolated after purification. Surprisingly, when TEA as base was used (3 equivalents of methyl iodide was employed) no reaction was observed after 4 days (Table 5, entry 4). Then, it was decided to try with phase transfer conditions (Table 5, entry 3) but, compound **101a-2** was predominantly found, and some degree of starting material was also recuperated after 48h at RT.

In another attempt to be more successful, a reaction using TBAB as PTC catalyst was attempted (Table 5, entry 6) with 3 equivalents of methyl iodide but, unfortunately, a new unknown compound was obtained.

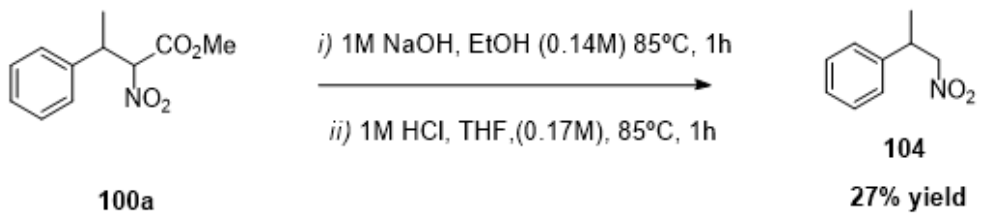
Although the synthetic strategy proposed was promising, I had to face several difficulties in the alkylation step and it proved inefficient to keep on investigating further. This unexpected challenge made us change the initial approach and look for another methodology for the experimental determination of the absolute configuration of nitroalkane **100** though.

The decarboxylation of the ester moiety of compound **100a** was then used to afford the corresponding trisubstituted nitroalkene **104** (Scheme 44) as a new synthetic strategy to reach our goal.[73]



Scheme 44: New synthetic route for the experimental determination of the absolute configuration

The nitroalkane **100a** was treated with a 1M solution of sodium hydroxide in Ethanol, followed by the reaction with 1M hydrochloric acid in THF to afford compound **104** as shown in Scheme 45.[73]



Scheme 45: Decarboxylation of compound **100a**

This new simple and faster methodology (involved only two reaction steps), worked properly and allowed to get the corresponding trisubstituted nitroalkane but with low yield. The optical rotation of the synthetized compound **104** was measured and the data obtained was compared with the published optical rotation values for the same compound found in the literature.[74] The positive sign of the experimental optical rotation observed, confirmed that compound ***R*-100a** was the one preferentially obtained, with *R* configuration at carbon 3 of compound **100a**. Since computational studies are not in agreement with the experimental ones, further studies will be necessary in order to find the transition states responsible of the stereochemistry of the reaction.

Based on this experiment also compounds **100e**, **100f** and **100g** are presumed to have *R* configuration at carbon 3 of these compounds. Importantly, the stereoselectivity of the generated stereocenter in the enantioselective reduction was successfully established.

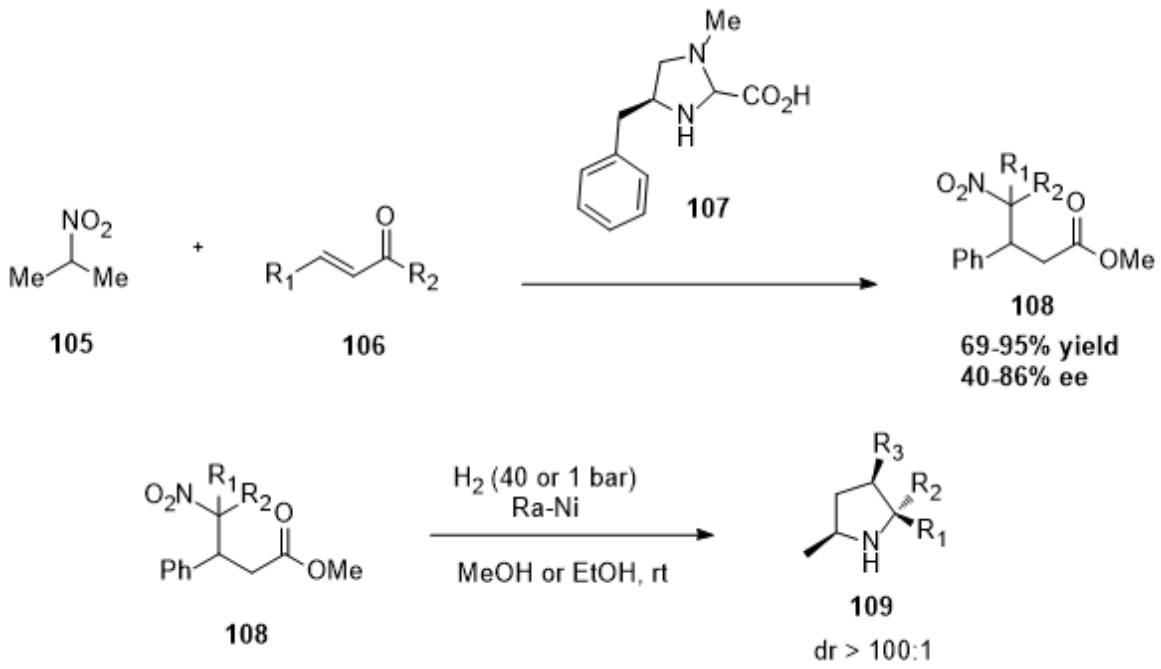
6.2 Organocatalyzed Michael addition of substitute nitropropionates to α,β-unsaturated ketones

Enantioselective construction of quaternary stereocenters is a complex process, due to the difficulties to obtain both high enantioselectivities and chemical efficiency. It remains a challenge developing new enantioselective methodologies for the synthesis of α,α-amino acids derivatives to this date.

One of the most useful and employed reactions for the construction of C-C bonds in organic chemistry is the Michael addition reaction. A large number of publications on this topic have been found based on the type of organic synthons associated with the reaction.[75]

In 2002, Jorgensen *et al*, reported an asymmetric conjugate addition of nitroalkanes **105** to α,β-unsaturated ketones **106**, catalyzed by a novel imidazoline catalyst **107** (Scheme 46).[76]

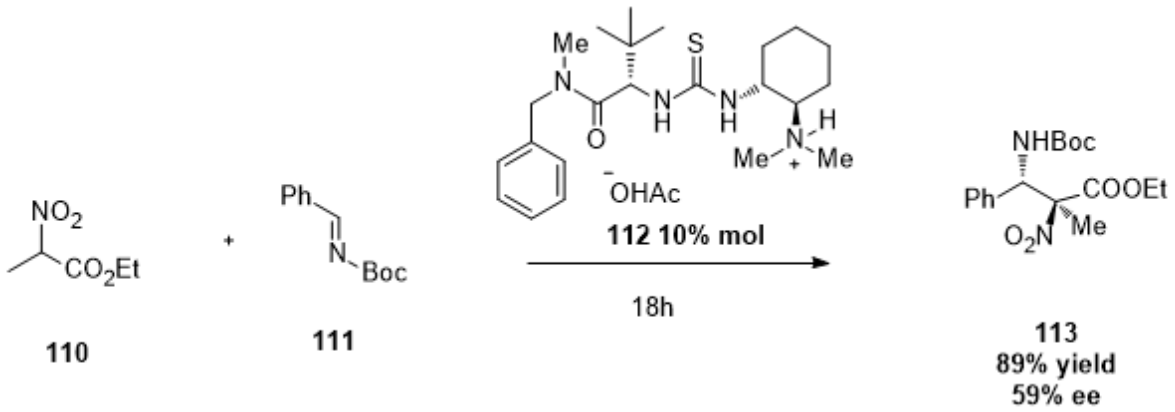
The corresponding compounds **108** were obtained with high yields and up to 83% of ee and were transformed into functionalized pyrrolines and pyrrolidines maintaining the enantioselectivity observed and with high diastereoselectivity (Scheme 46).



Scheme 46: Organocatalytic asymmetric conjugate addition of nitroalkanes to α,β-unsaturated enones

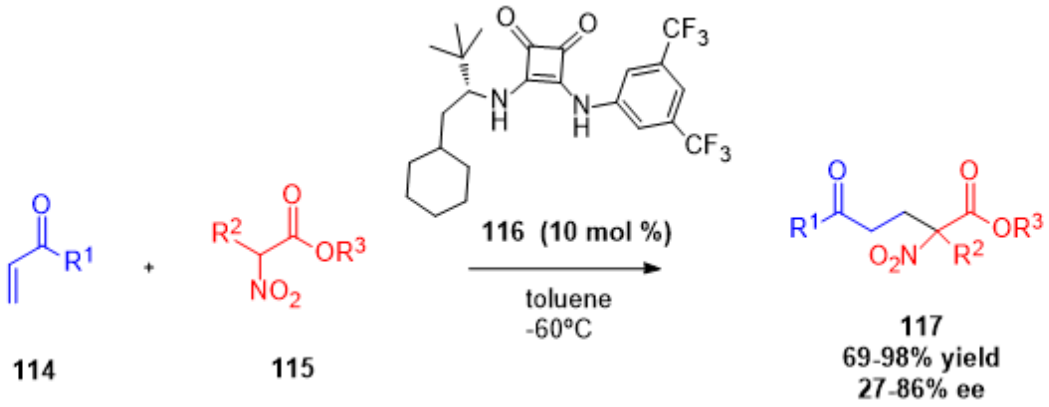
Despite the vast amount of scientific data on the organocatalyzed asymmetric Michael addition using acyclic or cyclic nitroalkanes, 1,3-dicarbonyl compounds and substituted nitroalkanes such us 2-nitropropane as Michael donors,[75,76] there are only a few examples regarding the use of nitroesters.

For example, in 2009 Puglisi *et al*,[77] reported the use of a low-cost bifunctional catalyst **101** as an efficient promotor of the conjugate addition of nitroesters **110** to imines **111** (Scheme 47) with high yield and good enantioselectivities. The positive charge located on the nitrogen of the organocatalyst **112** can stabilize the interaction between the enolic form of the nitroester and the imine by H-bonding interaction.



Scheme 47: Enantioselective addition of ethyl-2-nitropropionate to N-Boc-imine

More recently, Namboothiri and co-workers[78] reported in 2016 an enantioselective Michael addition of tertiary α-amino acids **115** to β-unsubstituted vinyl ketones **114** using a L-*tert*-leucine derived squaramide catalyst **116** (Scheme 48) and obtained the corresponding α-quaternary nitroesters **117** with good yields and good enantioselectivities.

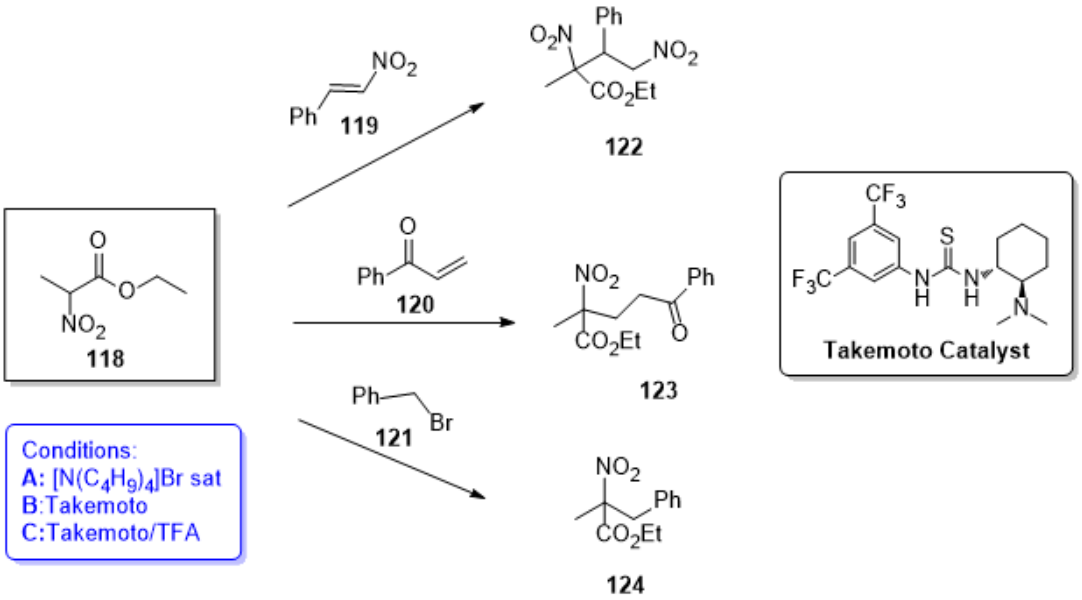


Scheme 48: Enantioselective Michael addition of tertiary α-amino acids

The versatility of this reaction and the well-tolerance of the substrates encouraged us to base the next experiments on this chemistry but, initially different Michael acceptors were used, such us nitrostyrene, α,β-unsaturated ketones and benzyl bromide and ethyl-2-nitropropionate as substrate.

Following a discussion with my PhD tutor regarding the best choice of conditions for my reaction and which catalyst I need, I was advised to use a Takemoto's catalyst, a well-known thiourea catalyst that was designed and produced by Takemoto's group when they developed the first enantioselective and organocatalytic addition of dimethyl malonates to nitroalkenes.[79]

Takemoto's catalyst was the first bifunctional amine thiourea organocatalyst reported in the literature.[79] It is a very potent and highly efficient and as a bifunctional catalyst, it can activate simultaneously nitroalkenes and the nucleophile through its tertiary amine group so, we decided to proceed with it when I made the very first preliminary studies on the organocatalytic Michael addition of ethyl-2-nitropropionate **118** with different Michael acceptors **119-121** using different conditions as shown in Scheme 49. The results are summarized in Table 6.



Scheme 49: Organocatalyzed Michael addition of ethyl-2-nitropropionate **118** using different Michael acceptors **119-121**

Table 6: Organocatalyzed Michael addition of ethyl-2-nitropropionate **118** using different Michael acceptors **119-121**

Entry	Conditions	Product	Time (h)	Yield[a] (%)
1	B	**119**	24	87
2	B	**120**	24	56
3	B	**121**	24	<10
4	C	**119**	24	49
5	C	**120**	24	<10
6	C	**121**	24	----
7	A	**119**	48	19
8	A	**120**	72	33
9	A	**121**	48	25

Reaction conditions: 0.2 mmol of ethyl-2-nitropropionate, 0.2 mmol of micheal acceptor 10%mol of catalyst and 200μL of Toluene; a= after purification with column chromatography

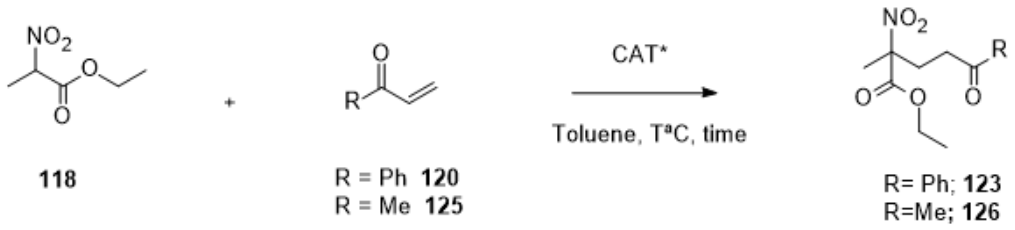
The reactions were initially investigated using Conditions *B* in the absence of catalyst, and it was demonstrated that no product formation could be observed after 24h at RT. In contrast, when Takemoto catalyst was used, products **119** and **120** were obtained with moderate yield after purification, while only traces of product **121** were detected. The addition of a catalytic amount of TFA to the mixture of Michael donor, Michael acceptors and Takemoto catalyst (Conditions C) led to the formation of compound **119** with good yield after purification but, in the case of compounds **120** and **121**, the reaction did not work as expected and only traces of the desired products were detected after 24h at RT.

Phase transfer conditions A (Michael donor, Michael acceptors, TBAB, CsOH, solvent) were also tested, providing an improvement of conversion for products **120** and **121** compared to conditions C. However, the yields were very low after purification. It should be noted that out of all the conditions tested, conditions A proved to be the best ones for the synthesis of compound **121**, while conditions B were the best ones for the synthesis of compounds **119** and **120**.

Based on those preliminary data and on the published works in the literature, it was decided to focus on the less investigated transformation, the synthesis of compound **123** that was not previously reported in literature in an enantioselective manner. Therefore, the results obtained on the enantioselective organocatalyzed Michael addition of ethyl-2-nitropropionate **118** to α,β-unsaturated ketones **109** and **114** catalyzed by different organocatalysts is described in the next sections.

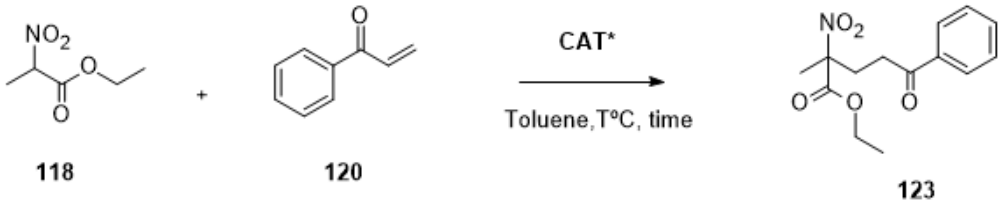
6.2.1 Organocatalyzed Michael addition of ethyl-2-nitropropionate to α,β-unsaturated ketones

Using conditions B, the organocatalyzed Michael addition of ethyl-2-nitropropionate **118** to α,β-unsaturated ketones **120** and **125** using different bifunctional catalysts was studied in an enantioselective manner (Scheme 50).[80]



Scheme 50: Organocatalyzed Michael addition of ethyl-2-nitropropionate to α,β-unsaturated ketones

The reaction was firstly investigated using phenylvinyl ketone **118** to obtain the corresponding compound **120** (Scheme 51a) using the organocatalysts represented in Figure 15. The results are summarized in Table 7.



Scheme 51: Organocatalyzed Michael addition of ethyl-2-nitropropionate **118** and phenilvynil ketone **120**: Synthesis of compound **123**

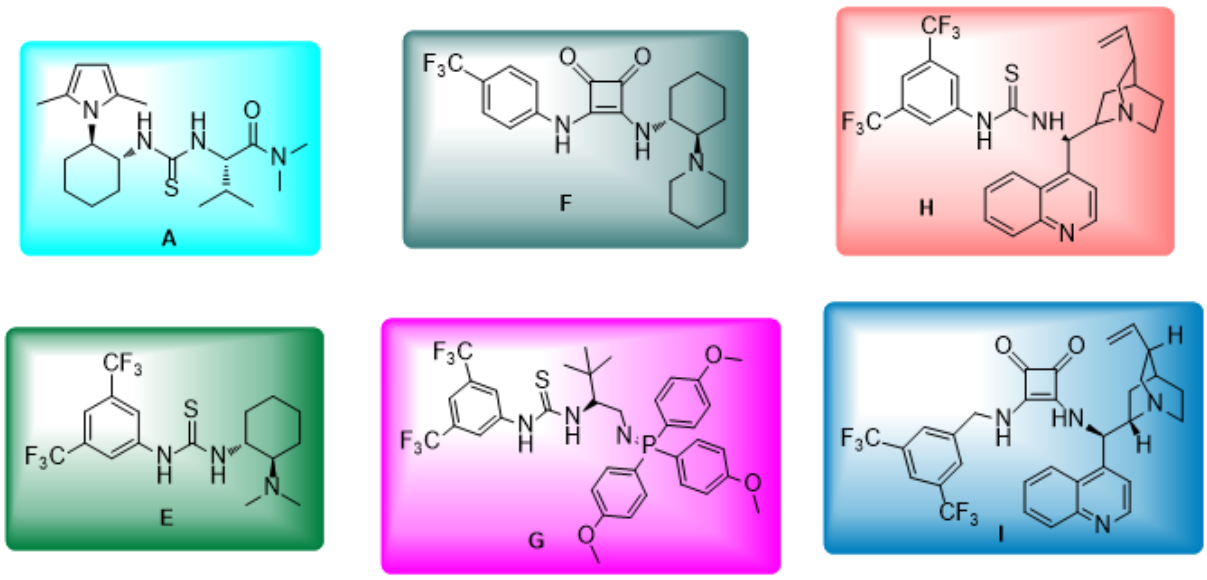


Figure 15: Structures of the Organocatalysts employed in the Michael addition of ethyl-2-nitropropionate

Table 7: Organocatalyzed Michael addition of ethyl-2-nitropropionate and phenylvinyl ketone: Synthesis of compound **123**

Entry	T°C/time	Catalyst	Yield[a] %	ee[b]
1	RT/48	none	----	----
2	RT/48	E	56	16
3	RT/48	A	60	1
4	0°C/48	A	39	7
5	RT/48	F	29	11
6	RT/ 15	G	67	5
7	-20/24	G	7	8
8	-20/48	H	23	2
9[c]	RT/18	I	50	16
10[c]	-20/24	I	65	20

Conditions: 0.25 mmol of ethyl-2-nitropropionate, 0.25 mmol of ketone, 10% of catalyst in 1mL of Toluene; a= after purification by column chromatography; b= using chiral column Phenomenex Cellulose 3 Hexane/IPA 90:10 1 mL/min; c= using DCM as solvent RT= room temperature

The Michael addition of ethyl-2-nitropropionate **118** and phenylvinyl ketone **120** was studied using different **organocatalysts A-I** which are represented in Figure 15. The thiourea catalyst **A** was employed in these experiments, the squaramide catalyst **F** was commercially available whereas the thiourea catalyst **E** and the iminophosphorane catalyst **G** were available in my laboratory. The thiourea catalysts **H** and the squaramide catalyst **I** were synthetized according with literature procedures (references 7 and 8 of the Materials and Method section). Control experiment of this reaction was performed, and no reaction occurred in the absence of catalyst. However, when **catalysts A-I** were used, compound **112** was obtained with good to moderate yield after purification with column chromatography. The use of the thiourea **catalyst E** (Table 7, entry 2) promoted the formation of the product with good yield but, only a maximum of 16% ee was observed.

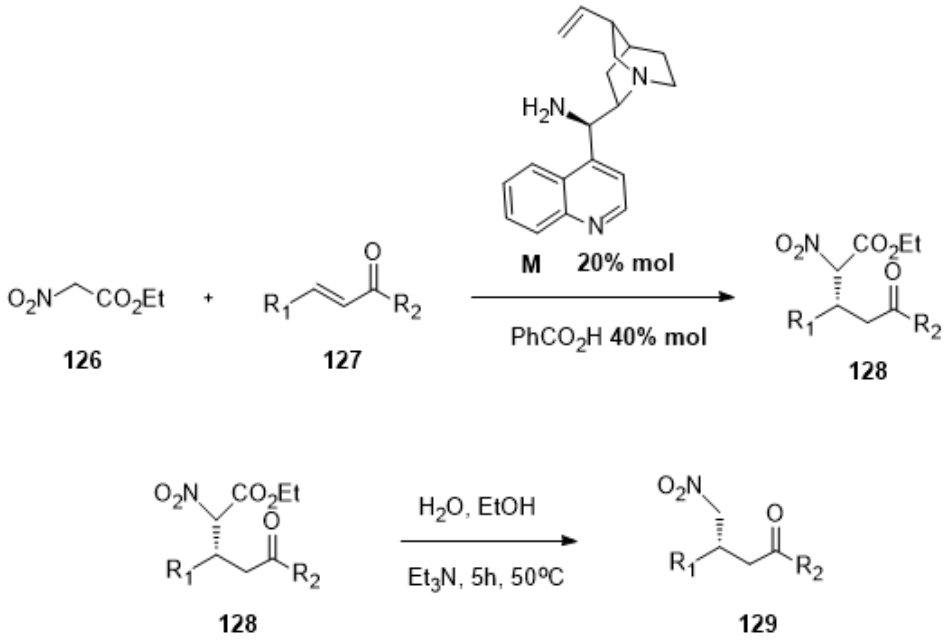
Unfortunately, a lower enantiomeric excess was observed with **catalyst A** (Table 7, entries 3,4) and despite the product was formed with moderate yield, only 7% ee was observed. The iminophosphorane **catalyst G** (Table 7, entry 6) which allowed to obtain the product with very high yield, gave disappointing results for the enantioselectivity (5% of ee at RT). This value was slightly improved to 8% when the reaction was performed at -20ºC (Table 7, entry 7) but the yield was drastically reduced. Lastly, I tested the thiourea **catalyst H** (Table 7, entry 8) and obtained the product with low yield and as almost a racemic mixture.

Furthermore, the reaction was also studied with squaramide **catalyst F** (Table 7, entry 5) which led to the formation of the product with 29% yield, however only 11% ee was found. In addition, the squaramide **catalyst I**, was not found completely dissolved in toluene, so the reactions were conducted using DCM as solvent instead (Table 7, entries 9, 10) which resulted in good yields of the product after filtration of the catalyst followed by preparative TLC purification. In this case, a maximum of 16% ee at RT was achieved, only slightly improved when the reaction was carried out at lower temperature, reaching 20% ee.

Despite of different type of bifunctional catalysts used in these experiments were successful in promoting the required reactions, the enantioselectivity observed was very low. In view of this, I had to search for another type of activation for this transformation which was more effective and produced better enantioselectivities and decided to try aminocatalysis conditions (see Experimental Section for further details) for this reaction. Unfortunately,

when the reaction was tested with L-Proline **L** as a catalyst, it took three days to identify traces of product. A similar result was observed when a combination of morpholine and L-Proline was used.

The epi-9-deoxyaminocinchona **M** was also tried based on the Kim and co-workers' work regarding the use of this amine as catalyst for the enantioselective organocatalyzed conjugate addition of ethyl nitroacetate **126** to α,β-unsaturated ketones **127**, under aqueous reaction conditions (Scheme 52).[81]



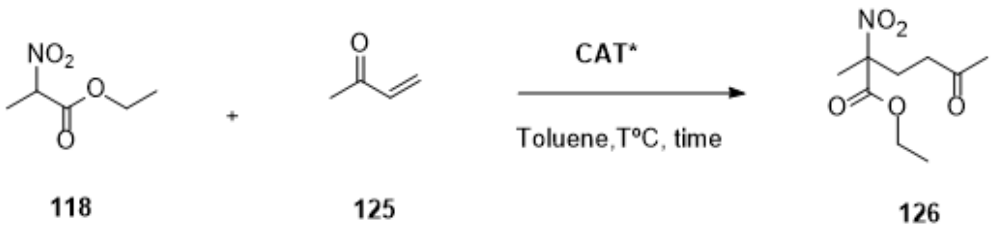
Scheme 52: Enantioselective organocatalytic conjugate addition of α-nitroacetate to α,β-unsaturated ketones

The corresponding chiral γ nitro ketones **128** were obtained with high yields and enantioselectivities under mild reaction conditions. Decarboxylation of the ester moiety yielded the corresponding keto nitroalkanes **129** with high yields.

At this point, the reaction between ethyl-2-nitropropionate **118** and methylvinyl ketone **125** (Scheme 53) was also studied using the organocatalysts **A-I** and the results are summarized in Table 8.

The organocatalyzed Michael addition of ethyl-2-nitropropionate **118** with ketone **125** was performed using catalysts **A-I** represented in Figure 15. As in the case of the previous example, control experiment of this reaction was carried out, but no reaction was observed

in the absence of catalyst. However, catalysts **A-I** were able to promote the reaction leading to the formation of the corresponding compound **126** with good to excellent yields after purification with column chromatography.



Scheme 53: Organocatalyzed Michael addition of ethyl-2-nitropropionate: Synthesis of compound **126**

Table 8: Organocatalyzed Michael addition of ethyl-2-nitropropionate: Synthesis of compound **126**

Entry	T°C/time	Catalyst	Yield[a] %	ee[b]
1	RT/24	none	----	----
2	RT/24	A	----	----
3	RT/48	F	69	32
4	0°C/72	F	31	33
5	RT/15	G	82	9
6	-20/72	G	60	15
7	RT/48	H	53	2
8	-20/48	H	62	10
9[c]	RT/18	I	88	49
10[c]	-20/24	I	59	54

Conditions: 0.25 mmol of ethyl-2-nitropropionate, 0.25 mmol of ketone, 10% of catalyst in 1mL of Toluene; a= after purification by column chromatography; b= using chiral column Phenomenex Cellulose 5 Hexane/IPA 90:10 0.5mL/min; c= using DCM as solvent RT= room temperature

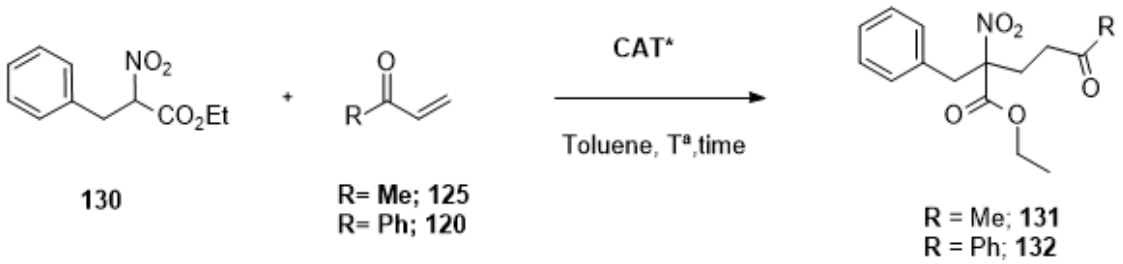
Furthermore, when thiourea catalyst **A** was tested (Table 8, entry 2), no reaction was observed. The squaramide **catalyst F** (Table 8 entries 3, 4) led to the formation of the product with good yield, obtaining an interesting value of 33% ee. An excellent yield was observed using the iminophosphorane **catalyst G** (Table 8 entry 5, 6), but, unfortunately, the enantioselectivity observed was only 15%. The same tendency was found using thiourea **catalyst H** (Table 8, entries 7, 8) obtaining a 10% ee. The squaramide **catalyst I** (Table 2 entries 9-10), was found to be the best one in terms of enantioselectivity, obtaining an excellent yield after 18h at RT and a promising 49% ee. This value was improved to 54% when the reaction was performed at lower temperature.

The replacement of a phenyl for a methyl group in the α,β-unsaturated ketone meant an improvement in the enantioselectivity observed when comparing the results obtained in both experiments. However, the values were still quite low for this transformation. Thus, also for this reaction, other activation modes were tested in order to improve the enantioselectivity observed (see experimental section).

Although phase transfer catalysts **J** and **K** was able to promote the reaction, the enantioselectivities observed were less than those observed during the reactions performed with organocatalysts. In addition, when proline **L** was used as catalyst, no reaction occurred (neither when 9-epi-9-deoxyaminocinchona **M** was used as catalyst).

6.2.2 Organocatalyzed Michael addition of benzyl nitropropionate to α,β-unsaturated ketones

So far, the Michael addition reaction of nitroesters to α,β-unsaturated ketones has been studied by changing the functional group in the Michael acceptor (ketone); it would be interesting to determine the effect and influence on the enantioselectivity of the substituent on the nitroester; therefore, the organocatalytic Michael addition of benzylnitropropionate **130** to α,β-unsaturated ketones **120** and **125** was studied using different organocatalysts **A-I** (Scheme 54) represented in Figure 16.



Scheme 54: Organocatalyzed Michael addition of benzyl nitropropionate **130** to α,β-unsaturated ketones **125** and **120**

The thiourea catalyst **A** which was previously synthetized (reference 3 of the Materials and methods section), was also employed in these experiments, the squaramide catalyst **F** was commercially available whereas the iminophosphorane catalyst **G** was available in the laboratory. The thiourea catalysts **H** and the squaramide catalyst **I** were synthetized

according with literature procedures.

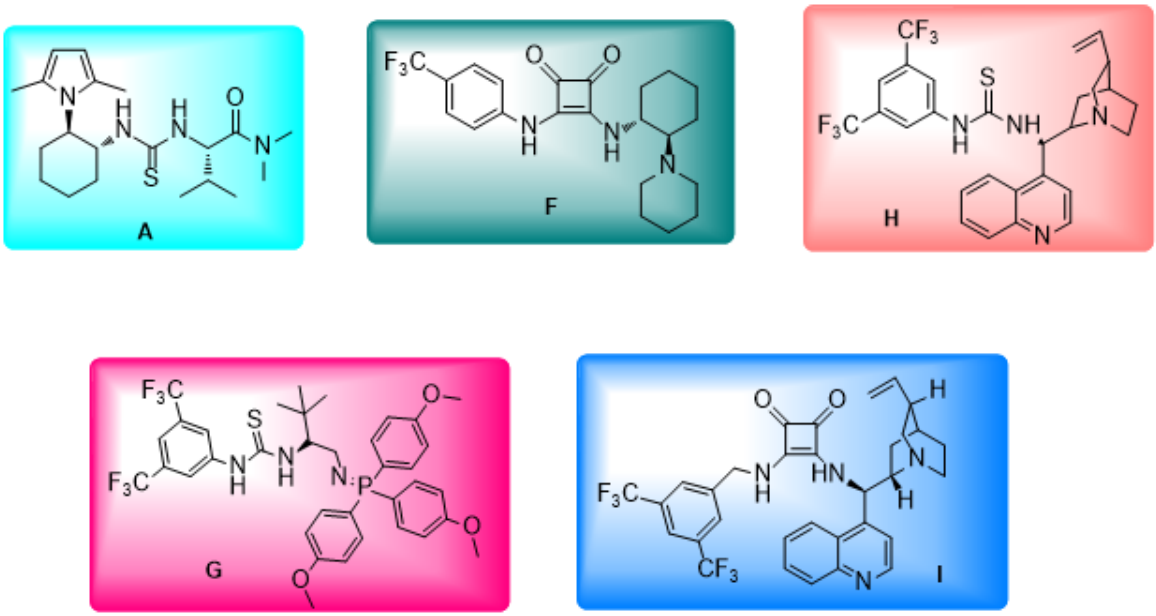
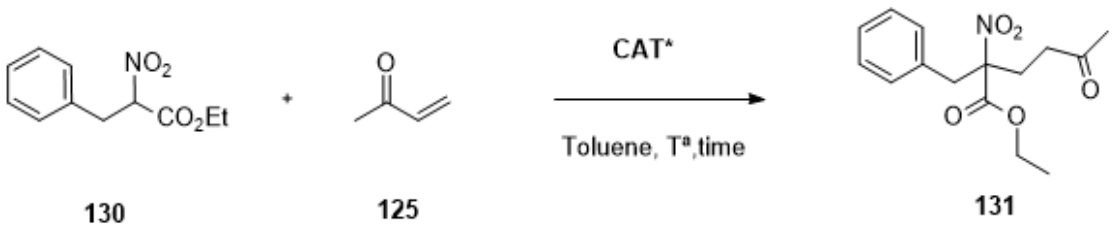


Figure 16: Structures of the Organocatalysts employed in the Michael addition of benzyl nitropropionate



Scheme 55: Organocatalyzed Michael addition of benzyl nitropropionate: Synthesis of compound **131**

Table 9: Organocatalyzed Michael addition of benzyl nitropropionate: Synthesis of compound **131**

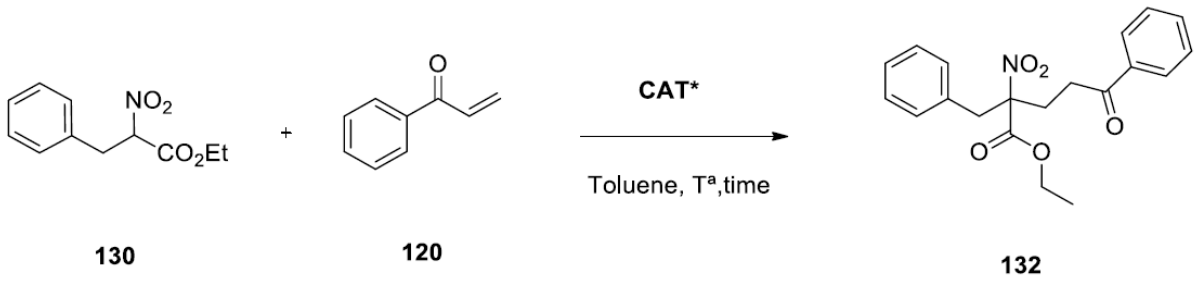
Entry	T°C/time(h)	Catalyst	Yield[a]	ee[b]
1	RT/24	----	NR	----
2	-20/40	A	NR	----
3	-20/60	F	27	40
4	-20/24	G	70	2
5	-20/40	H	43	9
6[c]	RT/18	I	82	41
7[c]	-20/18	I	35	53

Conditions: 0.25 mmol of nitroester, 0.25 mmol of ketone, 10% of catalyst in 1mL of solvent a= after preparative TLC purification; b= using a chiral column Cellulose 5Hex/iPA 90:10 1 mL/min; c= using DCM as solvent NR= no reaction

The reaction between benzyl nitropropionate **130** and methylvinyl ketone **125** using the organocatalysts represented in Figure 8 was firstly investigated (Scheme 55a). The results obtained are summarized in Table 9.

The organocatalyzed Michael addition of benzyl nitropropionate **130** and ketone **125** led to the formation of compound **131** with low to moderate yield after purification with preparative TLC. No product was formed when the reaction was performed in the absence of catalyst (Table 9, entry 1). The same happened when **thiourea catalyst A** (Table 9, entry 2) was used, no product was found to be formed. However, an interesting 40% ee was observed with squaramide catalyst F (Table 9, entry 3) whereas with the **iminophosphorane catalyst G** and the **thiourea catalyst H** (Table 9, entries 4, 5) only 2 and 9% ee were observed even despite the products were obtained with moderate and good yields.

The **squaramide catalyst I** was found to be the best catalyst for this transformation leading to the formation of the product with excellent yield at RT and a promising 41% ee. This value was also improved to 53% ee when the reaction was performed at a lower temperature.



130 **120** **132**

Scheme 56: Organocatalyzed Michael addition of benzyl nitropropionate: Synthesis of compound

Table 10: Organocatalyzed Michael addition of benzyl nitropropionate: Synthesis of compound 132

Entry	T°C/time (h)	Catalyst	Yield (%)	ee
1	-20/72	A	50	4
2	-20/72	F	34	32
3	-20/48	G	33	14
4	-20/48	H	37	2
5	RT/24	I	31	2
6	-20/36	I	47	2

Conditions: 0.25 mmol of nitroester, 0.25 mmol of ketone, 10% of catalyst in 1mL of solvent a= after preparative TLC purification; b= using a chiral column Cellulose 3 Hex/iPA 90:10 1 mL/min; c= using DCM as solvent NR= no reaction

Following this, the organocatalyzed Michael addition of benzyl nitropropionate **130** and phenylvinyl ketone **120** was also performed using the organocatalysts represented in Figure 16 (Scheme 56). The results are summarized in Table 10.

The organocatalyzed Michael addition of benzyl nitropropionate **130** and ketone **120** was performed and the corresponding compound **132** was synthetized with low yield after preparative TLC purification due to starting material also being recovered. The thiourea catalyst A led to the formation of the product with good yield but only 4% of ee. A higher ee was noted when squaramide **catalyst F** was tested (32% ee).

When the iminophosphorane **catalyst G** was used, the product was obtained with low yield and a maximum of 14% ee. A same tendency was found when thiourea **catalyst H** was used obtaining only 2% ee. Surprisingly, the squaramide catalyst I which was found to be the best catalyst for the synthesis of compounds **123**, **126** and **131**, did not work as expected obtaining only a 2% ee.

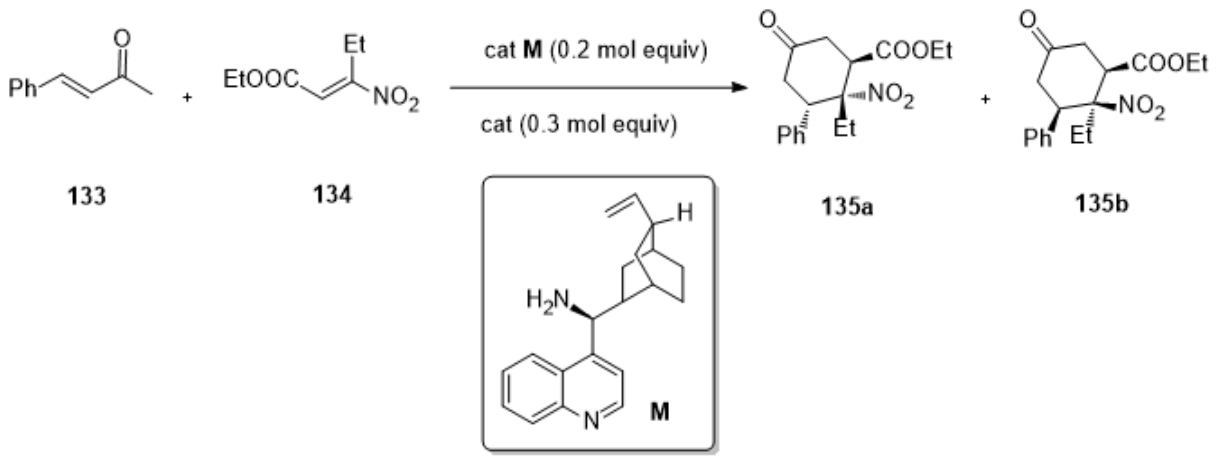
This could be most likely due to the presence of a second phenyl group in the molecule, which might not be very suitable for the interaction with the catalyst which was also very bulky.

The Michael addition of substituted nitropropionates **118** and **130** to α,β-unsaturated ketones **120** and **125**, was accomplished and compounds **123**, **126**, **131** and **132** were synthetized with good to moderate yields. Although the enantioselectivity observed was not very high, it should be noted that it was demonstrated that it is possible to achieve this transformation to afford functionalized nitroesters bearing a quaternary stereocenter in an enantioselective manner. Further studies aimed to optimize the catalyst structure are needed to improve the stereoselectivity of the process.

6.3 Reactivity experiments of tetrasubstituted nitroalkenes

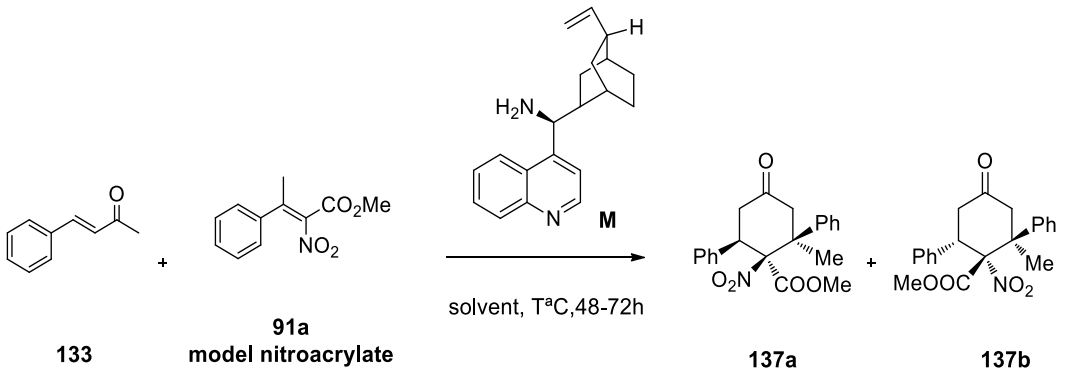
Despite the difficulties found during the synthesis of tetrasubstituted nitroalkenes **91** described previously, it was possible to prepare these compounds successfully. Indeed, their reactivity in the enantioselective reduction was demonstrated, and enantioenriched nitroalkanes **100** were obtained.

In an attempt to further explore the reactivity of tetrasubstituted nitroalkenes, their use in another reaction was preliminary explored. Considering that only a few examples are known for the Michael addition to nitroacrylates,[82] we decided to start from a recent publication by Massolo *et al*,[83] reporting an organocatalyzed reaction of trisubstituted nitroacrylates **134** to *in situ* generated dienamine of unsaturated ketone **133** using amino Cinchona derivatives **M** as catalyst (Scheme 57).



Scheme 57: Organocatalyzed reaction of nitroacrylates with *in situ* generated dienamine

This innovative protocol without the use of a metal catalyst, allows to obtain the corresponding 2-nitrocyclohexanecarboxylic esters **135** bearing two tertiary stereocenters and one quaternary stereocenter in good yields and up to 98% ee, and typically 90/10 diastereoselectivity. Compounds **135a** and **135b** are present in different natural bioactive compounds and are very relevant in drug discovery as they are key intermediates in the synthesis of critical pharmaceutical compounds such as β-lactam antibiotics.[84]



Scheme 58: Reactivity experiments of tetrasubstituted nitroacrylates

Based on this example, the reaction between benzalacetone **133** and nitroacrylate **91a**, in the presence of amino Cinchona **M** was studied (Scheme 58).

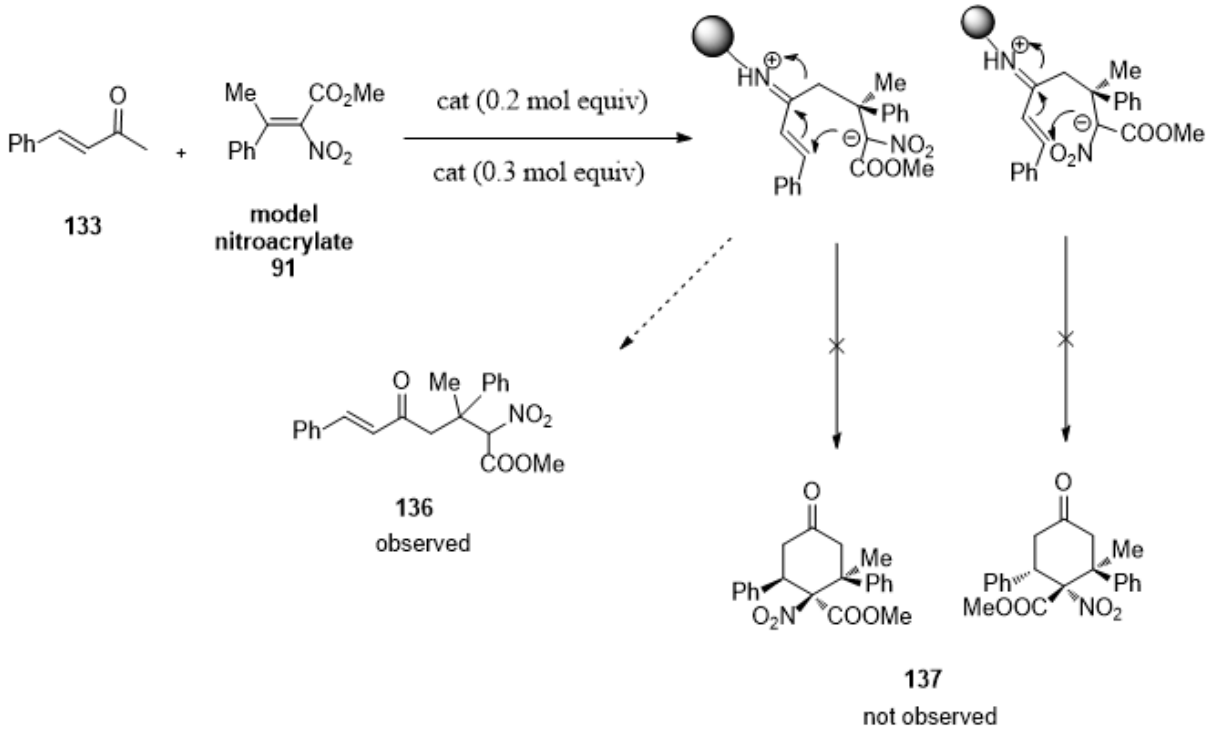


Figure 17: Suggested synthetic mechanism of the reaction of ketone **119** and the tetrasubstituted nitroacrylates **82**

The suggested mechanism for this reaction is represented in Figure 17 and involves two reaction steps: in the first step the ketone **119** is activated by the catalyst **M** by forming the dienamine system which reacts with the nitroacrylate **91a** to form the Michael adduct intermediate **136**, that should further evolve by an intramolecular reaction between the iminium species and the in situ generated carbanion (stabilized by the nitro group), resulting in the formation of the corresponding cyclohexanone derivatives **137a** and **137b**, as two possible stereoisomers that, among others, could been preferably formed, in analogy with the reaction of Scheme 58.

The reaction was studied starting from different fractions of starting material **91**. In Figure 18 the conversion vs time curves of the experiments conducted is represented. The blue line corresponds with the experiment starting from the less reactive isomer (LR) of starting material, the green line represents the experiment using the more reactive isomer (MR) as starting material, both at 40°C, while the orange line corresponds with the experiment starting from a mixture (60:40 ratio between MR/LR) of starting material performed at higher temperature (80°C).

The initial temperature for the first two experiments was based on the original paper by Massolo *et al*[81] where the reaction was run was 40ºC but, after 24h of reaction time the conversion was around 10% for the less reactive isomer and around 20% for the more reactive isomer. Thus, temperature was increased to 60ºC with the aim of improving these results and this resulted in a significant improvement of conversion in the reaction of the

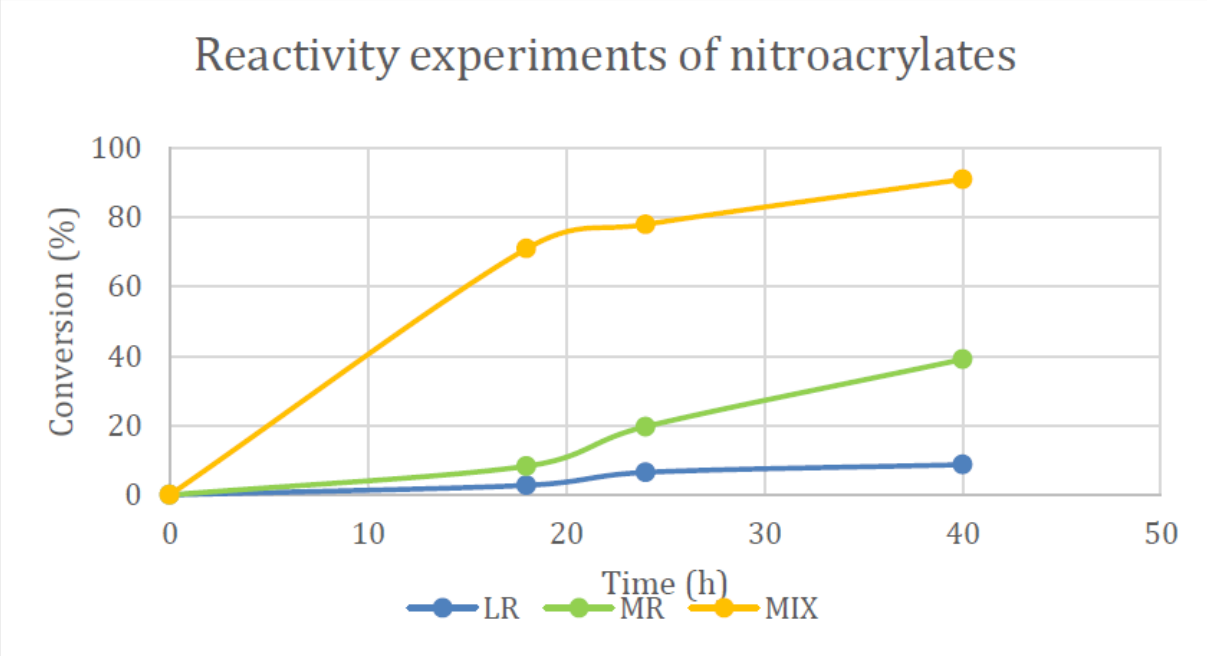


Figure 18: Conversion vs Time curves of experiments conducted

MR up to 40% after 40h whereas in the reaction of LR it was only possible to obtain 15% of conversion, confirming that this isomer reacts very slowly.

With this initial information, a new experiment starting from a mixture of isomers of starting material (60:40 MR/LR ratio) was conducted at 80ºC as the starting temperature. A remarkable improvement compared with the other two experiments was observed for this reaction, obtaining an up to 80% conversion after only 24h and almost 95% conversion after 40h of reaction time. All reactions showed the formation of several products and were purified by column chromatography; however, the only compound that could be isolated was the Michael adduct **136**, as mixture of isomers. Further attempts of cyclization of this compound to obtain the cyclohexanone **123**, using DBU as base and heating the mixture at 80ºC for 48h, did not lead to satisfactory results and formation of mostly decomposition compounds was detected.

Materials and Methods

7. Materials and Methods

7.1 General Methods

Chemical reagents

All chemical reagents used in this PhD research work were obtained from commercially available sources such as Sigma Aldrich, TCI chemicals and Combi-Blocks.

Solvents

All solvents were obtained from commercially available sources and had HPLC grade.

Chromatography

Flash chromatography was performed using Silica gel (70-230 mesh). For the thin layer chromatography (TLC) I used Macharery-Nagel cat No.818333 (20 x 20) plates on aluminum, silica layer thickness of 0.2 mm and is Silica 60 with UV254 indicator.
The enantiomeric excess of the synthetized compounds was measured under the corresponding reported conditions with Agilent 1100 series HPLC.

Nuclear magnetic resonance spectroscopy

The 1HNMR and 13CNMR experiments were measured using 300MHz Brucker equipment. Proton chemical shifts are showed in ppm (δ) and referenced considering the solvent peak (CDCl3= 7.26 ppm) as internal standard. Carbon chemical shifts are reported in ppm (δ) and referenced using the solvent resonance as the internal standard (CDCl3 = 77.0 ppm). Data are reported as: s = singlet; d = doublet; t= triplet; q= quartet; s= septuplet; m= multiplet.

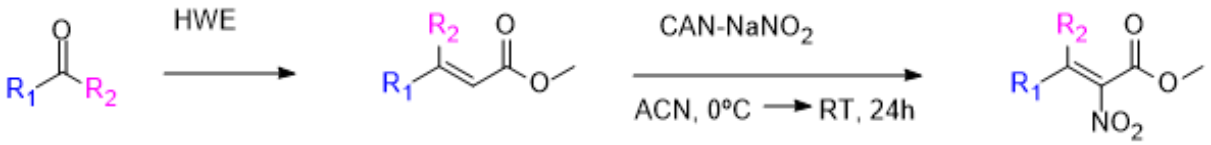
Mass spectroscopy

Mass spectra (MS) were carried out at CIGA (Centro Interdipartimentale Grandi Apparecchiature) with mass spectrometer APEX II Xmass software (Brucker Daltonics).

Polarimetry

Optical rotations were obtained employing a polarimeter at 589 nm using 1 mL cell 1dm long.

7.2 Synthesis and enantioselective reduction of tetrasubstituted nitroalkenes



HWE = NaH, $(CH_3O)_2P(O)CH_2CO_2CH_3$, THF,RT, 24h

The synthesis of tetrasubstituted nitroalkenes 91a-g was performed in two steps which involved the formation of an acrylate 89 starting from commercially available ketones 88 followed by their reaction of nitration using CAN-NaNO2 as nitration reagent to afford the desired compounds 91a-g

Step 1: Synthesis of intermediates 89 a-g

Compounds **89 a-g** were synthetized using conditions reported in literature.[55] First, a solution of trimethyl phosphonoacetate in 20 mL of THF was cooled to 0°C. Then, NaH was added portion wise and the mixture was stirred for 30 min. After this time, the appropriate ketone **79** was added at the same temperature and the reaction mixture was allowed to warm to room temperature and stirred for 24h at the right temperature (Figure 1). Then, 20 mL of saturated solution of ammonium chloride was added dropwise and the mixture was extracted with Et2O.

The combined organic phases were dried using $MgSO_4$, filtered and concentrated in vacuo. The solvent was eliminated under reduced pressure and the crude was purified using column chromatography and Hexanes/EtOAc as eluent. The 1HNMR of compounds **88a-g** were in agreement with the published ones. Compounds **88a-g** were directly used in the next step after purification.

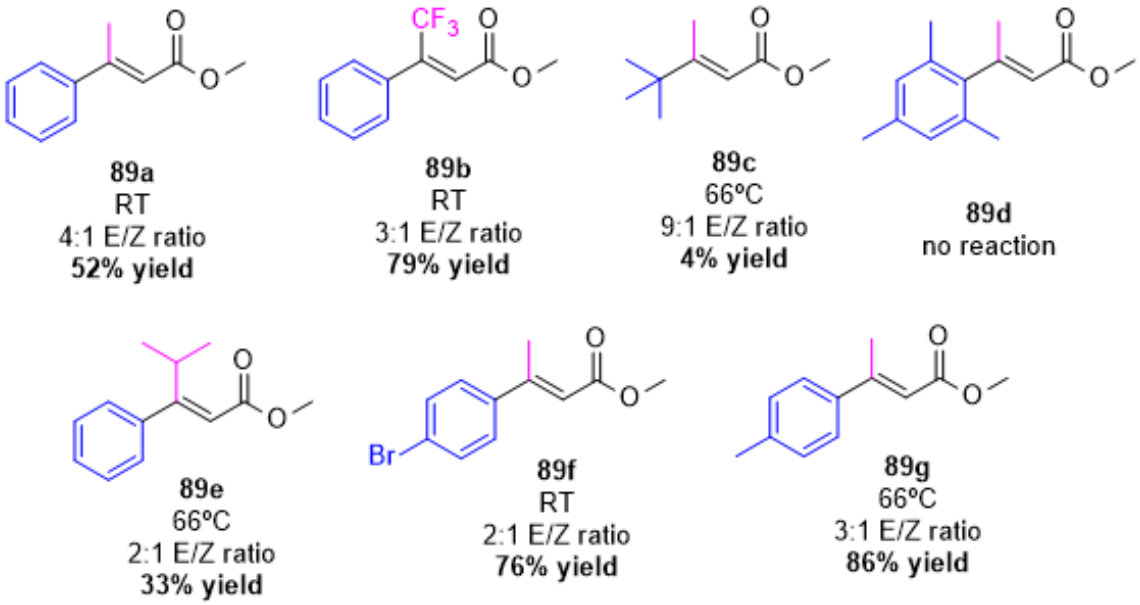
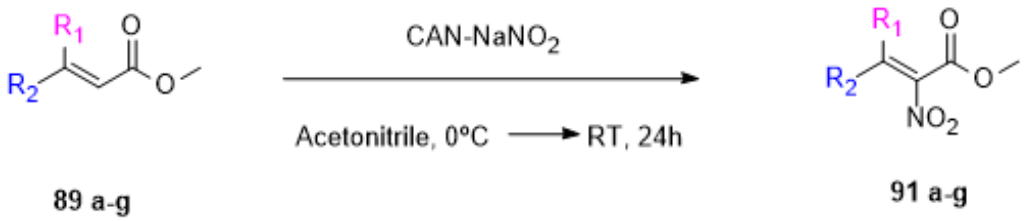


Figure 18: Chemical structures of compounds **89** a-g

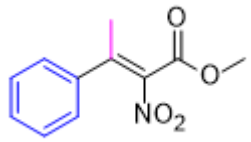
Step 2: Nitration of intermediates 89 a-g 62



The corresponding acrylates **89a**, **89b**, **89c**, **89e**, **89f** and **89g** (1 eq, 1mmol) were dissolved in 20 mL of Acetonitrile and cooled to 0°C. Then, sodium nitrite (3 eq, 3 mmol) and cerium ammonium nitrate (3 eq, 3mmol) were added at the same temperature, and the reaction mixture was allowed to warm to room temperature and stirred for 24h. After this time, the reaction was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was poured into cold water and extracted with DCM (3 x 50 mL). The combined organic layers were dried using $MgSO_4$, filtered and concentrated in vacuo.

The crude was purified by column chromatography using an appropriate mixture of solvents to afford nitroacrylates **91a**, **91d**, **91f** and **91g** in enriched mixtures of isomers as well as separate fractions of isomers. The reaction of nitration of acrylate **89c** did not lead to the formation of the corresponding nitroacrylate **91c** whereas when the reaction of nitration of acrylate **89b** was performed, the *p*-nitroacrylate was obtained as major compound.

Methyl 2-nitro-3-phenylbut-2-enoate 91a



Compound **91a** was obtained in 46% yield as colorless oil after column chromatography using Cyclohexane/Dichloromethane 1:1 as eluent. Both isomers were obtained.

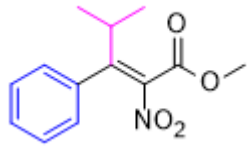
^{1}HNMR first isomer (CDCl3, 300 MHz) 2.55 (s, 3H) 3.85 (s, 3H) 7.21-7.25 (m, 2H) 7.35-7.37 (m, 3H)

^{1}HNMR second isomer (CDCl3, 300 MHz) 2.35 (s, 3H) 3.66 (s, 3H) 7.26-7.29 (m, 2H) 7.42-7.45 (m, 3H)

^{13}CNMR (CDCl3, 300MHz) 22.82, 52.80, 126.60, 128.53, 129.47, 137.20, 141.84, 149.26, 159.96

ESI MS (+) m/z = 244.0591 (M^{+} + Na)

Methyl 4-methyl-2-nitro-3-phenylpent-2-enoate 91d



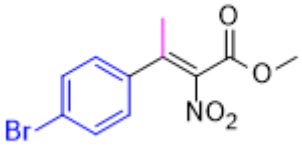
Compound **91d** was obtained in 25% yield as colorless oil after column chromatography using Cyclohexane/Diethyl ether (from 99:1 to 95:5) as eluent. In this case, one isomer pure and a mixture of both isomers were isolated.

^{1}HNMR (CDCl3 300 MHz) 1.04 (d, 6H) 3.87 (s, 3H) 3.93-4.02 (s, 1H) 7.07-7.10 (m, 2H) 7.34-7.36 (3H)

^{13}CNMR (CDCl3, 300MHz) 20.37, 29.57, 52.97, 127.38, 127.88, 132.37, 141.55, 158.48, 159.51

ESI MS (+) m/z = 272.0893 (M^{+} + Na)

Methyl 3-(4-bromophenyl)-2-nitrobut-2-enoate 91f



Compound **91f** was obtained as colorless oil in 47% yield after column chromatography in Cyclohexane / Dichloromethane 1:1. Both isomers were obtained.

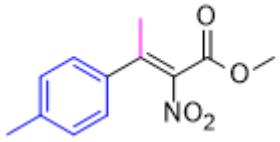
^{1}HNMR first isomer (CDCl3, 300 MHz) 2.54 (s, 3H) 3.87 (s, 3H) 7.11 (d, 2H) 7.52 (d, 2H)

^{1}HNMR second isomer (CDCl3, 300 MHz) 2.28 (s, 3H) 3.66 (s, 3H) 7.13 (d, 2H) 7.55 (d, 2H)

^{13}CNMR (CDCl3, 300 MHz) 22.90, 53.14, 124.00, 128.45, 131.97, 136.10, 142.06, 148.07, 159.67

ESI MS (+) m/z = 321.9691 (M+ + Na)

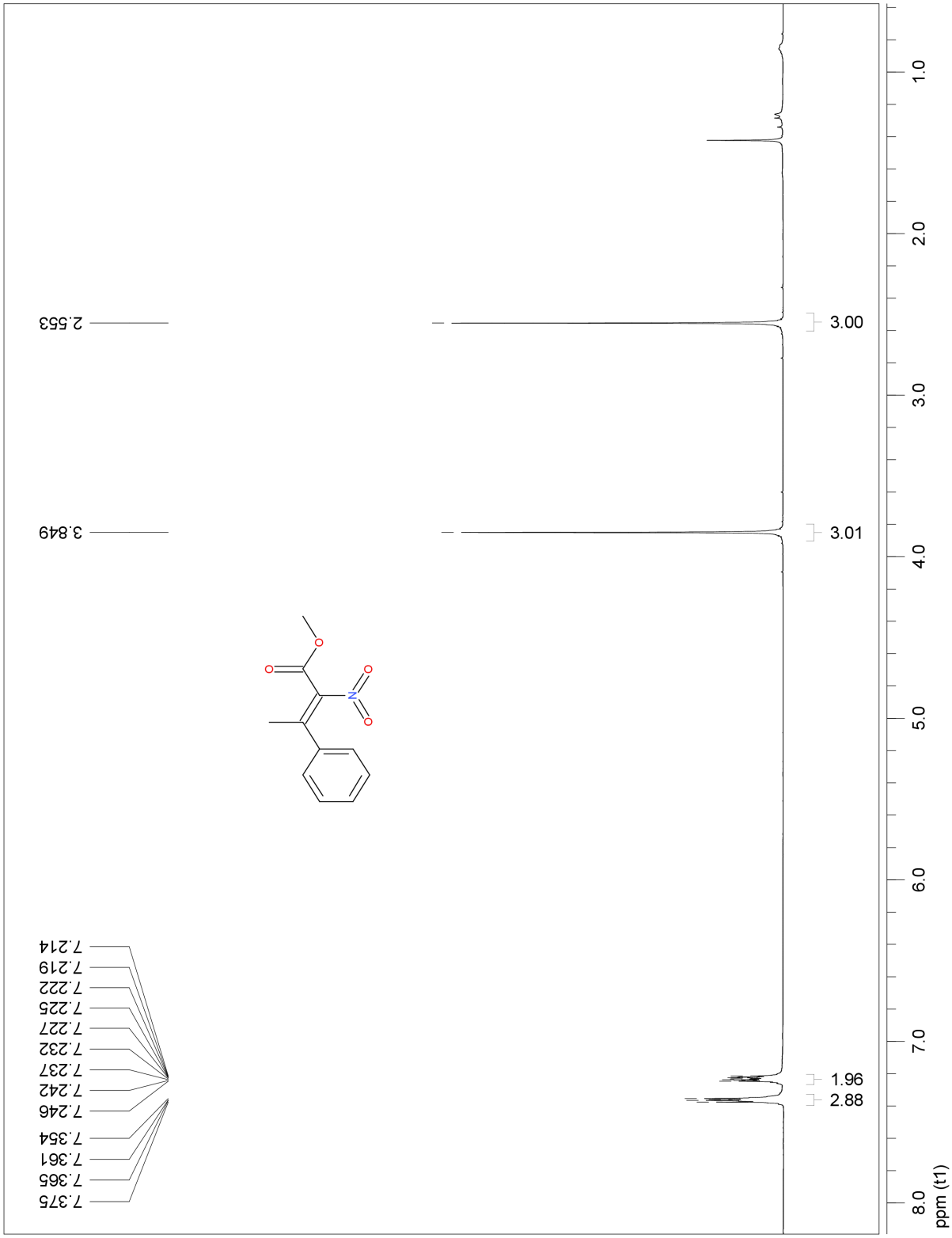
Methyl 2-nitro-3-(p-tolyl)-2-butenoate 91g

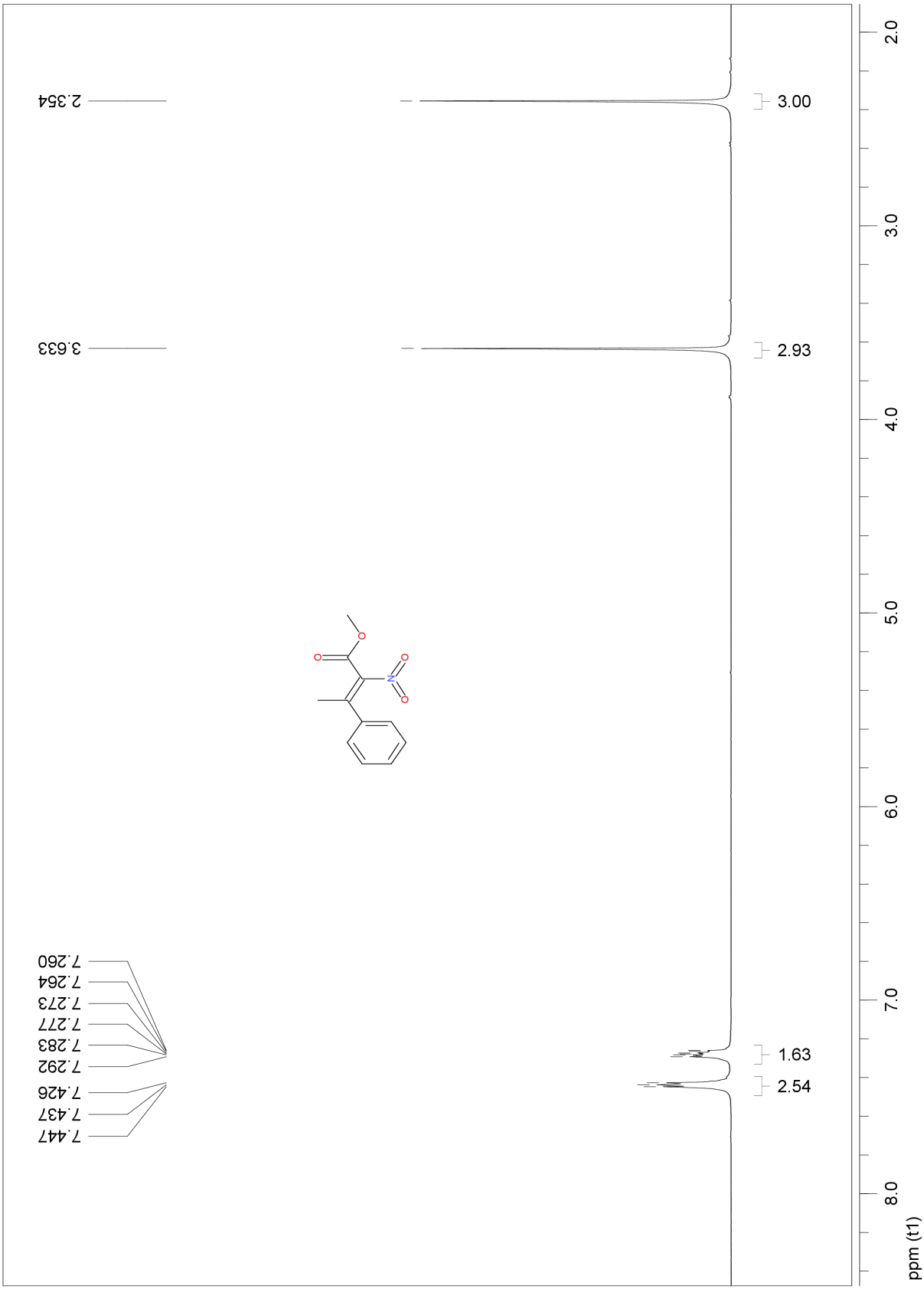


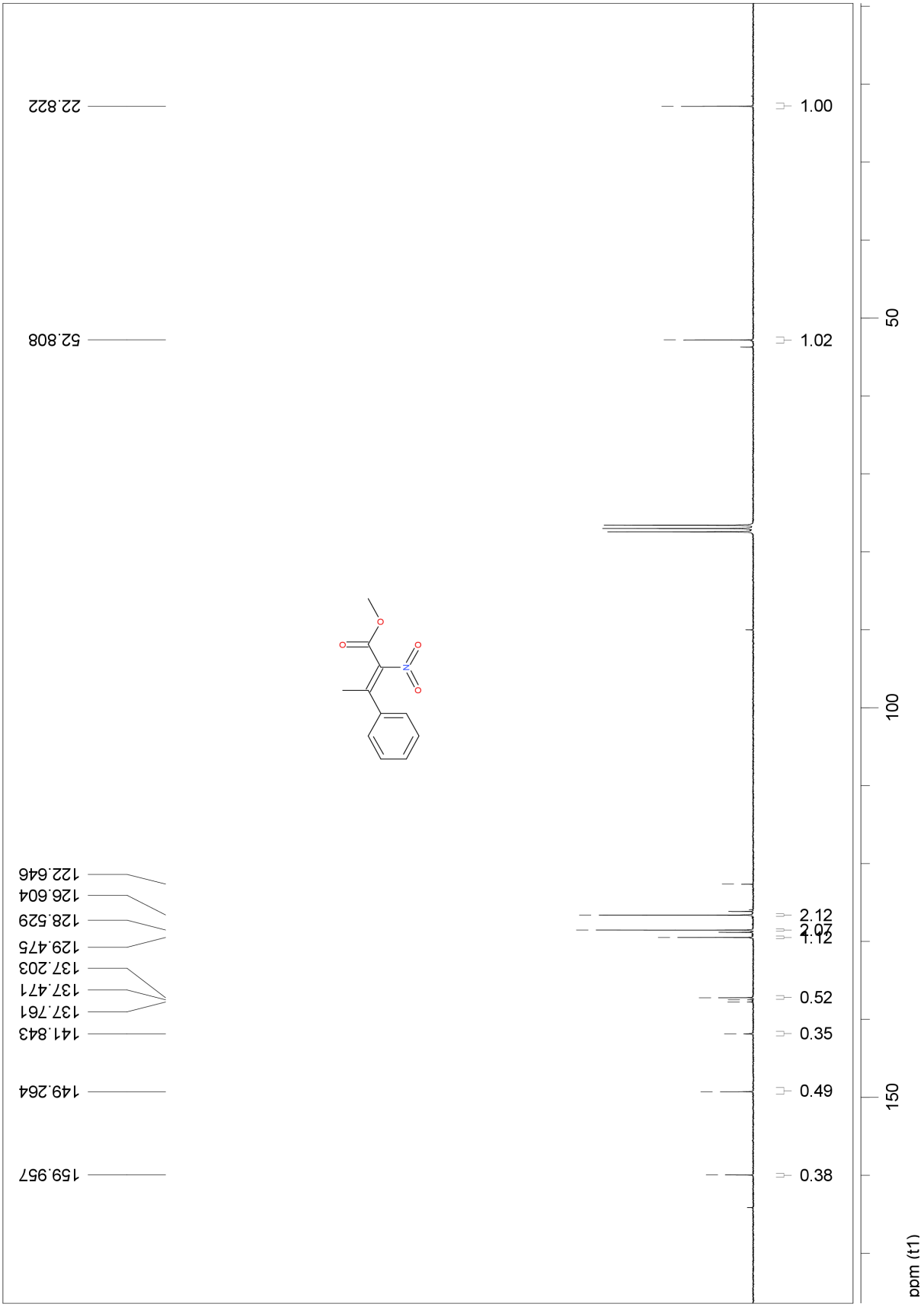
Compound **91g** was obtained as colorless oil in 48% yield after purification with column chromatography and Cyclohexane/ Dichloromethane 1:1. One isomer and a mixture of both isomers were obtained.

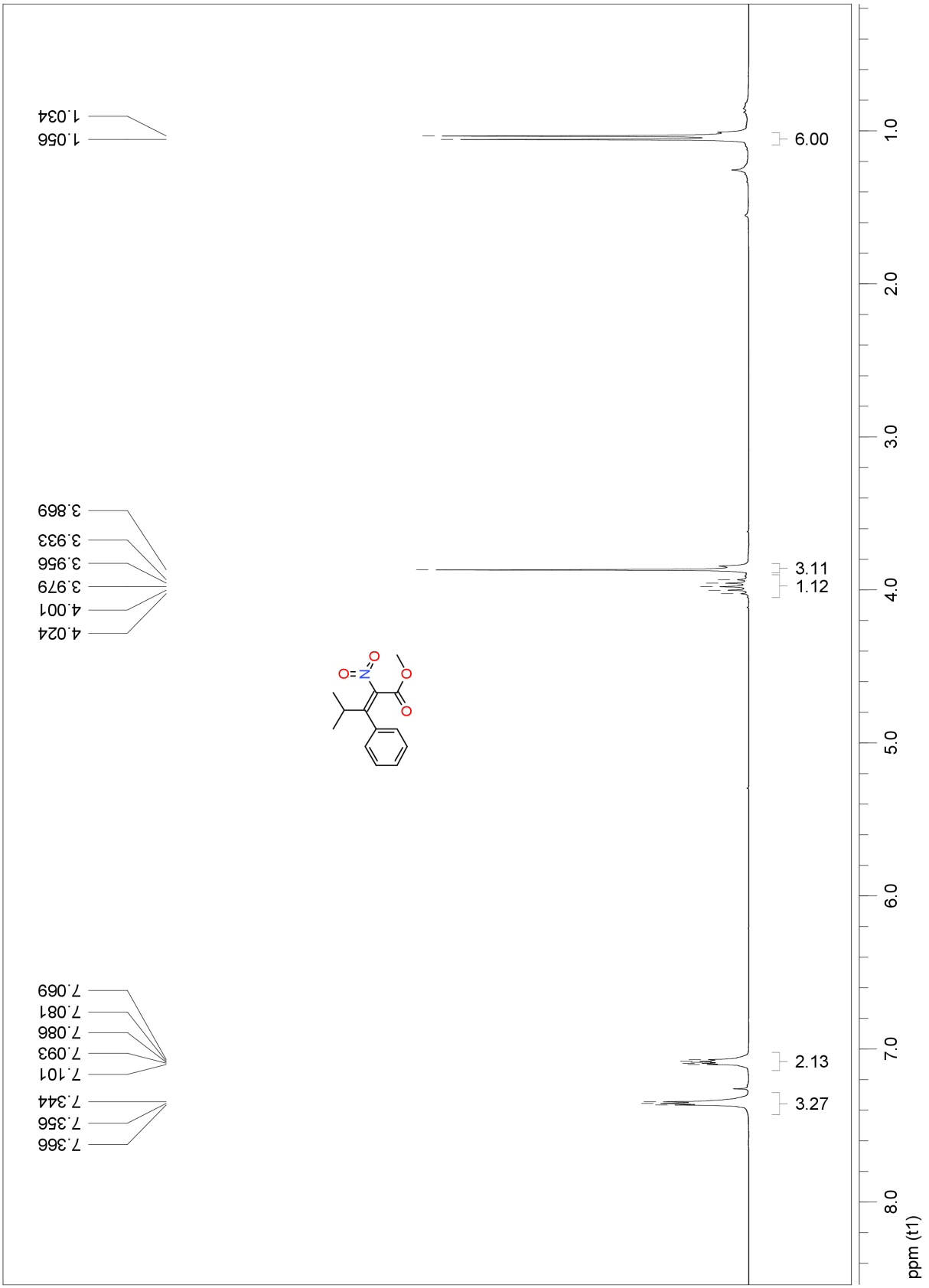
^{1}HNMR (CDCl3, 300 MHz) 2.35 (s, 3H) 2.55 (s, 3H) 3.86 (s, 3H) 7.12-7.20 (m, 4H)

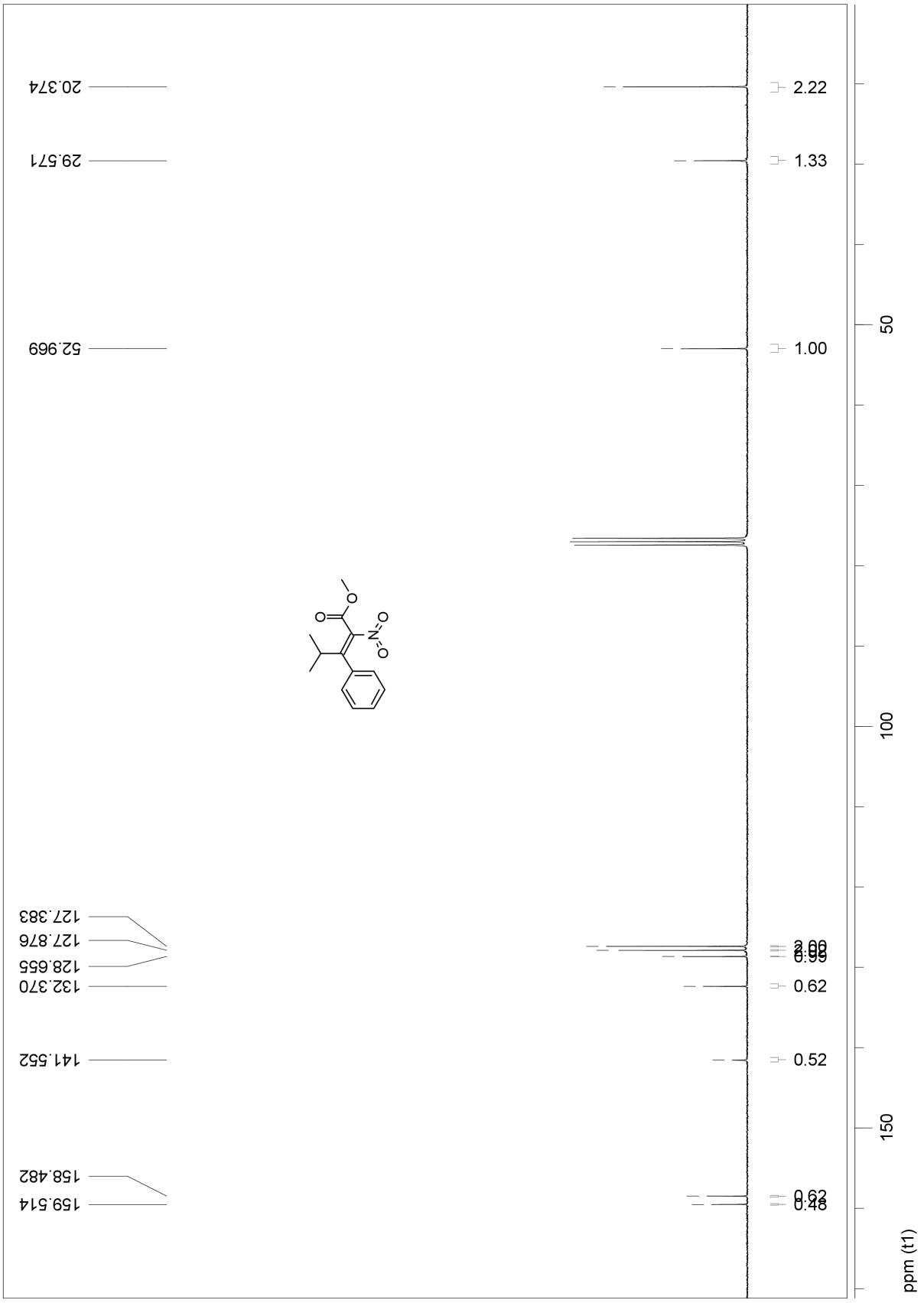
^{13}CNMR (CDCl3, 300 MHz) 21.27, 21.58, 52.89, 125.95, 129.55, 134.78, 139.95, 150.44, 160.00

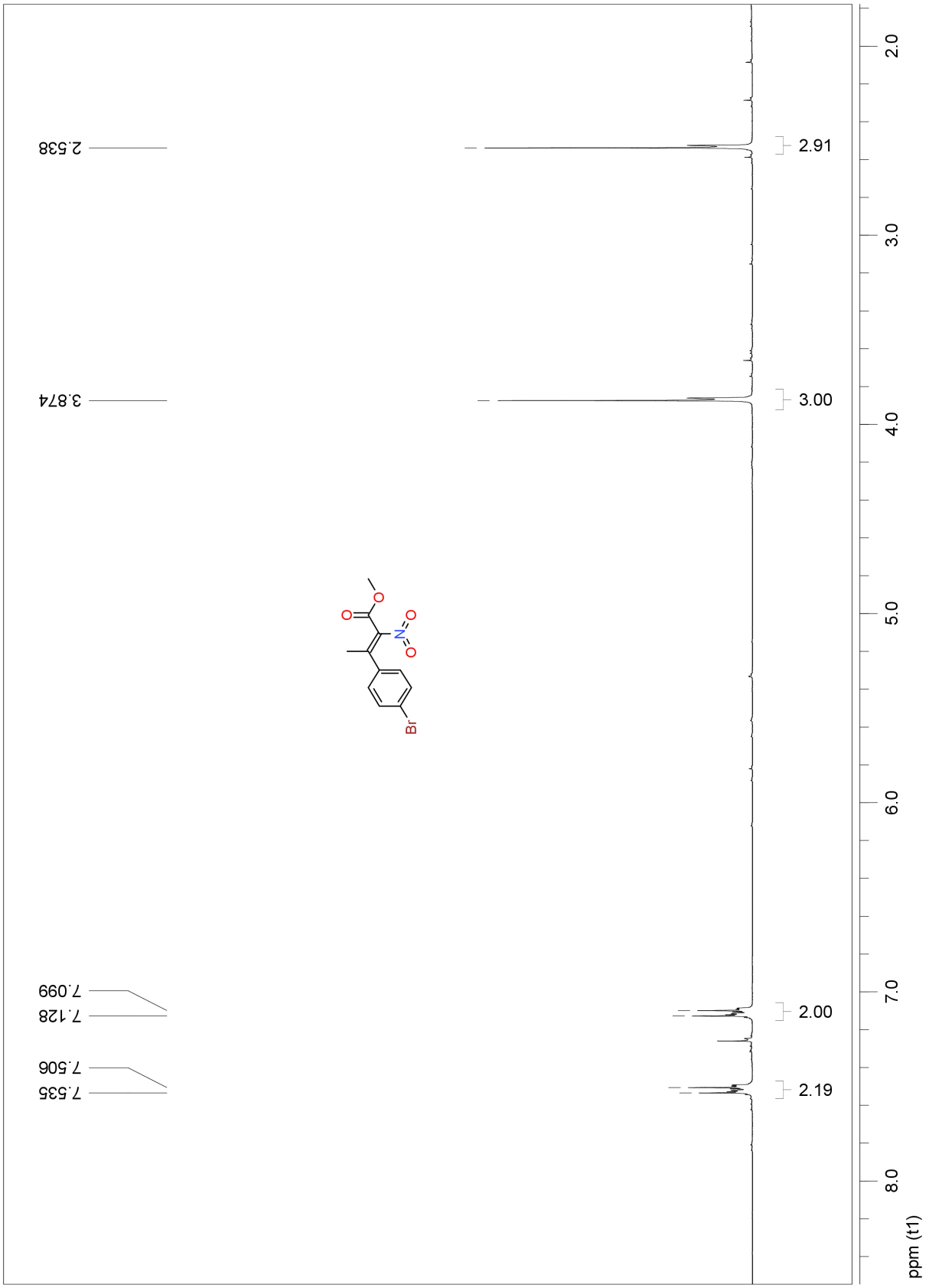

2.553
3.849
7.214
7.219
7.222
7.225
7.227
7.232
7.237
7.242
7.246
7.354
7.361
7.365
7.375
3.00
3.01
1.96
2.88
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

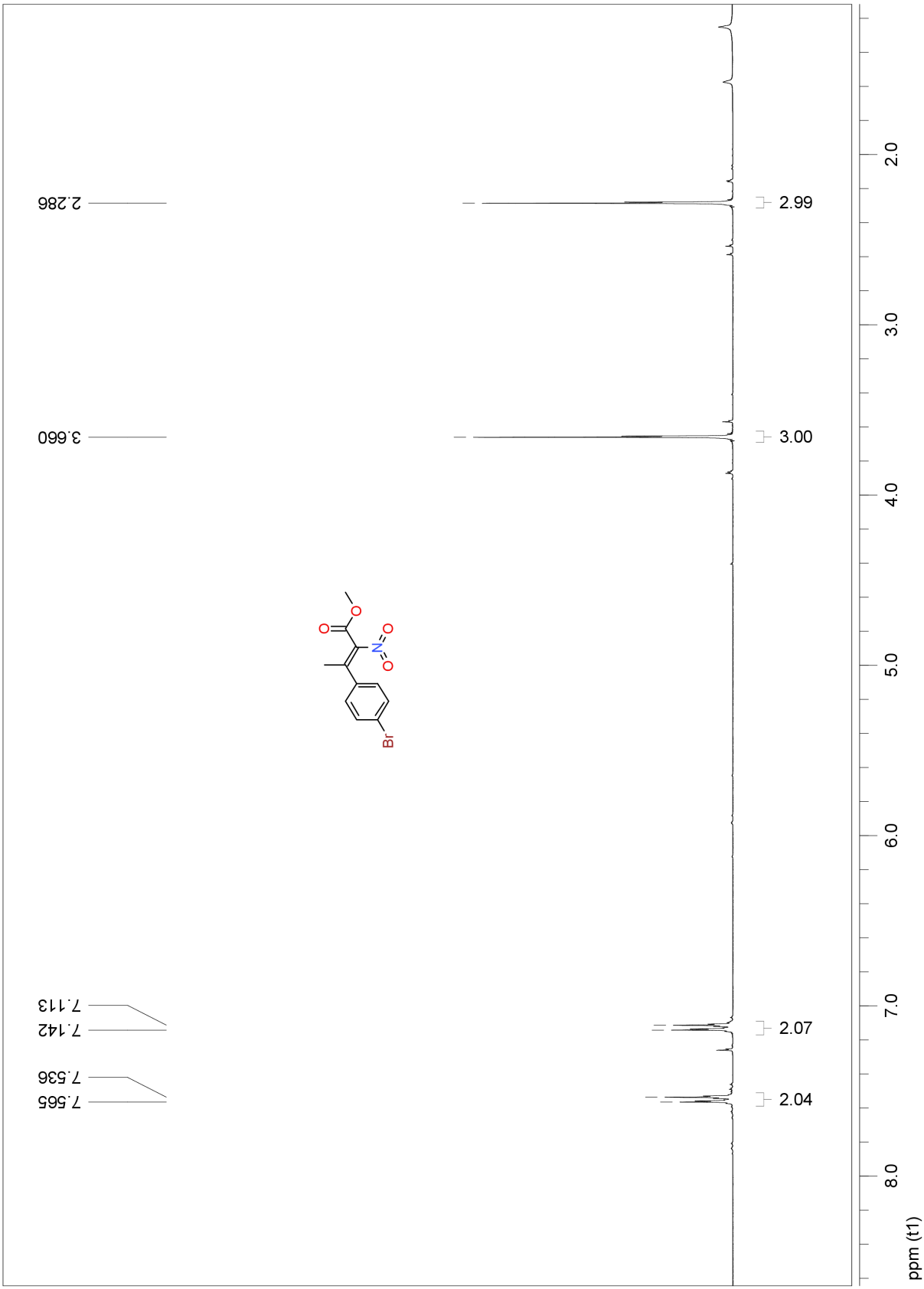

2.354
3.633
7.260
7.264
7.273
7.277
7.283
7.292
7.426
7.437
7.447
3.00
2.93
1.63
2.54
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

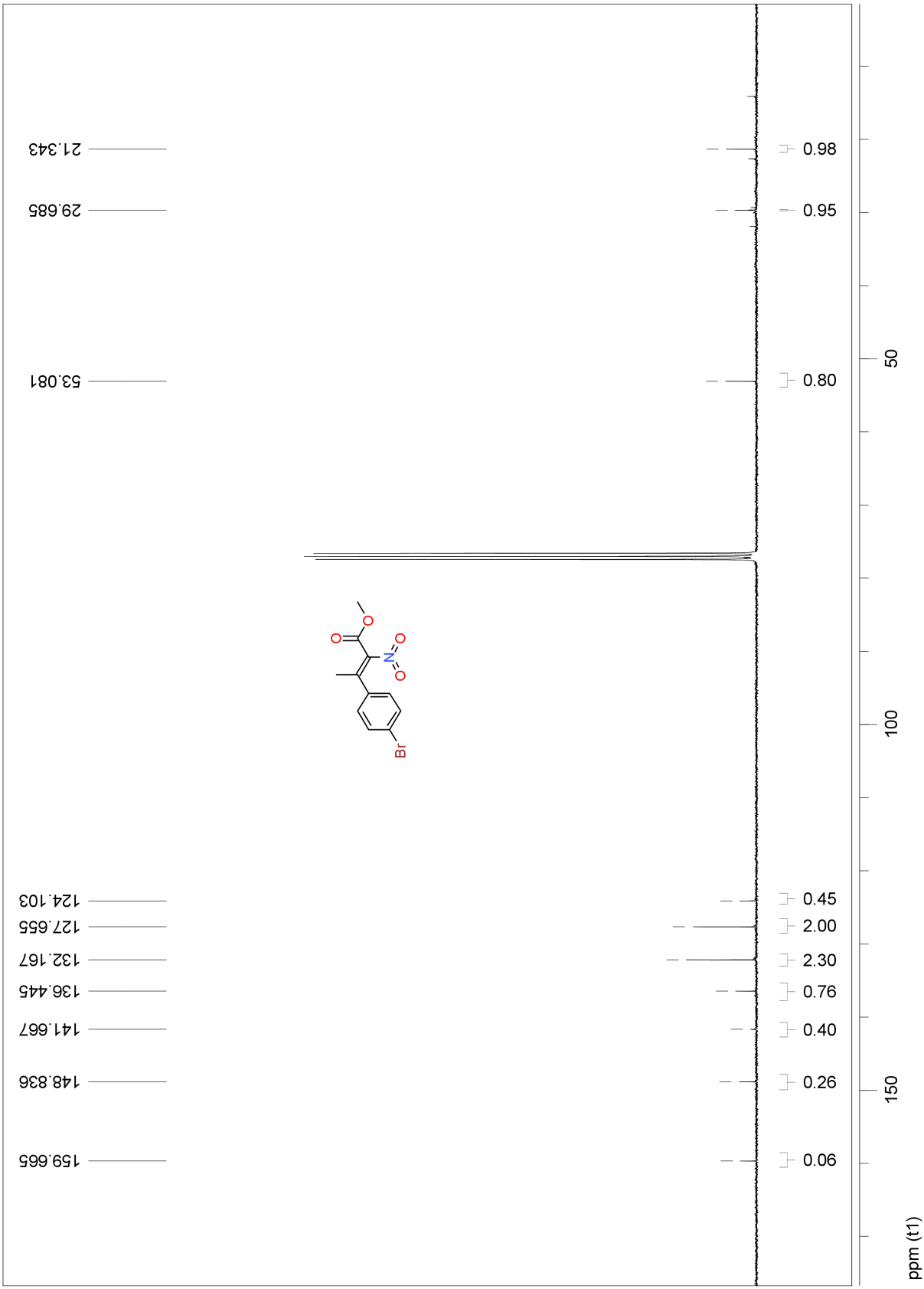

22.822
52.808
159.957
149.264
141.843
137.761
137.471
137.203
129.475
128.529
126.604
122.646
1.00
1.02
2.12
2.07
1.12
0.52
0.35
0.49
0.38
50
100
150
ppm (t1)

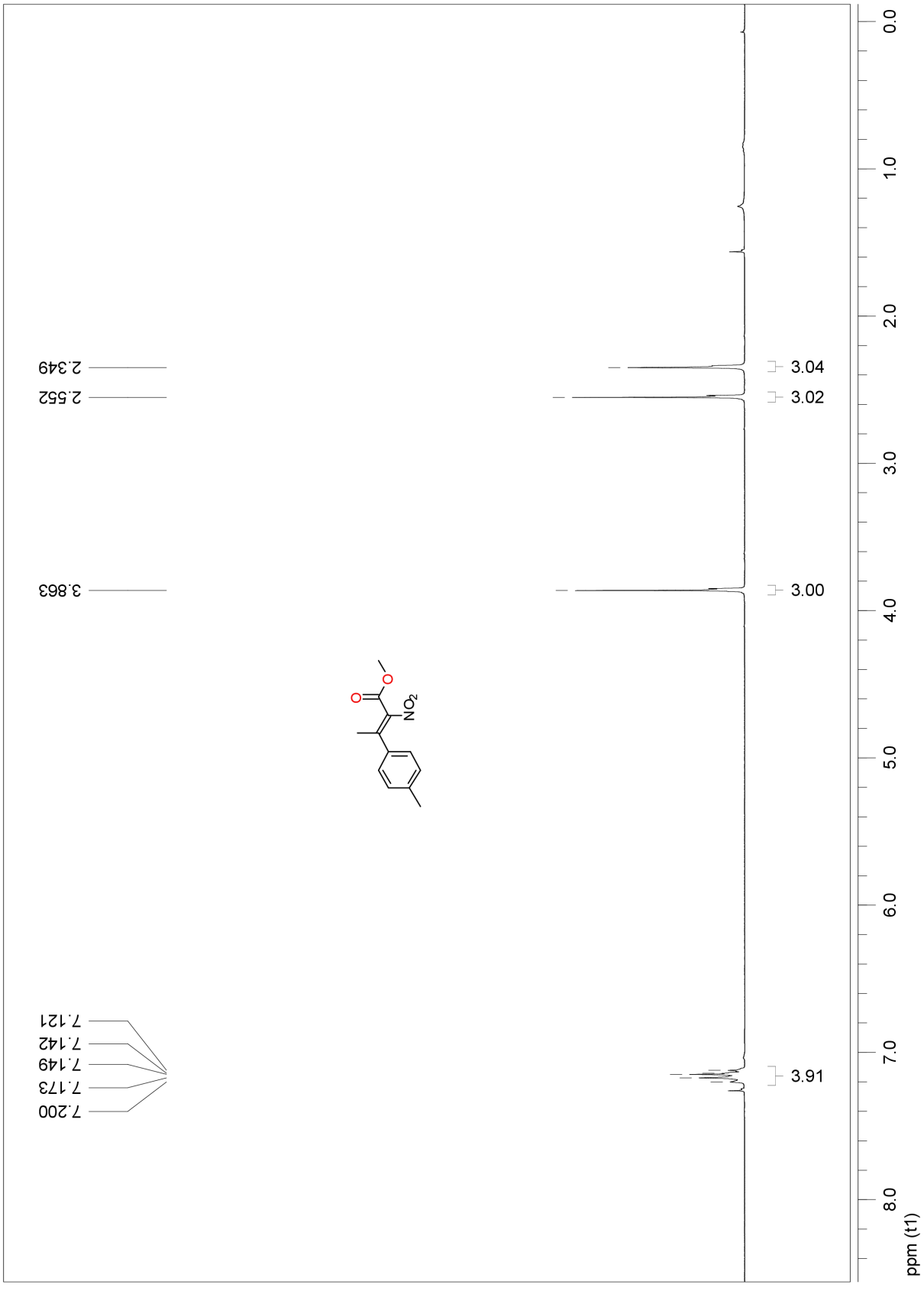

1.034
1.056
3.869
3.933
3.956
3.979
4.001
4.024
7.069
7.081
7.086
7.093
7.101
7.344
7.356
7.366
6.00
3.11
1.12
2.13
3.27
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

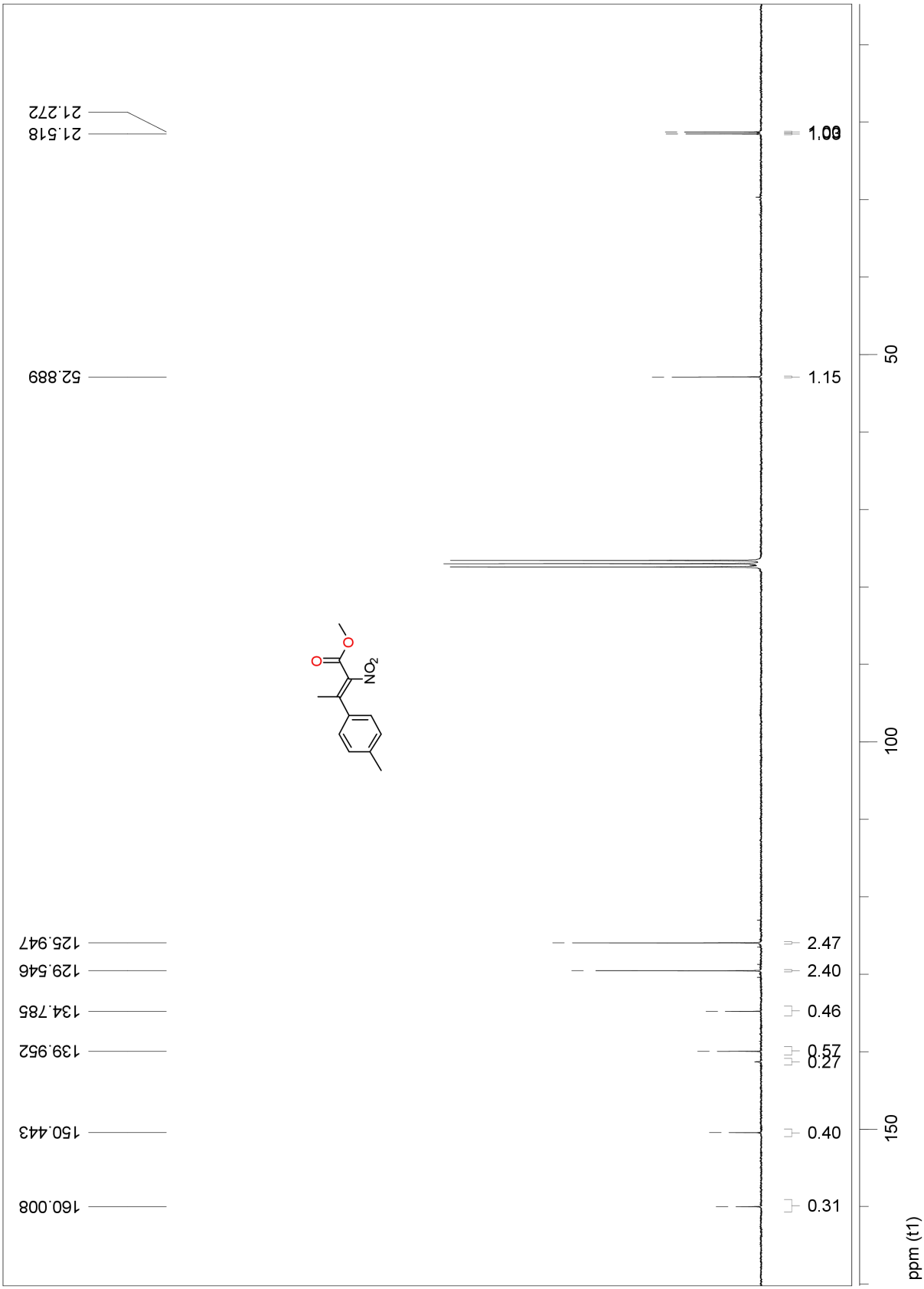

20.374
29.571
52.969
127.383
127.876
128.655
132.370
141.552
158.482
159.514
2.22
1.33
1.00
0.62
0.52
0.62
0.48
50
100
150
ppm (t1)


2.538
3.874
7.099
7.128
7.506
7.535
2.91
3.00
2.00
2.19
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
O
O
O
N
O
Br

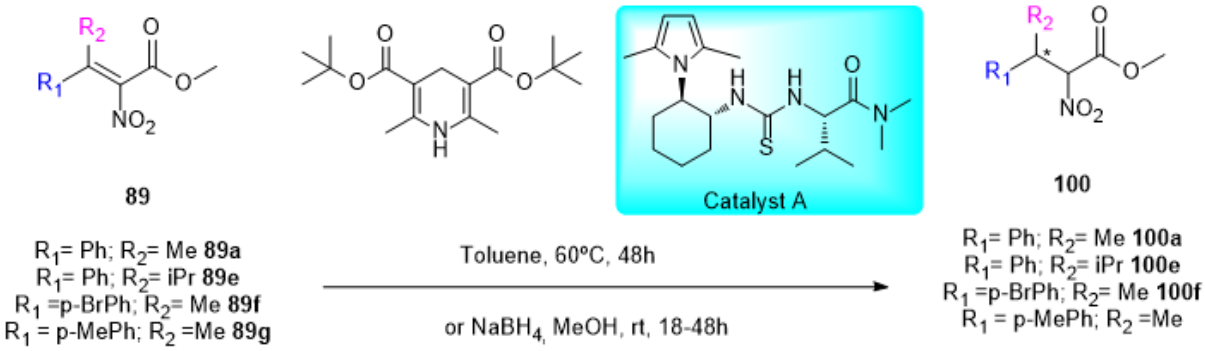

2.286
3.660
7.113
7.142
7.536
7.565
2.99
3.00
2.07
2.04
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
O
O
O
N
O
Br


21.343
29.685
53.081
124.103
127.655
132.167
136.445
141.667
148.836
159.665
0.98
0.95
0.80
0.45
2.00
2.30
0.76
0.40
0.26
0.06
O
O
N
O
O
Br
50
100
150
ppm (t1)


7.200
7.173
7.149
7.142
7.121
3.863
2.552
2.349
3.91
3.00
3.02
3.04
O
O
NO2
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

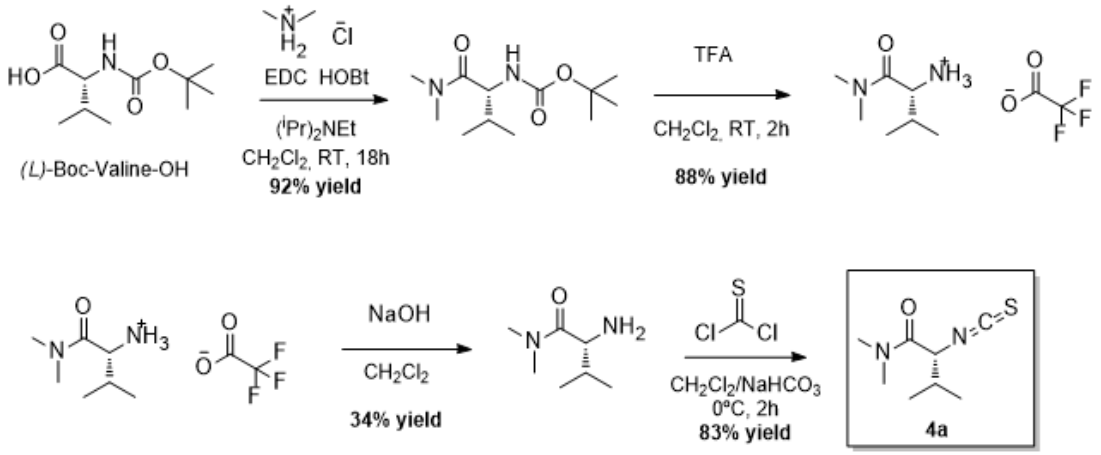

21.272
21.518
52.889
125.947
129.546
134.785
139.952
150.443
160.008
1.00
1.15
2.47
2.40
0.46
0.57
0.27
0.40
0.31
50
100
150
ppm (t1)
O
O
NO2

7.3 Enantioselective reduction of tetrasubstituted nitroalkenes



7.3.1 Preparation of Catalyst A: The catalyst A was prepared in three steps following the literature procedure.[67]

Part A: ***Synthesis of intermediate 4a***



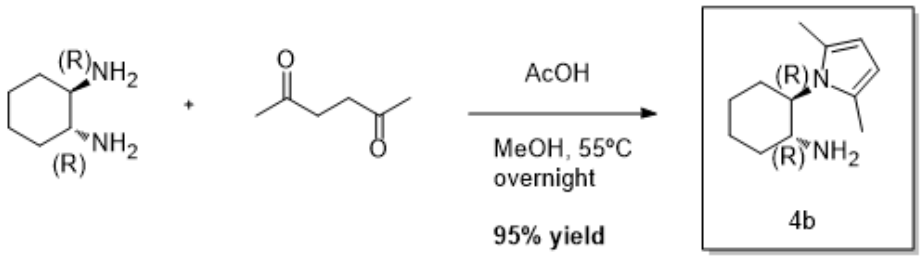
N,N-Diisopropylethylamine (1.5 eq., 2.1 mmol) was added to a 0.1M solution of the N-Boc-(L)-Valine-OH (1 eq., 1.38 mmol), HOBt (1.1 eq., 1.5 mmol), EDC (1.1 eq., 1.5 mmol) and *N,N*-dimethylamine hydrochloride (1.1 eq. 1.5 mmol) in dichloromethane. The reaction mixture was stirred at room termperature overnight, then treated with 1N HCl and with $NaHCO_3$ ss. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure.

TFA (10 eq., 2 mmol) was added to a 0.3M solution of amide (1 eq., 0.2 mmol) in dichloromethane at room temperature. The mixture was stirred for 2 hours, after which it was

concentrated under reduced pressure. The trifluroacetic acid salt was diluted in dichloromethane and treated with a stoichiometric amount of 5.5M NaOH. The solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the corresponding amide – featuring free NH_2.

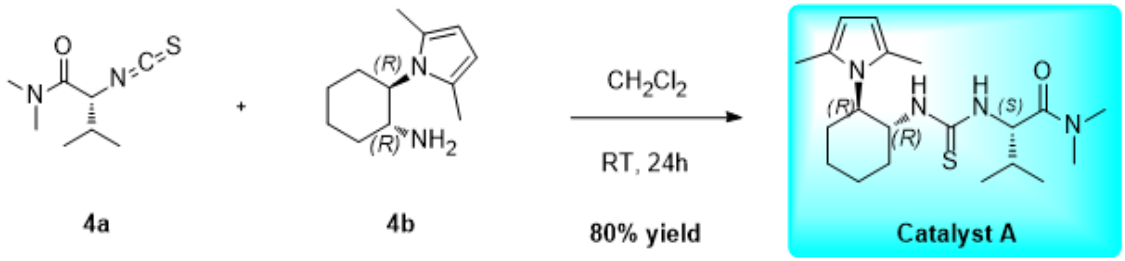
To a 0.05M solution of amide (1 eq., 0.5 mmol) in CH_2Cl_2:$NaHCO_3$ ss 1:1, kept at 0°C, thiophosgene (1.1 eq., 0.55 mmol) was added directly into the organic phase. The reaction mixture was stirred for 2 hours at 0°C; after this period, the organic phase was separated and the aqueous one extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product **4a** was purified through flash column chromatography on silica gel using Hexane: Ethyl Acetate 8:2 as eluent.

***Part B:* Synthesis of intermediate 4b**



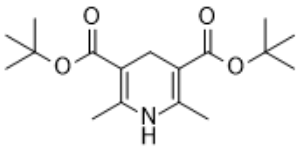
Acetic acid (1 eq., 0.7 mmol) and 2,6-hexaandione (1 eq., 0.7 mmol) were added to a 0.2M solution of diaminocyclohexane (1 eq., 0.7 mmol) in methanol. The reaction mixture was heated to 50°C and stirred overnight. After this period, it was allowed to cool to room temperature and the solvent was removed under reduced pressure. The reaction mixture was treated with 5.5M NaOH and extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product **4b** was used in the next step without any further purification.

***Part C:* Synthesis of Catalyst A**



Working under inert atmosphere, a 0.1M solution of compound **4b** (1.2 eq., 0.18 mmol) in dichloromethane was added to a solution of compound **4a** (1 eq., 0.15 mmol) in dichloromethane at room temperature. The reaction mixture was stirred 48 hours and subsequently concentrated under reduced pressure. The product was purified though flash column chromatography on silica gel. ^{1}HNMR of Catalyst 2, was in agreement with the published one.[67]

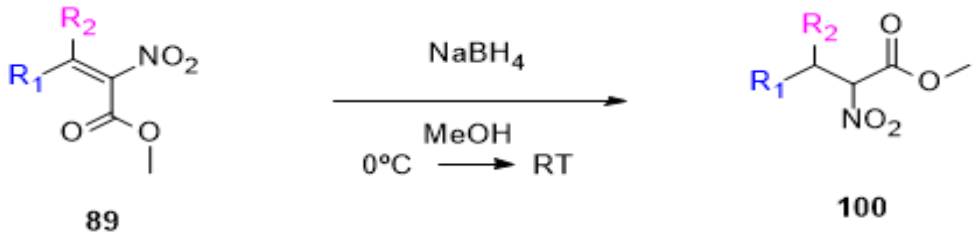
7.3.2 Synthesis of di-tert-Butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Hantzsch ester)



The tert-butyl Hantzsch ester was synthetized according to a procedure found in the literature.[68] A solution of paraformaldehyde (0.75 g, 25 mmol), tert-butyl acetoacetate (8.25 mL, 50 mmol), and aqueous NH_4OH (15 mL of a 5 M solution, 75 mmol) in Ethanol (20 mL) was heated at reflux (oil bath at 85°C) for 2 h. The mixture was then cooled to RT, poured into ice-water (75 mL) and extracted with Et_2O (100 mL). The ether phase was washed successively with 10% aqueous solution of NaOH (50 mL), water (50 mL), 5% aqueous solution of HCl (50 mL) and water (50 mL). The ether solution was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuum* to afford a yellow solid. The crude product was crystallized with MeOH (about 6-8 mL). To avoid oxidation of the dihydropyridine to the corresponding pyridine derivative, the solubilization of the crude product with MeOH was promptly done and the recrystallization was carry out under nitrogen atmosphere for up to 2 h. The *tert*-butyl Hantzsch ester was obtained as yellow solid in 45%

yield. [1]HNMR of pure compound agreed with the published one.[68]

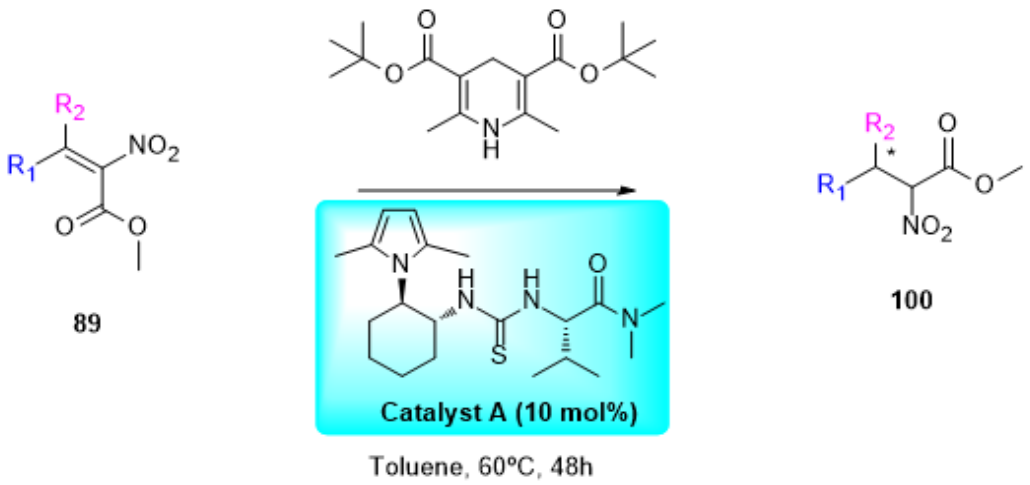
7.3.3 General procedure for the synthesis of racemic nitroalkanes 94



89 100

A solution of the corresponding nitroalkene 89 (1 eq, 0,5 mmol) in MeOH (0.5 mL, 0.2M) was cooled to 0ºC. Then, NaBH4 (2 eq, 1 mmol) was added and the mixture was allowed to warm to room temperature and stirred at RT for 18-48h. After this time, a saturated solution of ammonium chloride was added and the mixture was extracted with dichloromethane. The combined organic layers were dried using MgSO4, filtered and concentrated in vacuo. The crude was purified using column chromatography or preparative HPLC purification.

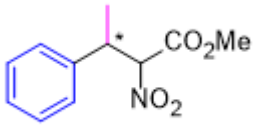
7.3.4 General procedure for the synthesis of chiral nitroalkanes 94



89 100

To a stirred solution of nitroalkenes 89 in Toluene (0,3 mmol 0.3M), catalyst A (10 mol%) and Hanztsch ester (1.2 eq, 0,36 mmol) were added. The reaction mixture was heated at 60ºC for 48h. Then, the mixture was allowed to warm to room temperature and the solvent was eliminated under reduced pressure, and the crude was purified using column chromatography and an appropriate mixture of eluents.

Methyl 2-nitro-3-phenylbutanoate 100a



Yield racemic 75%

Yield chiral 85%

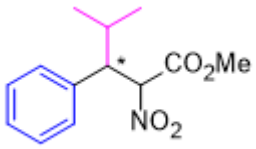
Compound **100a** was obtained as colorless oil and a 1:1 mixture of syn/anti products after column chromatography using Cyclohexane/Dichloromethane 7:3 as eluent. Enantiomeric excess was measured using chiral HPLC column Phenomenex-Cellulose 5_Hexane_IPA_98_2_0.5 mL/min

^{1}HNMR (CDCl3, 300 MHz) 1.35-1.41 (m, 6H) 3.54 (s, 3H) 3.76-3.78 (m, 2H) 3.84 (s, 3H) 5.22-5.32 (m, 2H) 7.20-7.31 (m, 10 H)

^{13}CNMR (CDCl3, 300 MHz)

ESI MS (+) m/z = 246.0742 (M+ + 23)

Methyl 4-methyl-2-nitro-3-phenylpentanoate 100e



Yield racemic 3%*

Yield chiral 32%

**after preparative HPLC purification*

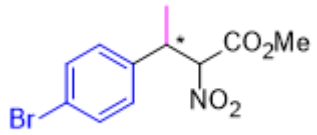
Compound **100e** was obtained as colorless oil and a 1:1 mixture of *syn/anti* products after column chromatography using Cyclohexane/ Diethyl ether 9:1 as eluent. Enantiomeric excess was measured using chiral HPLC column Phenomenex-Cellulose 5_Hexane_IPA_95_5_1 mL/min

^{1}HNMR (CDCl3, 300 MHz) 0.83-0.88 (m, 12H) 3.50 (s, 3H) 3.60-3.65 (m, 2H) 3.86 (s, 3H) 5.59-5.67 (m, 2H) 7.14-7.18 (m, 4H) 7.26-7.31 (m, 6H)

^{13}CNMR (CDCl3, 300 MHz) 17.82, 20.95, 29.19, 52.19, 53.18, 90.58, 127.71, 128.25, 129.15, 134.90, 163.74, 164.53

ESI MS (+) m/z = 274.1050 (M+ + 23)

Methyl 3-(4-bromophenyl)-2-nitrobutanoate 100f



Yield racemic 53%

Yield chiral 59%

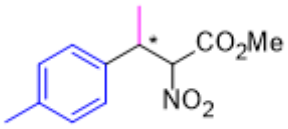
Compound **100f** was obtained as colorless oil and a 1:1 mixture of syn/anti products after column chromatography using Cyclohexane /DCM 7:3 as eluent. Enantiomeric excess was measured using chiral HPLC column Phenomenex-Cellulose 5_Hexane_IPA_95:5_1 mL/min

^{1}HNMR (CDCl3, 300 MHz) 1.35-1.41 (m, 6H) 3.61 (s, 3H) 3.73 (m, 2H) 3.86 (s, 3H) 5.20-5.26 (m, 2H) 7.11-7.14 (m, 4H) 7.43-7.46 (m, 4H)

^{13}CNMR (CDCl3, 300 MHz) 18.01, 40.60, 53.38, 92.73, 121.81, 129.02, 129.40, 132.06, 137.98, 138.77, 163.79

ESI MS (+) m/z = 323.9853 (M+ + 23)

Methyl 2-nitro-3-(p-tolyl)-butanoate 100g



Yield racemic 20%

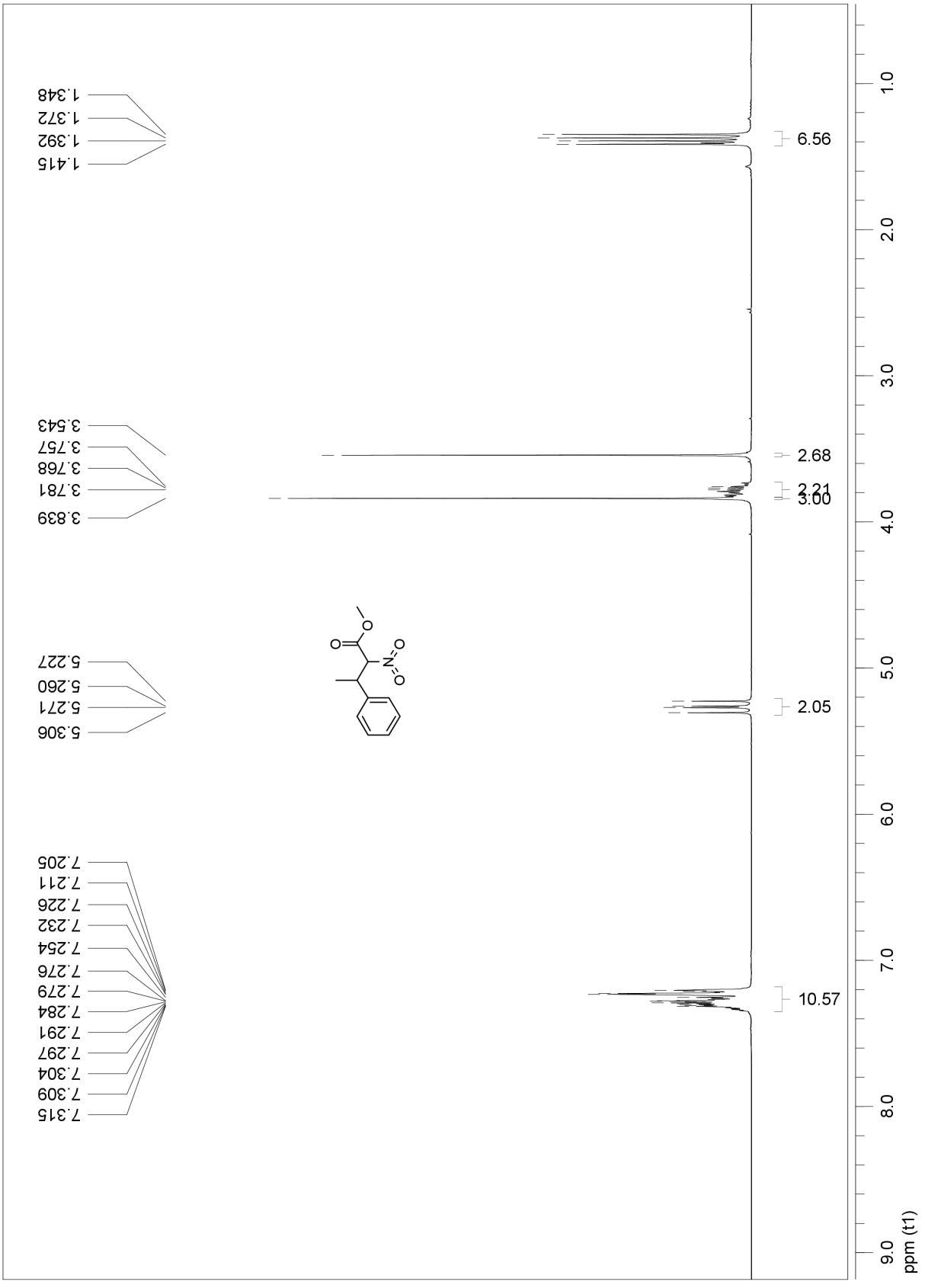
Yield chiral 51%

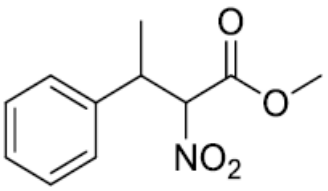
Compound **100g** was obtained as colorless oil and a 1:1 mixture of syn/anti products after column chromatography using Cyclohexane/DCM as eluent. Enantiomeric excess was measured using chiral HPLC column Phenomenex-Cellulose 5_Hexane_IPA_95:5_1 mL/min.

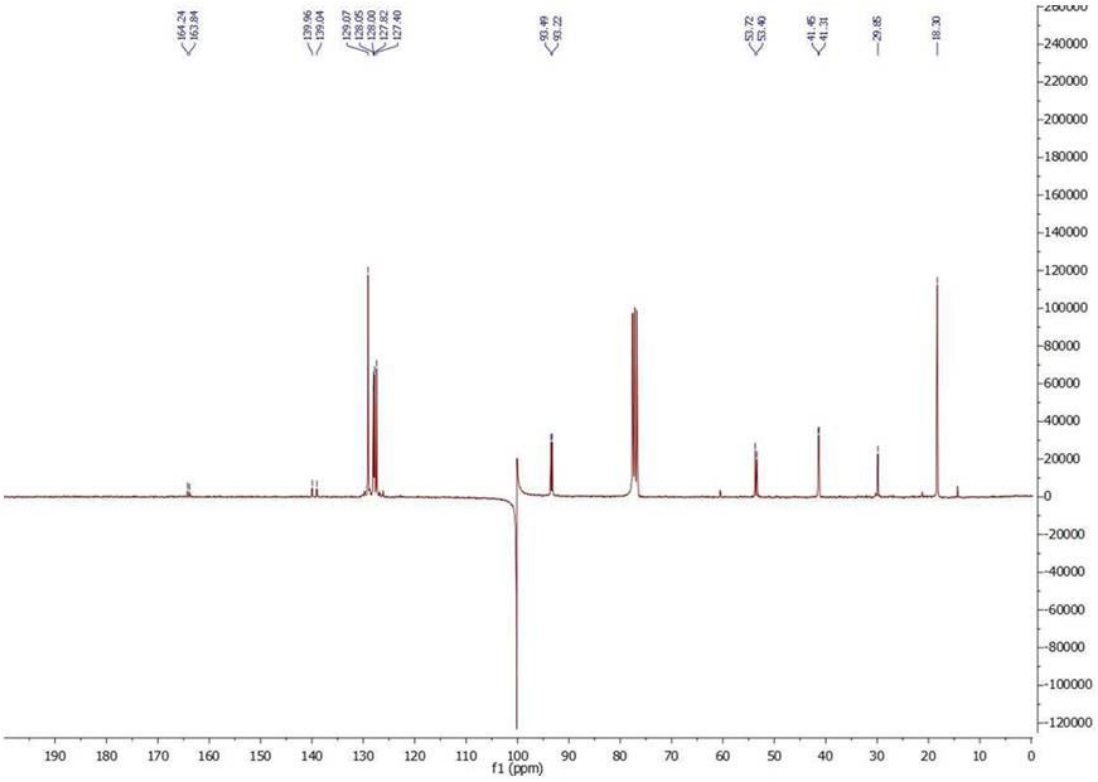
^{1}HNMR (CDCl3, 300 MHz) 1.35-1.41 (m, 6H), 2.31 (d, 6H), 3.59 (s, 3H) 3.74-3.80 (m, 2H) 3.86 (, 3H) 5.22-5.29 (m, 2H) 7.12 (s, 8H)

^{13}CNMR (CDCl3, 300 MHz) 18.11, 20.96, 40.87, 53.08, 93.29, 127.15, 127.55, 129.61, 136.09, 136.95, 137.54, 137.58, 164.15

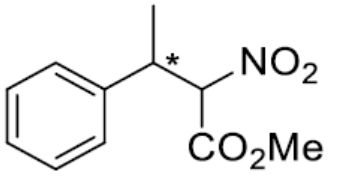
ESI MS (+) m/z = 260.1001 (M+ + 23)

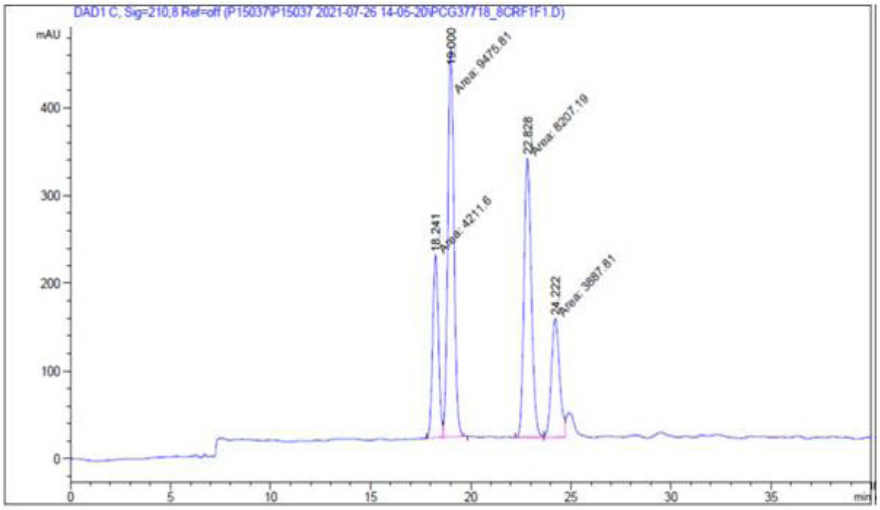

1.348
1.372
1.392
1.415
3.543
3.757
3.768
3.781
3.839
5.227
5.260
5.271
5.306
7.205
7.211
7.226
7.232
7.254
7.276
7.279
7.284
7.291
7.297
7.304
7.309
7.315
6.56
2.68
2.21
3.00
2.05
10.57
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)


O
O
NO2

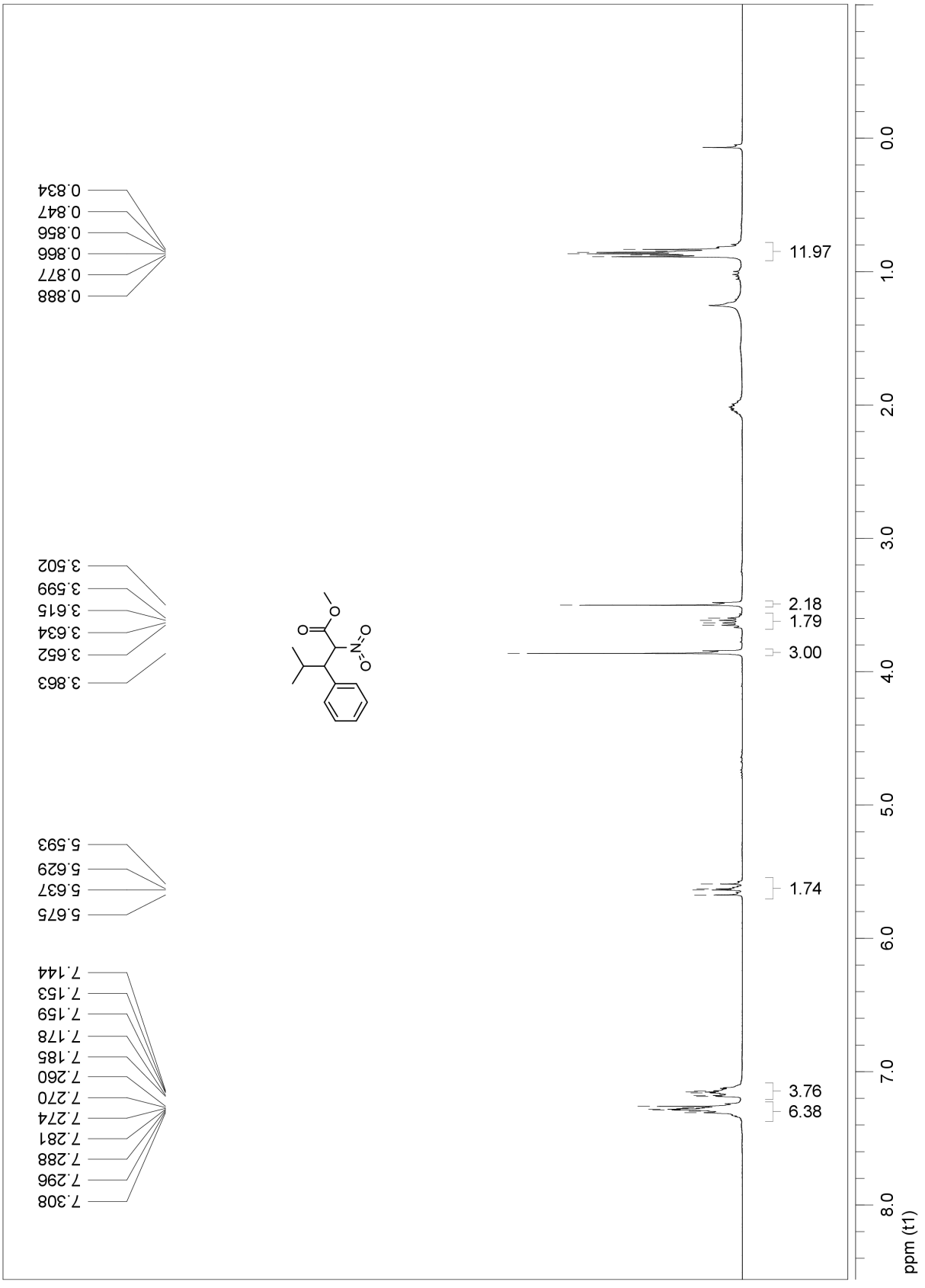

164.24
163.84
139.96
139.04
129.07
128.05
128.00
127.82
127.40
93.49
93.22
53.72
53.40
41.46
41.31
29.85
18.30
f1 (ppm)

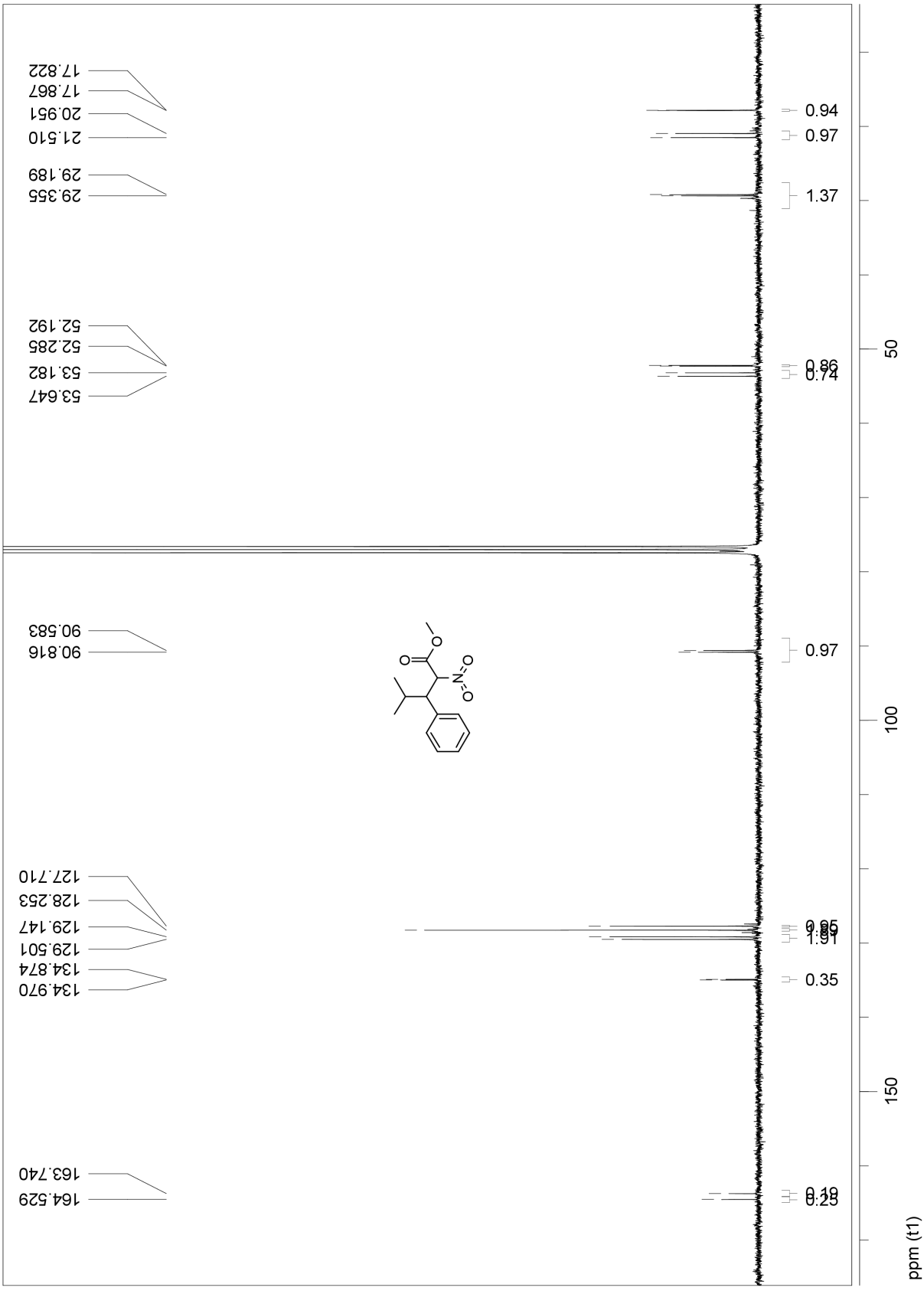
Chiral HPLC data of compound 100a



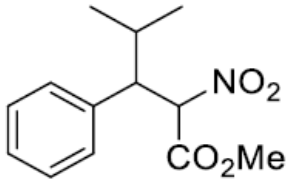


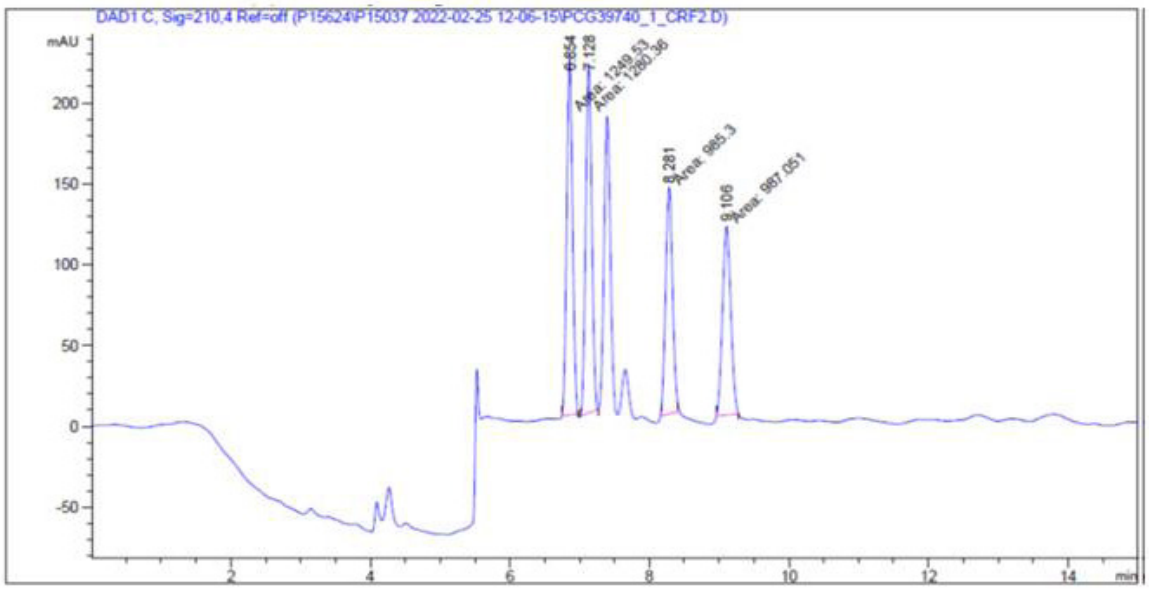
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.241	MF	0.3379	4211.59766	207.76465	16.3352
2	19.000	FM	0.3560	9475.81445	443.66376	36.7530
3	22.828	MF	0.4293	8207.19238	318.64307	31.8325
4	24.222	MF	0.4767	3887.80957	135.91457	15.0793


0.834
0.847
0.856
0.866
0.877
0.888
3.502
3.599
3.615
3.634
3.652
3.863
5.593
5.629
5.637
5.675
7.144
7.153
7.159
7.178
7.185
7.260
7.270
7.274
7.281
7.288
7.296
7.308
11.97
2.18
1.79
3.00
1.74
3.76
6.38
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

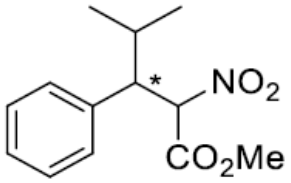

17.822
17.867
20.951
21.510
29.189
29.355
52.192
52.285
53.182
53.647
90.583
90.816
127.710
128.253
129.147
129.501
134.874
134.970
163.740
164.529
0.94
0.97
1.37
0.86
0.74
0.97
1.91
0.35
0.19
0.25
50
100
150
ppm (t1)

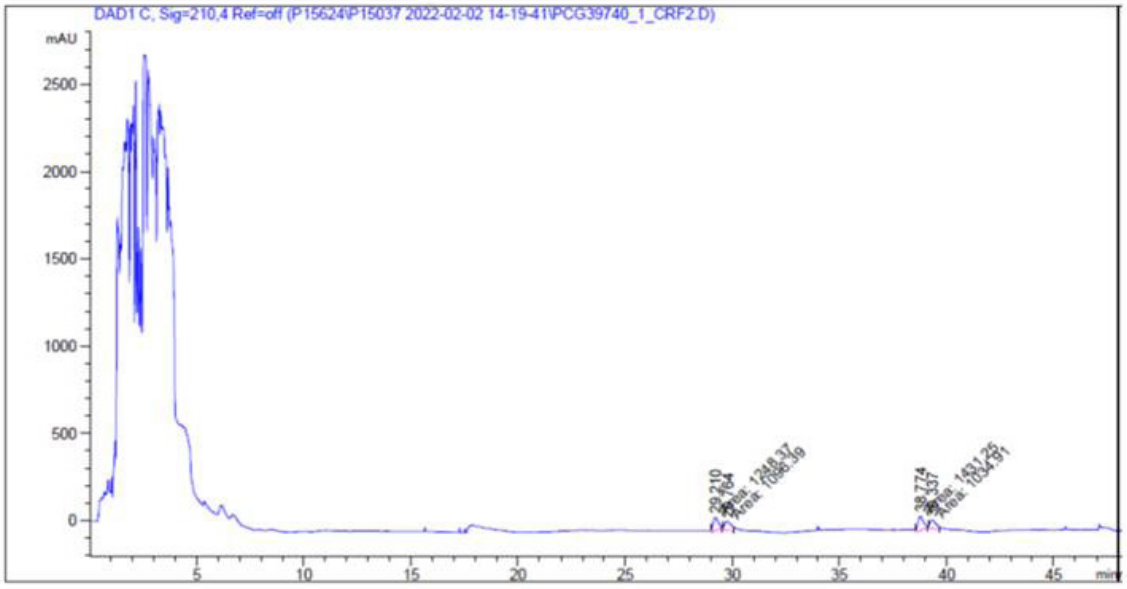
Chiral HPLC data of Compound 100e



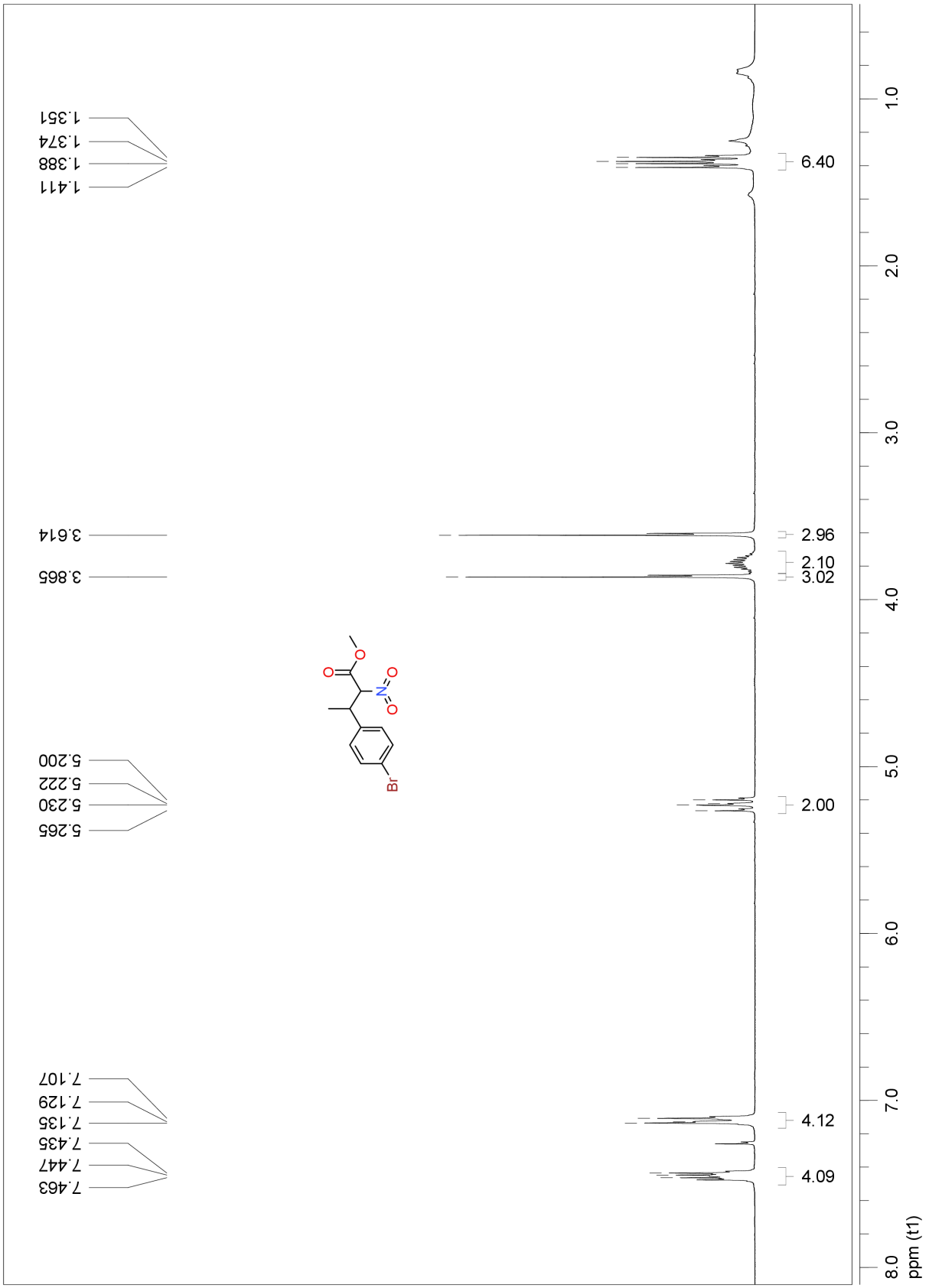


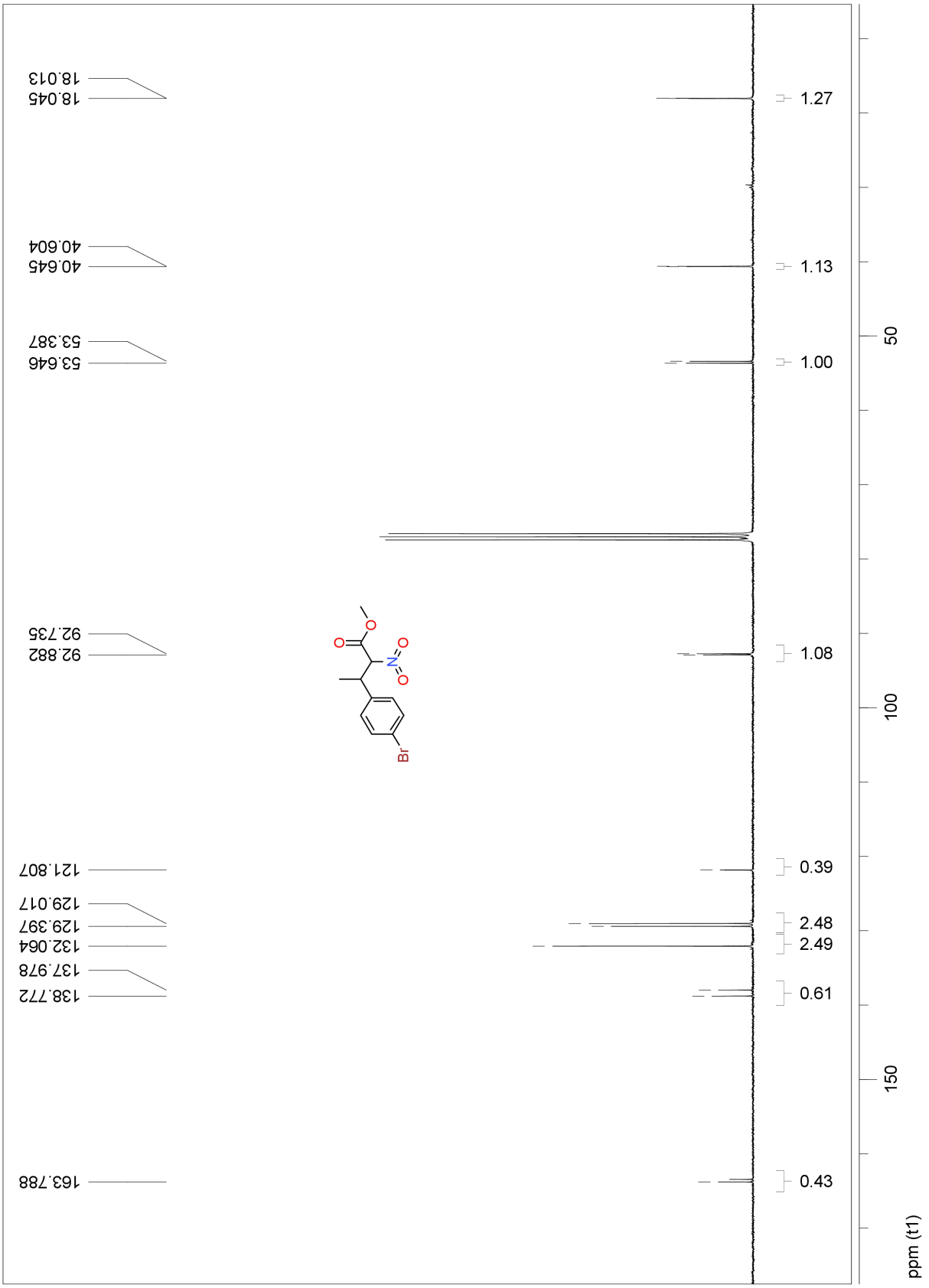
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.854	MM	0.0940	1249.53137	221.47246	27.7535
2	7.128	MM	0.0990	1280.36475	215.46544	28.4383
3	8.281	MM	0.1170	985.29993	140.30157	21.8846
4	9.106	MM	0.1403	987.05127	117.26270	21.9235



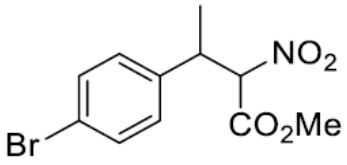


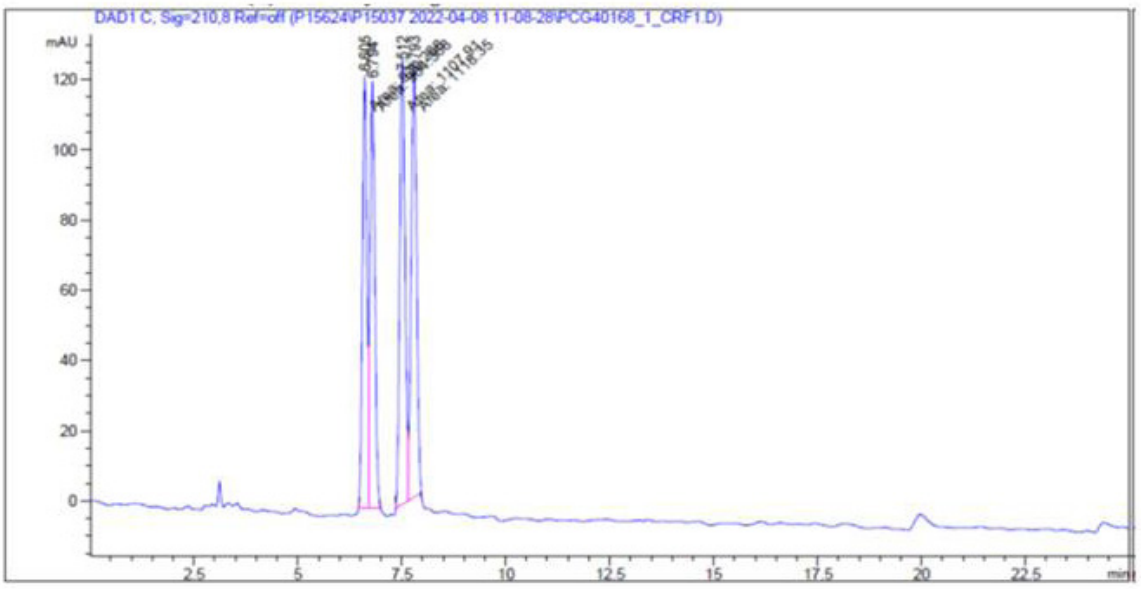
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.210	MM	0.2773	1248.37207	75.02459	25.9487
2	29.764	MM	0.3641	1096.39026	50.18269	22.7896
3	38.774	MM	0.2975	1431.24573	80.19376	29.7499
4	39.337	MM	0.3529	1034.91284	48.87428	21.5117


1.351
1.374
1.388
1.411
3.614
3.865
5.200
5.222
5.230
5.265
7.107
7.129
7.135
7.435
7.447
7.463
6.40
2.96
2.10
3.02
2.00
4.12
4.09
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
O
O
N
O
O
Br

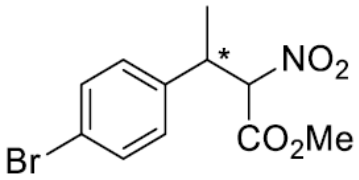

18.013
18.045
40.604
40.645
53.387
53.646
92.735
92.882
121.807
129.017
129.397
132.064
137.978
138.772
163.788
1.27
1.13
1.00
1.08
0.39
2.48
2.49
0.61
0.43
O
O
O
N
O
Br
50
100
150
ppm (t1)

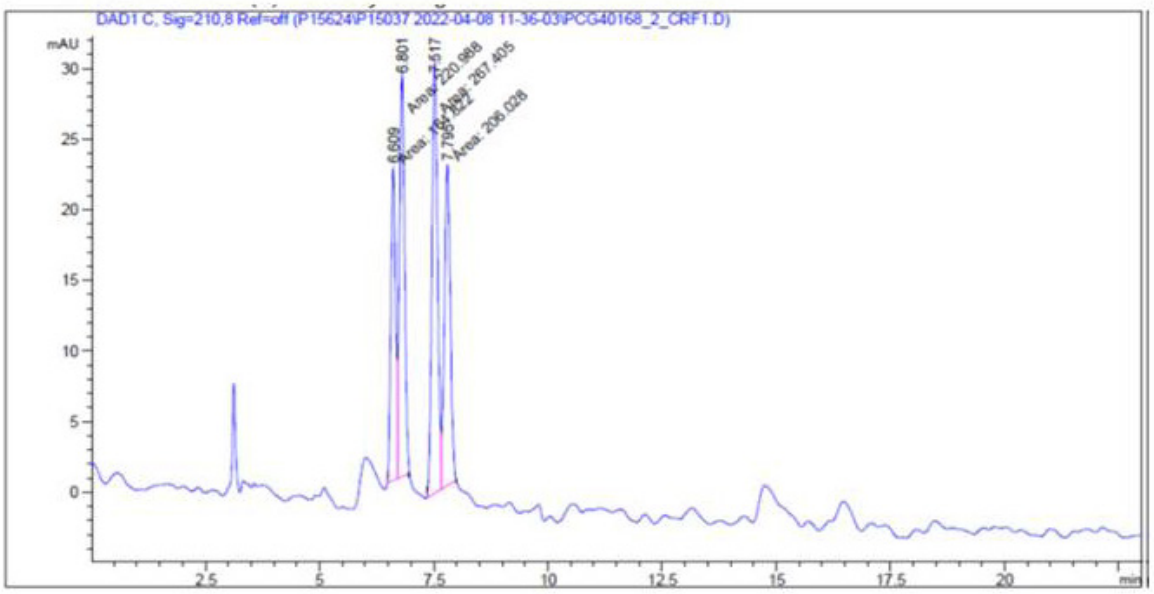
Chiral HPLC data of Compound 100f



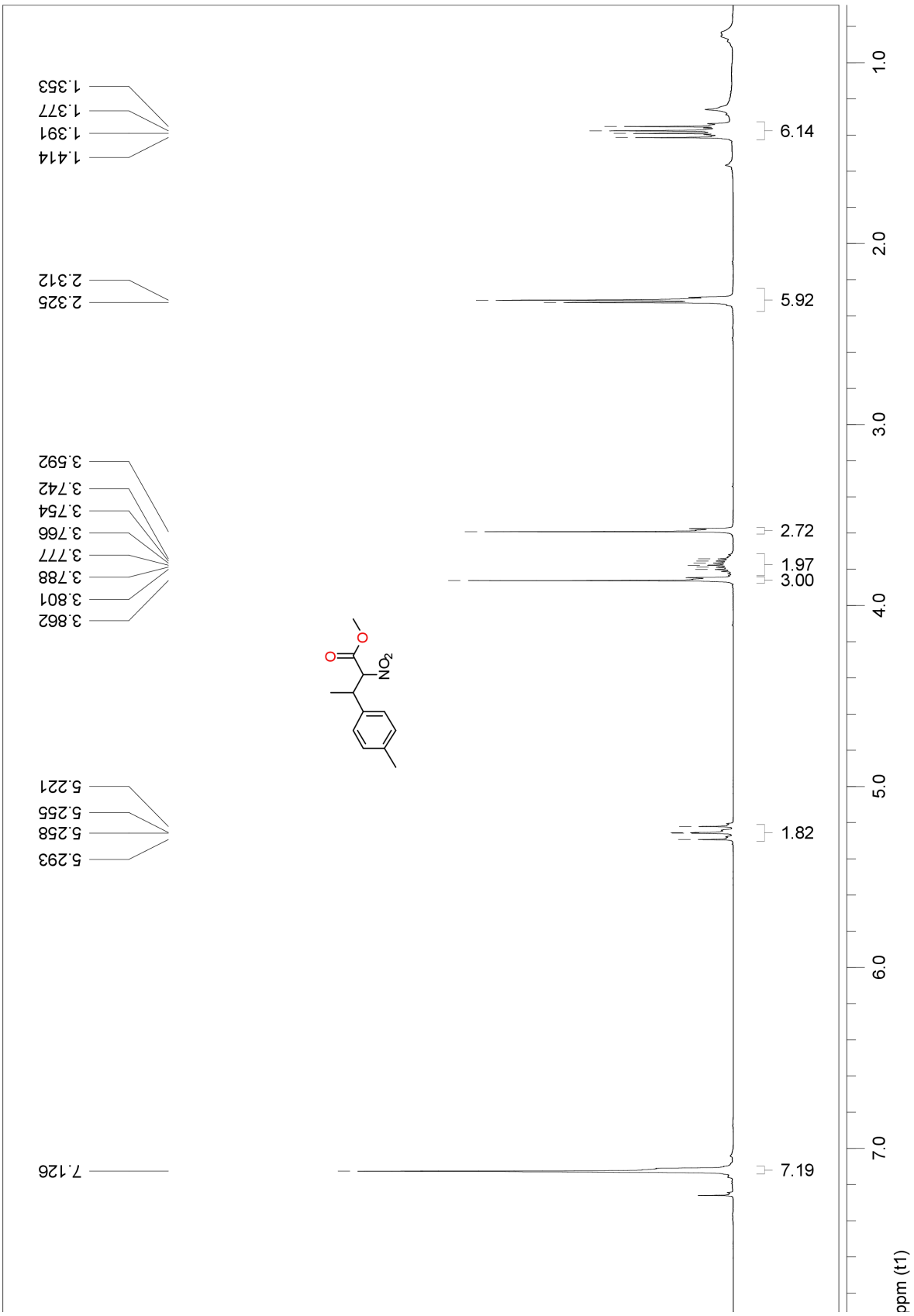


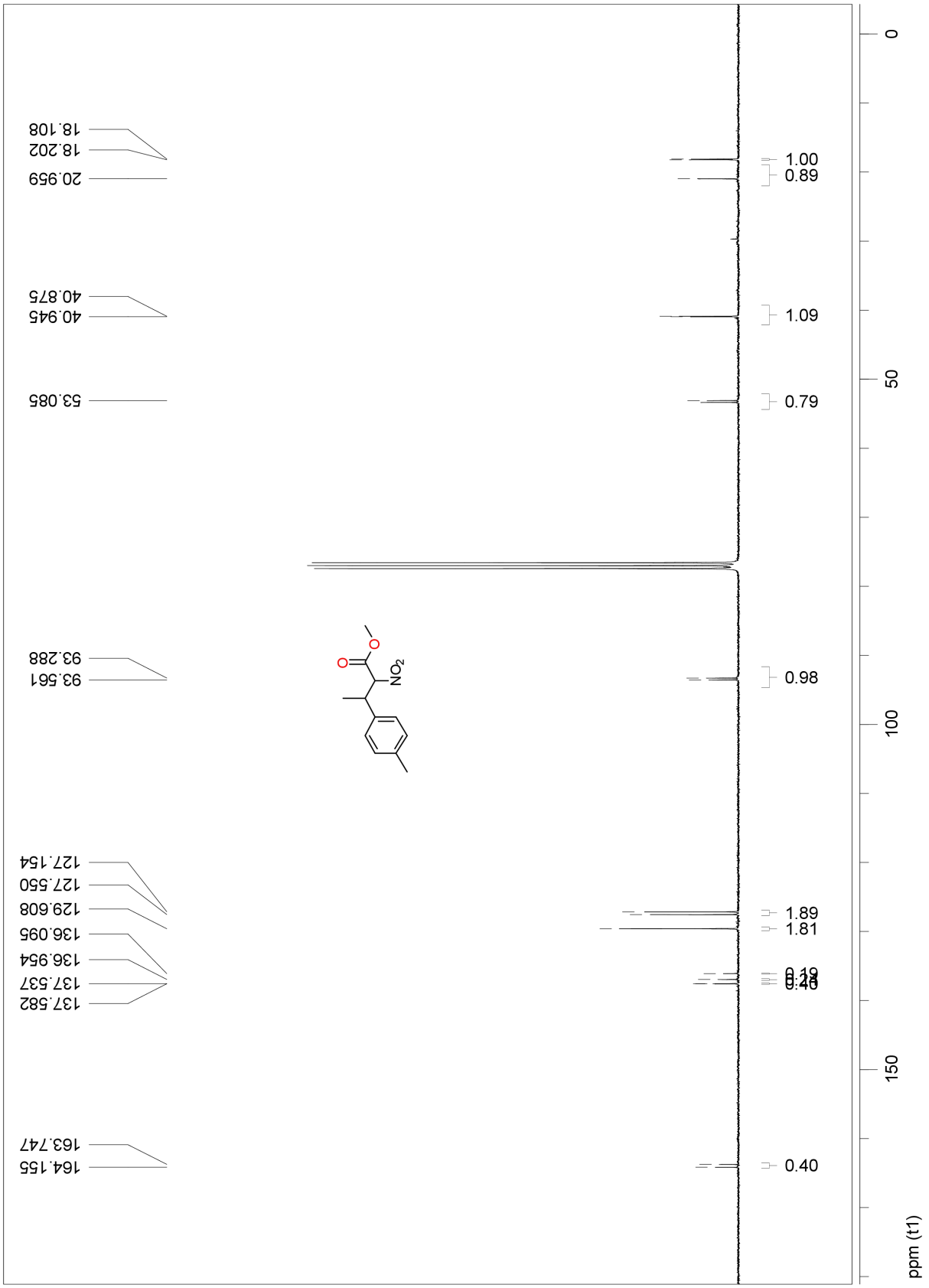
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.605	MF	0.1256	929.28839	123.30390	22.5560
2	6.794	FM	0.1324	964.36804	121.41569	23.4075
3	7.512	MF	0.1452	1107.90845	127.16387	26.8916
4	7.793	FM	0.1504	1118.34741	123.93054	27.1449



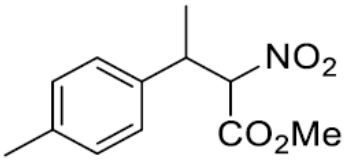


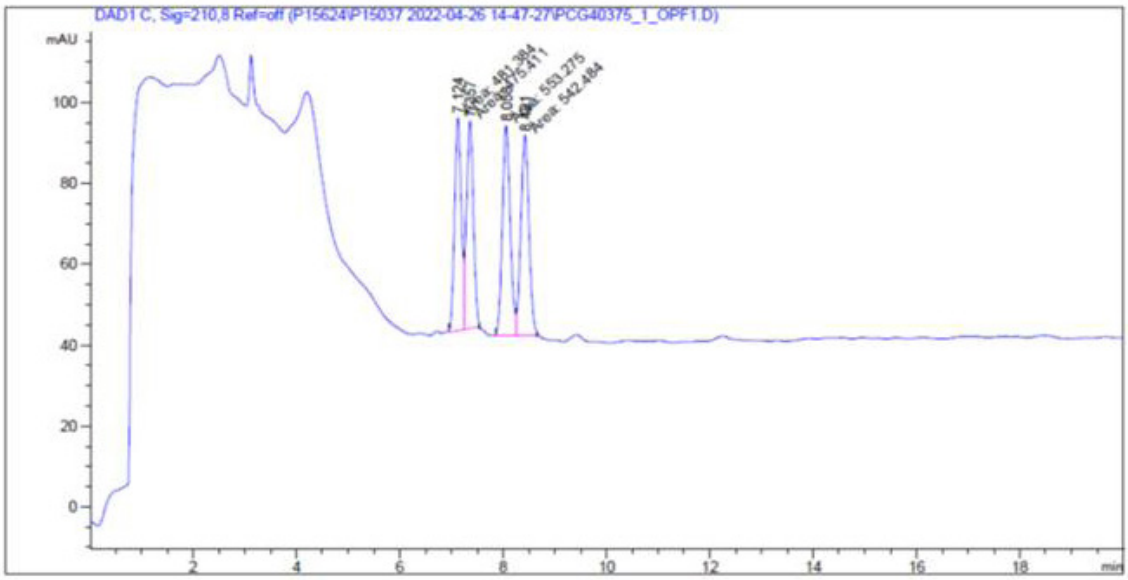
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.609	MF	0.1240	164.82224	22.14586	19.1823
2	6.801	FM	0.1286	220.98792	28.64508	25.7189
3	7.517	MF	0.1452	267.40518	30.69749	31.1210
4	7.795	FM	0.1510	206.02779	22.74287	23.9778


1.353
1.377
1.391
1.414
2.312
2.325
3.592
3.742
3.754
3.766
3.777
3.788
3.801
3.862
5.221
5.255
5.258
5.293
7.126
6.14
5.92
2.72
1.97
3.00
1.82
7.19
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)
O
O
NO2

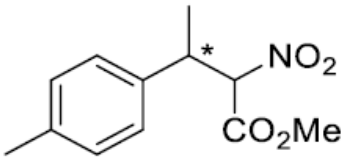

18.108
18.202
20.959
40.875
40.945
53.085
93.288
93.561
127.154
127.550
129.608
136.095
136.954
137.537
137.582
163.747
164.155
1.00
0.89
1.09
0.79
0.98
1.89
1.81
0.40
0
50
100
150
ppm (t1)

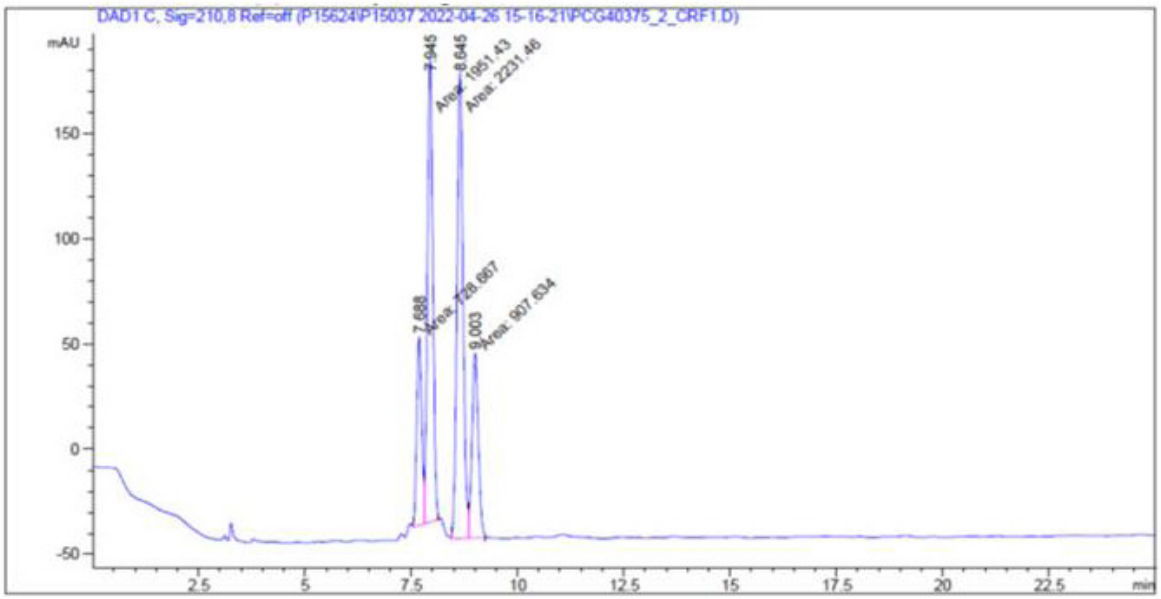
Chiral HPLC data of Compound 100g





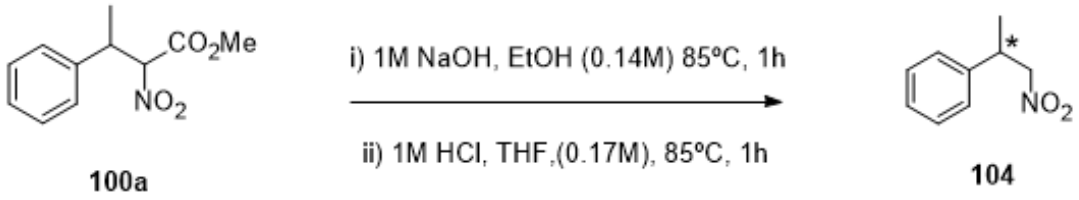
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.124	MF	0.1522	481.38358	52.72947	23.4529
2	7.357	FM	0.1543	475.41125	51.33826	23.1619
3	8.058	MF	0.1774	553.27496	51.98196	26.9554
4	8.421	FM	0.1826	542.48425	49.52488	26.4297





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.688	MF	0.1357	728.66669	89.46865	12.5218
2	7.945	FM	0.1475	1951.42749	220.53372	33.5343
3	8.645	MF	0.1679	2231.46240	221.48985	38.3466
4	9.003	FM	0.1724	907.63434	87.72820	15.5973

7.4 Determination of the absolute configuration of compound 100



100a **104**

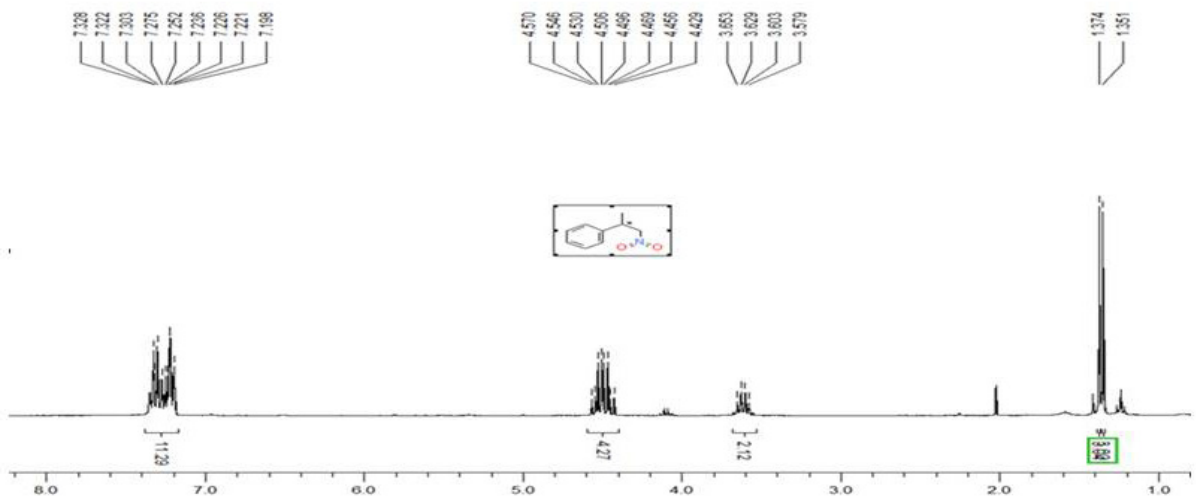
Figure 1: Xelsius apparatus

The reaction was performed using a Xelsius apparatus (Figure 1) based on data extracted from a literature procedure.[73] In a Xelsius vial, a solution of compound **100a** in Ethanol (0.14M) 1M solution of sodium hydroxide was dropwise added and the mixture was heated at 85°C for 1h and, monitored by TLC after disappearance of starting material. Then, the mixture was allowed to warm to room temperature and the solvent was eliminated under reduced pressure. The remaining salts were dissolved in tetrahydrofuran (0.17 M respect compound **100a**) and an equal volume of 1M hydrochloric acid was added. The mixture was heated at 85°C for 1h. After this time, the mixture was allowed to warm to room temperature and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried using Na_2SO_4, filtered and concentrated in vacuo. Compound **104** was obtained as colorless oil in 27% yield.

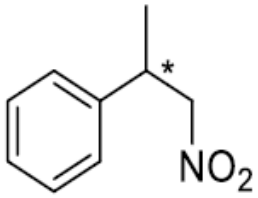
^{1}HNMR (CDCl3, 300 MHz) 1.35 (s, 3H) 1.37 (s, 3H) 3.57-3.65 (m, 2H) 4.43-4.57 (m, 4H) 7.19-7.33 (m, 10H)

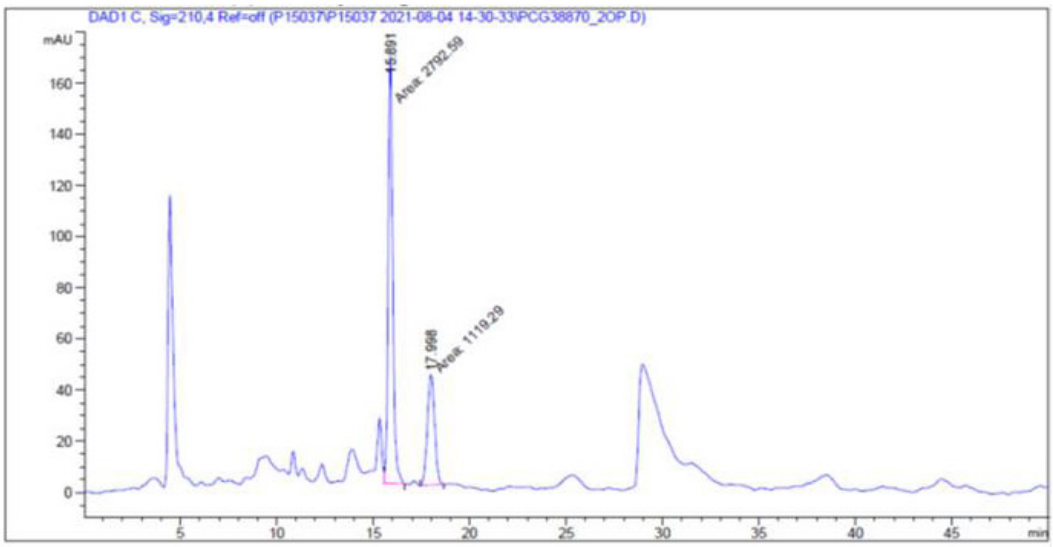
GC-MS 4.15 min; m/z = 165.19

The optical rotation of compound **104** was measured using a polarimeter obtaining an experimental value of $[\alpha]^{25}D$ = +18 (c = 0.5 in $CHCl_3$). Enantiomeric excess was measured using chiral HPLC column Phenomenex Cellulose 3_Hex_IPA_95:5_0.75 mL/min.



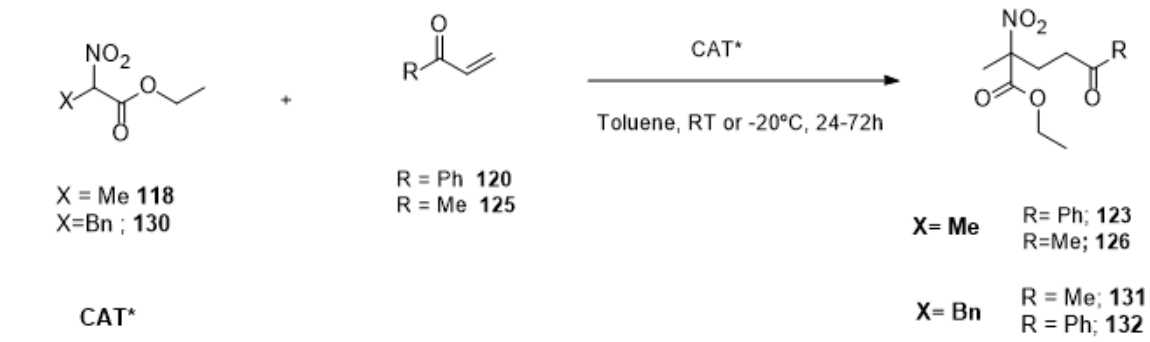
Chiral HPLC data Compound 104

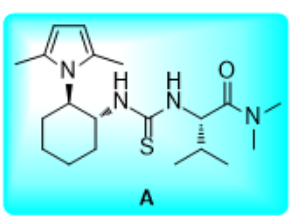


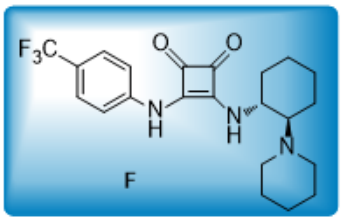


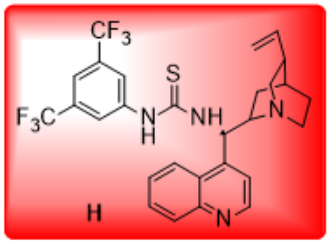
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.891	FM	0.2760	2792.58862	168.66377	71.3875
2	17.998	MM	0.4324	1119.28711	43.14579	28.6125

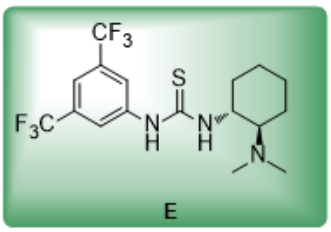
7.5 Organocatalyzed Michael addition of substituted nitropropionates to α,β-unsaturated ketones

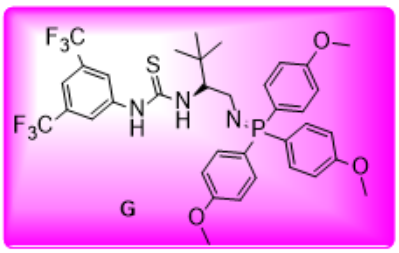


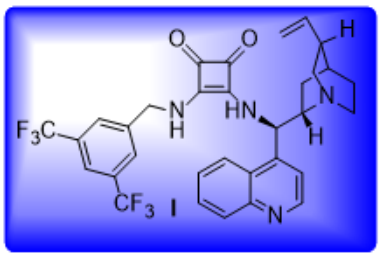








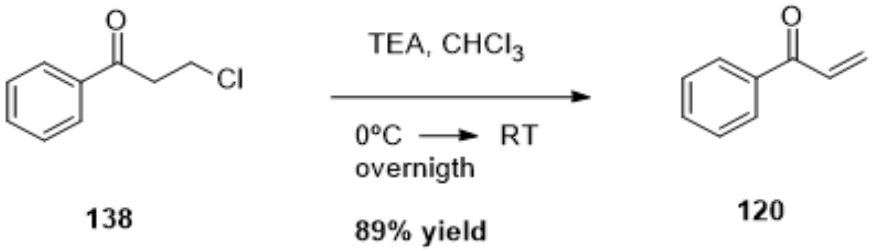




Catalysts employed in Organocatalyzed Michael addition of substituted nitropropionates to α,β-unsaturated ketones

7.5.1 Preparation of starting materials

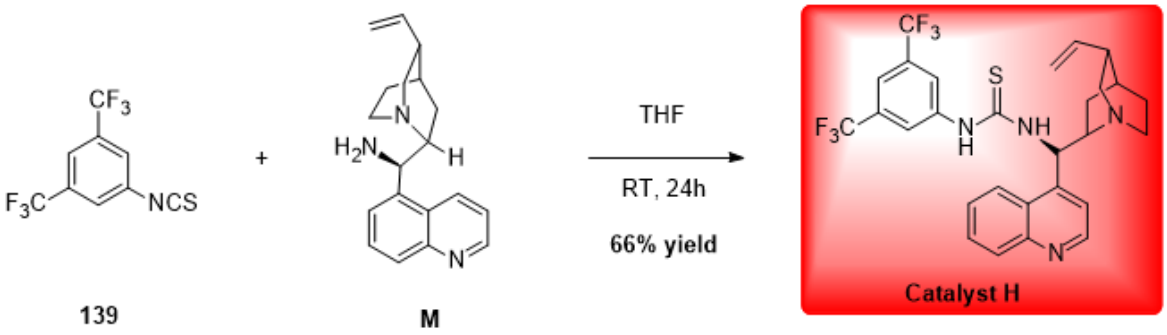
7.5.1.1 Synthesis of ketone 120



138 **120**

Ketone **120** was synthetized using the conditions reported in literature.[85] A solution of 3-chloropropiophenone **138** in $CHCl_3$ was cooled to 0°C. Then, TEA was slowly added at the same temperature. The mixture was allowed to warm to room temperature and stirred at RT for 24h. After this time, a saturated solution of HCl was slowly added and the mixture was extracted with dichloromethane. The organic layer was washed with H_2O, $NaHCO_3$ and Brine. The combined organic layers were dried using $MgSO_4$, filtered and concentrated in vacuo. The crude was purified using column chromatography and Cyclohexane/Ethyl Acetate 98:2 as eluent.

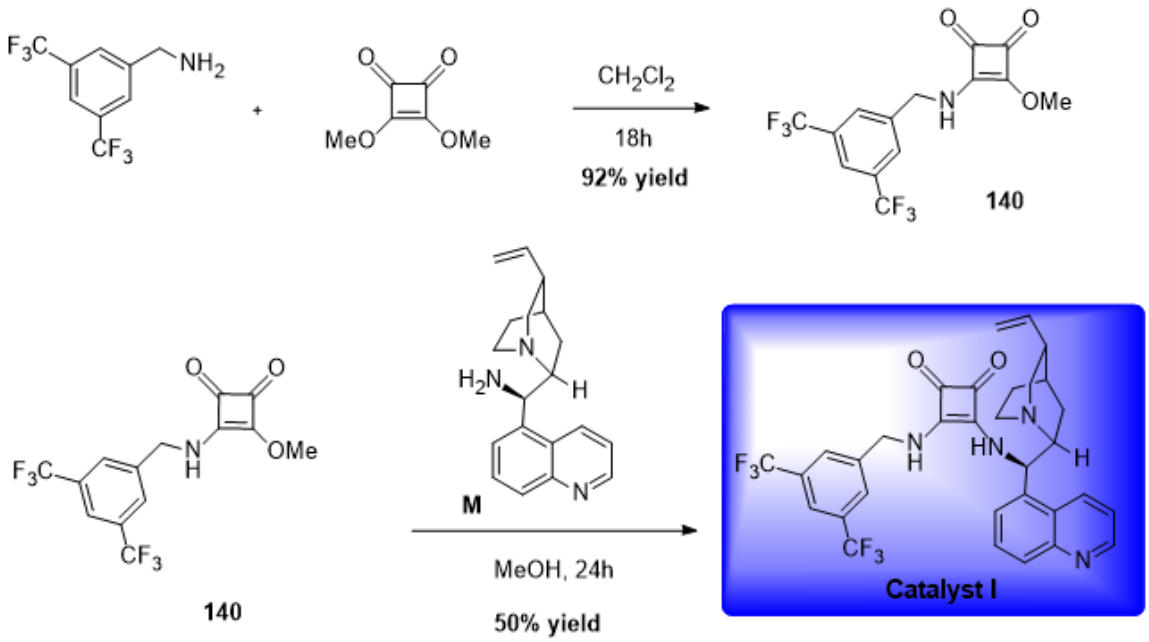
7.5.1.2 Synthesis of Catalust H



139 **M**

Catalyst **H** was synthetized using the conditions reported in literature.[86] To a solution of phenyl isothiocyanate **139** (3.7 mmol) in dry THF (2 mL) a solution of amino chinchona **M** (3.4 mmol) in dry THF (5 mL) was added at 0°C. The reaction mixture was stirred for 4h at RT. After this time, the solvent was removed under reduced pressure and the crude was purified using column chromatography and Ethyl Acetate/Methanol/Triethylamine (from 100:2:3 to 100:10:3) to afford Catalyst **H** as white solid.

7.5.1.3 Synthesis of Catalyst I

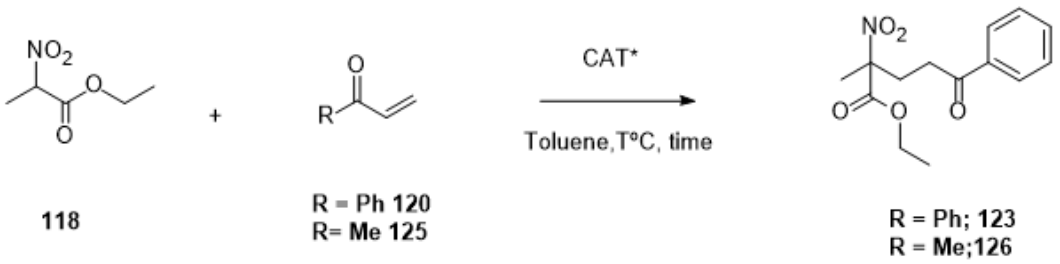


Catalyst **I** was synthetized in two steps according to literature procedure.[87]

Synthesis of intermediate 140: To a solution of dimethylsquarate (1 mmol) in dichloromethane (4 mL) was added a solution of 3,5-bis(trifluormethyl)-benzylamine (1.05 mmol) in dichloromethane (1 mL). After 18h, the reaction mixture was filtered and the filtrate was washed with 1M HCl (1x 10 mL). The organic layer was dried using $MgSO_4$, filtered and concentrated in vacuo to afford **126** as white solid which was used in the next step without any further purification.

Synthesis of catalyst I: To a solution of compound **140** (0.360 mmol) in MeOH (4 mL), a solution of amine **M** (0.300 mmol) in MeOH (1 mL). After 24h, the reaction mixture was filtered and the precipitate was washed with cold methanol to afford catalyst **I** as white solid.

7.5.2 General procedure for the synthesis of compounds 112 and 115



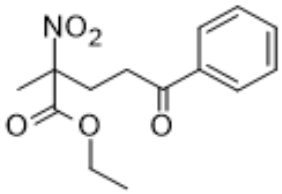
118

R = Ph 120
R= Me 125

R = Ph; 123
R = Me;126

To a stirred solution of ethyl-2-nitropropionate **118** (0.25 mmol), catalysts A-I (10 mol% represented in Figure 1) and the appropriate ketone **120** or **125** (0.25 mmol) were added. The mixture was stirred at RT or -20°C for 24-72h. Then, solvent was eliminated under reduced pressure and the crude was purified using column chromatography and Cyclohexane/Ethyl acetate as eluent. The reactions performed with catalyst I, were filtered before running the purification (in case of compound 113, no purification was required).

Ethyl 2-methyl-2-nitro-5-oxo-5-phenylpentanoate 123



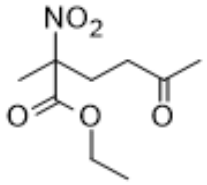
Compound **123** was synthetized using ketone **120** and catalysts A-I as colorless oil. The enantiomeric excess was determinate employing chiral HPLC column Phenomenex- Cellulose 3_Hex_IPA_90_10_1mL/min

^{1}HNMR (CDCl3, 300 MHz) 1.24 (t, 3H) 1.72 (s, 3H) 2.11 (s, 3H) 2.38-2.51 (4H) 4.22 (q, 2H)

^{13}CNMR (CDCl3, 300 MHz) 13.68, 21.90, 30.34, 37.86, 62.80, 91.96, 166.99, 205.28

ESI MS (+) m/z = 302.0999 (M+ + 23)

Ethyl 2-methyl-2-nitro-5-oxohexanoate 126

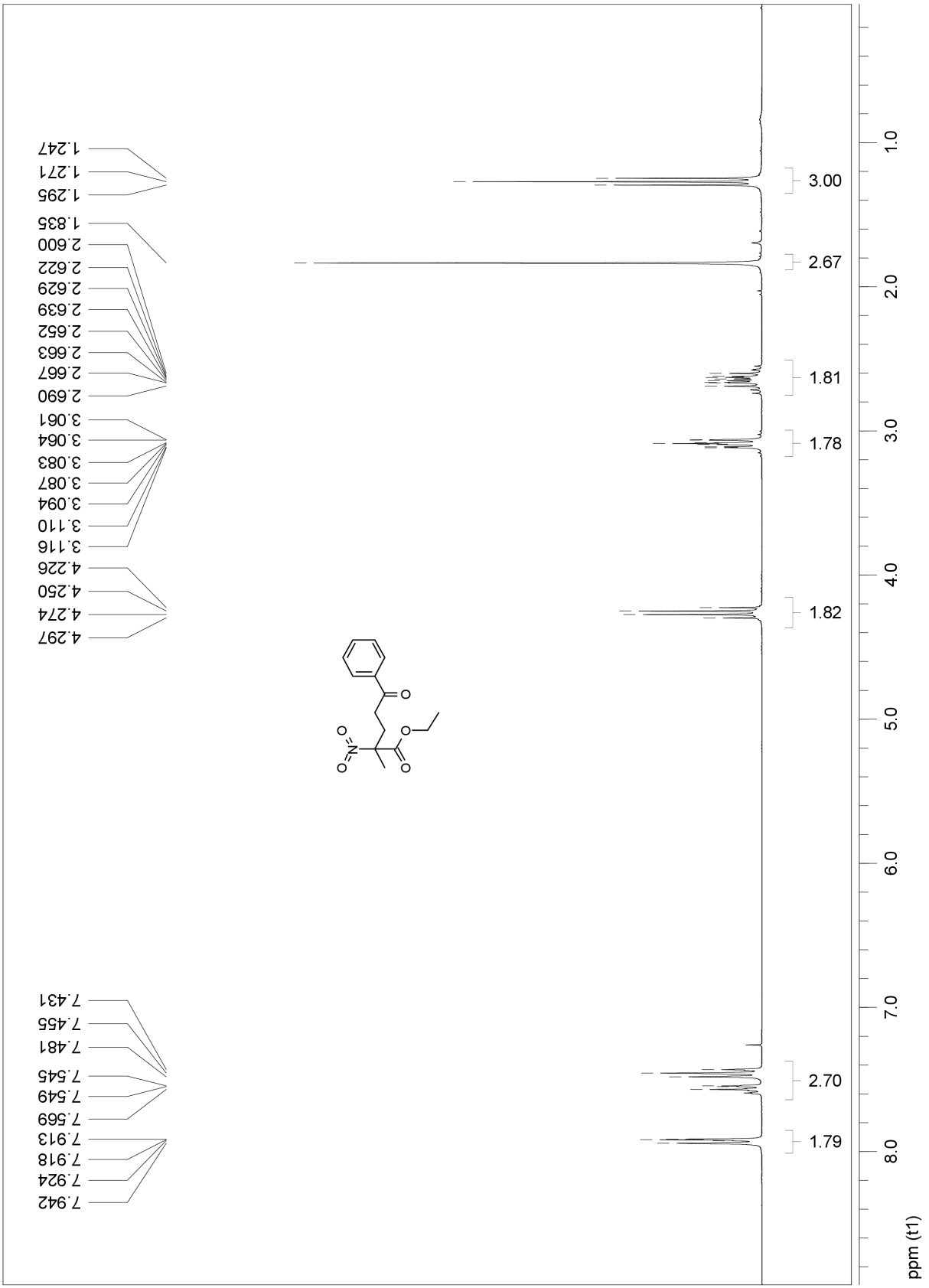


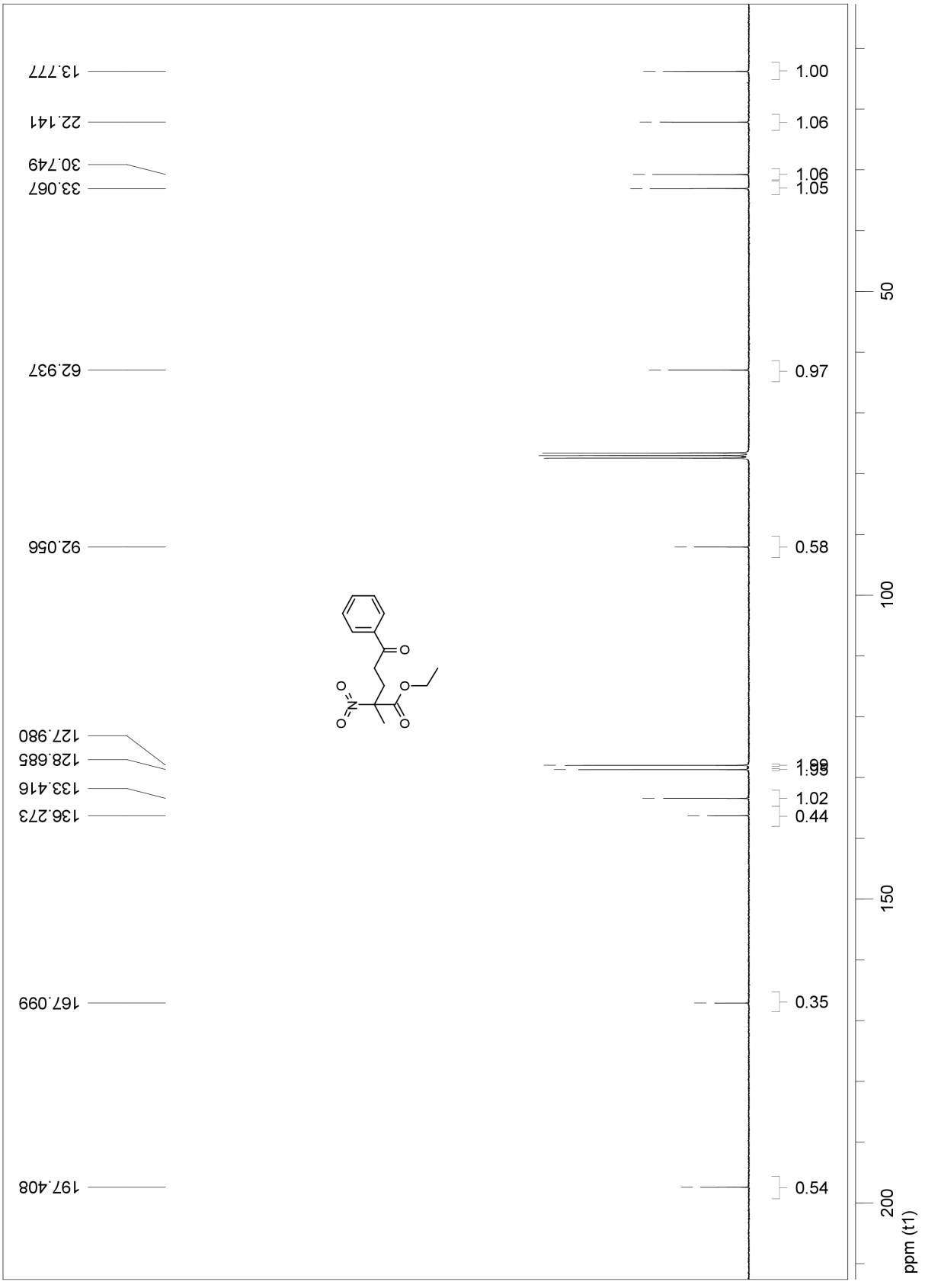
Compound **126** was obtained using ketone **125** and catalysts **A-I** as colorless oil. The enantiomeric excess was determined using chiral HPLC column Phenomenex- Cellulose 5 Hex_IPA_ 90_10 1 mL/min.

^{1}HNMR (CDCl3, 300 MHz) 1.24 (t, 3H) 1.72 (s, 3H) 2.11 (s, 3H) 2.38-2.51 (m, 4H) 4.22 (q, 2H)

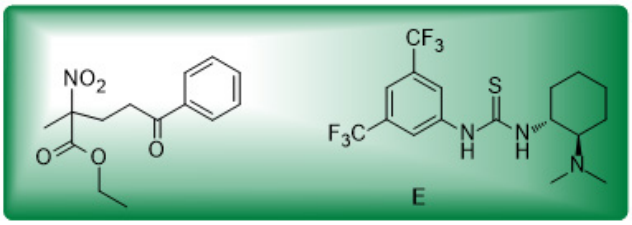
^{13}CNMR (CDCl3, 300 MHz) 13.69, 21.90, 30.34, 37.86, 62.80, 91.96, 166.99, 205.28

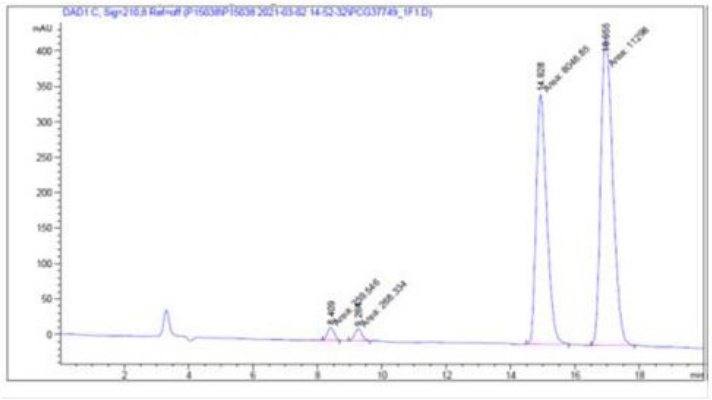
ES MS (+) m/z = 240.0847 (M+ + 23)


1.247
1.271
1.295
1.835
2.600
2.622
2.629
2.639
2.652
2.663
2.667
2.690
3.061
3.064
3.083
3.087
3.094
3.110
3.116
4.226
4.250
4.274
4.297
7.431
7.455
7.481
7.545
7.549
7.569
7.913
7.918
7.924
7.942
3.00
2.67
1.81
1.78
1.82
2.70
1.79
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

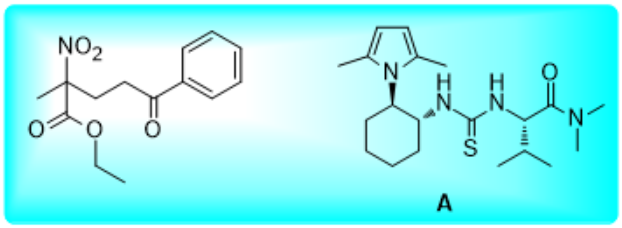

13.777
22.141
30.749
33.067
62.937
92.056
127.980
128.685
133.416
136.273
167.099
197.408
1.00
1.06
1.06
1.05
0.97
0.58
1.99
1.02
0.44
0.35
0.54
50
100
150
200
ppm (t1)

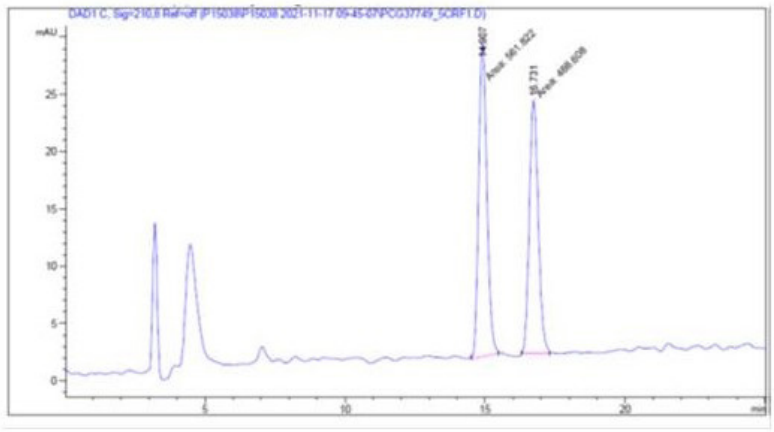
Chiral HPLC data for Compound 123



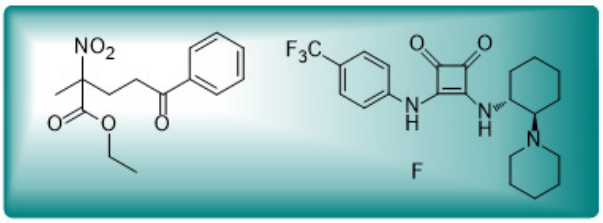


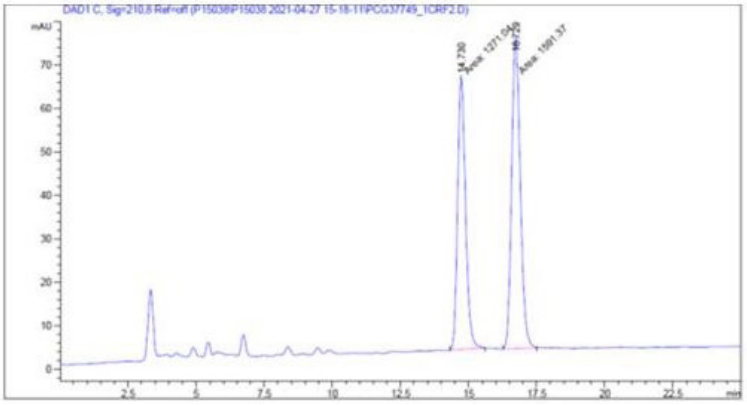
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.409	MM	0.2416	259.54593	17.90578	1.3060
2	9.264	MM	0.2626	268.33362	17.03277	1.3503
3	14.928	MM	0.3802	8046.84863	352.74008	40.4920
4	16.955	MM	0.4343	1.12980e4	433.53467	56.8517



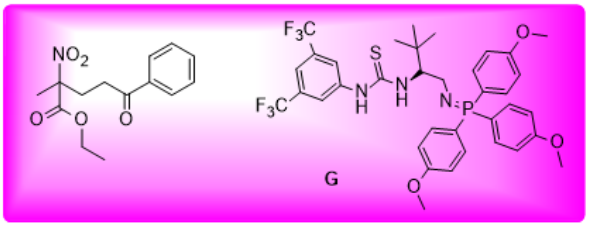


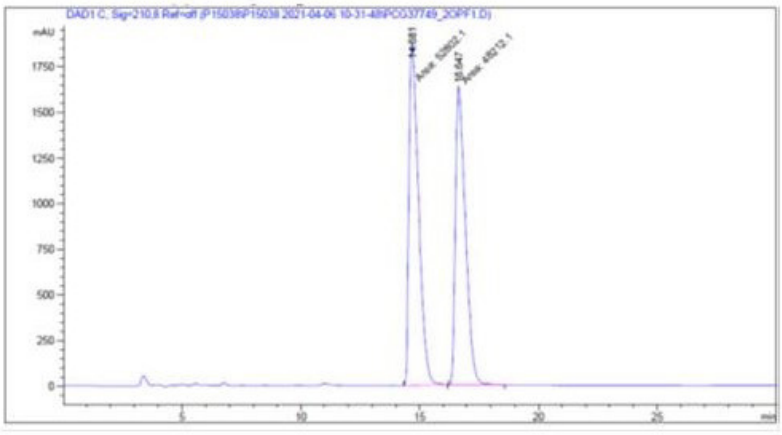
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.907	MM	0.3407	561.82239	27.48350	53.4850
2	16.731	MM	0.3676	488.60837	22.15115	46.5150



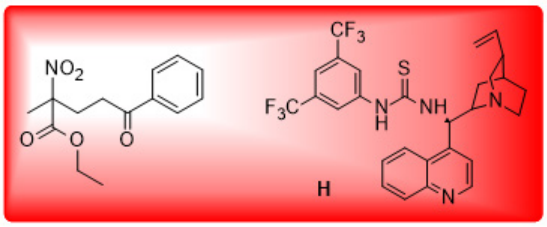


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.730	MM	0.3367	1271.03564	62.92096	44.4044
2	16.729	MM	0.3700	1591.37341	71.68045	55.5956

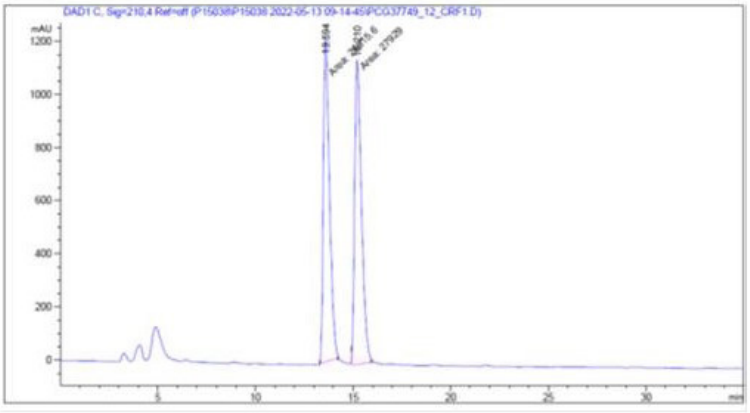




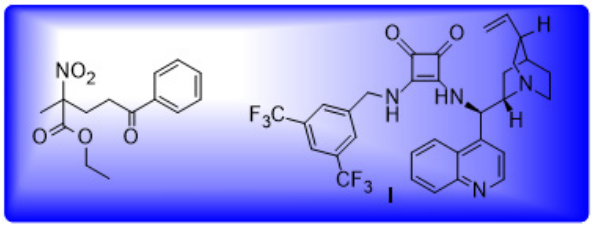
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.681	MM	0.4676	5.28021e4	1881.98511	52.2720
2	16.647	MM	0.4903	4.82121e4	1638.94971	47.7280



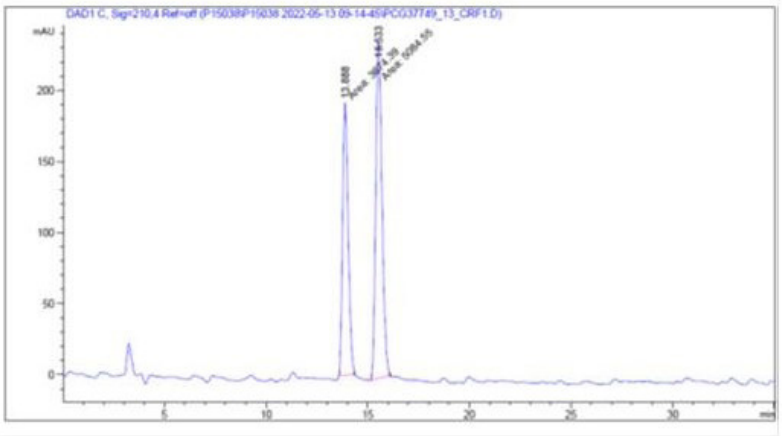
H



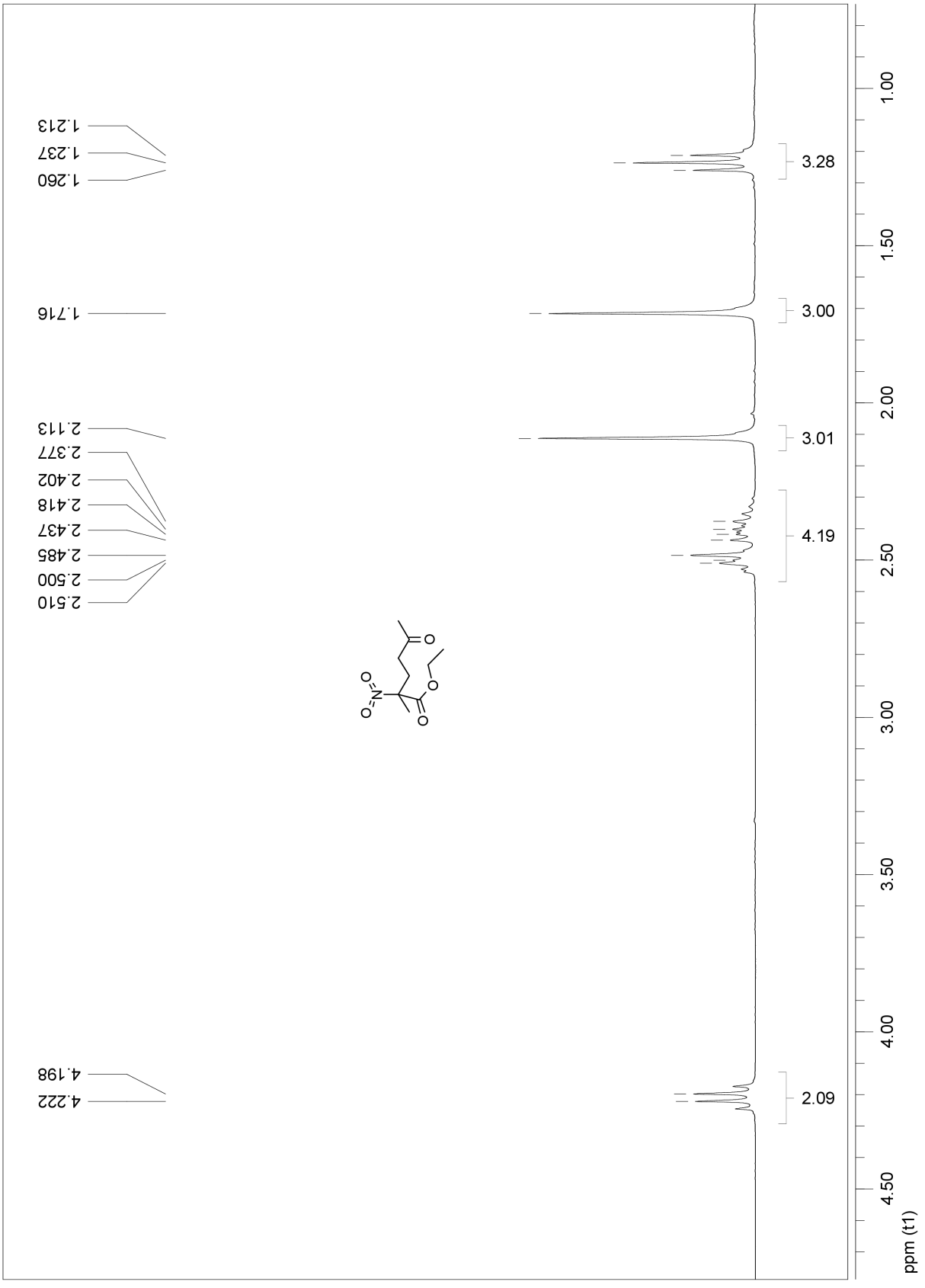
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.594	MM	0.3669	2.68156e4	1218.03760	48.9831
2	15.210	MM	0.4050	2.79290e4	1149.24780	51.0169

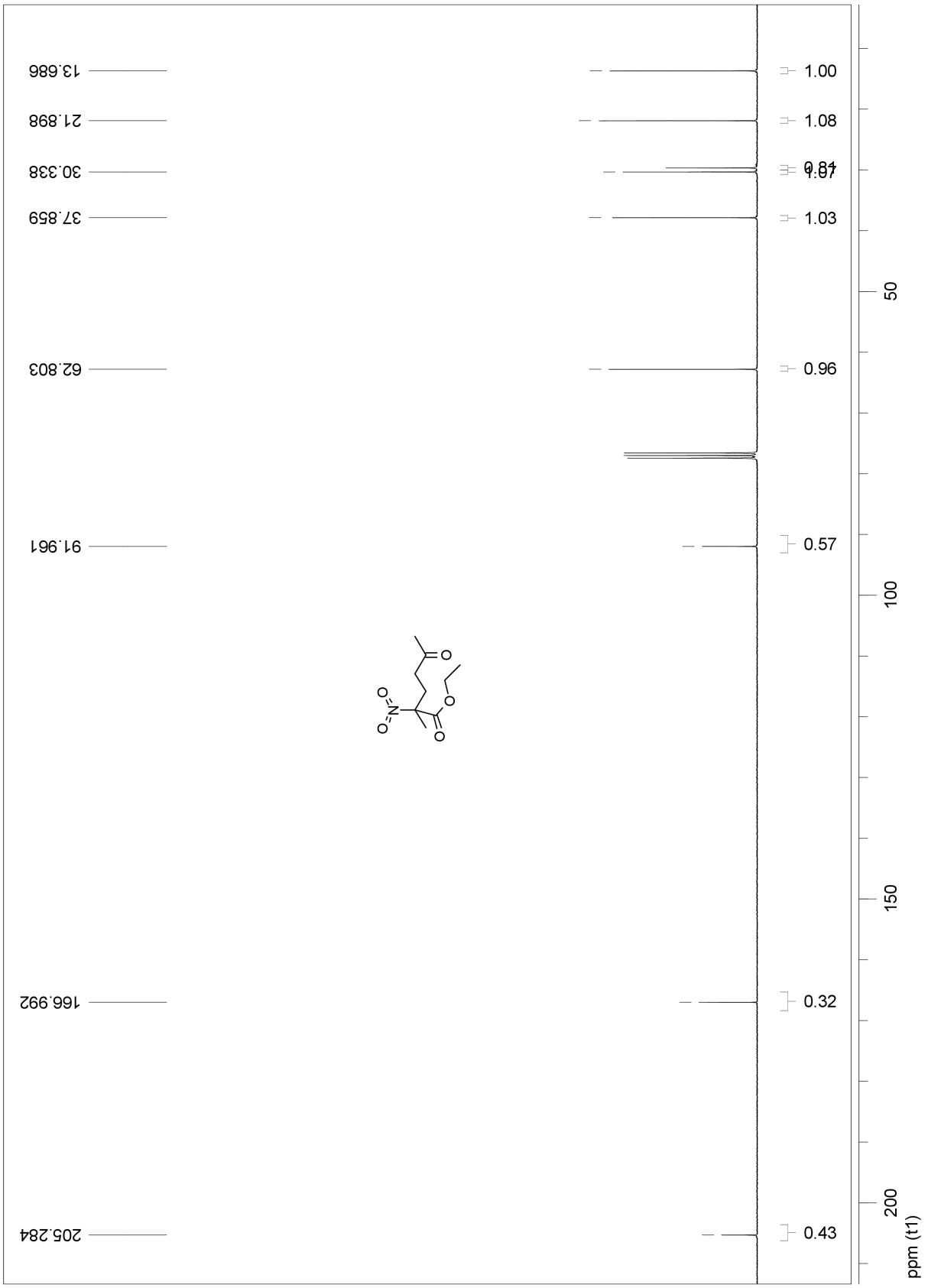


I

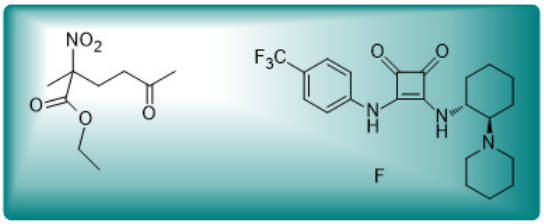


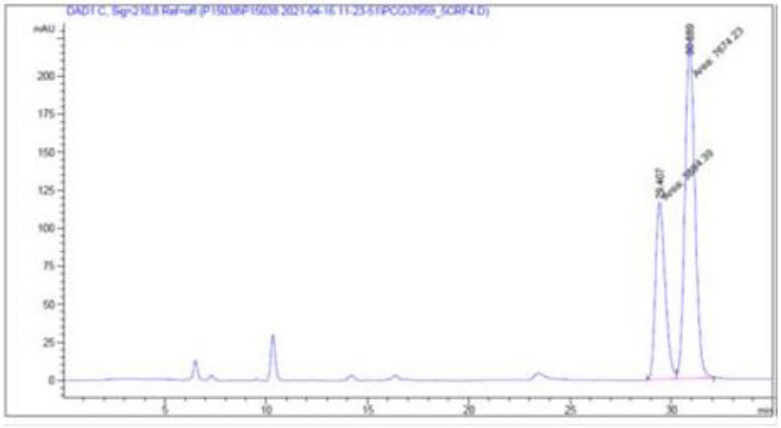
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.888	MM	0.3178	3674.39453	192.70122	41.9502
2	15.533	MM	0.3561	5084.55273	237.96233	58.0498


1.213
1.237
1.260
1.716
2.113
2.377
2.402
2.418
2.437
2.485
2.500
2.510
4.198
4.222
3.28
3.00
3.01
4.19
2.09
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
ppm (t1)

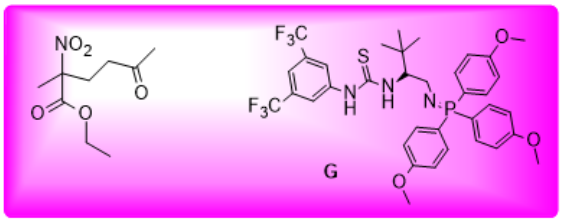

205.284
166.992
91.961
62.803
37.859
30.338
21.898
13.686
1.00
1.08
0.81
1.07
1.03
0.96
0.57
0.32
0.43
200
150
100
50
ppm (t1)

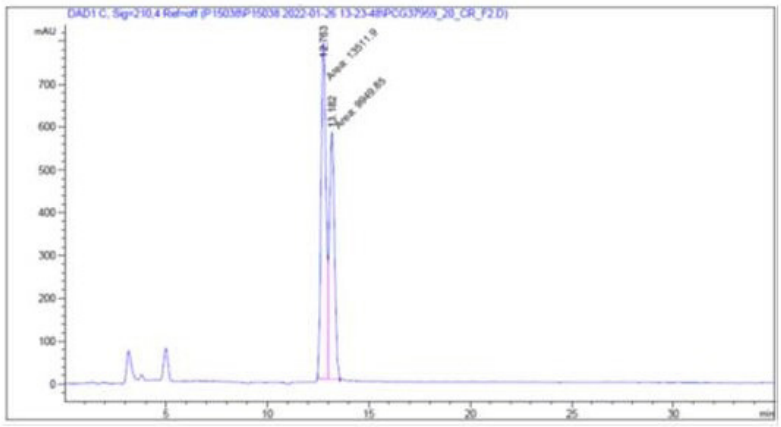
Chirel HPLC data of Compound 126



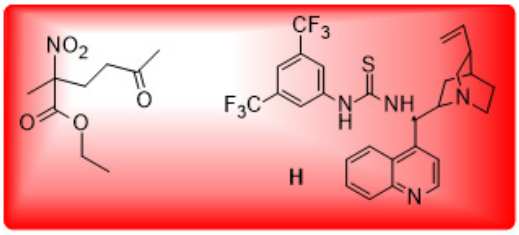


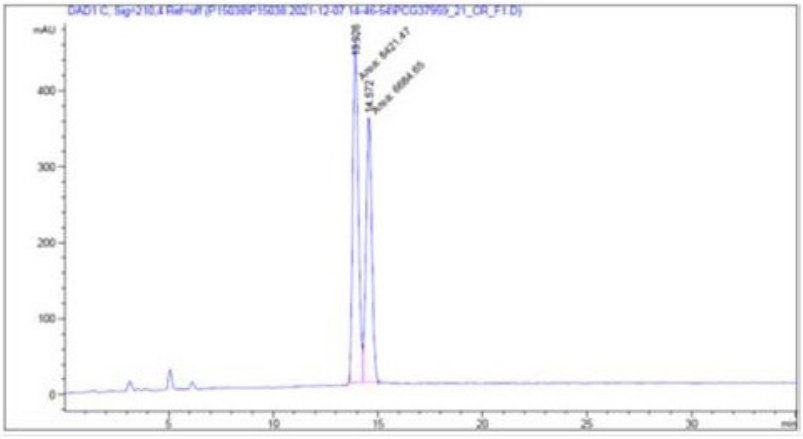
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.407	MF	0.5574	3894.39160	116.44279	33.6634
2	30.889	FM	0.5749	7674.22559	222.48636	66.3366



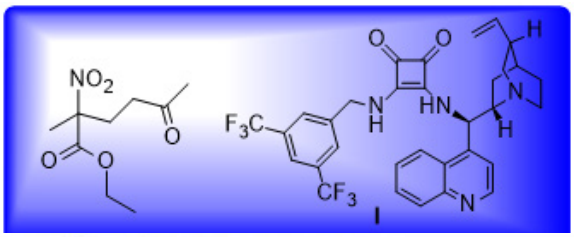


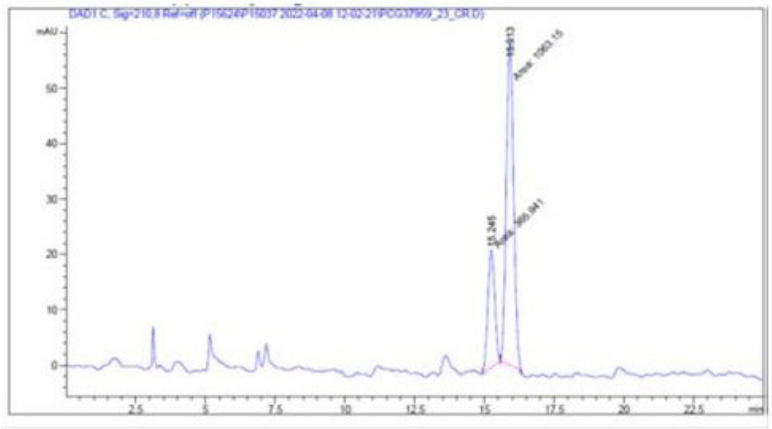
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.763	MF	0.2859	1.35119e4	787.65613	57.5912
2	13.182	FM	0.2864	9949.85352	579.09430	42.4088





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.926	MF	0.3114	8421.46875	450.68347	55.7487
2	14.572	FM	0.3182	6684.64648	350.09384	44.2513





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.245	MM	0.2873	365.94150	21.22903	25.6066
2	15.913	MM	0.3047	1063.14795	58.15679	74.3934

7.5.2.1 Additional experiments conducted for the synthesis of compounds 123 and 126

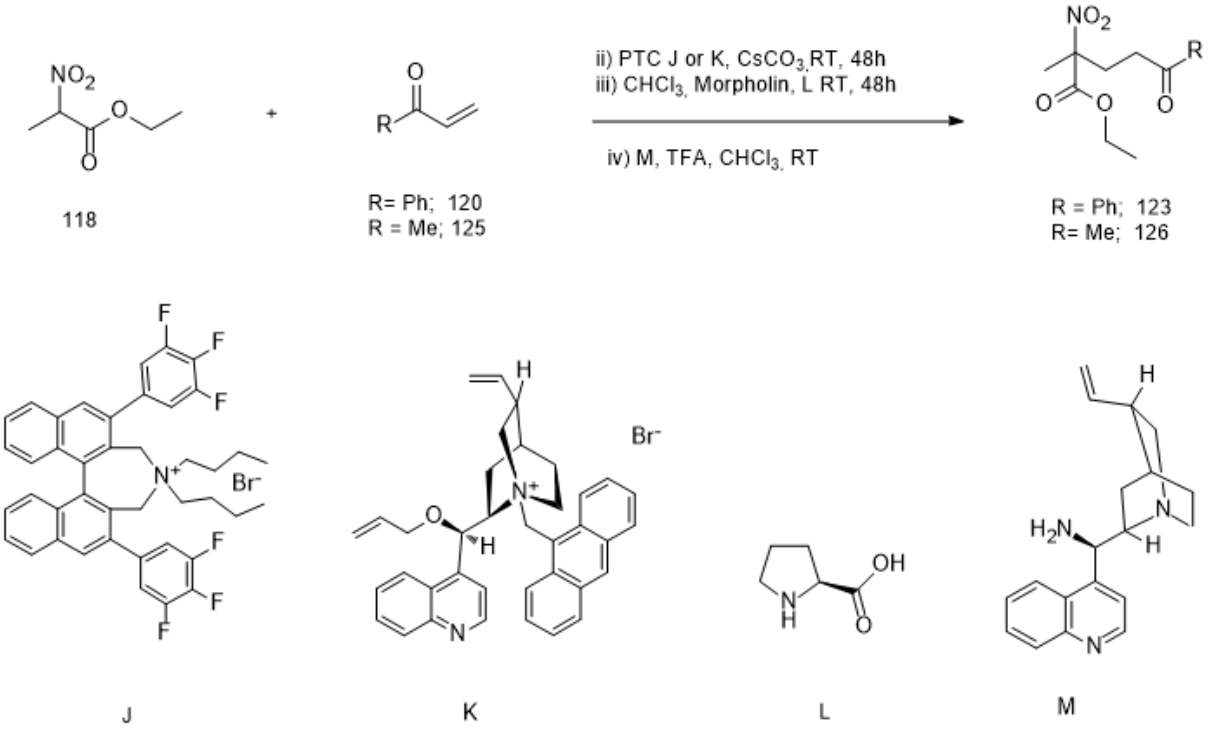


Table 1: Additional experiments performed for the synthesis of Compound 112

Entry	Conditions	Catalyst	Yield	ee
1	*iii*	L	traces	----
2[a]	*iii*	L	NR	----
3[b]	*iii*	---	NR	----
4	*iv*	M	NR	----

a= reaction performed without Morpholin; b= reaction performed without Catalyst 9

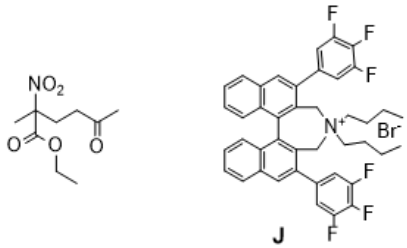
Table 2: Additional experiments performed for the synthesis of Compound 115

Entry	**Conditions**	**Catalyst**	**Yield**	**ee**[c]
1	*ii*	J	31	8
2	*ii*	K	56	4
3	*iii*	L	35	15
4[a]	*iii*	L	traces	ND
5	*iv*	M	traces	ND

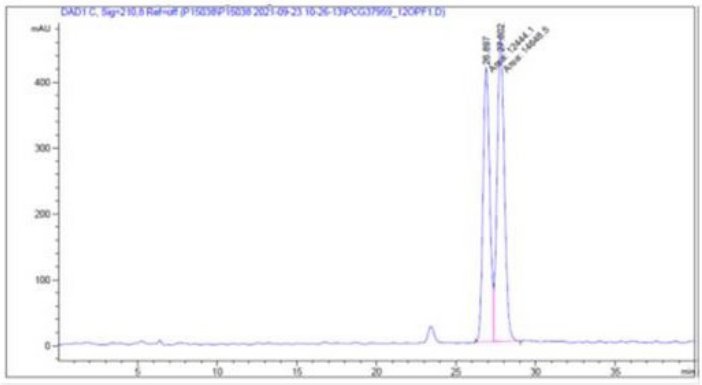
a= reaction performed without Morpholin; ND = not determinated; c= using chiral HPLC column Cellulose 5_Hex_IPA_90_10_1mL/min

Chiral HPLC data of the additional experiments conducted for Compound 126

Tale 2, entry 1

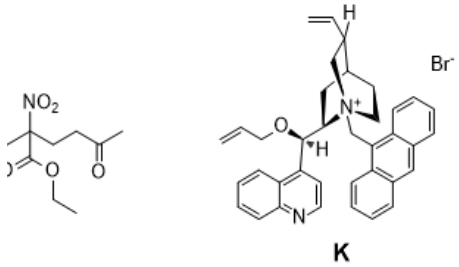


J

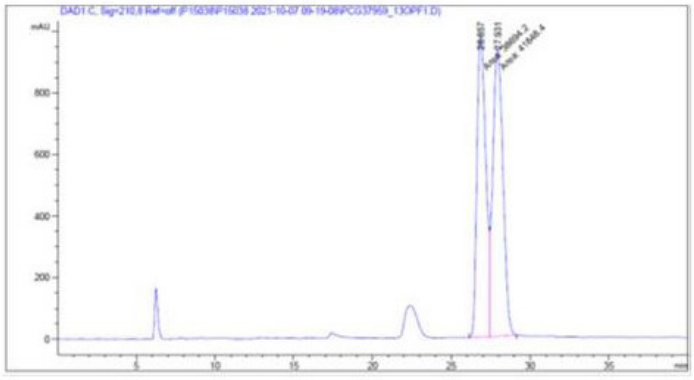


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.897	MF	0.4979	1.24441e4	416.53583	45.9317
2	27.802	FM	0.5303	1.46485e4	460.37006	54.0683

Tale 2, entry 2

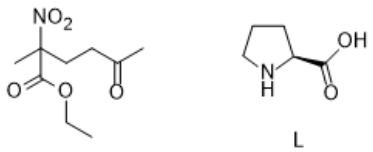


K

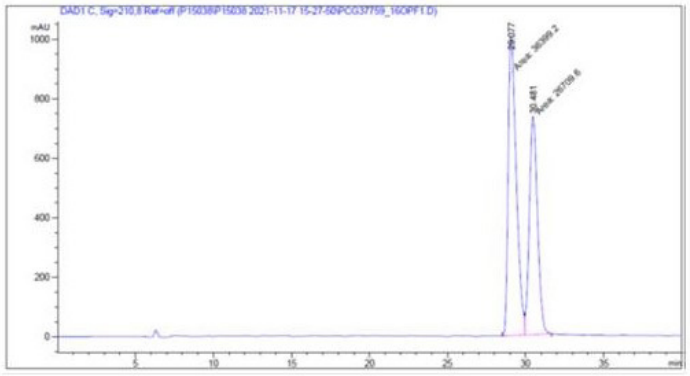


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.857	MF	0.6593	3.86942e4	978.09814	48.0419
2	27.931	FM	0.7462	4.18484e4	934.74493	51.9581

Tale 2, entry 3



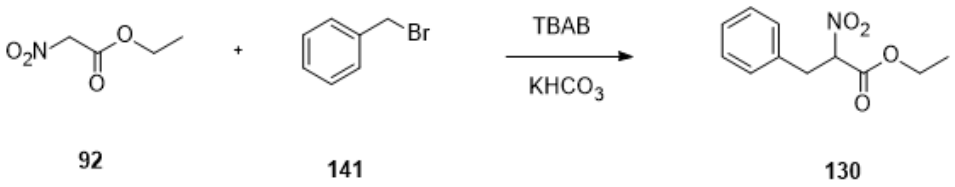
L



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.077	MF	0.6039	3.63992e4	1004.51453	57.6769
2	30.481	FM	0.6062	2.67096e4	734.37671	42.3231

7.5.3 Organocatalytic Michael addition of benzyl-2-nitropropionate to α,β-unsaturated ketones: Synthesis of compounds 131 and 132

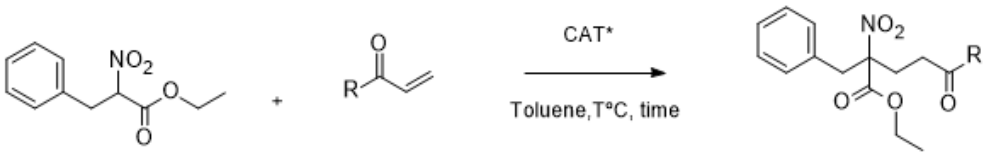
7.5.3.1 Synthesis of ethyl 2-nitro-3-phenylpropanoate 130



92 141 130

Compound **130** was prepared using the conditions reported in literature.[88] A solution of ethyl nitroacetate **92** (2 eq, 2 mmol), benzyl bromide **141** (1 eq, 1 mmol) and 2 mmol of tetrabutylammonium bromide (TBAB) was stirred 30 min at RT. Then, potassium bicarbonate was added, and the mixture was stirred at RT for 24h. After this time, the reaction mixture was extracted with dichloromethane. The combined organic layers were dried using $MgSO_4$, filtered and concentrated in vacuo. The crude was purified using column chromatography and Cyclohexane/Ethyl Acetate 8:2 as eluent to afford compound **116** as colorless oil in 19% yield.

7.5.3.2 General procedure for the Organocatalytic Michael addition of benzyl nitropropionate: Synthesis of compounds 131 and 132

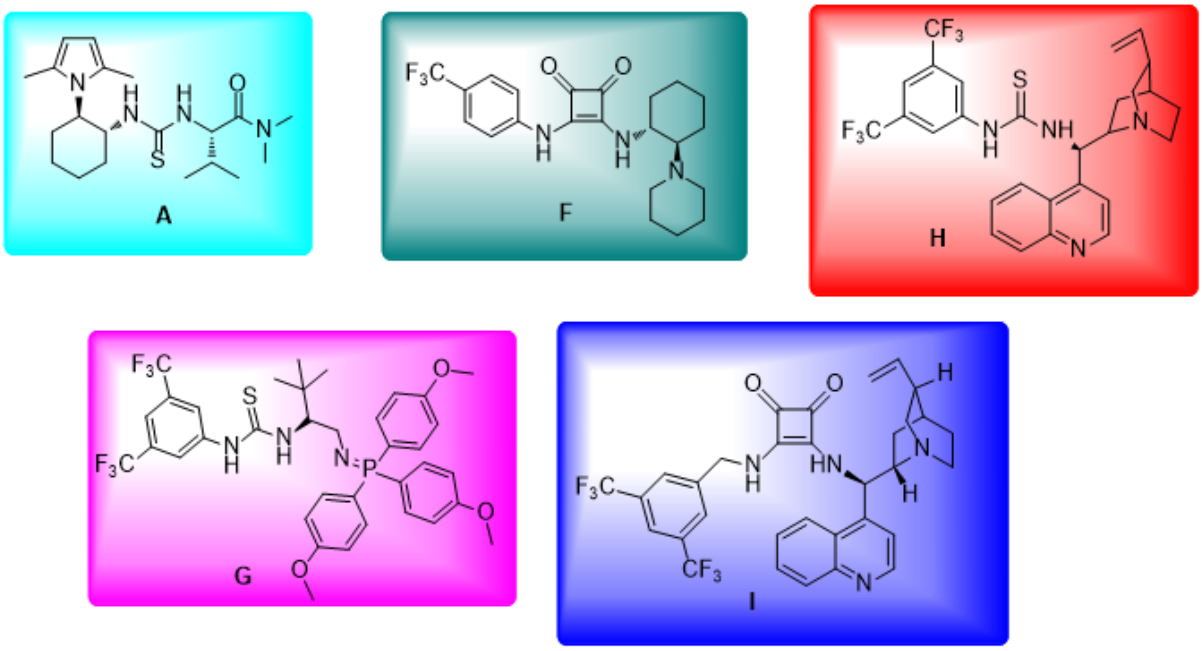


130

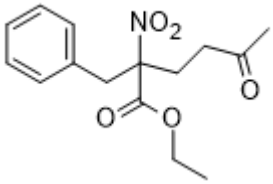
R= Ph; **120**
R = Me; **125**

R = Ph; **131**
R= Me; **132**

To a solution of benzyl nitro propionate **130** (0.25 mmol) in Toluene (1 mL), catalyst **A-I** and the appropriate ketone **120** or **125** (0.25 mmol) were added. The mixture was stirred at -20 for 18-72h. Then, the solvent was eliminated under reduced pressure and the crude was purified using preparative TLC purification and n-Hexane/Ethyl acetate 9:1 as eluent.



Ethyl 2-benzyl-2-nitro-5-oxohexanoate 131



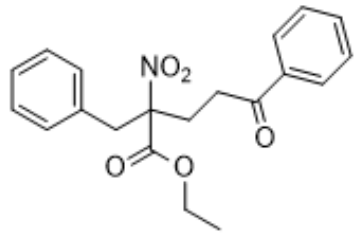
Compound **131** was obtained as colorless oil in 27-82% yield after preparative TLC purification. The enantiomeric excess was measured using chiral HPLC column Phenomenex-Cellulose 5_Hex_IPA_90:10_1mL/min

^{1}HNMR ($CDCl_3$, 300 MHz) 1.27 (t, 3H) 2.13 (s, 3H) 2.32-2.37 (m, 2H) 2.53-2.58 (m, 2H) 3.46-3.60 (q, 2H) 4.20-4.28 (m, 2H) 7-06-7.10 (m, 2H) 7.27-7.30 (m, 3H)

^{13}CNMR ($CDCl_3$, 300 MHz) 13.73, 27.66, 29.73, 37.94, 41.19, 62.87, 95.79, 127.99, 128.76, 130.00, 132.85, 166.29, 205.27

ESI MS (+) m/z = 316.1158 (M^+ + 23)

Ethyl 2-benzyl-2-nitro-5-oxo-5-phenylpentanoate 132

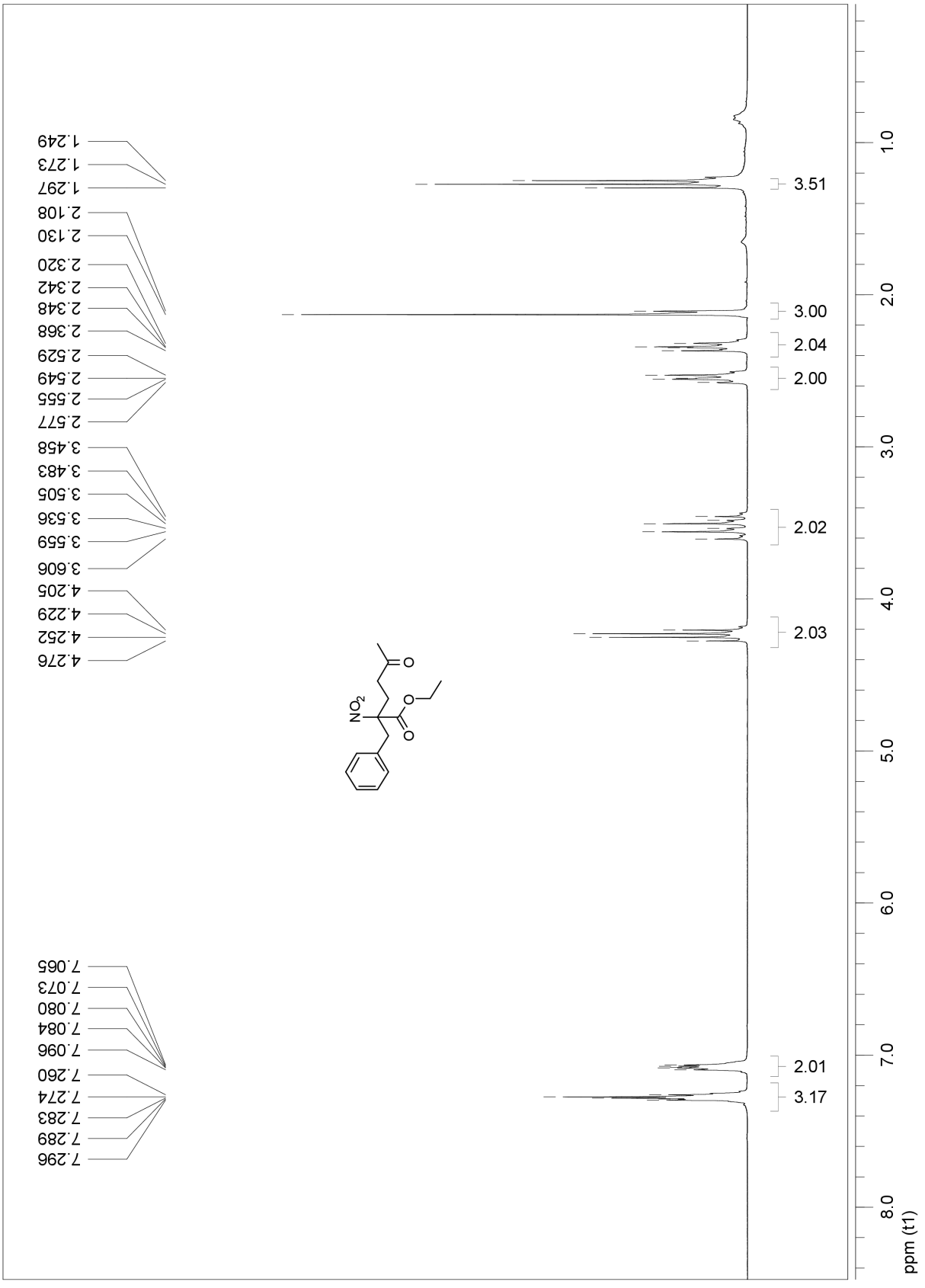


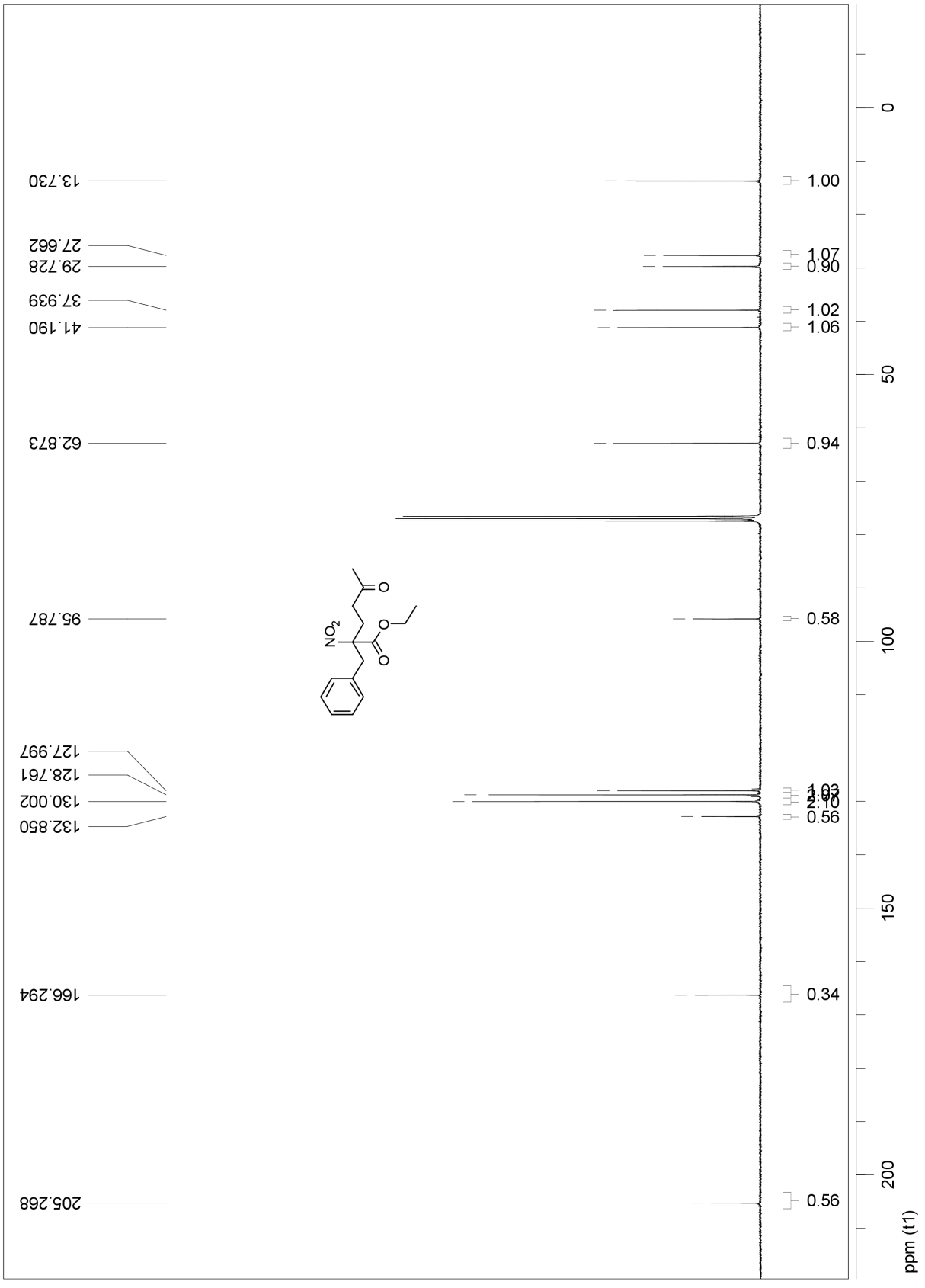
Compound **132** was obtained as colorless oil in 31-50% yield after preparative TLC purification. The enantiomeric excess was measured using a chiral HPLC column Phenomenex Cellulose 3_Hexane_IPA_90:10_1mL/min

^{1}HNMR ($CDCl_3$ 300 MHz) 1.22-1.27 (t, 3H) 2.52-2.58 (m, 2H) 3.07-3.14 (m, 2H) 3.54-369 (q, 2H) 4.21-4.29 (m, 2H) 7.11-7.15 (m, 2H) 7.26-7.32 (m, 3H) 7.43-7.58 (m, 2H) 7.91-7.93 (d, 2H)

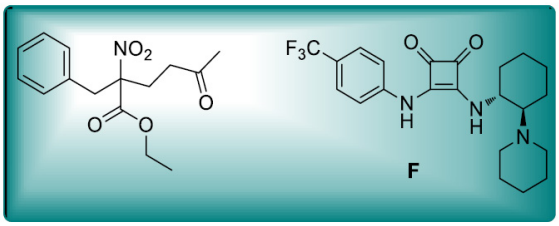
^{13}CNMR ($CDCl_3$ 300 MHz) 13.64, 28.21, 33.13, 41.39, 62.84, 95.97, 127.93, 128.62, 128.72, 130.00, 133.23, 136.53, 166.30, 197.27

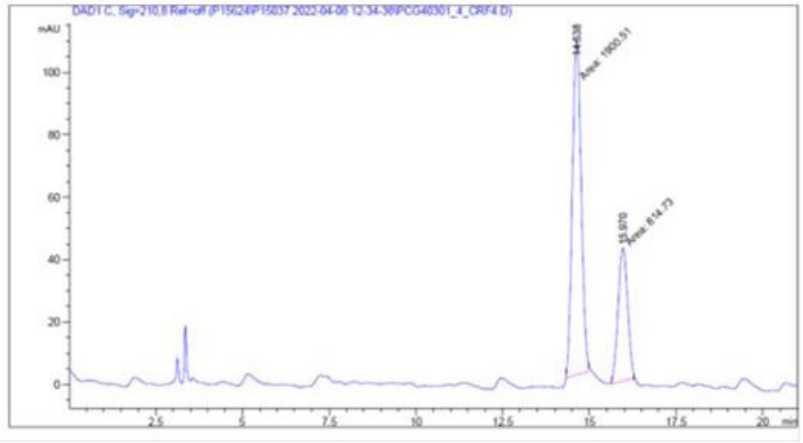
ESI MS (+) m/z = 378.1314 (M^+ + 23)


1.249
1.273
1.297
2.108
2.130
2.320
2.342
2.348
2.368
2.529
2.549
2.555
2.577
3.458
3.483
3.505
3.536
3.559
3.606
4.205
4.229
4.252
4.276
7.065
7.073
7.080
7.084
7.096
7.260
7.274
7.283
7.289
7.296
3.51
3.00
2.04
2.00
2.02
2.03
2.01
3.17
O
O
O
NO2
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

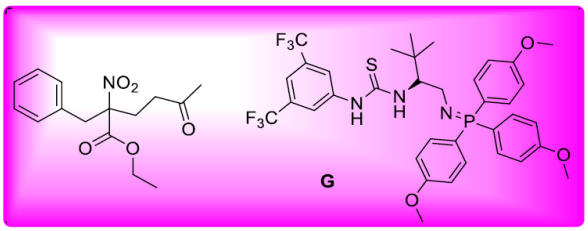

13.730
27.662
29.728
37.939
41.190
62.873
95.787
127.997
128.761
130.002
132.850
166.294
205.268
1.00
1.07
0.90
1.02
1.06
0.94
0.58
0.56
0.34
0.56
0
50
100
150
200
ppm (t1)

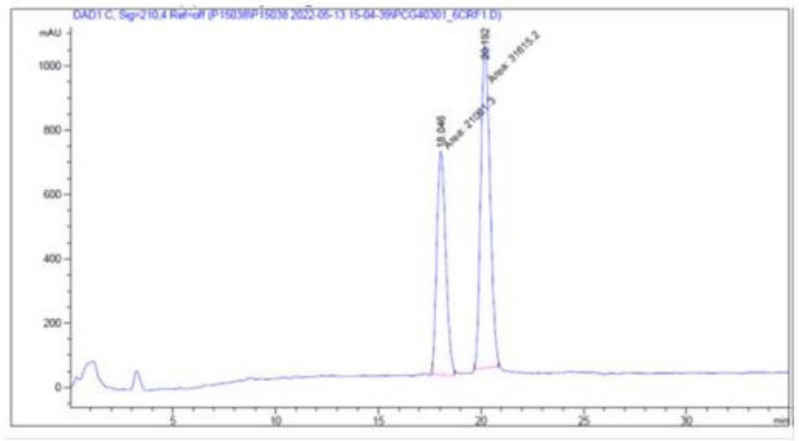
Chiral HPLC data of Compound 131



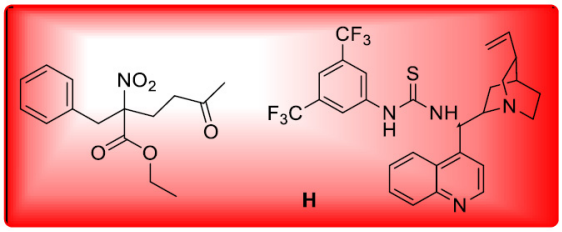


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.638	MM	0.2960	1900.51062	107.00484	69.9942
2	15.970	MM	0.3181	814.73029	42.68269	30.0058

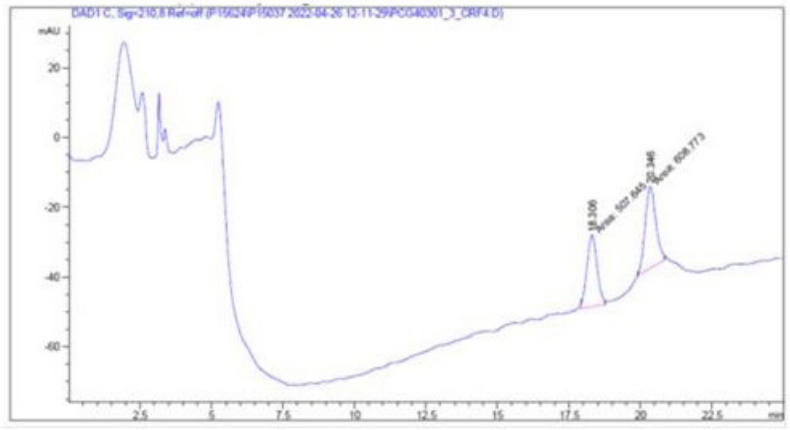




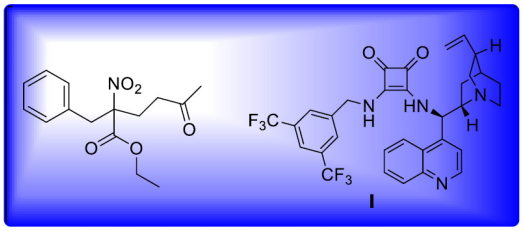
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.046	MM	0.5040	2.10613e4	696.48621	39.9824
2	20.192	MM	0.5234	3.16152e4	1006.65588	60.0176



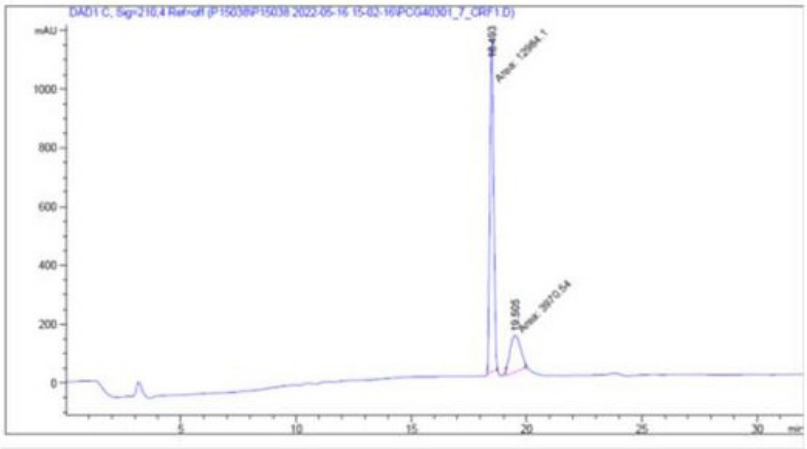
H



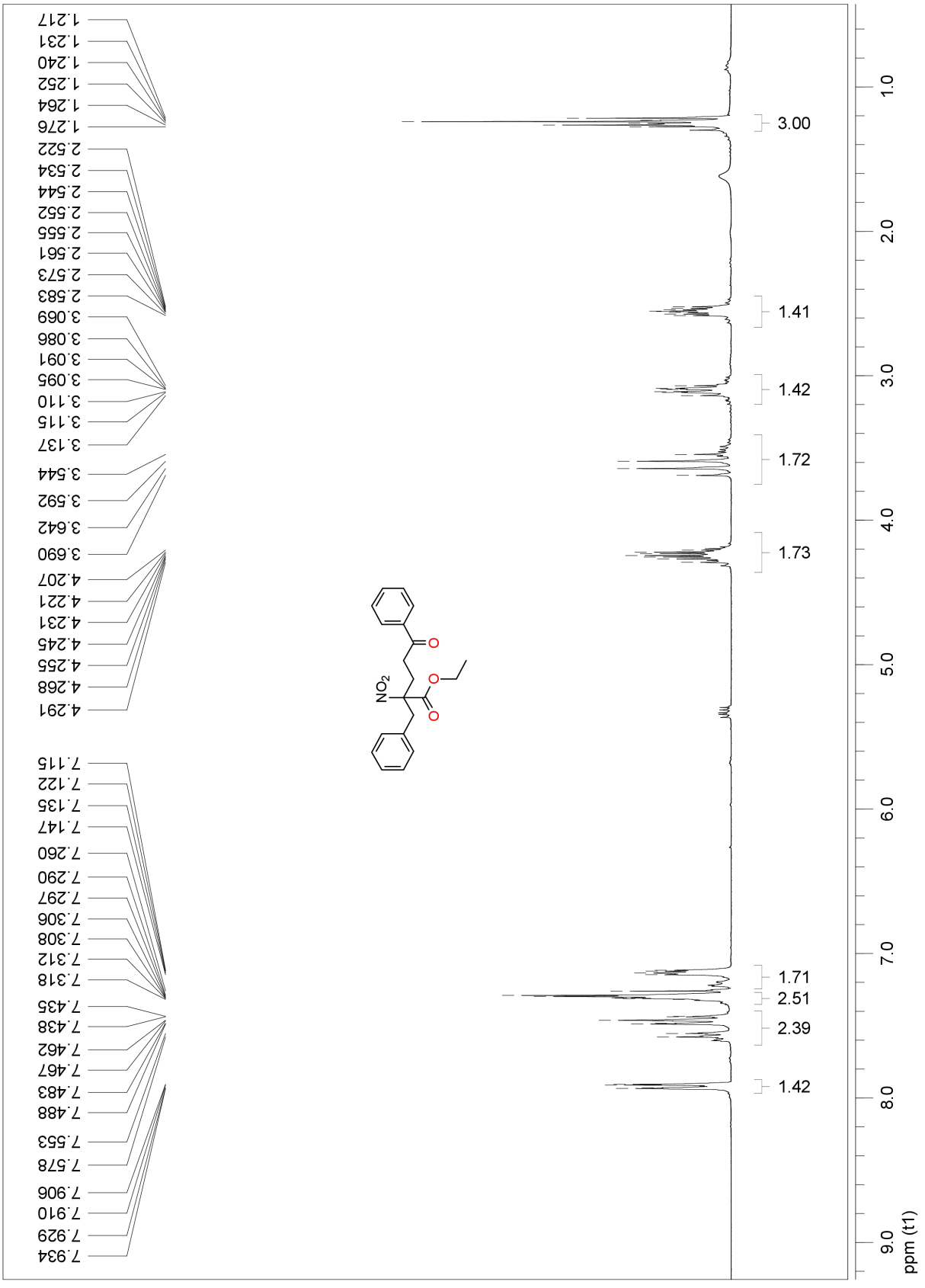
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.306	MM	0.4132	507.64481	20.47766	45.4709
2	20.346	MM	0.4328	608.77252	23.44251	54.5291

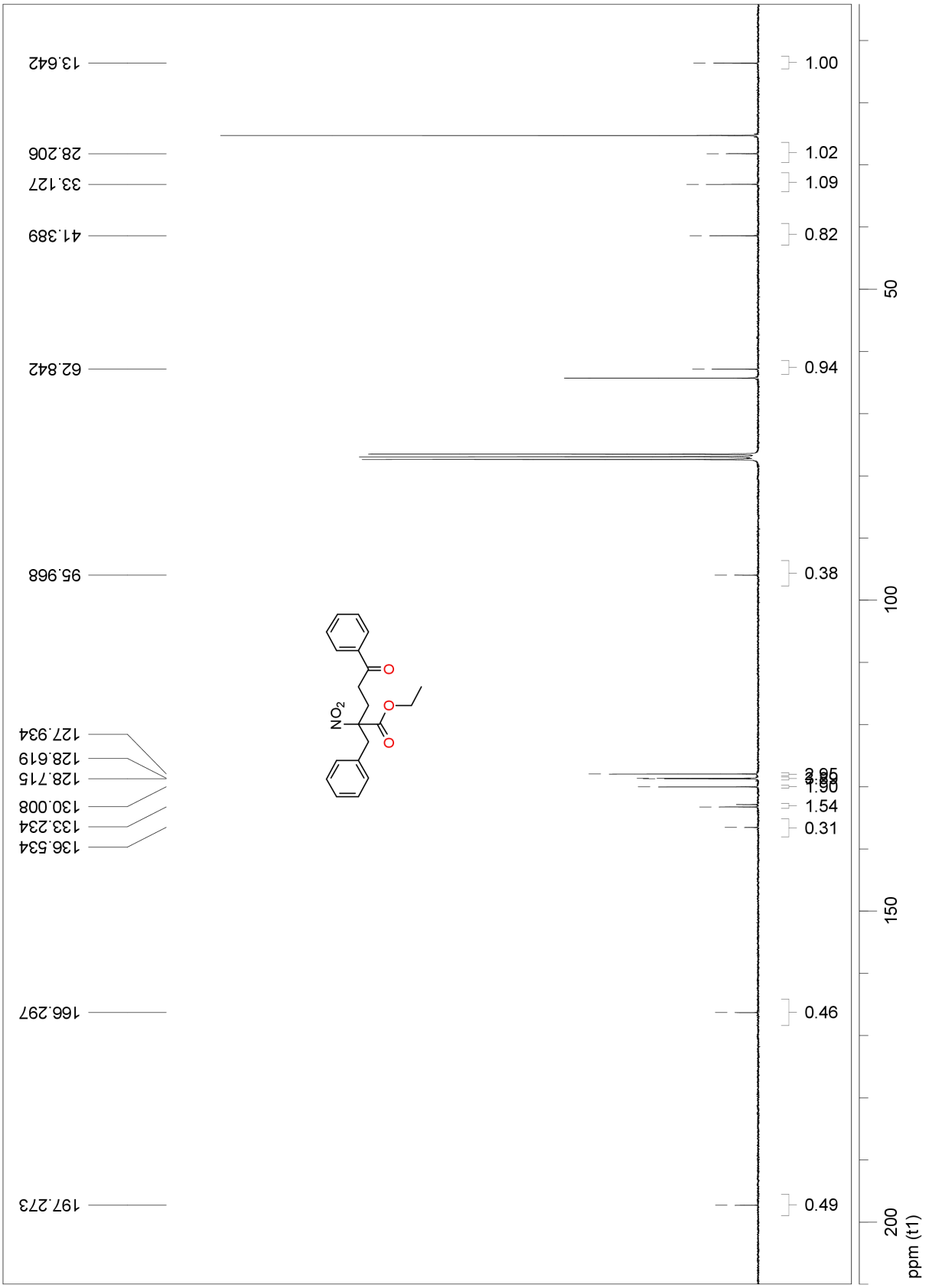


I

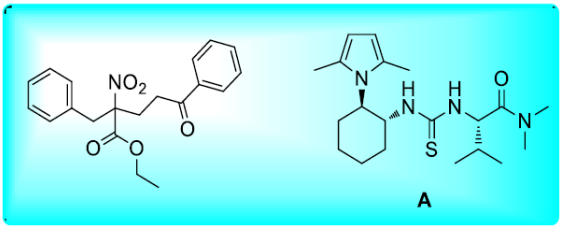


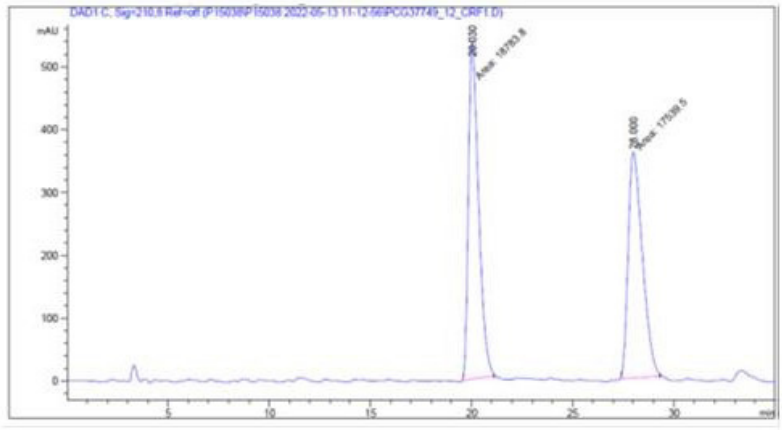
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.493	MM	0.1906	1.29841e4	1135.42322	76.5814
2	19.505	MM	0.5303	3970.54053	124.79681	23.4186


1.217
1.231
1.240
1.252
1.264
1.276
2.522
2.534
2.544
2.552
2.555
2.561
2.573
2.583
3.069
3.086
3.091
3.095
3.110
3.115
3.137
3.544
3.592
3.642
3.690
4.207
4.221
4.231
4.245
4.255
4.268
4.291
7.115
7.122
7.135
7.147
7.260
7.290
7.297
7.306
7.308
7.312
7.318
7.435
7.438
7.462
7.467
7.483
7.488
7.553
7.578
7.906
7.910
7.929
7.934
3.00
1.41
1.42
1.72
1.73
1.71
2.51
2.39
1.42
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
NO2
O
O
O
O

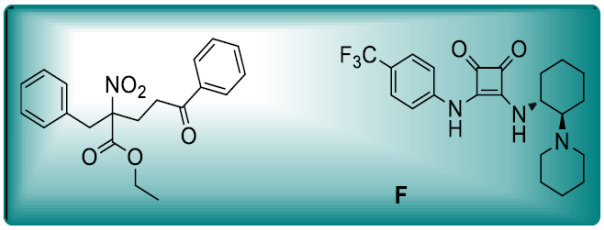

13.642
28.206
33.127
41.389
62.842
95.968
127.934
128.619
128.715
130.008
133.234
136.534
166.297
197.273
1.00
1.02
1.09
0.82
0.94
0.38
1.90
1.54
0.31
0.46
0.49
50
100
150
200
ppm (t1)
NO2
O
O
O
O

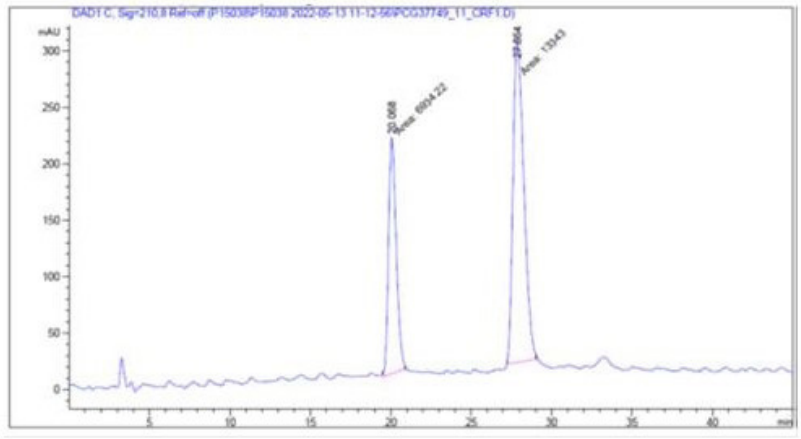
Chiral HPLC data of Compound 132



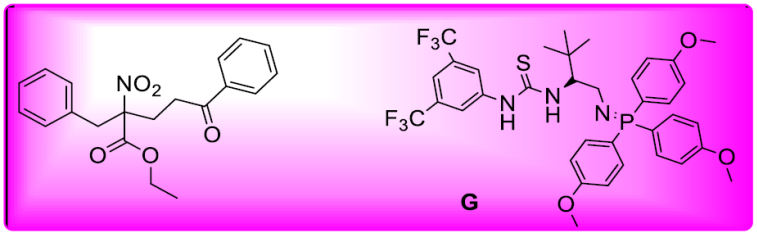


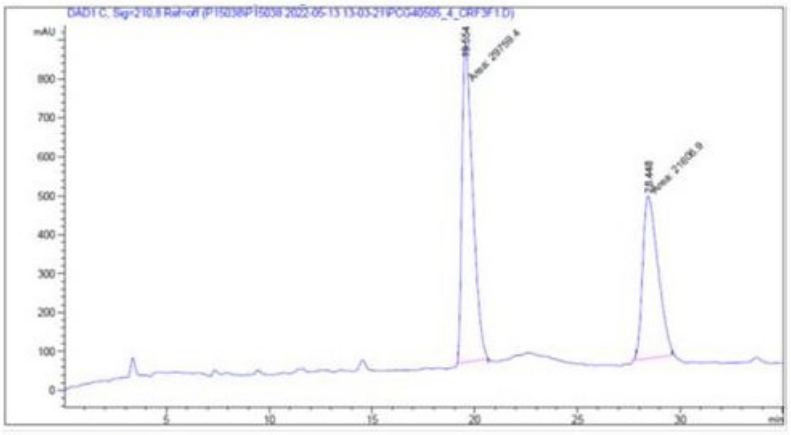
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.030	MM	0.5824	1.87838e4	537.52393	51.7127
2	28.000	MM	0.8119	1.75395e4	360.03284	48.2873



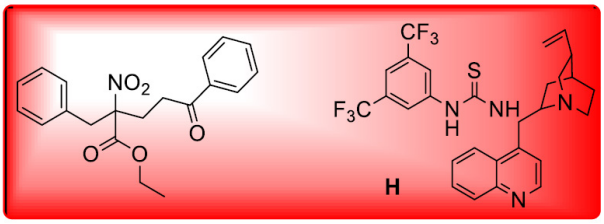


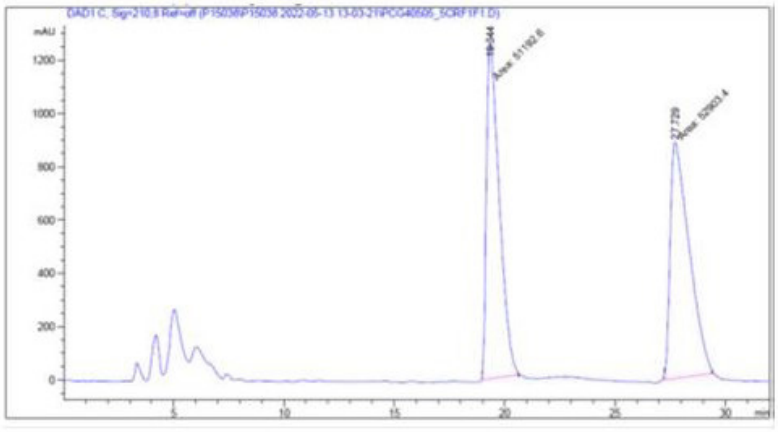
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.068	MM	0.5512	6934.21631	209.66016	34.1970
2	27.864	MM	0.7853	1.33430e4	283.17157	65.8030



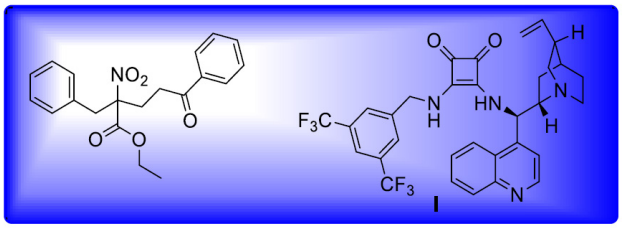


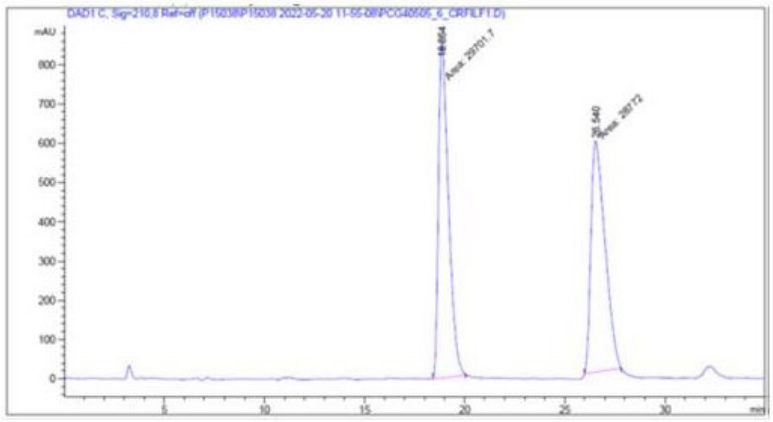
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.554	MM	0.6031	2.97594e4	822.33691	57.9357
2	28.448	MM	0.8615	2.16069e4	418.03195	42.0643





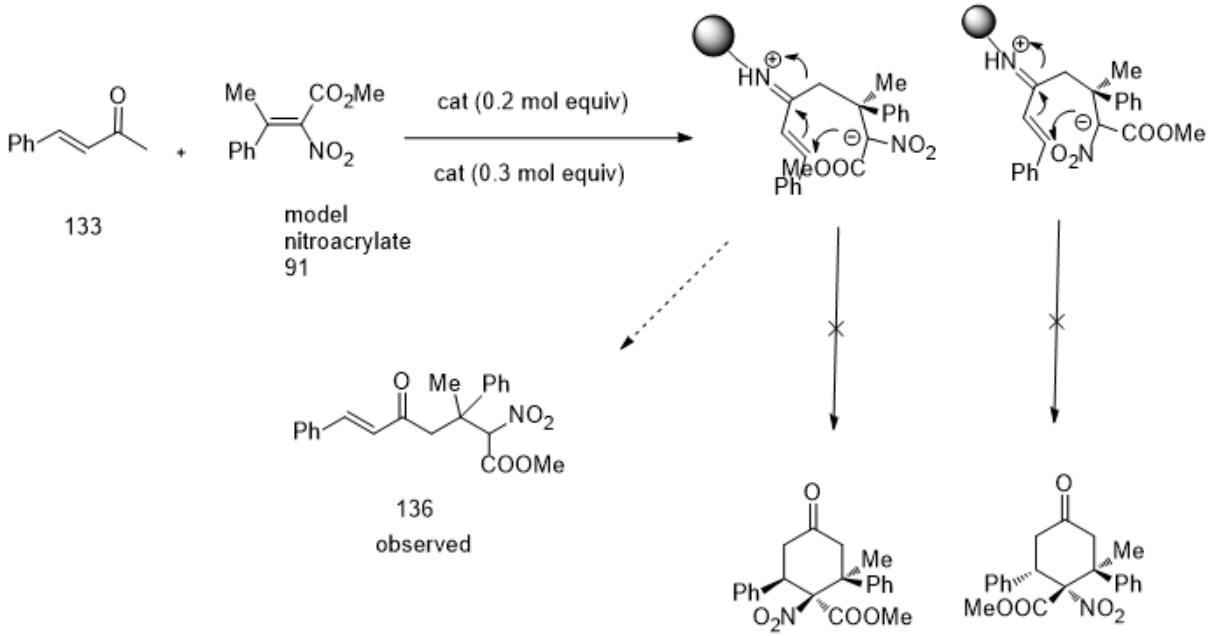
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.344	MM	0.6750	5.11926e4	1263.92224	49.1783
2	27.729	MM	0.9939	5.29034e4	887.13470	50.8217





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.864	MM	0.5779	2.97017e4	856.59729	50.7950
2	26.540	MM	0.8133	2.87720e4	589.61670	49.2050

7.6 Reactivity experiments of nitroacrylates: Synthesis of compound 137

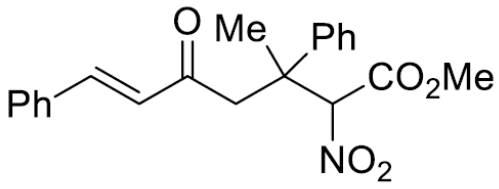


Compound **137** was synthetized according to literature procedure.[83] The primary amine catalyst **M** (0.2 equiv.) and the acidic cocatalyst (0.3 equiv.) were dissolved in dry solvent (1M solution) under N_2 atmosphere and stirred at room temperature for 10 min. After this period, the α,β-unsaturated ketone **133** and the nitroacrylate **91** were added. The reaction mixture was heated at 60°Cand stirred for the reported time, after which solvent was removed at reduced pressure.

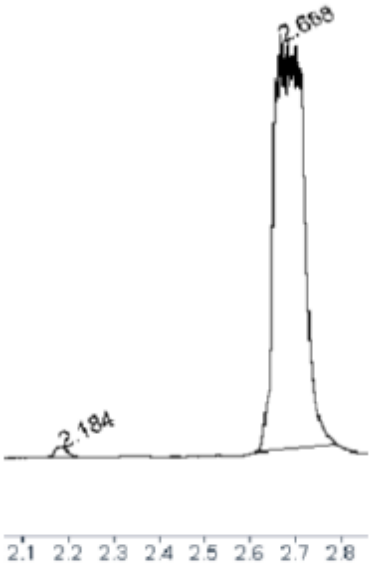
Compound **136** (Michael adduct) was obtained as colorless oil in 3% yield. The desired cyclohexanone derivative **137** was not possible to isolate.

^{1}HNMR of compound 136 ($CDCl_3$, 300 MHz) 1.98 (s, 2H) 2.04 (s, 3H) 2.77-2.86 (m, 4H) 3.77 (s, 3H) 3.78 (s, 3H) 3.88-3.93 (m, 2H) 5.86 (d, 2H) 6.18 (d, 2H) 7.14-7.17 (m, 10H) 7.35-7.43 (m, 10H)

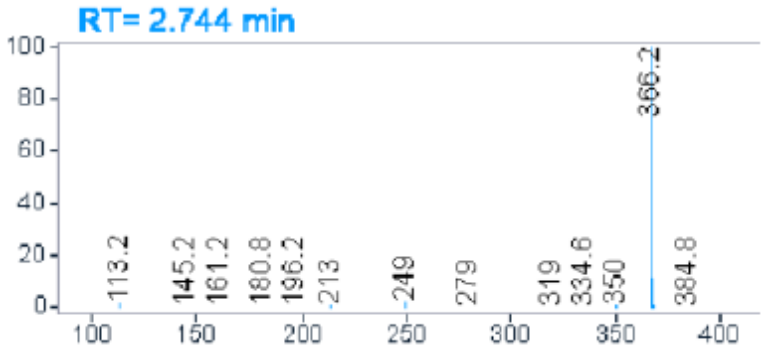
uHPLC compound 136 (exact mass 367,14) RT= 2.668 min m/z= 366.2



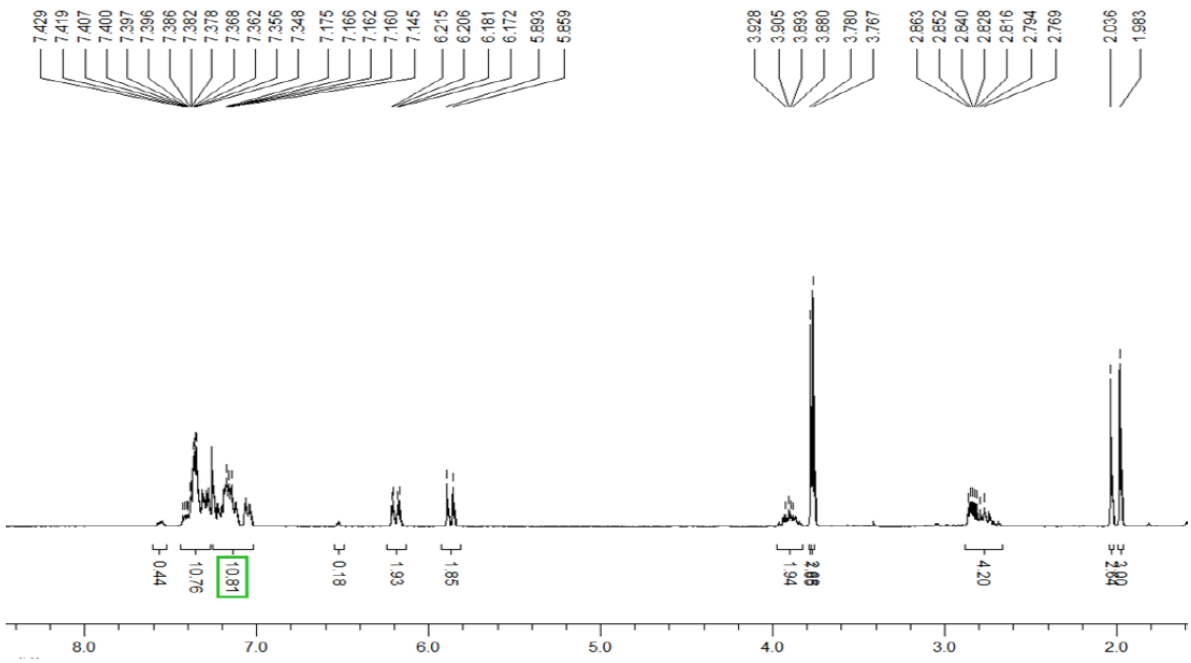
uHPLC compound 136 (positive mode ESI)



RT [min]	Peak Area Percent
2.184	1.17
2.668	98.83



1HNMR compound 136 ($CDCI_3$, 300 MHz)



Final remarks and Conclusions

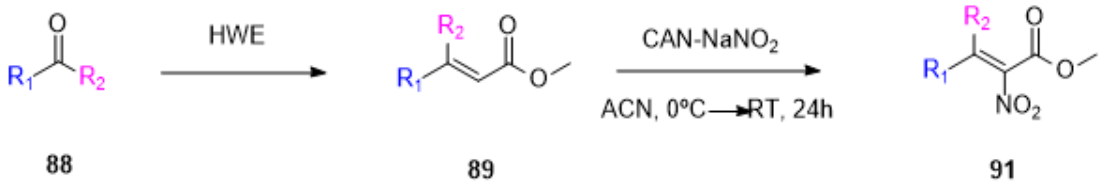
8. Final remarks and conclusions

During my research work for this PhD I faced synthetic challenges related to the synthesis and enantioselective reduction of tetrasubstituted nitroalkenes, the organocatalyzed Michael addition of substituted nitropropionates to different α,β-unsaturated ketones and to the preliminary investigation of the use of tetrasubstituted nitroalkenes in cyclisation reactions.

Although the initial goal of the PhD thesis was to explore unprecedented synthetic strategies for the synthesis of α,α-disubstituted-α-amino acids or critical precursors, I could not obtain α,α-disubstituted-α-amino acids. However, I was able to obtain tetrasubstituted nitroalkenes successfully, as key intermediates, not previously described in the literature, and to accomplish the enantioselective reduction of such substrates in up to 65% e.e.

Firstly, I focused on the synthesis of tetrasubstituted nitroalkenes. As the compounds of interest were not previously reported in literature, I needed to base my research on the reported synthetic routes for trisubstituted nitroalkenes[53,54] with the aim to propose different approaches for their synthesis involving the formation of acrylates and their reaction of nitration or the condensation between a ketone or an alkyne with ethyl nitroacetate.[59,60,61] Despite the initial limitations found with the proposed strategies (mostly regarding the nitration step) such us poor yields, low reproducibility and difficult separation, this goal was finally accomplished by the optimization of the nitration step using a mixture of CAN/$NaNO_2$ as an effective nitration reagent which allowed to obtain the desired tetrasubstituted nitroalkenes in moderate yields but in a reproducible manner.

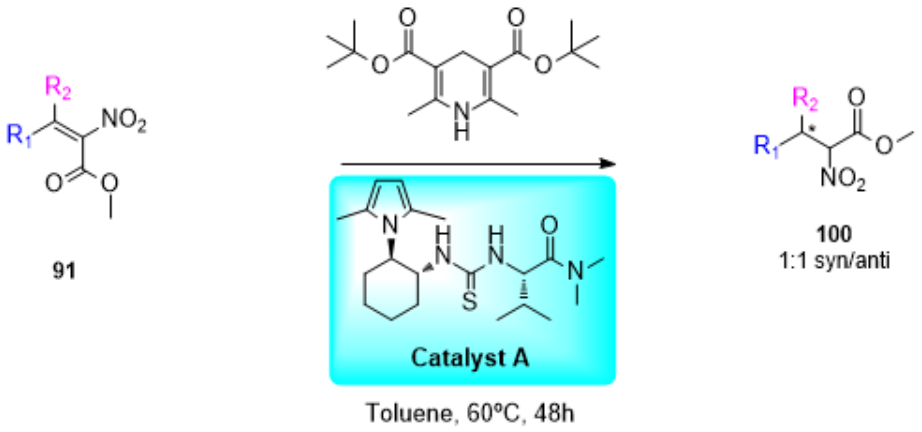
Therefore, the initial challenges were solved by the development of a reproducible synthetic strategy for the synthesis of tetrasubstituted nitroalkenes in two steps, involving the formation of an acrylate **89** starting from commercially available ketones **88** followed by their reaction of nitration employing CAN-$NaNO_2$ as effective nitration reagent for the synthesis of tetrasubstituted nitroalkenes **91** (Scheme 59).



Scheme 59: Novel synthetic strategy developed for the synthesis of tetrasubstituted nitroalkenes **82**

The next reaction I studied was the enantioselective reduction of these synthetized tetrasubstituted nitroalkenes **91** to access the functionalized tetrasubstituted nitroalkanes **100** and use them as the starting materials for further synthetic elaboration.[67]

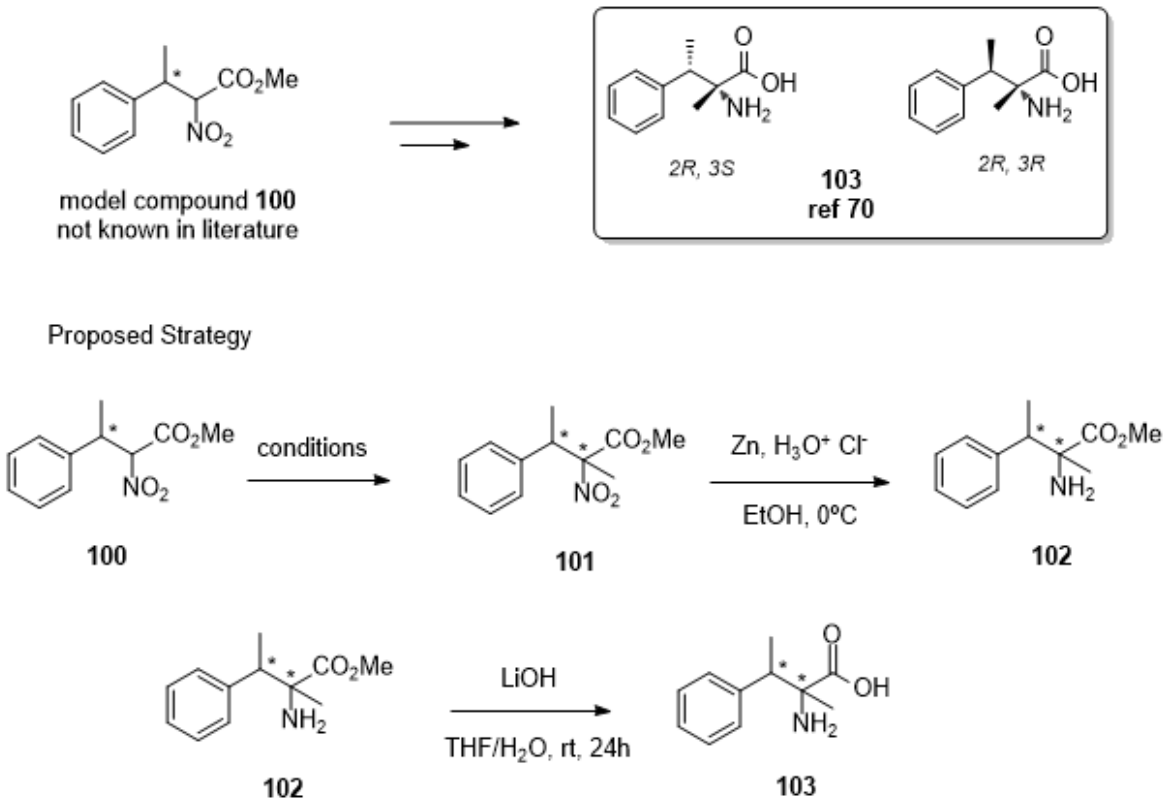
The nitroalkanes **100** were obtained after reaction of nitroalkenes **91** with Hanztsch ester as reductive agent and a thiourea based catalyst **A** with good to moderate yields in a 1:1 mixture of *syn/anti* products (Scheme 60).



Scheme 60: Enantioselective reduction of tetrasubstituted nitroalkenes **91**

Moreover, starting from different mixtures of starting material, **a different reactivity of the isomers of starting material was detected** meaning that one isomer reacted more quickly than the other one. This interesting discovery was confirmed when the reaction was performed with a pure fraction of the less reactive isomer as material and no reaction was observed.

The absolute configuration of the major enantiomer obtained in the enantioselective reduction was established by converting the already synthetized nitroalkane **100** into a known product.[70] However, several attempts to convert **100** into the known amino acid **103** were unsuccessful (Scheme 61).



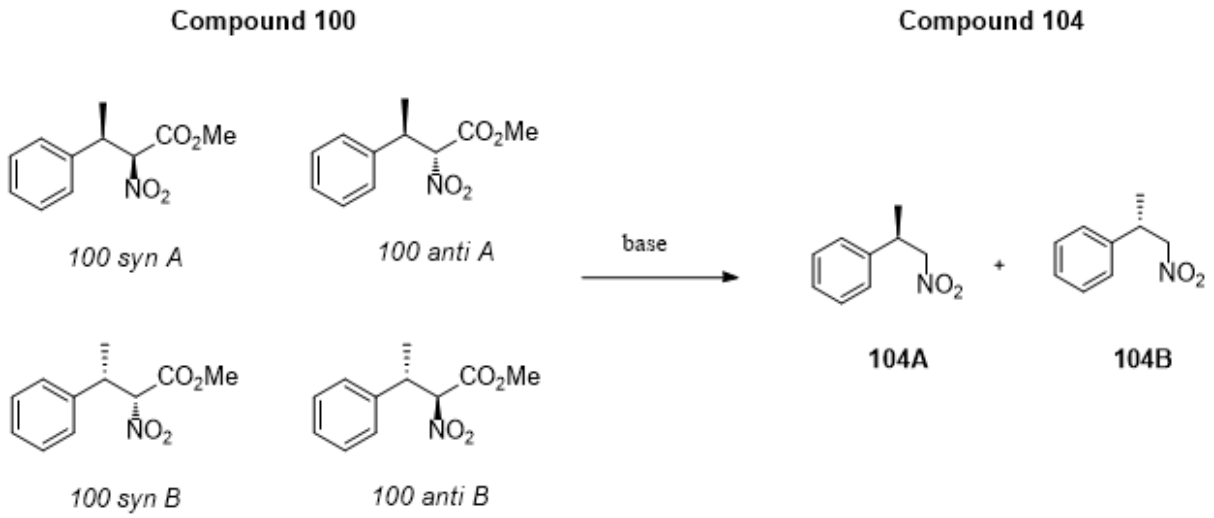
Scheme 61: First synthetic procedure for the experimental determination of the absolute configuration.

The first step of the initial synthetic strategy was an important challenge for me. Although I tested a wide variety of conditions for the alkylation of the nitroalkane **100**, the formation of the *O*-methylation compound of the oxygen of the ester group was, unfortunately, observed as the major compound in most of all the conditions tested,[71,72] whereas the goal was to obtain the C-alkylated product. This product was only observed as minor compound and despite big efforts to isolate it, it was extremely difficult to do so and, I also kept noticing the formation of other sub-products when repeating the experiment several times so, I was unable to proceed with this route.

After discussing possible alternatives and further suitable actions with my PhD supervisor, we agreed that the decarboxylation of the ester moiety to afford the corresponding trisubstituted nitroalkane **104** could be a suitable synthetic pathway to reach our purpose (Scheme 62).[73]

This simple approach was found to be effective and the **desired decarboxylated nitroalkane 104** was finally synthetized after two steps with low yield. The experimental optical rotation was measured using a polarimeter and the result obtained was compared with the

published rotation values for this compound giving us a confirmation that the synthetizing trisubstituted nitroalkane **104 was preferentially obtained with R-configuration** at carbon 3 of the molecule.



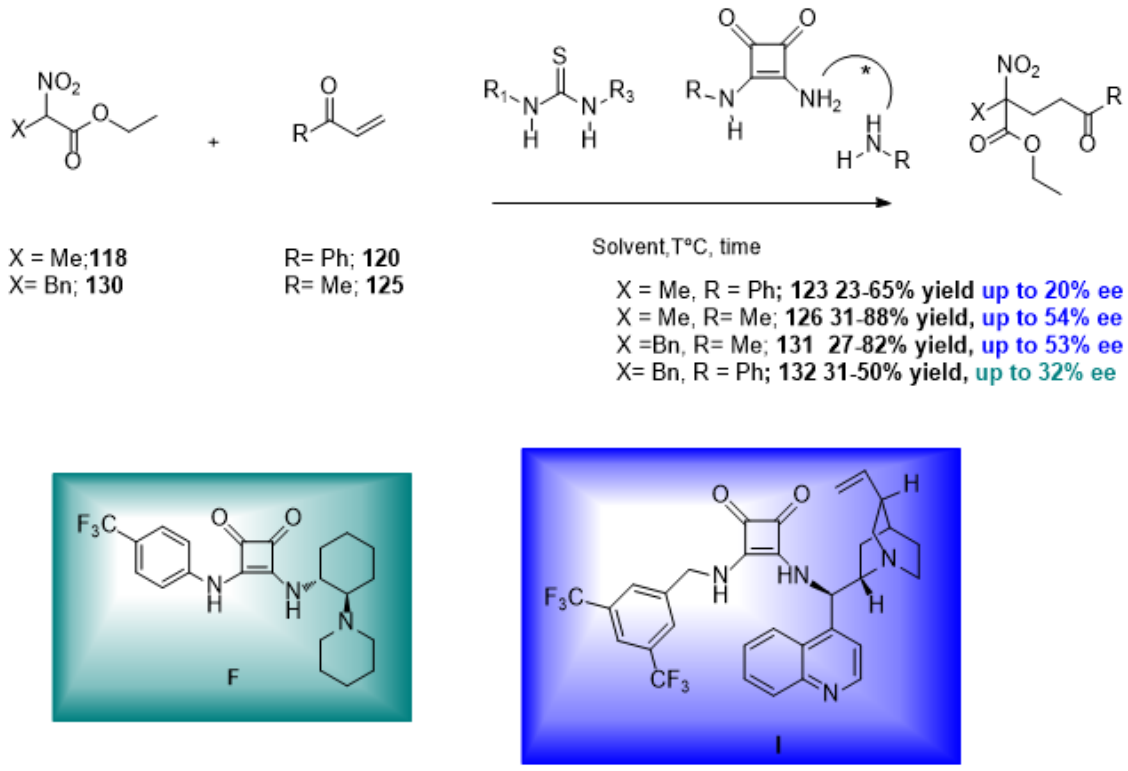
Scheme 62: Decarboxylation of compound **100** as an effective strategy for the determination of the absolute configuration of the generate stereocenter.

DFT calculations of this reaction were conducted by our colleagues Dr Sergio Rossi and Prof. Laura Raimondi to predict which would be the predominant configuration of the formed nitroalkane. However, the Takemoto model, that involves the coordination of the thiourea of the catalyst to the nitro group, was not able to correctly rationalize the stereochemical outcome of the reaction. Further studies which will consider other alternative coordination modes between the catalyst and the substrate, will be necessary in order to understand the stereocontrol of the reaction.

Furthermore, the organocatalyzed **Michael addition of substituted nitropropionates 118 and 130** to α,β-unsaturated ketones **120** and **125**, was also another project within my PhD work that I was involved in. Preliminary studies of this reaction using several Michael acceptors such us nitroolefins **119** benzyl bromide **121** or α,β-unsaturated ketones **120**, under different reaction conditions, were run. Then, we decided to focus on the reaction between nitroesters and α,β-unsaturated ketones, because of the high synthetic potential of this strategy and of the formed products.

The experiments were conducted using different thiourea or squaramide derived catalysts

A-I yielding the corresponding Michael adducts **112**, **115**, **117** and **118** bearing a quaternary stereocenter with good to moderate yields (Scheme 63).



Scheme 63: Michael addition of substituted nitropropionates **118** and **130** to α,β-unsaturated ketones **120** and **125**

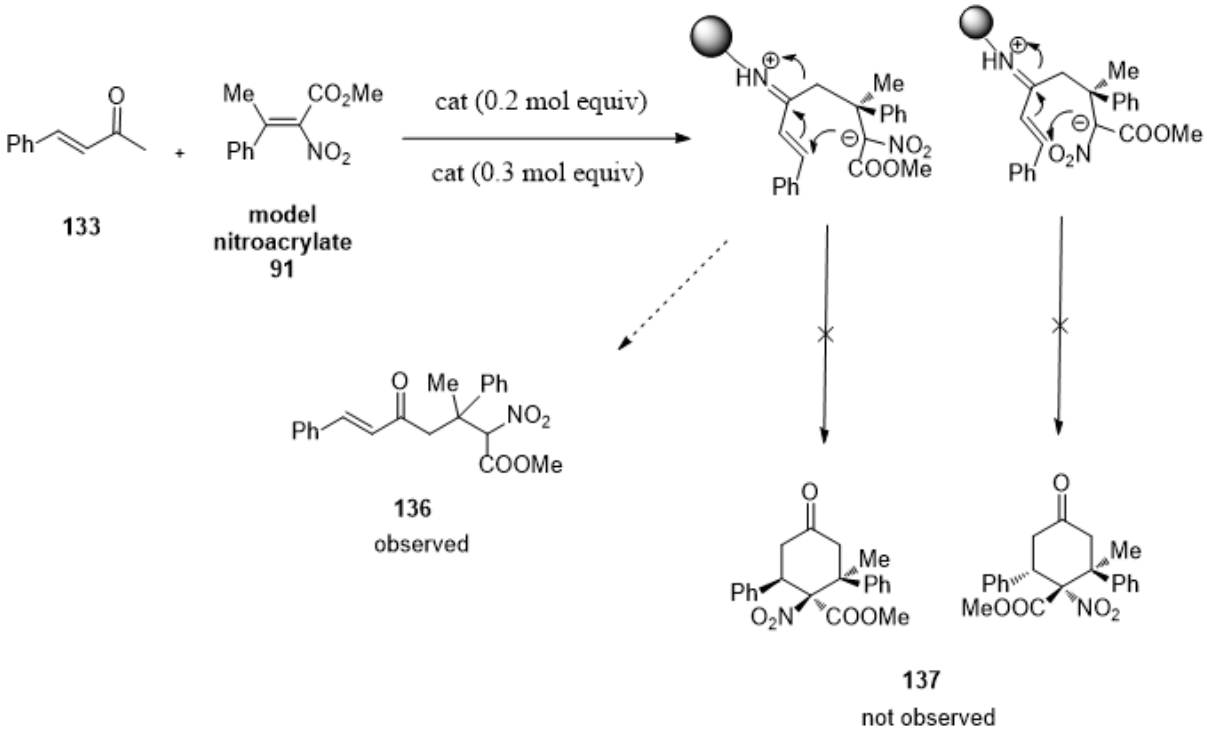
The enantioselectivity was measured using chiral HPLC and, although the best results were obtained using a squaramide derived catalyst I, the observed values were low. Thus, other activation modes such us aminocatalysis and phase transfer catalysis were also tested in order to check if this could improve the enantioselectivity observed. Enamine catalysis using proline as catalyst was found to not be so effective for this transformation, leading to the formation of traces of product after long reaction times. In contrast, phase transfer catalysis demonstrated to work efficiently, but the enantioselectivity observed was less than that observed with organocatalysts so, we agreed it was best not to continue with phase transfer catalysis.

Overall, the corresponding Michael adducts **123**, **126**, **131** and **132** were obtained in good to moderate yields employing different thiourea or squaramide derived catalysts. In terms of enantioselectivity, the squaramide derived catalyst I was found to be the best catalyst for the enantioselective synthesis of compounds 123 (20% ee) 126 (54% ee) and **131** (53% ee) whereas the squaramide catalyst **F** was found to be the best for the synthesis of

compound **132** (32% ee). The nitroester compounds **131** and **132** had not been published prior to this work and one of these **(131)** showed a 53% ee. Therefore, this approach showed promising results.

Sadly, due to limited time I had at this point, I could not further optimize this synthetic route to improve the enantioselectivity further but, although with moderate ee results, I was able to prove these compounds can be synthetized in an enantioselective manner which is of vital importance because they have a great potential as precursors of bioactive therapeutic compounds.

During my third year of PhD, based on previous studies,[83] I also studied the reactivity of tetrasubstituted nitroalkenes in a multistep cyclisation reaction catalyzed by an aminocinchona **M** (Scheme 64), in the attempt to synthesize highly functionalized cyclohexanones **137** bearing two contiguous quaternary stereocenters.



Scheme 64: Reactivity experiments of tetrasubstituted nitroacrylate

Using different fractions of the synthetized tetrasubstituted nitroalkene **91a** as starting material, I explored its reactivity using the reaction described in Figure 6. However, even after 3 days of reaction, the expected products were not observed while it was possible to

isolate in very minor amount the Michael adduct **136** as mixture of isomers. Thus, a cyclization experiment was then carried out using a widely available base (DBU) and heating the reaction at 85ºC, but, unfortunately, decomposition products were mainly found, and no desired cyclohexanone was observed. The results are a further demonstration that tetrasubstituted nitroacrylates are indeed poorly reactive substrates, compared to trisubstituted nitroolefins. In addition, higher temperatures seemed to be necessary to promote reactions in reasonable times, but this seemed to affect the stability of the nitroacrylates, which show often decomposition products when high temperatures are used to perform the organic transformation.

Literature References

9. Literature References

1. Saghyan, A. S., & Langer, P. **2016**. *Asymmetric synthesis of non-proteinogenic amino acids*. Retrieved from The Willey Online Library

2. Narancic, T., Almahboub, S.A. O'Connor, K.E. *Unnatural amino acids: production and biotechnological potential*. World J Microbiol Biotechnol 35, 67 **2019**

3. Yin, X., Wu, J., Yang, L. *Efficient reductive amination process for enantioselective synthesis of L-phosphinothricin applying engineered glutamate dehydrogenase*. *Appl Microbiol Biotechnol* **2018** *102*, 4425–4433

4. Zhang, KC., Li, H., Cho, KM., Liao, JC *Expanding metabolism for total biosynthesis of the nonnatural amino acid L-homoalanine*. *Proc Natl Acad Sci USA* **2010**, *107*, 6234–6239

5. Causey TB, Zhou S, Shanmugam KT, Ingram LO *Engineering the metabolism of Escherichia coli W3110 for the conversion of sugar to redox-neutral and oxidized products: Homoacetate production*. *Proc Natl Acad Sci USA* **2003** *100*, 825–832

6. Williams. R. M, Im. M. N *Asymmetric synthesis of monosubstituted and .alpha.,.alpha.-disubstituted .alpha.-amino acids via diastereoselective glycine enolate alkylations J. Am. Chem. Soc.* **1991**, *113*, 24, 9276–9286

7. Bøgevig, A., Juhl, K., Kumaragurubaran, N., Zhuang, W. and Jørgensen, K.A. *Direct Organo-Catalytic Asymmetric α-Amination of Aldehydes—A Simple Approach to Optically Active α-Amino Aldehydes, α-Amino Alcohols, and α-Amino Acids*. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790-1793

8. Osberger, T., Rogness, D., Kohrt, J. *et al. Oxidative diversification of amino acids and peptides by small-molecule iron catalysis*. *Nature* **2016**, *537*, 214–219

9. Li. B, Zhang. J, Xu. Y, Yang. X, Li. L, *Improved synthesis of unnatural amino acids for peptide stapling, Tetrahedron Letters*, **2017**, *58*, 24-28

10. Bisht A, Juyal D. *Unnatural amino acids (UAA'S): A trendy scaffold for pharmaceutical research* JDDT **2019**

11. Inoue, Y., Takashima, S., Nogata, Y., Yoshimura, E., Chiba, K., Kitano, Y *Isocyanides Derived from α,α-Disubstituted Amino Acids: Synthesis and Antifouling Activity Assessment. Chem. Biodiversity*, **2018**, 15-21

12. Vogt. H, Bräse. S *Recent approaches towards the asymmetric synthesis of α,α-disubstituted α-amino acids. Org Biomol Chem* **2007**, 406-430

13. Ravikumar, Y., Nadarajan, S.P., Hyeon Yoo, T., Lee, C.-S. and Yun, H. *Incorporating unnatural amino acids to engineer biocatalysts for industrial bioprocess applications. Biotechnology Journal*, **2015**, *10*, 1862-1876.

14. Ufaz S, Galili G. *Improving the content of essential amino acids in crop plants: goals and opportunities. Plant Physiol.* **2008** ;*147,* 954-61

15. Ohfune. Y, Shinada. T *Enantio- and Diastereoselective Construction of α,α-Disubstituted α-Amino Acids for the Synthesis of Biologically Active Compounds. Eur. J. Org. Chem.* **2005**, 5127–5143

16. Chung. C. P, Parker. P. D, Dong. V. M *Towards α,α-disubstituted amino acids containing vicinal stereocenters via stereoselective transition-metal catalyzed allylation Arkivoc* **2021**, 138-157

17. Metz. A. E, Kozlowski. M. C *Recent Advances in Asymmetric Catalytic Methods for the Formation of Acyclic α,α-Disubstituted α-Amino Acids J. Org. Chem.* **2015**, 80, 1–7

18. Bera, K. and Namboothiri, I.N.N. *Asymmetric Synthesis of Quaternary α-Amino Acids and Their Phosphonate Analogues. Asian Journal of Organic Chemistry*, **2014**, *3*, 1234-1260.

19. Niimi. L, Serita. K. I, Hiraoka. S, Yokozawa. T, *Lewis acid-catalyzed three-component condensation reactions of aldehydes, N-silylcarbamates, and allylsilane: synthesis of N-homoallylcarbamates Tetrahedron Lett.* **2000** 41 7075

20. Heydari. A, Arefi. A, Khaksar. S, Shiroodi. R. K *Guanidine hydrochloride: An active and simple catalyst for Strecker type reaction Journal of Molecular Catalysis A: Chemical 271* **2007** 142–144

21. Vachal. P, Jacobsen. E. N *Enantioselective Catalytic Addition of HCN to Ketoimines. Catalytic Synthesis of Quaternary Amino Acids Org. Lett.*, **2000**, 867-870

22. Buyck, T., Wang, Q, Zhu, J. *Catalytic Enantioselective Michael Addition of α-Aryl-α-Isocyanoacetates to Vinyl Selenone: Synthesis of α,α-Disubstituted α-Amino Acids and (+)- and (–)-Trigonoliimine A. Angew. Chem. Int. Ed.*, **2013**, *52*, 12714-12718

23. Zhang. X, Cividino. P, Poisson. J. F, Kraievskyi. P. S, Laurent. M. Y, Martel. A, Dujardin. G, Py. S *Asymmetric Synthesis of α,α-Disubstituted Amino Acids by Cycloaddition of (E)-Ketonitrones with Vinyl Ethers Org. Lett.* **2014**, *16*, 1936–1939

24. Clark, J. S.; Hodgson, P. B. *Intramolecular generation and rearrangement of ammonium ylides from copper carbenoids: a general method for the synthesis of cyclic amines J. Chem. Soc., Chem. Commun.*, **1994**, 2701-2702

25. West, F. G.; Naidu, B. N. *Piperidines via Ammonium Ylide [1,2]-Shifts: A Concise, Enantioselective Route to (-)-Epilupinine from Proline Ester J. Am. Chem.Soc.* **1994**, *116*, 8420-8422

26. Clark. J. S; Middleton. M. D *Synthesis of Novel α-Substituted and α,α-Disubstituted Amino Acids by Rearrangement of Ammonium Ylides Generated from Metal Carbenoids Org. Lett.* **2002**, *4*, 765–768

27. Das. J. P, Marek. I *Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems Chem Commun.*, **2011**, *47*, 4593–4623

28. Qu. J, Helmchen. G *Applications of Iridium-Catalyzed Asymmetric Allylic Substitution Reactions in Target-Oriented Synthesis Acc. Chem. Res.* **2017**, *50*, 2539–2555

29. Xiong. Y, Zhang. G *Enantioselective Synthesis of Quaternary Stereocenters via Chromium Catalysis Org. Lett.* **2016**, *18*, 5094–5097

30. Husain FM, Ahmad I, Khan FI, Al-Shabib NA, Baig MH, Hussain A, Rehman MT, Alajmi MF, Lobb KA. *Seed Extract of Psoralea corylifolia and Its Constituent Bakuchiol Impairs AHL-Based Quorum Sensing and Biofilm Formation in Food- and Human-Related Pathogens. Front Cell Infect Microbiol.* **2018,** *25*, 351-359.

31. Lv L; Lv L: *Anti-tumor effects of bakuchiol on human gastric carcinoma cell lines are mediated through PI3K/AKT and MAPK signaling pathways. Mol Med Rep* **2017**, *16*, 8977-8982

32. Gao. J. R, Wu. H, Xiang. B, Yu. W. B, Han. L, .Jia. Y. X *Highly Enantioselective Construction of Trifluoromethylated All-Carbon Quaternary Stereocenters via Nickel-Catalyzed Friedel–Crafts Alkylation Reaction J. Am. Chem. Soc.* **2013**, *135*, 2983–2986

33. Mahadu. Y, Mithula. K, Sankaranarayanan. S, Kondapalli. M, Gowri. V, Sekhar. C *Oxindole and its derivatives: A review on recent progress in biological activities Biomedicine & Pharmacotherapy* **2021**, 111842-111860

34. Sun. W, Hong. L, Liu. C, Wang. R *Asymmetric construction of quaternary stereocenters by direct conjugate addition of oxindoles to enone Tetrahedron: Asymmetry,* **2010**, *21*, 2493–2497

35. Quintard, A. and Alexakis, A. *Organocatalytic Conjugate Addition in Stereoselective Synthesis. In Stereoselective Synthesis of Drugs and Natural Products* (eds V. Andrushko and N. Andrushko) **2013**

36. Wang. Z *Construction of all-carbon quaternary stereocenters by catalytic asymmetric conjugate addition to cyclic enones in natural product synthesis Org. Chem. Front.*, **2020**, *7*, 3815-3841

37. Ricci, P., Carlone, A., Bartoli, G., Bosco, M., Sambri, L. and Melchiorre, P. *Organocatalytic Asymmetric Sulfa-Michael Addition to α,β-Unsaturated Ketones. Adv. Synth. Catal.*, **2008**, *350*, 49-53.

38. Fernández. M, Vicario. J. L, Reyes. E, Carrilloa. L, Badía. D *Organocatalytic enantioselective synthesis of 2,3-dihydropyridazines Chem. Commun.*, **2012**, *48*, 2092-2094

39. Sönmez M, Berber I, Akbaş E. *Synthesis, antibacterial and antifungal activity of some new pyridazinone metal complexes. Eur J Med Chem.* **2006** *41*, 101-5

40. Demirayak S, Karaburun AC, Beis R. *Some pyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities. Eur J Med Chem.* **2004,** *39*, 1089-95.

41. Gyoten. M, Nagaya. H, Fukuda. S, Ashida. Y, Kawano. Y *Synthesis of Eosinophil Infiltration Inhibitors with Antihistaminic Activity Chem. Pharm. Bull.*, **2003**, *51*, 122.

42. Halskov. K. S, Kniep. F, Lauridsen. V. H, Iversen. E. H, Donslund. B. S, Jørgensen. K. A *Organocatalytic Enamine-Activation of Cyclopropanes for Highly Stereoselective Formation of Cyclobutanes J. Am. Chem. Soc.* **2015**, *137*, 1685−1691

43. Wen. K.G, Peng. Y. Y, Zeng. X. P *Advances in the catalytic asymmetric synthesis of quaternary carbon containing cyclobutanes. Organic Chemistry Frontiers* **2020**: 2576-2597

44. Van der Kolk. M. R, Janssen. M.A.C.H, Rutjes. F.P.J.T, Blanco-Ania. D, *Cyclobutanes in Small-Molecule Drug Candidates ChemMedChem* **2022**

45. Yang. X, Phipps. R. J, Toste. F. D *Asymmetric Fluorination of α-Branched Cyclohexanones Enabled by a Combination of Chiral Anion Phase-Transfer Catalysis and Enamine Catalysis using Protected Amino Acids J. Am. Chem. Soc.* **2014**, *136*, 5225−5228

46. Bartfai, T.; Lu, X.; Badie-Mahdavi, H.; Barr, A. M.; Mazarati, A.; Hua, X.-Y.; Yaksh, T.; Haberhauer, G.; Ceide, S. C.; Trembleau, L.; Somogyi, L.; Krö ck, L.; Rebek, J., *Proc Natl Acad Sci USA* **2004**, *101*, 10470−10475

47. Lee. A, Oh. S, Kim. H *Synthesis of α-(4-Oxazolyl)amino Esters via Brønsted Acid Catalyzed Tandem Reaction Org. Lett.* **2018**, *20*, 3319−3322

48. Rueping, M., Sugiono, E. Azap, C A *Highly Enantioselective Brønsted Acid Catalyst for the Strecker Reaction. Angew Chem Int Ed,* **2006**, *45*, 2617-2619

49. Lee. Y. J, Park. Y, Kim. M. H, Jew. S. S, Park. H. G *An Enantioselective Synthesis of (+)-Polyoxamic Acid via Phase-Transfer Catalytic Conjugate Addition and Asymmetric Dihydroxylation J. Org. Chem.* **2011**, *76*, 740–743

50. Kano. T, Hayashi. Y, Maruoka. K *Construction of a Chiral Quaternary Carbon Center by Catalytic Asymmetric Alkylation of 2-Arylcyclohexanones under Phase-Transfer Conditions J. Am. Chem. Soc.* **2013**, *135*, 7134–7137

51. Bugaut. X, Glorius. F *Organocatalytic umpolung: N-heterocyclic carbenes and beyond Chem. Soc. Rev.*, **2012**, *41*, 3511-3522

52. Breslow. R *On the Mechanism of Thiamine Action. IV.1 Evidence from Studies on Model Systems J. Am. Chem. Soc.* **1958**, *80*, 3719–3726

53. Noboru. O, *Chapter 2: Preparation of Nitro Compounds, The Nitro Group in Organic Synthesis,* **2001**, 3-29, Retrieved from Willey-VCH;

54. Gabrielli. S, Chiurchiù. E, Palmieri. *A β-Nitroacrylates: A Versatile and Growing Class of Functionalized Nitroalkenes, Adv. Synth. Catal.* **2019**, *361*, 630-651.

55. Wen. J, Jiang. J, Zhang. X *Rhodium-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Carbonyl Compounds via Thiourea Hydrogen Bonding Org. Lett.* **2016**, *18*, 4451–4453

56. Sharma. V, Kelly. G. T, Watanabe. C. M. H Exploration of the Molecular Origin of the Azinomycin Epoxide: Timing of the Biosynthesis Revealed Org. Lett. 2008, 10, 21, 4815–4818

57. Maity. S, Manna. S, Rana. S, Naveen. T, Mallick. A, Maiti. D *Efficient and Stereoselective Nitration of Mono- and Disubstituted Olefins with AgNO2 and TEMPO J. Am. Chem. Soc.* **2013**, *135*, 3355–3358,

58. Rodríguez. J. M, Pujol. M. D *Straightforward synthesis of nitroolefins by microwave- or ultrasound-assisted Henry reaction Tetrahedron Lett.* **2011**, *52*, 2629–2632

59. Zhu. L, Yan. P, Zhang. L, Chen. Z, Zeng. X, Zhong. G *TiCl4/DMAP mediated Z-selective knovenagel condensation of isatins with nitroacetates and related compounds RSC Adv.* **2017**, *7*, 51352–51358

60. Zhang. J, Blazecka. P. G, Mark. P. A, Lovdahl, T, Curran. T *Indium (III) mediated Markovnikov addition of malonates and β-ketoesters to terminal alkynes and the formation of Knoevenagel condensation products Tetrahedron* **2005**, *61*, 7807–7813

61. Nakamura. M, Fujimoto. T, Endo. K, Nakamura. E *Stereoselective Synthesis of Tetra-Substituted Olefins via Addition of Zinc Enolates to Unactivated Alkynes Org. Lett* **2004,** *6*, 4837-4840

62. Buevich. A. V, Wu. Y, Chan. T. M, Stamford. A *An unusual contra-Michael addition of NaNO2–ceric ammonium nitrate to acrylic esters Tetrahedron Lett* **2008**, *49*, 2132-2135

63. Nolwenn J. A. Ozores. M. L, List. B *Organocatalytic Asymmetric Transfer Hydrogenation of Nitroolefins J. Am. Chem. Soc.* **2007**, *129*, 8976-8977

64. Bernardi L, Fochi M. *A General Catalytic Enantioselective Transfer Hydrogenation Reaction of β,β-Disubstituted Nitroalkenes Promoted by a Simple Organocatalyst. Molecules.* **2016**, *21*, 1000.

65. Zheng. C, You. S. L *Transfer hydrogenation with Hantzsch esters and related organic hydride donors Chem. Soc. Rev.*, **2012**, *41*, 2498–2518

66. Simón. L, Goodman. J. M *Theoretical Study of the Mechanism of Hantzsch Ester Hydrogenation of Imines Catalyzed by Chiral BINOL-Phosphoric Acids J. Am. Chem. Soc.* **2008**, *130*, 27, 8741–8747

67. Massolo, E., Benaglia, M., Orlandi, M., Rossi, S Celentano, G. *Enantioselective Organocatalytic Reduction of β-Trifluoromethyl Nitroalkenes: An Efficient Strategy for the Synthesis of Chiral β-Trifluoromethyl Amines. Chem Eur J* **2015**, *21*, 3589-3595

68. Ferraro, A., Bernardi, L. Fochi, M. *Organocatalytic Enantioselective Transfer Hydrogenation of β-Amino Nitroolefins Adv Synth Catal,* **2016**, *358*, 1561-1565

69. Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, *Gaussian, Inc., Wallingford CT*, **2016**.

70. Davis. F. A, Liang. C. H, Liu. H *Asymmetric Synthesis of β-Substituted α-Amino Acids Using 2H-Azirine-2-carboxylate Esters. Synthesis of 3,3-Disubstituted Aziridine-2-carboxylate Esters J. Org. Chem.* **1997**, *62*, 3796-3797

71. Gagnot, G.; Hervin, V.; Coutant, E. P.; Desmons, S.; Baatallah, R.; Monnot, V.; Janin, Y. L *Synthesis of unnatural α-amino esters using ethyl nitroacetate and condensation or cycloaddition reactions Beilstein J Org Chem.* **2018**; *14*, 2846-2852

72. Harel. T, Rozen. S *Transforming Natural Amino Acids into α-Alkyl-Substituted Amino Acids with the Help of the HOF·CH3CN Complex J. Org. Chem.* **2007**, *72*, 6500-6503

73. Metz. A. E, Kozlowski. M. C *2-Aryl-2-nitroacetates as Central Precursors to Aryl Nitromethanes, α-Ketoesters, and α-Amino Acids J.Org.Chem* **2013**, *78*, 717-722

74. Hostmann. T, Molloy. J. J, Bussmann. K, Gilmour. R *Light-Enabled Enantiodivergence: Stereospecific Reduction of Activated Alkenes Using a Single Organocatalyst Enantiomer Org. Lett,* **2019**, *21*, 10164-10168

75. Ballini. R, Bosica. G, Fiorini. D, Palmieri. A, Petrini. M *Conjugate Additions of Nitroalkanes to Electron-Poor Alkenes: Recent Results Chem. Rev.* **2005**, *105*, 933–971

76. Halland N, Hazell RG, Jørgensen KA. *Organocatalytic asymmetric conjugate addition of nitroalkanes to alpha,beta-unsaturated enones using novel imidazoline catalysts. J Org Chem.* **2002.** *67*, 8331-8338

77. Raimondi. L, Benaglia. M, Bonsignore. M, Rossi. S, Puglisi. A *Enantioselective catalytic addition of nitroesters to N-carboalkyloxy imines: a route to quaternary stereocenters Tetrahedron Letters,* **2009**, *50*, 4340–4342

78. Bera. K, Satam. N. S, Namboothiri. I. N. N *Enantioselective Synthesis of Quaternary α-Amino Acids via l-tert-Leucine-Derived Squaramide-Catalyzed Conjugate Addition of α-Nitrocarboxylates to Enones J. Org. Chem.* **2016**, *81*, 5670–5680

79. Okino. T, Hoashi. Y, Takemoto. Y *Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

80. Martínez, J. I.; Uria, U.; Muñiz, M.; Reyes, E.; Carrillo, L.; Vicario, J. L *Organocatalytic and enantioselective Michael reaction between α-nitroesters and nitroalkenes. Syn/anti-selectivity control using catalysts with the same absolute backbone chirality Beilstein J. Org. Chem.* **2015**, *11*, 2577–2583

81. Moon. H. W, Kim. D. Y *Enantioselective organocatalytic conjugate addition of a-nitroacetate to α,β-unsaturated ketones in water Tetrahedron Letters,* **2010**, *51*, 2906–2908

82. Bencivenni. G, Galzerano. P, Mazzanti. A, Bartoli. G, Melchiorre. P *Direct asymmetric vinylogous Michael addition of cyclic enones to nitroalkenes via dienamine catalysis Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642–20647

83. Massolo, E., Benaglia, M., Annunziata, R., Palmieri, A., Celentano, G. Forni, *A Stereoselective Synthesis of Functionalized Chiral 2-Nitrocyclohexanecarboxylic Esters via Catalytic Dienamine Addition to β-Substituted β-Nitroacrylates Adv. Synth. Catal.* **2014**, *356*, 493–500

84. Fülöp F. *The chemistry of 2-aminocycloalkanecarboxylic acids. Chem. Rev.* **2001,** *101*, 2181-2204.

85. Zhang. B, Chakma. P, Shulman. M. P, Ke. J, Digbya. Z. A, Konkolewicz. D *Probing the mechanism of thermally driven thiol-Michael dynamic covalent chemistry Org. Biomol. Chem,* **2018**, *16*, 2725-2730

86. Ye. J, Dixon. D. J, Hynes. P. S *Enantioselective organocatalytic Michael addition of malonate esters to nitroolefins using bifunctional cinchonine derivatives Chem. Commun,* **2005**, 4481-4483

87. Malerich. J. P, Hagihara. K, Rawal. V. H *Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts J. Am. Chem. Soc,* **2008**, *130*, 14416-14417

88. Diez-Barra. E, De la Hoz. A, Moreno. A *Alkylation of Ethyl Nitroacetate in the Absence of Solvent Synthetic Communications,* **1994**, *24*, 1817-1821

Aknowledgments

10. Aknowledgments

I started my PhD in June 2019, I was enjoying the "start" of my first year, but in 2020 all changed: a very well unknown and terrible pandemic arrived and put the world on hold, having an effect in our health and lives. I was living in Milan where everything started, I was alone without my family, friends and only my neighbors and work colleagues from the lab. Therefore, I want to dedicate my first Acknowledgements to my family, for being there to support me with my thesis work during such a difficult time.

· To my family, specially my sister Maria for their continuous support and help, my mum, my brother-in-law and my niece and nephew. It was very hard to spend the beginning of a pandemic away from you. Thank you for your un-conditional love and support during these last three years. You have been my best support with this work when facing challenges and difficulties and I am very grateful for your love and understanding. Moreover, I felt safe, also feeling the support from the people who unfortunately were not with us.

· I would like to thank the 2018 MSCA project (Marie Sklodowska Curie Actions) and the ITN-EID (European Industrial Doctorate) to have funded and supported my PhD work under the research program: **TECHNOTRAIN**

· To my supervisors **Dr. Maurizio Benaglia** and **Dr. Miguel A. Sanz Franco**: thank you very much for all your help and continuous support during my PhD, specially at challenging times when results were not going as expected, guiding me with your knowledge, suggestions, and recommendations. I could not have done it without you. A big big GRAZIE and GRACIAS!!!

. To my TECHNOTRAIN colleagues Milena and Fabian, it was a pleasure to meet you and work together in this amazing European program. Thank you to you both for your support as close colleagues over the last three years.

· To all the people from the TECHNOTRAIN Program: Alessandra Puglisi, Sergio Rossi, David Bevck, Sumaira Umbreen, thank you very much to you all for your continuous support and assistance whenever I needed it during the three years.

· To the people from Benaglia´s group: Elisabetta Massolo e Margherita Pirola grazie mille per il vostro aiuto quando ho iniziato il mio percorso di Dottorato, vi ringrazio tanto per il vostro tempo ed indicazioni sintetiche inziali. Gaia, Giulia, Alessandro, Daniele, Mauro, Francesca, Simonetta, Fabrizio, Margherita Gazzotti, Emanuela, Chiara, Monica Mariam, Piero, Fabrizia e tutti quelli che han terminato il loro programma di studi e a tutti quelli che lo stanno svolgendo e che mi avete conosciuto, grazie per sopportarmi e per il vostro aiuto durante il mio percorso nell'Università degli studi di Milano, vi ringrazio tanto per tutti i momenti insieme, rimarrà con me sempre.

· To the people from Taros Chemicals: Iryna Kurpil, thank you very much for taking part of your time in doing small purifications and chiral HPLC´s for my project, I really appreciate it. Bogdan, Tamal, Florian, Svenja, Michael Kostka, Elena, Mira, Mattia, Nacho, Pepe, people from purification department, thank you for your continuous support and ideas during my period in the company, I really appreciate it.

· Gracias Marina Velado por tu esfuerzo y dedicación en enseñarme el maravilloso mundo de la investigación en el 2014 durante mi estancia en tu laboratorio del CSIC aprendiendo a saber trabajar correctamente en un laboratorio de investigación científica. Contigo aprendí a descubrir que este mundo realmente me interesaba y durante este año decidí proseguir con mi carrera investigadora. Muchas gracias también por escucharme y ser mi "paño de lágrimas" cuando necesitaba desahogarme científicamente durante mis años de Doctorado. Espero que podamos volver a trabajar juntas en el futuro.

· María Frutos, Marta, Carmen, Mayca, María: Muchas gracias por ayudarme a crecer como investigadora durante mi estancia en el CSIC. Vuestros sabios consejos de investigadoras expertas me han ayudado mucho en los momentos peores del Doctorado, os lo agradezco mucho.