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"Conjugate Additions and Organocatalytic Sequential Reactions - New Approaches to Old Reactions"

Karla Santos Feu

Tese apresentada como parte dos requisitos para obtenção do título de DOUTOR EM CIÊNCIAS, área de concentração: QUÍMICA ORGÂNICA

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“First and foremost, synthesis has to be viewed as an art and a science that needs to be advanced for its own sake.”

K. C. Nicolaou

“Never lose the holy curiosity”

Albert Einstein

Dedicated to my dear Family

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At last, and most importantly I could not finish without thanking my Holy Mother of God and GOD Almighty for supporting me in all moments with his graces and blessings, giving me peace in the hard moments, patience, health and strength in order to finish this research!

List of Abreviatures

ILs = Ionic Liquids

APIs = Active pharmacological ingredients

[Bmim]OH = 1- butyl-3- methylimidazolium hydroxide

[EMIM]OAc = 1-ethyl-3-methylimidazolim acetate

GABA = Gamma – AminoButyric Acid

PTC = Phase Transfer Catalysis

PEG = Polythylene glycols

VOCs = Volatile Organic compounds

ESI = Electrospray ionisation mass spectrometry

BOC = tert-butyloxycarbonyl protecting group

CSA = Camphorsulfonic acid

HOMO = Highest occupied molecular orbital

LUMO = Lowest unoccupied molecular orbital

SOMO = Single occupied molecular orbital

ee: Enantiomeric excess

dr: diastereomeric ratio

DABCO = 1,4-diazabicyclo [2.2.2] octane

DIPEA = *N.N* – Diisopropylethylamine

DMF = Dimethylformamide

$[DHQ]_2PHAL$ = Hydroquinine 1,4-Phtalazinediyl diether

BINOL = 1,1'-Bi-2-naphtol

$[DHQ]_2PYR$ = Hydroquinine 2,5- diphenyl-4,6-pyrinidinediyl diether

UPC^2 = UltraPerformance Convergence Chromatography

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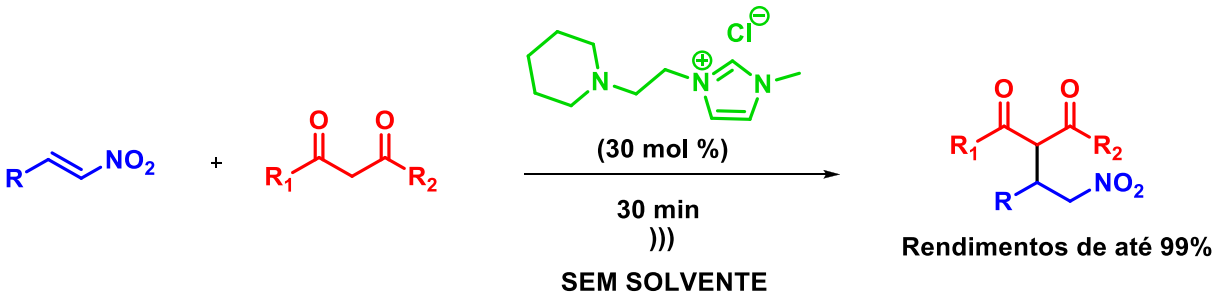
Resumo

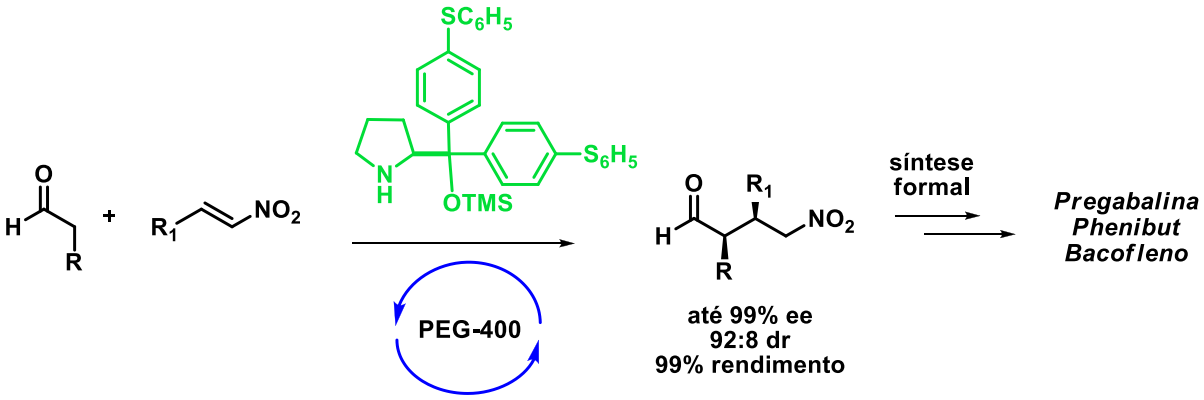
“Adições Conjugadas e Reações Sequenciais Organocatalíticas- Uma Nova Abordagem para Reações Antigas. ”

Essa tese consiste em uma coleção de projetos cujo foco central foi a aplicação de organocatalisadores tanto para acelerar as reações, sua função primária, quanto para induzir assimetria aos alvos sintéticos, dentro de uma ótica da química sustentável. Assim, a presente tese foi organizada em quatro capítulos, sendo os dois primeiros envolvendo reações de adições conjugadas, o terceiro referente a uma reação cascata tipo Friedel-Crafts seguida de oxa-Michael e por fim o quarto referente a uma reação de cicloadição formal [3+3].

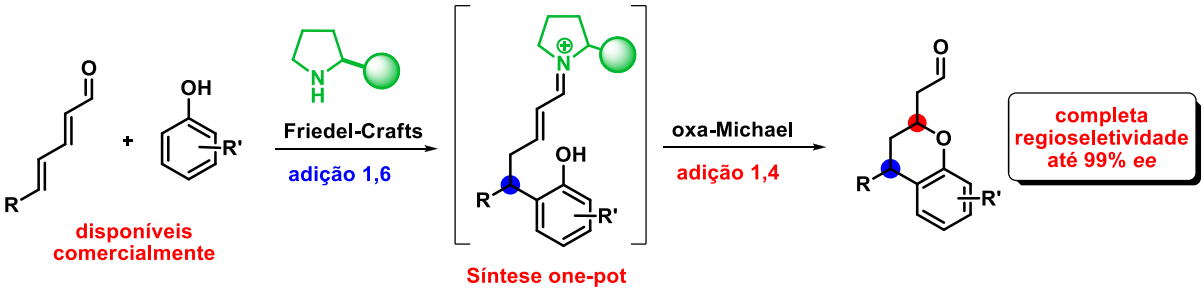
O primeiro capítulo refere-se a aplicação de uma classe de líquidos iônicos de tarefa específica, como catalisadores básicos em reações de adição conjugada de dicetonas à nitroolefinas irradiadas por ultrassom. Desta forma, em uma condição livre de solventes, foram sintetizados de forma eficiente, uma coleção de adutos de Michael, os quais são importantes blocos de construção sintéticos.



No segundo capítulo apresenta-se a síntese formal dos fármacos Pregabalina, Phenibut e Bacofleno. O intermediário sintético dos medicamentos citados são produtos de adição conjugada de aldeídos à nitroolefinas, os quais foram facilmente sintetizados utilizando um organocatalisador desenvolvido pelo próprio grupo em PEG-400, como solvente reciclável. Assim foi sintetizado uma coleção de adutos de Michael em bons rendimentos e seletividades, dentro dos príncipios da química verde.

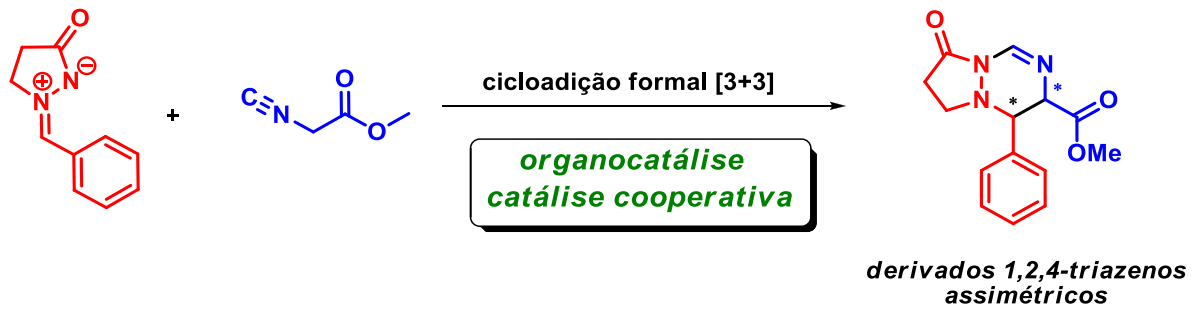


O terceiro capítulo descreve o primeiro exemplo de adição-1,6 tipo Friedel-Crafts seguida de adição- 1,4 Oxa-Michael organocatalítica assimétrica de hidroxiarenos a 2,4-dienais para a construção de cromanos enantioenriquecidos. Foram sintetizados uma coleção de cromanos quirais com altos rendimentos e seletividades (94-99% ee), os quais, posteriormente sofreram uma série de manipulações, incluindo uma macrolactamização.



Por fim, o quarto capítulo dedica-se a cicloadição formal [3+3] de azometina imina com isocianoacetato de metila, levando a produtos derivados do 1,2,4 triazenos, heterocíclicos de relevante atividade biológica. Utilizou-se tanto a organocatálise, quanto a catálise cooperativa (organocatálise e catálise metálica) como ferramentas sintéticas. Este trabalho está ainda nas etapas iniciais, sendo os

resultados preliminares, entretanto o produto já foi obtido com até (42% de ee e 69%) de rendimento, sendo a síntese diastereoseletiva.



derivados 1,2,4-triazenos assimétricos

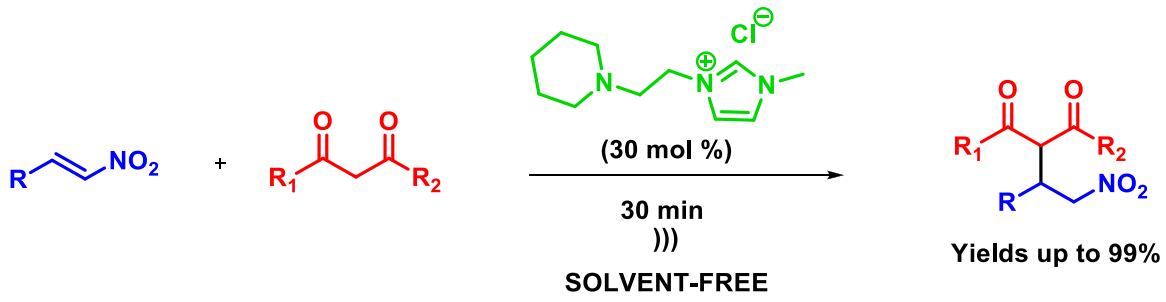
Abstract

“Conjugate Additions and Organocatalytic Sequential Reactions - New Approaches to Old Reactions.”

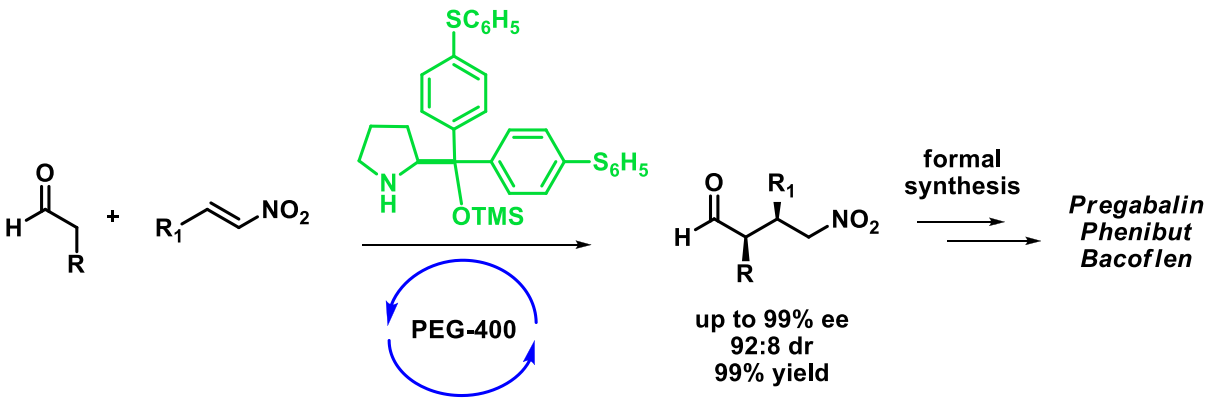
This thesis consists in a collection of projects wherein the focus is the application of organocatalysts to accelerate the reactions, its primary function, as to induce asymmetry to the synthetic targets, within a perspective of sustainable chemistry.

Thus, this thesis was arranged in four sections, the first two being about conjugate additions reactions; the third one related to 1,6-Friedel-Crafts/ 1,4-oxa-Michael cascade, and finally the fourth related to a formal [3 + 3] cycloaddition reaction.

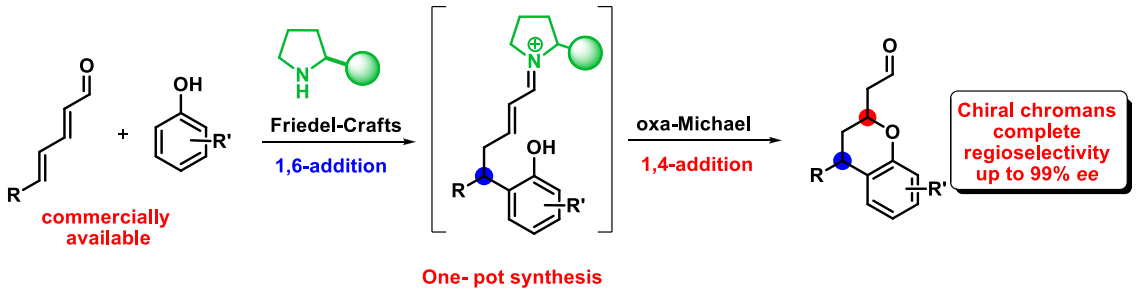
The first chapter describes the application of ionic liquids as basic catalysts in the conjugate addition of diketones to nitroolefins irradiated by ultrasound. Thus, the Michael adducts, which are important synthetic building blocks were synthesized efficiently under solvent free conditions.



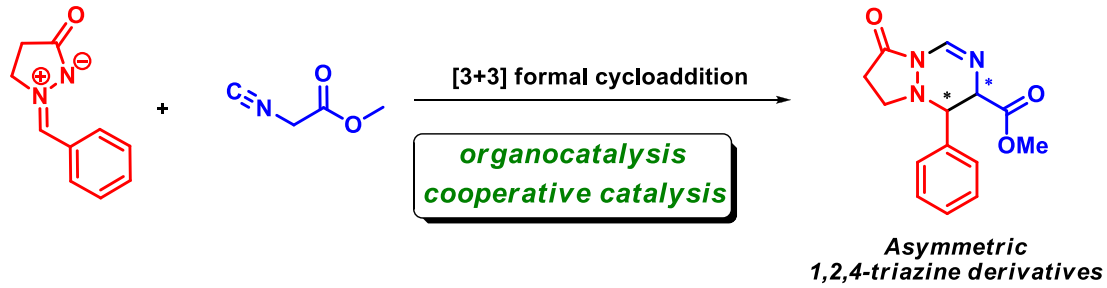
In the second chapter is presented the formal synthesis of Pregabalin Phenibut and Bacoflen. The synthetic intermediate of theses are obtained via a conjugate addition of aldehydes to nitroolefins, using an organocatalyst developed by our group in PEG-400, as recyclable solvent. In this regard, a collection of Michael adducts was synthesized within the principles of green chemistry in good yields and selectivities.



The third section describes the first organocatalytic asymmetric cascate 1,6- Friedel-Crafts / 1,4- Oxa-Michael of hydroxyarenes to 2,4-dienal for the construction of chiral chromans, which are important bioactive compounds. A collection of chiral chromans was synthesized with high yields and selectivities (94-99% ee). Furthermore, several manipulations were made including the formation of a macrocyclic lactam.



Finally, the fourth section dedicated to the formal [3 + 3] cycloaddition of azomethine imine with methyl isocyanoacetates leading to 1,2,4 triazines derivatives, which are relevant biological activity heterocyclic. We used either organocatalytic approach as cooperative catalysis (organocatalysis and metal catalysis). This work is still in the primary stages, however the product has been obtained with up to (42% ee, 69% yield), as just one diastereomer.



Asymmetric
1,2,4-triazine derivatives

Summary

Chapter 1

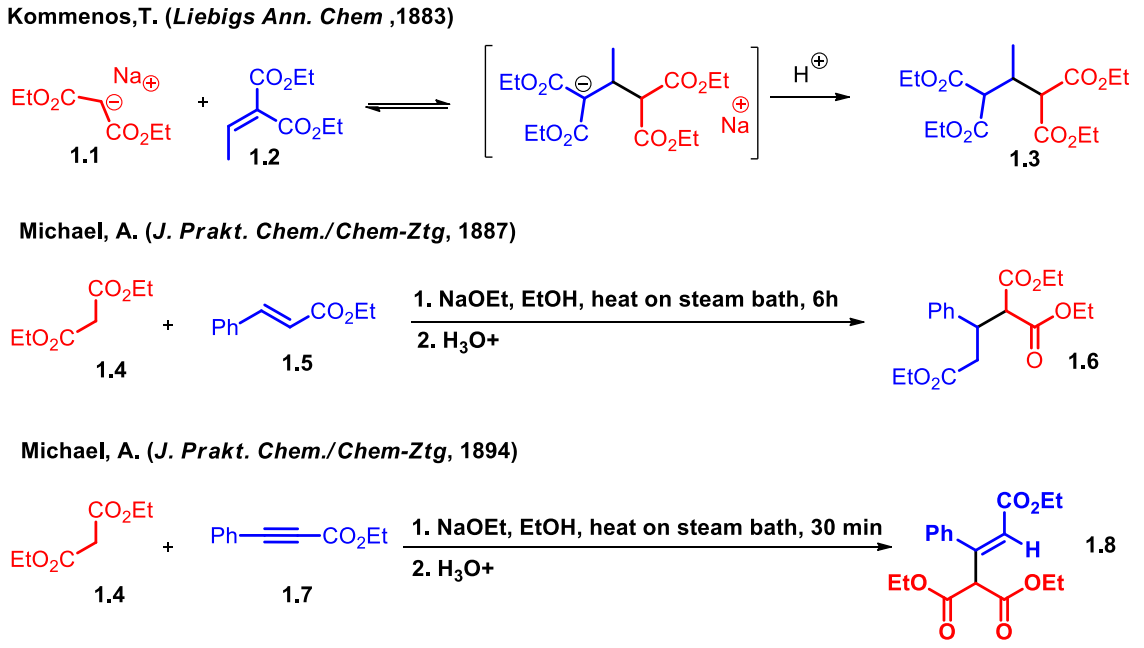
1 Chapter 1

In this chapter, historical and theoretical aspects of the Michael reaction and ionic liquids will be briefly revisited. Then, the chapter objectives will be presented, followed by the discussion of obtained results and final remarks on this section.

1.1 Introduction

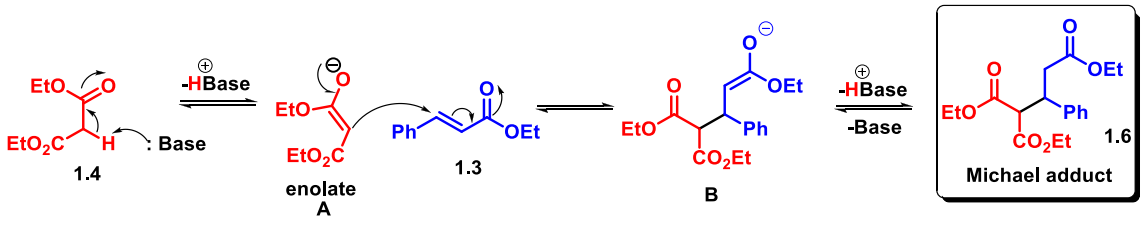
1.1.1 Conjugate Addition: 133 years of history (1883-2016)

The first example of a conjugate addition was made about 133 years ago, when Kommenos disclosed the conjugate addition of sodium diethylmalonate (1.1) to diethyl ethylidenemalonate (1.2).[1] However, this reaction remained almost unexplored until 1887, when Arthur Michael started his research with stabilized carbanions and α,β-unsaturated compounds. His studies regarded the conjugate addition of diethyl malonate (1.4) to the β-carbon of ethyl cinnamate (1.5) in the presence of sodium ethoxide, leading to the product - the so called Michael Adduct. The same author also published few years later a reaction in which were also used alkynes (1.7) with carbon nucleophiles (Scheme 1.1).



Scheme 1.1 - Chronology discovery of the conjugate addition reactions.

The general mechanism of the Michael reaction is illustrated in Sheme 1.2. First, the diethyl malonate (1.4) suffers deprotonation leading to the enolate (A). Then, this nucleophilic species, adds across the *β*-carbon of double bond of the ethyl cinnamate (1.3) followed protonation of (B). This reaction is reversible in protic solvents and the thermodynamically most stable product usually is the major.[2]



Scheme 1.2 - Michael addition mechanism.

Due to its performance, this carbon-carbon bond forming methodology has become very popular since the 1900s until nowadays. The addition of stabilized carbon nucleophiles to activated π-systems has been called ***Michael addition (or Michael reaction)*** and the products have been known as Michael adducts. In addition, conjugate additions refer to the addition of any class of nucleophile to double bonds conjugate with an electron withdrawing group.[3]

Despite of the age of Michael reactions, this chemistry has been a source of inspiration and study to many scientists. Atom economy and simple experimental procedures are among the reasons for the continuos interest in this particular reaction. The number of publications in the last 10 years on this subject proves that it still an open research field (Chart 1.1).

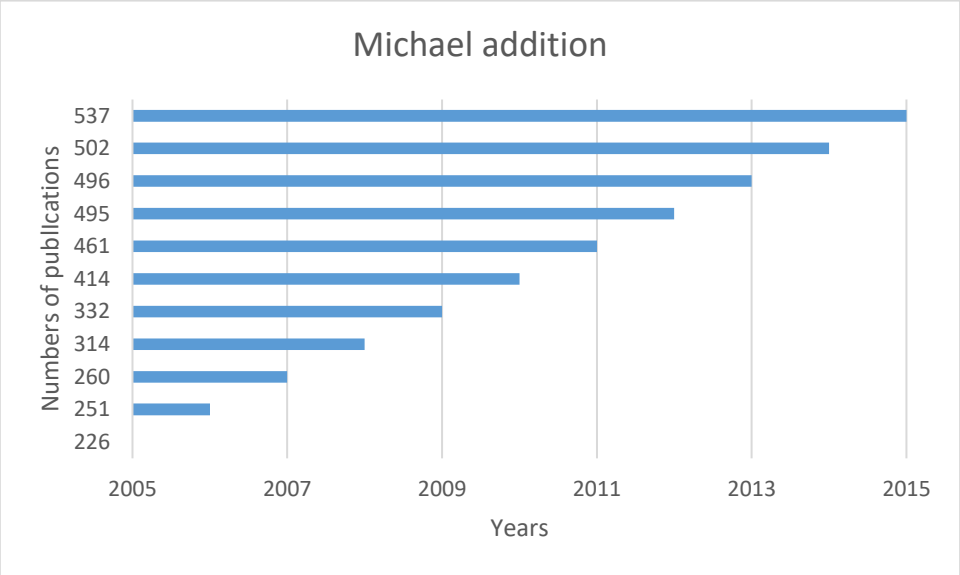
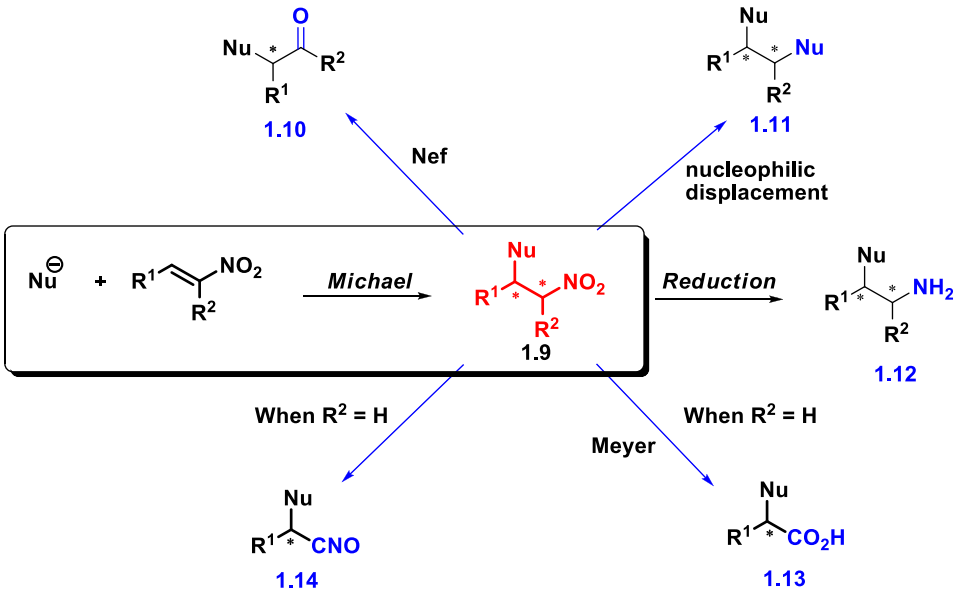


Chart 1.1 - Number of publications on Michael Addition per year (Jan 2005 – Dec 2015). Source: SciFinder (keyword "Michael addition").

Furthermore, the application of Michael adducts as synthetic building blocks in further transformations, also illustrates the importance of

the Michael reaction. Consequently, they have been used as initiating step of more complex inter- and intramolecular tandem processes (Scheme 1.3).

In a special way, nitroalkenes are very important Michael acceptors, which can be used as masked functional groups to be later transformed after the addition has taken place. Some examples are the Nef reaction (1.10), the nucleophilic displacement (1.11), the reduction to an amino group (1.12), the Meyer reaction (1.13), and the conversion into a nitrile oxide (1.14). Those are just samples of the several possible transformations that nitro groups can undergo (Scheme 1.3).[3]

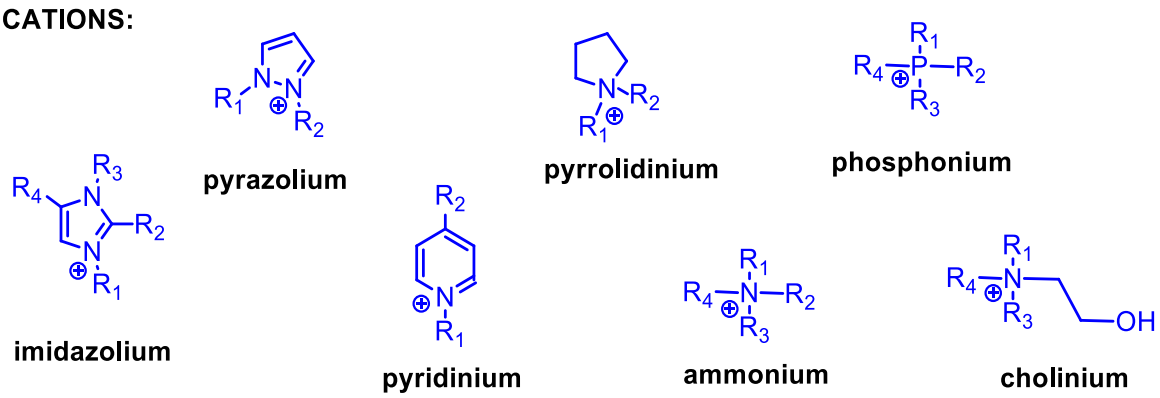


Scheme 1.3 - Selected examples of transformations of nitro groups.

1.1.2 Ionic Liquids

Several definitions have been found in literature for ionic liquids, and one of the most used states "*Ionic liquids are salts that have melting point below 100°C"*.[4] In order to illustrate, some examples of common ionic liquids are shown in Figure 1.1.

CATIONS:



ANIONS:

Cl^-, Br^-, I^-, $Al_2Cl_7^-$, $Al_3Cl_{10}^-$, $Sb_2F_{11}^-$, $Fe_2Cl_7^-$, $Zn_2Cl_5^-$, $Zn_3Cl_7^-$, $CuCl_2^-$, $SnCl_2^-$, NO_3^-, PO_4^{3-}, HSO_4^-, SO_4^{2-}, $CF_3SO_3^-$, $ROSO_3^-$, $CF_3CO_2^-$, $C_6H_5SO_3^-$, PF_6^-, SbF_6^-, BF_4^-, $(CF_3SO_2)_2N^-$, $N(CN)_2^-$, $(CF_3SO_2)_3C^-$, BR_4^-, $RCB_{11}H_{11}^-$.

Figure 1.1- Examples of structures of common ionic liquids.[5]

The definition of ionic liquids goes back to last century, when Paul Walden in 1914 discovered the ethylammonium nitrate, the first salt which behave as ionic liquid (1.15), (Figure 1.2, melting point 13-14ºC).[6]

After some years, in 1948, the ionic liquids regained attention, when Hurley and Wier synthesized a mixture of aluminium (III) chloride and 1-etylpyridinium bromide (1.16) used as baths solutions for electrodeposition of aluminum. In this way, Osteryoung and Wilkes also developed studies that generated great advances in the field; however, the chloroaluminates ionic liquids (1.17) in general still displayed some limitations, such as water sensibility, (Figure 1.2).[8]

The development of ionic liquids continued with Wilkes and Zaworotko in 1992, where 1-ethyl-3-methylimidazolium based ionic liquids were described (1.18). These new ionic liquids were reported to be more stable against hydrolysis and reduction than the first models, which promoted a real breakthrough in the field. Furthermore, these systems

present large tolerance to several functional groups, what enables their use in several applications and a full range of cations and anions combinations, (Figure 1.2).[8]

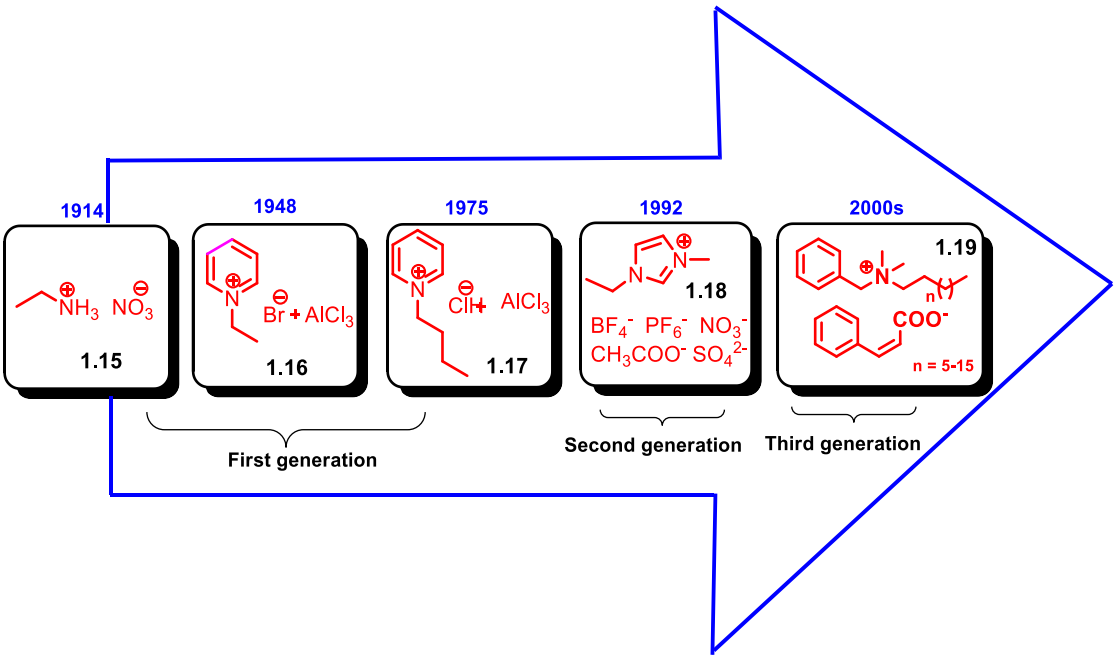


Figure 1.2- Chronology of ionic liquids: Since 1914 until today.

The recently designed ionic liquids, are known as task-specific ionic liquids, in which can be defined as ionic liquids wherein a functional group is covalently bonded to the cation or anion (or both) with the aim to assign particular properties, (Figure 1.2).[7]

Therefore, Rogers and Davis independently proposed a classification for ionic liquids into three generations based in their properties and applications. The first generation incorporates those ionic liquids used as ***solvents*** that are characterized by low or no volatility; thermal stability and large liquid ranges. A second generation it is about the ILs with potential application as ***energetic materials, lubricants, and scavenger materials***. In these cases, there are a combination of physical and chemical properties. Thus, the IL provide a platform where the properties of both cations and anions can be individually modified thus, allowing the design of new ionic

liquids. A third generation of ILs has been related to their ***biological activity***. The biological activity is the primary IL function, combined with the others physical and chemical characteristics, (Figure 1.2).[8]

As illustrated in Figure 1.3, the uses of ionic liquids have gone far beyond their utilization as solvents;[9] the tip of iceberg represents the initial use of ionic liquids as solvents while under the seawater the other possibilities that have been explored in the last decades are depicted. These applications include catalysis,[10] drugs,[11] analysis,[12] gas absortion,[13] valorization biomass: extraction, dissolution,[14] and others.

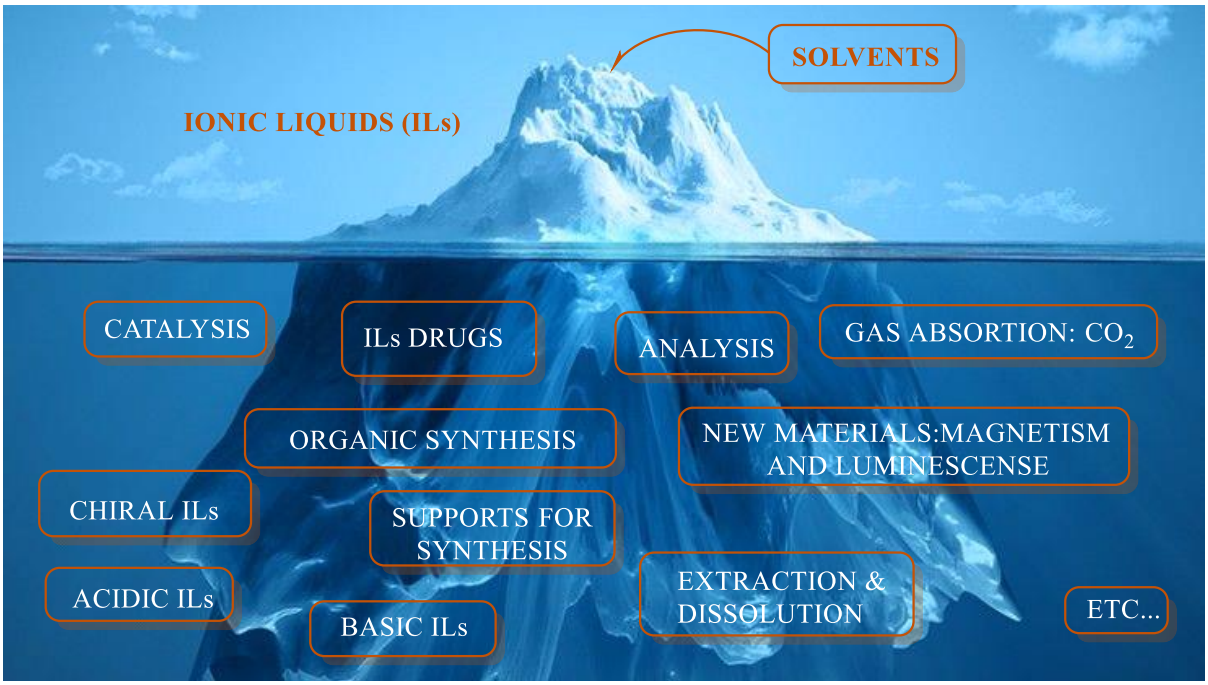


Figure 1.3 - Some applications of ionic liquids.

A selection of several structures of functionalized ionic liquids is shown in Figure 1.4.[15]

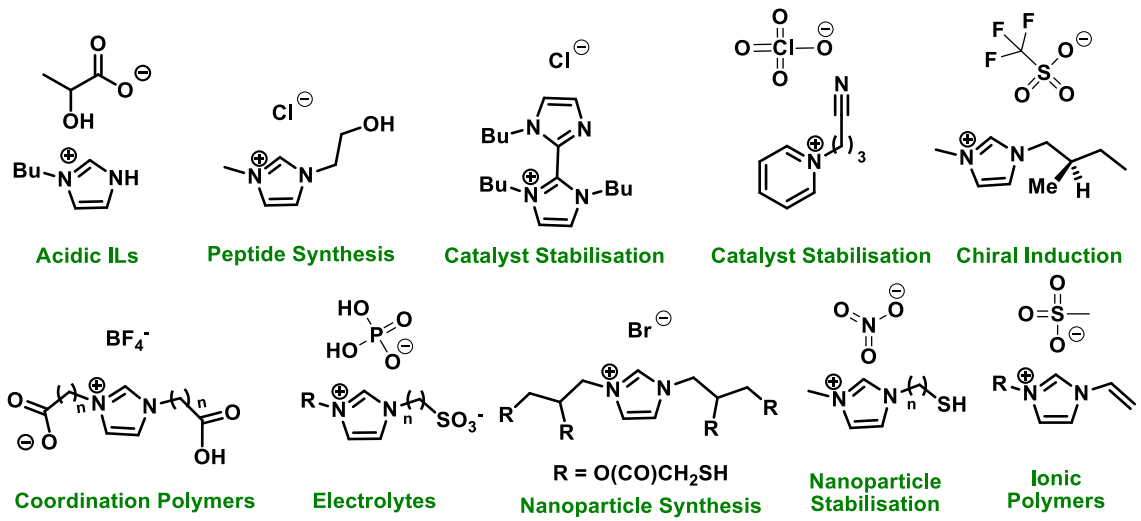


Figure 1.4 - Structures of some functionalized ionic liquids and their applications.

1.1.2.1 Ionic Liquids as catalysts

One of the major applications for ionic liquids aside from solvents is in catalysis. It is fairly common to find reports of ionic liquids being used as catalysts, catalyst activators, or co-catalysts for chemical reactions. In addition, there are many examples of ionic liquids showing significant improvements when compared to common molecular solvents or even catalyzing some processes that do not occur in common organic solvents.[16]

The direct use of ionic liquids as catalysts is often associated to their acidic or basic features. In this context, the use of ionic liquids as basic catalysts represents a great opportunity for developing environmentally friendly basic catalysts that combine the advantages of inorganic bases plus the stability in water and air, easy separation and high catalytic efficiency. Some examples of Basic-ILs are ilustrated in Figure 1.5.[17]

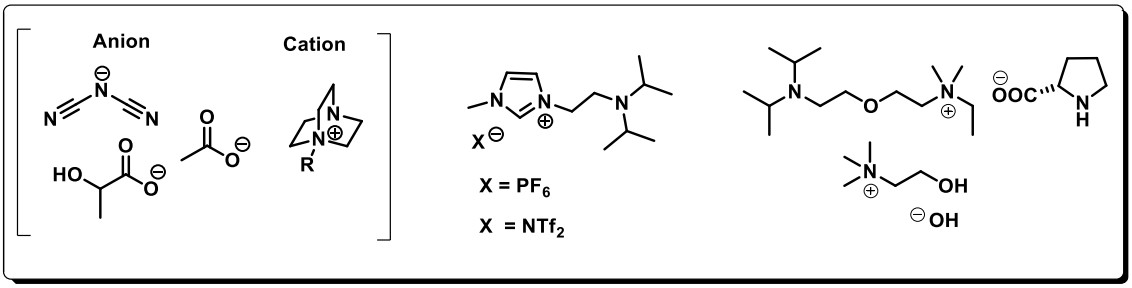
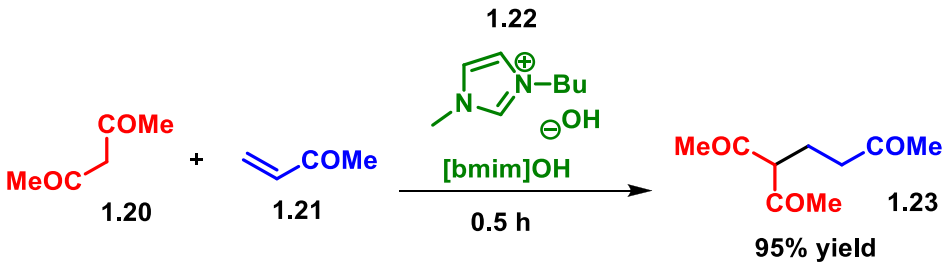


Figure 1.5 – Examples of basic ionic liquids

In 2005, Ranu and Banerjee described the application of a basic ionic liquid, [bmim]OH (1.22) as catalyst in the Michael addition of active methylene compound (1.20) to conjugated ketone (1.21), leading to the product (1.23) with high yield (Scheme 1.4).[18]

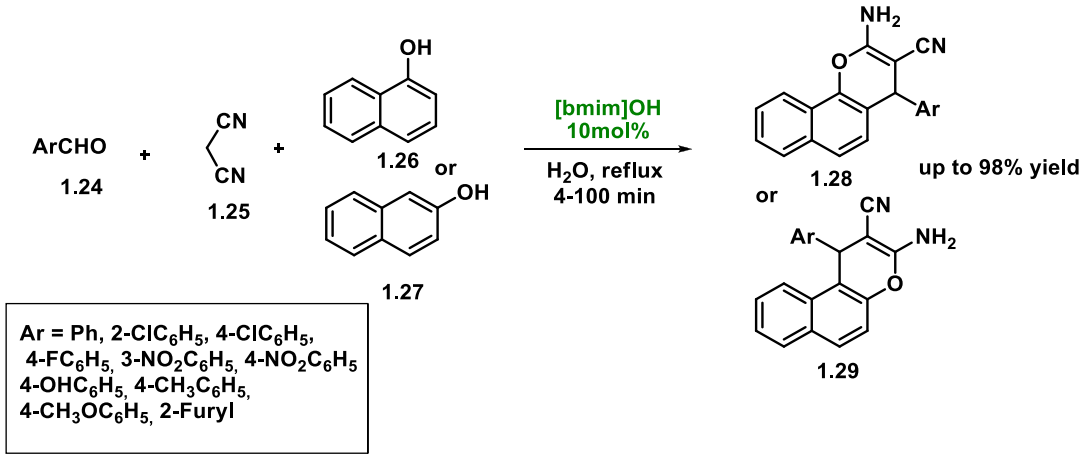


Scheme 1.4 - Michael addition using [bmim]OH as reaction media and catalyst.

Contrary to the traditional bases, such as sodium hydroxide or ammonia, [bmim]OH can be recycled and reused for many times without significant loss of catalytic activity and the reaction process is more environmentally benign.[9]

Another example using [bmim]OH was described by Gong and co-workers. The group synthesized substituted 2-amino-2-chromenes (1.28, 1.29) in high yields by the three-component condensation reaction of aromatic aldehydes (1.24), malononitrile (1.25) and α- or β-naphthol (1.26, 1.27) under reflux and [bmim]OH as catalyst. Furthermore, the greener protocol was found to be very versatile and the catalyst was recycled and

used in the next reactions with considerable catalytic activity (Scheme 1.5).[19]



Scheme 1.5 – Synthesis of choremes using [bmim]OH as catalyst.

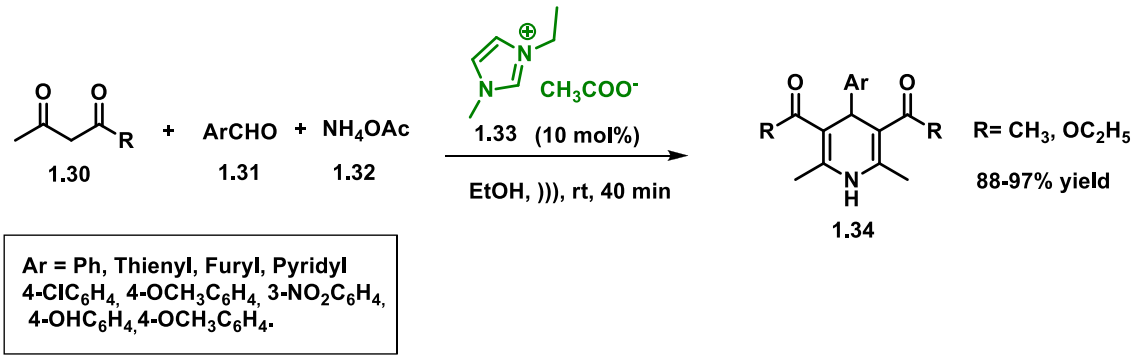
1.1.2.2 Ionic Liquids and ultrasound irradiation

In the last years, the use of ultrasound irradiation allied to ionic liquids have evolved progressively, not only in the synthesis of these salts, but also as alternative source of energy in a merging reactional system. The advantages of the use of ultrasonic irradiation are numerous, such as the easy processing and accessibility (ultrasonic baths or ultrasonic probes).[20]

Ionic liquids improve the physical effects of sonochemistry *e.g*. the generation of shockwaves, microjets, micro-convection, micro-emulsions, erosion, and others. Thus, the beneficial effects are the decrease of reaction/preparation times, increased yields, selectivity and/or quality of the products, in comparison with silent conditions. Sometimes, unexpected results can also be observed under ultrasonic irradiations, thereby contributing for new synthetic pathways starting from miscellaneous ionic liquids in combination ultrasound.[22]

In 2011, Vijayakumar and co-workers described an example of a successful combination of ionic liquids and ultrasound, (Scheme 1.6). The

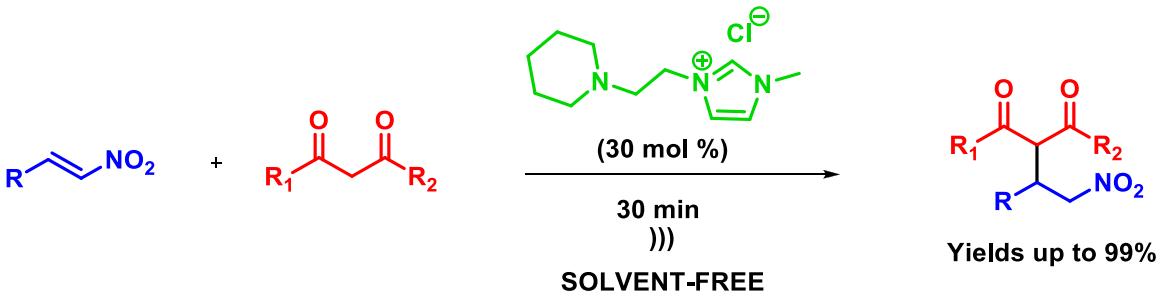
ionic liquid 1-ethyl-3-methylimidazole acetate [EMIM]OAc (1.33) was the catalyst of the one-pot three-component synthesis of 1,4-dihydropyridines (1.34), from arylaldehydes (1.31), ethylacetoacetate/acetylacetone (1.30) and ammonium acetate (1.32) at room temperature under sonication. This methodology afforded the product in high yield in one convenient and simple operation.[21]



Scheme 1.6 - Synthesis of 1,4-dihydropyridines using [EMIM]OAc as catalyst under ultrasound irradiation.

1.2 Objectives

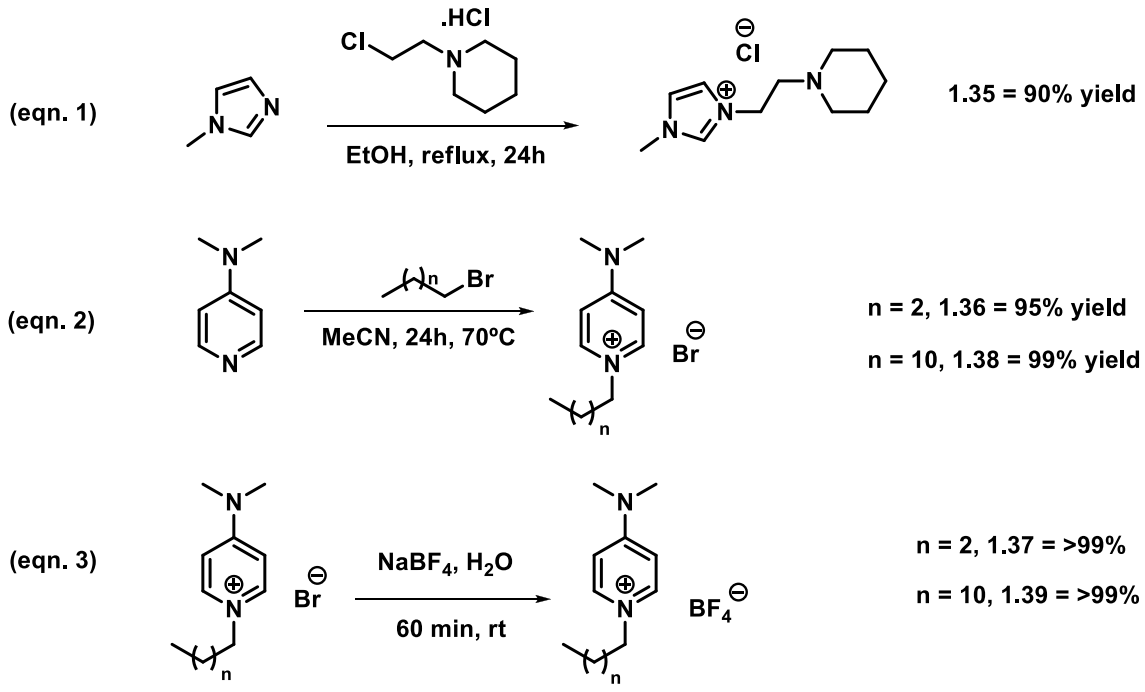
Inspired by the blooming development of ionic liquids and their increasing applications throughout history, and having in mind the pressing challenge for organic chemists to create new catalytic process, as that are not only efficient and high yielding, but also eco-compatible. The aim of this chapter is to describe and discuss the evaluation of some basic ionic liquids as catalysts under ultrasound irradiation. The reaction systems will be used in the Michael reactions of carbon nucleophiles to nitroalkenes using a new solvent-free approach. Besides that, another objective is the study of the possibility of reusing the ionic liquid catalysts in this reaction.



1.3 Results and Discussion

1.3.1 Synthesis of basic task-specific ionic liquids (IL 1-5)

The ionic liquid (1.35) was synthesized by using the procedure described by Gao and co-workers in 2010.[22] This ionic liquid is accessible by the alkylation of commercially available methylimidazole with chloro ethyl piperidine hydrochloride giving the corresponding (1.35) in 90% yield, (Scheme 1.7, Equation 1).



Scheme 1.7– Synthesis of ionic liquids IL1-5.

The ionic liquids (1.36 to 1.39) were synthesized by the procedure described by Sardroodi and co-workers in 2012 with some modifications.[23] The quaternization reaction to form the (1.36) and (1.38) was carried out with the desired alkyl bromide and 4-dimethylamino-pyridine, leading to the (1.36) with 95% yield and the (1.38) with 99% yield,

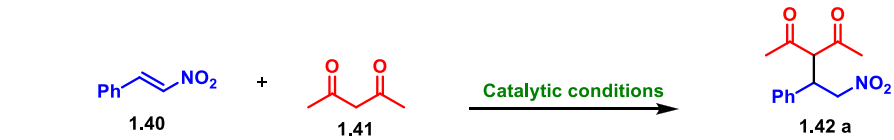
(Scheme 1.7, Equation 2). Then, (1.37) and (1.38) were obtained from (1.36) and (1.38), respectively, by a metathesis reaction with $NaBF_4$ (Scheme 1.7, Equation 3).

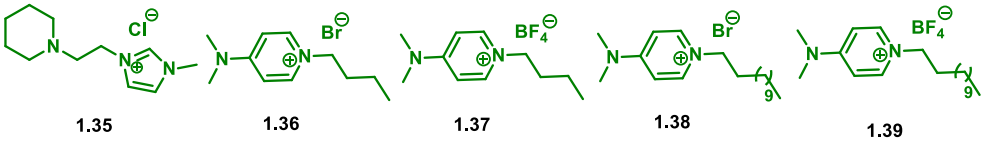
1.3.2 Evaluation of the catalytic activity of the basic ionic liquids in the Michael addition

The Michael addition between 2,4-pentanedione (1.41) and trans-β -nitrostyrene (1.40) was used as a model reaction for the evaluation of the catalytic activity of five basic ionic liquids (Table 1.1). The catalyst loading employed was 30 mol% and the reaction time was set on 30 min in a ultrasound bath.

Among the five task-specific ionic liquid with basic behavior evaluated in the model reaction, 1-methyl-3-(2-(piperidin-1-yl)ethyl)-1H-imidazol-3-ium chloride (1.35) was the best catalyst in terms of yield (98%, Table 1.1, Entry 1). Thus, IL (1.35) was selected to continue the optimization studies. The next step was the evaluation of the catalytic amount of ionic liquid required to promote the reaction. It was possible to notice that the decreased amount of the catalyst loading from 30 mol% to 20 and then to 10 mol% generated significant drops in the yields, which moved from 98% to 81% and then to 66% yield, respectively (Table 1.1, Entry 1 vs Entries 6 and 7). The reduction of the reaction time from 30 min to 15 min also showed a significant effect on the reaction yield, which decreased from 98% to 88% (Table 1.1, Entry 1 vs Entry 8).

Table 1.1 - Initial screening of the Michael addition between acetyl acetone and β-nitro-styrene under IL catalysis.





1.35 1.36 1.37 1.38 1.39

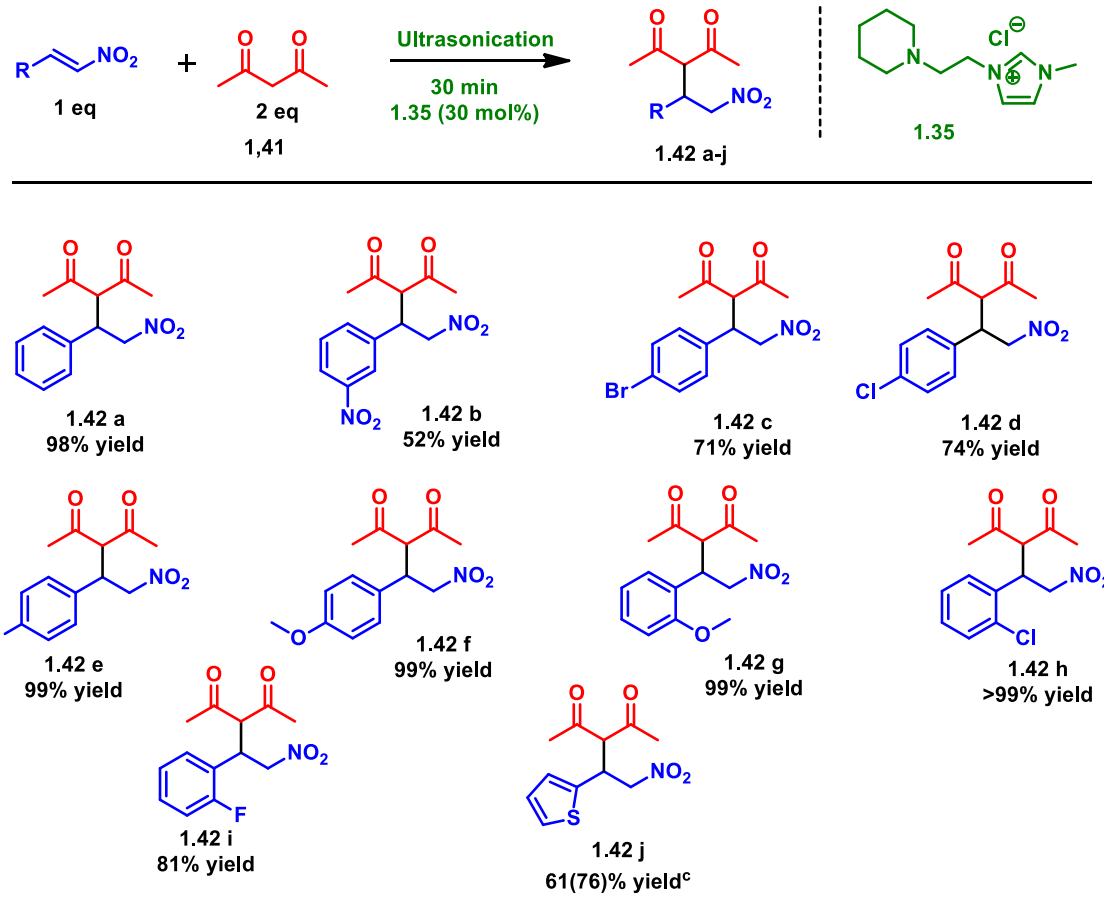
Entry	TSIL's	IL (%mol)	Time (min)	Yield (%)[a,b]
1	1.35	30	30	98
2	1.36	30	30	42
3	1.37	30	30	10
4	1.38	30	30	23
5	1.39	30	30	16
6	1.35	20	30	81
7	1.35	10	30	66
8	1.35	30	15	88
9[c]	1.35	30	120	73
10[d]	1.35	-	30	-

[a)] Unless otherwise specified, the reactions were performed using trans-*β*-nitrostyrene (0.25 mmol), 2,4-pentanedione (0.5 mmol), and ionic liquid (30 mol%) under ultrasonication for 30 minutes. [b)] Isolated yield. [c)] Reaction was performed without ultrasonication under room temperature for 120 min. [d)] Reaction was performed without ionic liquid.

Other parameter evaluated was the influence of ultrasound irradiation. When the model reaction was carried out in the absence of ultrasonication, the conjugate adduct was obtained in lower 73% of yield even when longer reaction times were employed (120 min) at room temperature under magnetic stirring (Table 1.1, entry 9). Subsequently, no product was formed in the absence of (1.35), (Table 1.1, entry 10).

Next, the scope of the newly developed procedure was evaluated. In order to accomplish that, a variety of nitroalkenes was evaluated in the reaction, considering the usefulness and versatility of the respective adducts in organic synthesis (Scheme 1.8).

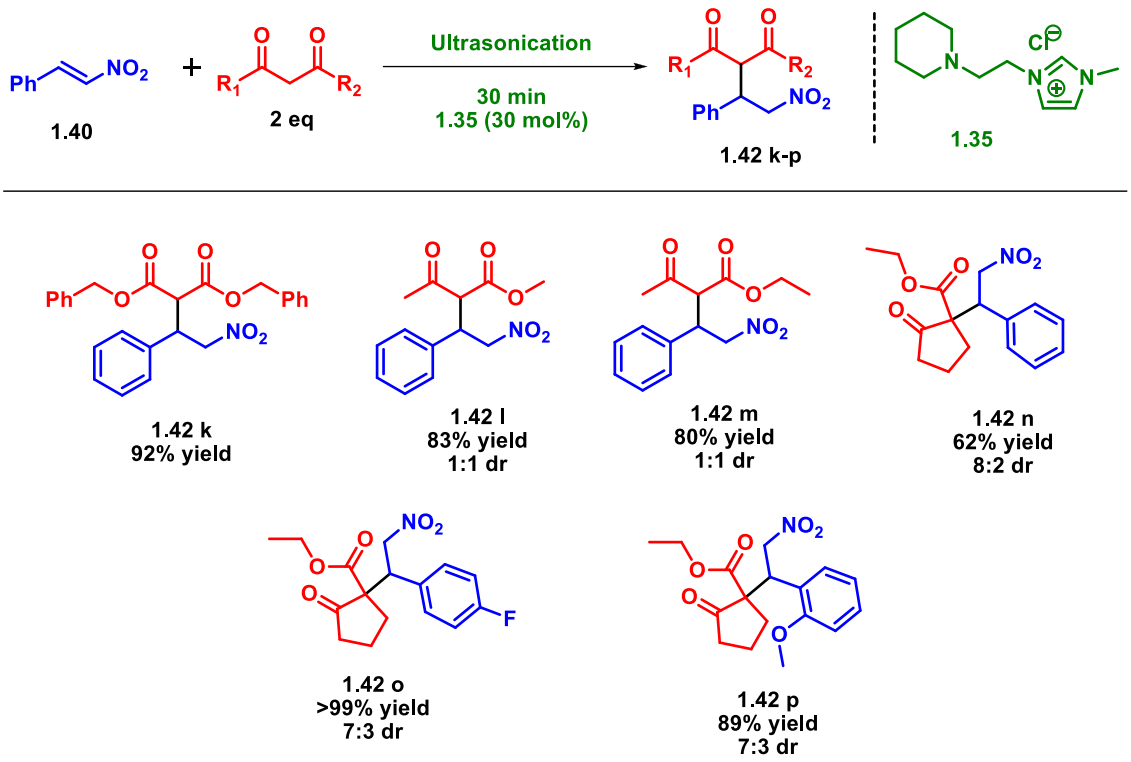
It is evident from the obtained results, that all reactions of nitroalkenes with 2,4-pentanedione (1.41) proceeded easily to afford the desired products with good to excellent yields. Electronic effects had small influence on the reaction course, with electron-withdrawing groups attached to the aromatic ring of β-nitrostyrenes leading to products with good to excellent yields (1.42a-d) and (1.42h-j). Moreover, the reactions of nitrostyrenes bearing ortho or para electron donating substituents with 2,4-pentanedione proceeded very well and afforded the corresponding Michael adducts in 99% yield (1.42f and 1.42g). It was possible to employ a nitroolefin bearing the group thiophene to give rise to the conjugate adduct in 76% yield (1.42j).



[a] Unless otherwise specified, the reactions were performed using nitrostyrene (0.25 mmol), 2,4-pentanedione (0.5 mmol), and 1.35 (30 mol%) under ultrasonication for 30 minutes at room temperature. [b] Isolated yield. [c] Yield in parenthesis refers to 1h reaction time under ultrasonication.

Scheme 1.8 - Michael addition reactions of 2,4-pentanedione to nitroalkenes.

The evaluation of different nucleophilic species was futher investigated, as shown in Scheme 1.9. For this study, various ketoesters were tested and effectively reacted with trans-β-nitrostyrene (1.40) in the presence of 30 mol% (1.35) to afford the products in good to excellent yields (1.42k-m). An important feature of this methodology is the possibility of the use of different nucleophiles such as cyclic-β-ketoester, giving the corresponding products in good yields (1.42n-p). In that way, these results demonstrate the potential broad ranging utility of this methodology by the preparation of various conjugate adducts.



[a] Unless otherwise specified, the reactions were performed using trans-*β*-nitrostyrene (0.25 mmol), nucleophile (0.5 mmol), and **1.35** (30 mol%) under ultrasonication for 30 minutes. [b] Isolated yield. [c] d.r. was determined by NMR analysis.

Scheme 1.9 - Evaluation of nucleophiles in the reaction with trans-β-nitrostyrene catalyzed by (1.35).

1.3.3 Recyclability of ionic liquids

Considering that the recyclability of the ionic liquids is one of the most important features, this parameter was then evaluated. For this purpose, a set of experiments were conducted to explore whether the ionic liquid can be reused for further reactions (Chart 1.2).

After completion of the first reaction, the task-specific ionic liquid catalyst was recovered and subjected to another run, affording the

product in 98% yield. This process was repeated four more times, leading the desired product without any significant decrease in yield.

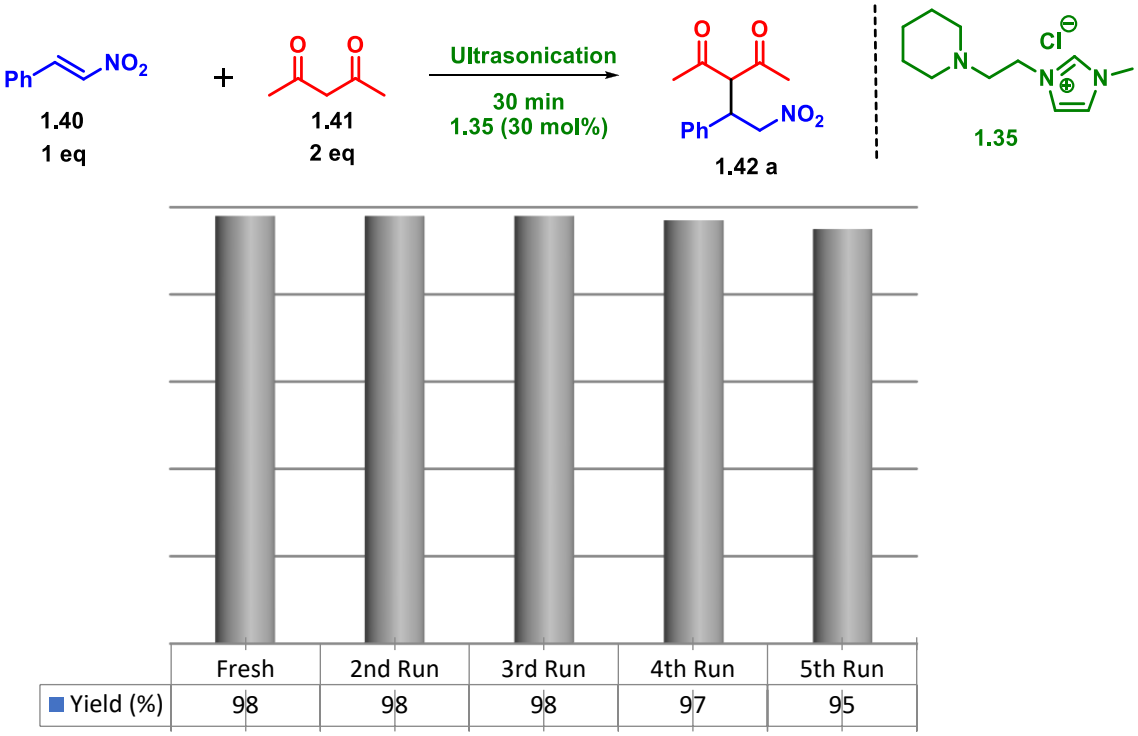


Chart 1.2 - Recyclability of ionic liquid catalyst for the conjugate addition.

1.4 Conclusions and outlook

In conclusion, an environmentally benign simple experimental protocol for the Michael addition of β-dicarbonyl compounds to nitroolefins was developed. The basic ionic liquid applied proved to be an efficient catalyst for this reaction, with the ease of recovery and reuse in further reactions; besides that, the protocol showed its versatility by tolerating a wide range of substrates.

Furthermore, in the future would be interesting develop an asymmetric approach for this reaction system using chiral ionic liquids as asymmetric inductor.

Chapter 2

2 Chapter 2

The asymmetric synthesis of Michael adducts is the focus of the present chapter. Thus, a short description about asymmetric synthesis, organocatalysis, green solvents and GABA derivatives will be presented. Then, the chapter objectives, discussion of results and final considerations of study will be exposed. .

2.1 Introduction

2.1.1 Asymmetric Synthesis

The asymmetric synthesis is a very important field of organic chemistry due to the characteristics of enantiomers, which often lead to different interactions within living organisms, and therefore show different pharmacological properties, different smells and tastes. This different behavior is because most biomolecules are chiral (Figure 2.1).[24]

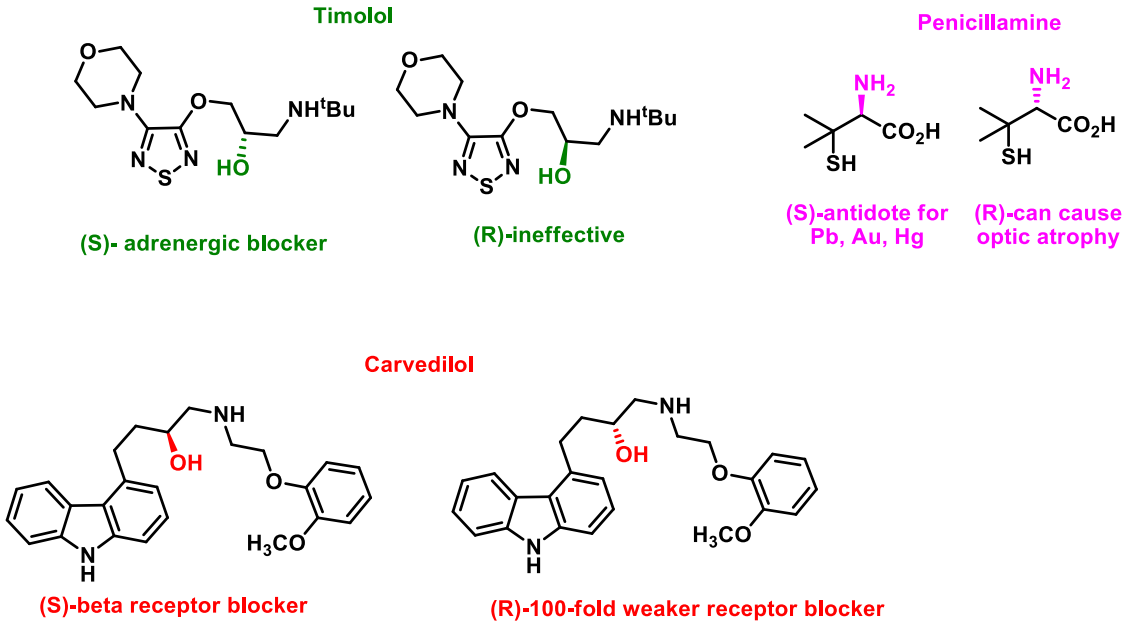


Figure 2.1– Example of chiral drugs.

The difference between two enantiomers of a chiral drug is illustrated in Figure 2.2, a hypothetical example of interaction between the drug and its chiral binding site.[25]

In this example, just one enantiomer is biologically active, and for the drug to have its pharmacologic effect, all the points of chiral drug A, B, and C must interact with the corresponding regions of the binding site labeled a, b, and c. If the enantiomer cannot be entirely aligned with the corresponding regions of the binding site, it is considered inactive against the chiral receptor (Figure 2.2). [25]

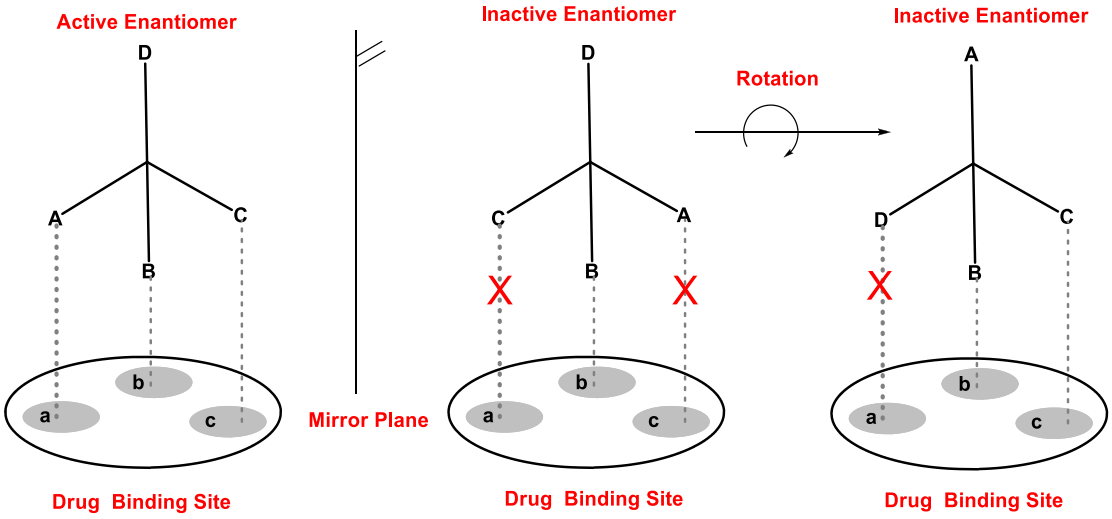


Figure 2.2 - Model of 3-points interaction between enantiomers and drug binding site.

Enantiomeric enriched compounds have been prepared via enzymatic kinetic resolution. However, catalytic asymmetric methodologies have expanded considerably in the last two decades, in particular the use of transition-metal complexes as chiral catalysts, which dominated the field. After the turn of the century, a new technology known as organocatalysis has been established as the third pillar of asymmetric catalysis.[26]

2.1.2 Organocatalysis

The use of small organic molecules as catalysts, the called "organocatalysts," has been widely explored by scientists around the world since its definition by MacMillan in 2000.[27]

The swift growth is mainly due to numerous advantages that the use of organocatalysis offer for synthetic organic chemistry. The organocatalysts are often of low cost, and allow the preparation of both enantiomers from the chiral pool, thus leading to broad possibilities for structural modification. Besides that, the prospect of performing reactions under an aerobic atmosphere, avoiding inert atmosphere, standard Schlenk and drybox techniques, dry and oxygen-free solvents make the experimental operations considerably simpler.[28]

The organocatalysts can be classified by means of their interaction with the substrate, the so-called 'mode of action'. In organocatalysis, there are two large modes of action: the covalent; and the non-covalent.[29]

Covalent organocatalysis is characterized by the formation of a covalent bond between the substrate and the catalyst, thus increasing the interaction among the substrate and the reagent in the reaction medium. For instance, aminocatalysts (2.1-2.3) and carbenes (2.4) belong in this category. In the case of non-covalent organocatalysis, the interactions between the substrate and the catalyst can occur *via* hydrogen bonds (e.g., thioureas, squaramides and phosphoric acids -2.5) or ionic interactions (e.g., phosphoric acids, chiral bases such as cinchona alkaloids and phase-transfer catalysts – 2.6), (Figure 2.3). [29]

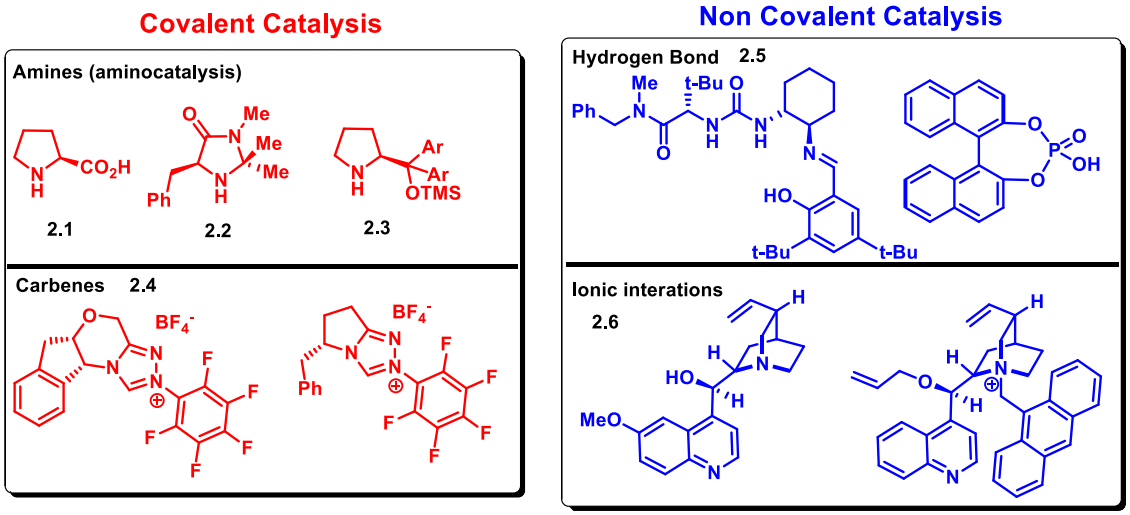
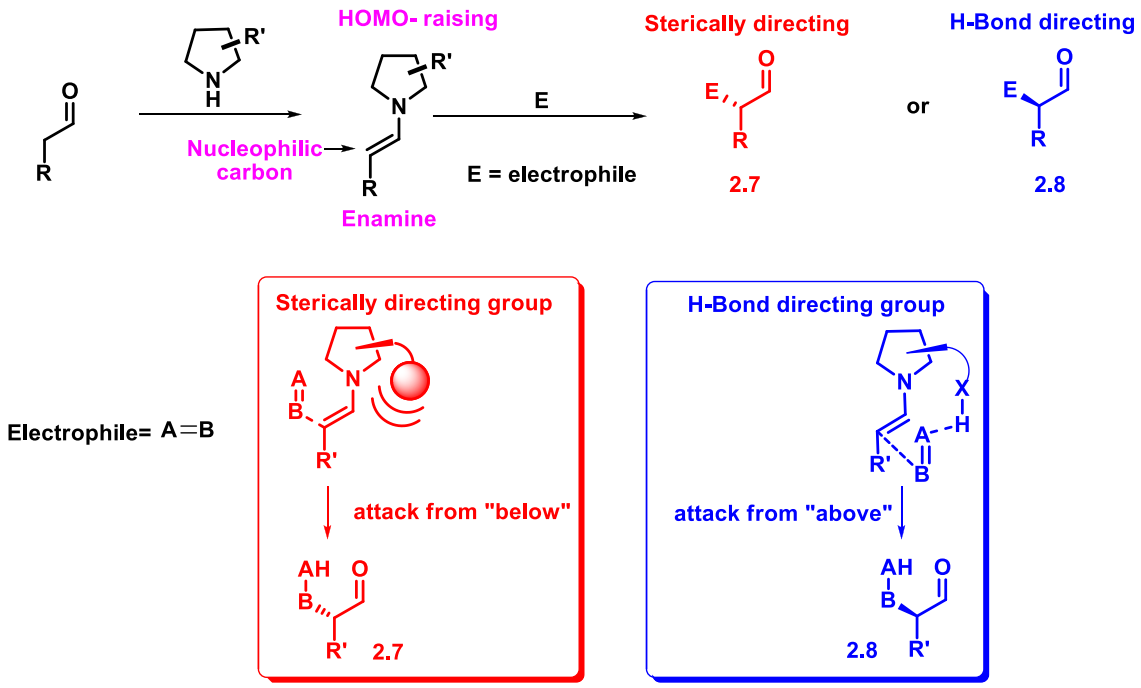


Figure 2.3 - General classification of the activation mode in organocatalysis.[29]

Organocatalysis is a vast field of study and possess numerous applications, for this reason, this chapter will be restricted to a short introduction on the use of the enamine activation mode via secondary amines.

2.1.2.1 Enamine activation

The employment of secondary amines to generate chirality in reactions such as Aldol, Michael, Mannich, conjugate additions to electron-deficient alkenes, as well α-functionalizations, *e.g.* α-Alkylation, α-Arylation, α-Fluorination, α-Bromination, α-Amination, and α-Oxygenation, among others has been extensively studied in the last decade (Scheme 2.1.[28,30,31]

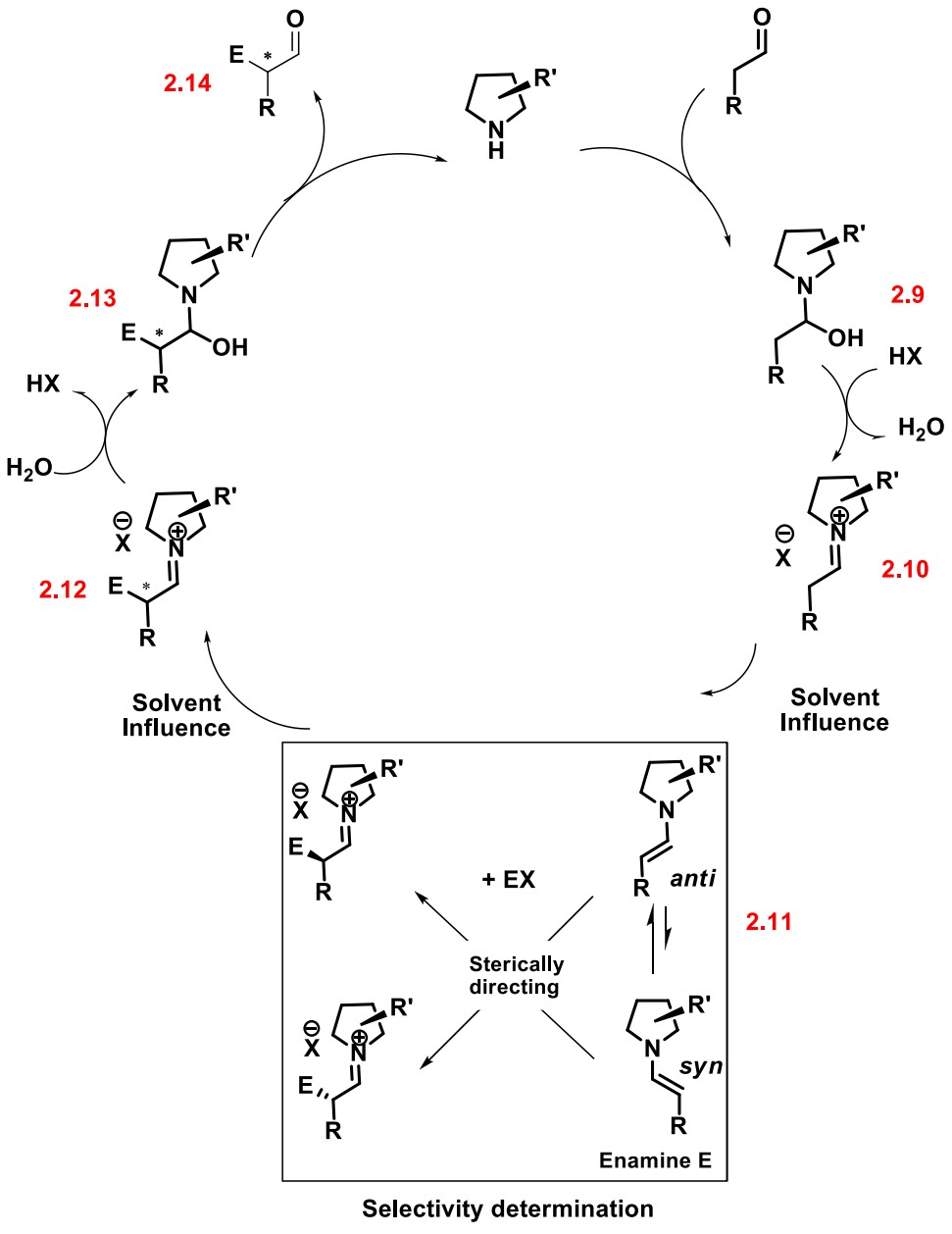


Scheme 2.1 - Aminocatalytic route via enamine activation. [31]

The stereoselectivity is originated by the chiral secondary amine, which can be classified according to their mode of stereochemical induction. The first class shields one face of the enamine by their steric bulk *e.g* imidazolidinone (2.2), diarylprolinol silyl ether (2.3) and promotes the approach of the electrophile from the opposite face, (*attack from ''below''*) (Scheme 2.1, 2.7). The second class *e.g*. proline (2.1) directs the electrophile to approach from one side of the enamines via electronic interactions (*attack from ''above''*) (Scheme 2.1, 2.8).[30]

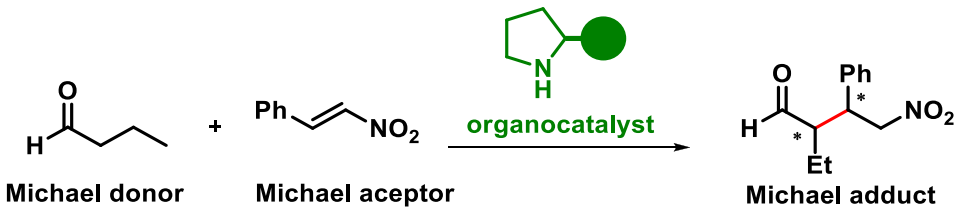
The detailed catalytic cycle of α-functionalisations with electrophiles mediated by secondary amine catalysts containing a steric bulk is presented in Scheme 2.2. Firstly, the aldehyde reacts with the catalyst leading to the formation of the hemiacetal (2.9), which in acid media goes to iminium-ion (2.10), followed of the tautomerisation to the enamine (2.11). The enamine formed has two possible configurational isomers (E and Z) in thermodynamic equilibrium, being that the enamine E is energetically most favored. Moreover, two rotational isomers (anti and syn) exist in the enamine

E, where by steric interactions the most favorable is the anti-enamine E. Thus, after reaction of the enamine with the electrophile, the iminium ion is formed (2.12), followed the hemicetal (2.13), which is hydrolysed to afford the addition product (2.14) and the free catalyst that returns to the catalytic cycle, (Scheme 2.2).[30]



Scheme 2.2 - Catalytic cycle for the α-functionalisation with mechanistic details (adapted from reference 30).

As stated earlier in Chapter 1, some reactions continue to inspire the chemists for years, as the case of Michael reaction, which in your asymmetrical version is the focus of this chapter. Here, we used organocatalysis, specifically enamine activation mode to induce asymmetry in the Michael adducts (Scheme 2.3).



Scheme 2.3 - Model organocatalized Michael addition between butiraldehyde and *β*-nitrostyrene.

The mechanism of the addition of linear aldehydes to nitroolefins has been discussed by many authors, and it is still an open discussion. Here, a model proposed by Seebach and Hayashi in 2011, one of the most accepted by the scientific community is presented (Scheme 2.4).[32]

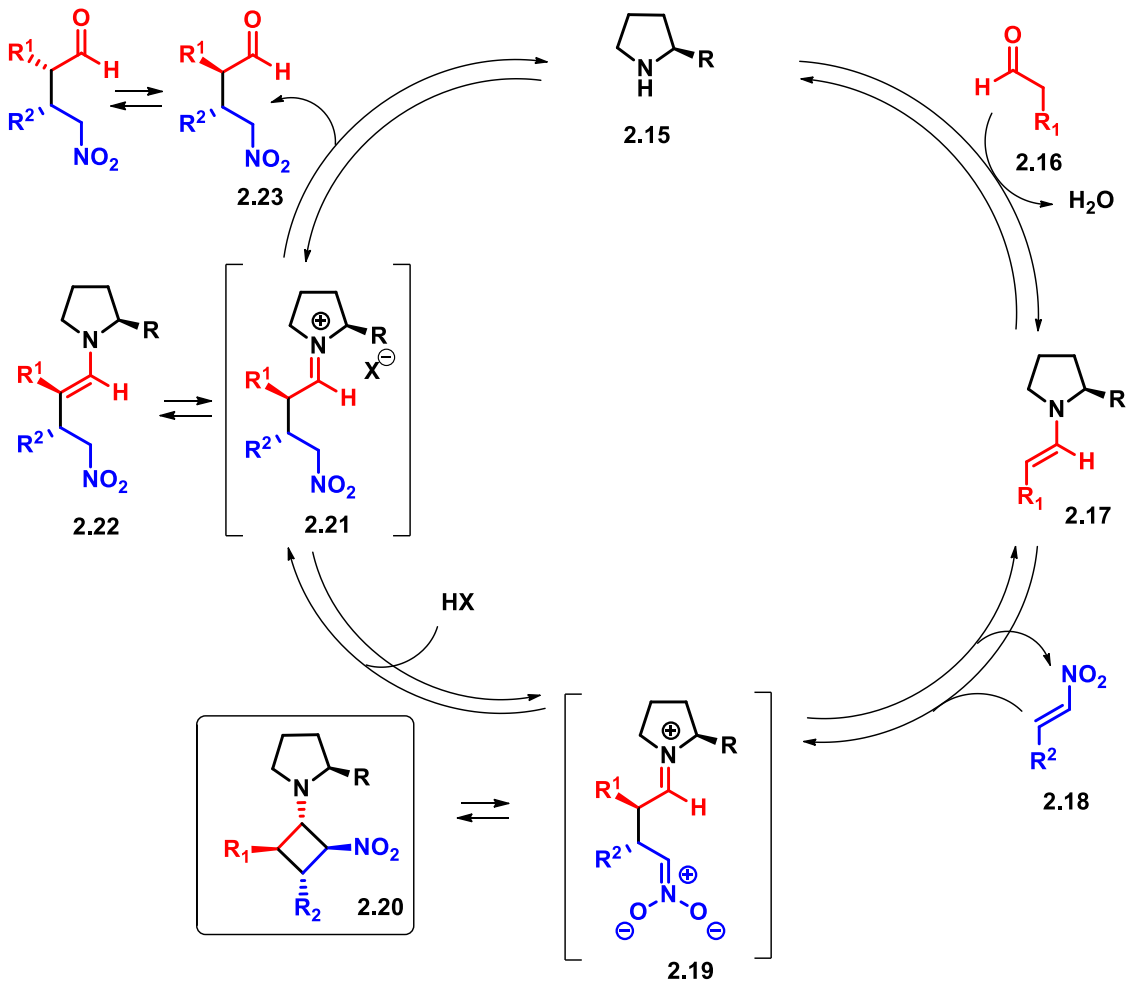
Firstly, the catalyst (2.15) reacts with the carbonyl partner (2.16), leading to the corresponding enamine (2.17), which further reacts with the nitroalkene (2.18) to afford the zwitterionic intermediate (2.19). Thereafter, two pathways are possible from (2.19):

a) cyclization to form a cyclobutane derivative (2.20) or;

b) protonation, leading to an iminium ion (2.21), which is hydrolyzed to the Michael addition product (2.23), with regeneration of the catalyst (2.15) or deprotonation of (2.21) to an enamine (2.22).

The cyclobutane (2.20) then undergoes a ring opening back to the zwitterion ion (2.19), providing access to the product-forming route.

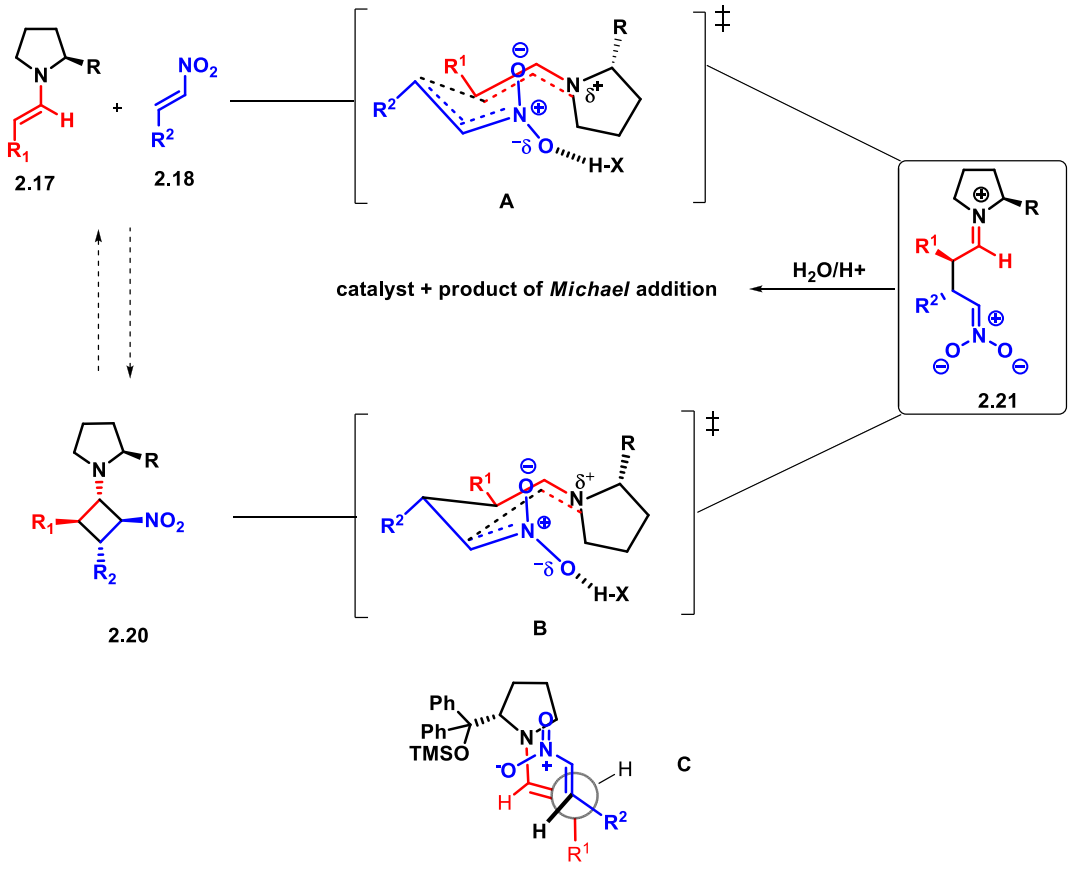
Finally, the nitroaldehyde product (2.23) can be epimerized at the α-carbonyl position by the organocatalyst (2.15), (Scheme 2.4).[32]



Scheme 2.4 - Mechanism of organocatalyzed addition of linear aldehydes to nitroolefins.

In addition, Seebach and Golinski proposed insights into the stereochemistry of this reaction, (Scheme 2.5). This process occurs in the *Si*-face of the nucleophilic s-trans-enamine atom (C), since the bulky group of the catalyst shields the *Re*-face, thus securing essentially exclusive *Si,Si*-coupling of the two trigonal centers, and hence the excellent enantioselectivity. After the C-C-bond formation, the resulting zwitterionic species can undergo a cyclization to form the cyclobutane (2.20) in a fast,

intramolecular step. The zwitterion can also be protonated forming (2.21), followed by hydrolysis or undergo a proton shift to afford the product-derived enamine (2.22). When this enamine is formed, the diastereoselectivity is at stake: the protonation of the enamine's C-C bond, back to the iminium ion, can lead to diastereoisomers. The acid co-catalyst is important to suppress the deprotonation of the iminium ion to the enamine. [33]



Scheme 2.5 - Transition States (A) and (B) of C-C-Bond Formation and of Cyclobutane Ring Opening, respectively, and Intermediate Zwitterion (2.21).

2.1.3 Green solvents

The exhaustion of natural resources and high degree of degradation of the environment has generated a world need to embrace sustainability.[34] In this context, Sustainable Chemistry is defined as the *''design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances.''* The 12 principles of green chemistry are ''design rules'' which direct the chemists towards the goal of achieving sustainability. Green Chemistry is also recognized as careful planning of chemical synthesis and molecular design to reduce adverse consequences.[35]

12 principles of green chemistry

1.*Prevention,*

2.*Atom Economy,*

3.*Less Hazardous Chemical Synthesis,*

4.*Designing Safer Chemicals,*

5. Safer Solvents and Auxiliaries,

6. *Design for Energy Efficiency,*

7. *Use of Renewable Feedstocks,*

8. *Reduce Derivatives,*

9. Catalysis,

10. *Design for Degradation,*

11. *Real-Time analysis for pollution prevention,*

12. *Inherently Safer Chemistry for Accident prevention*.

Therefore, chemical processes are being developed in the view of the environmental concerns. This also means that the more traditional chemical methods are being replaced for reformulated processes and

innovations.[36] One part of this reformulation involves re-thinking the use of specific solvents, which are universally recognized to be of great environmental concern. The reduction of their use is one of the most crucial aims of sustainable chemistry, since they often count for the vast majority of waste produced in syntheses and processes in both sections academia and industry (Figure 2.4).

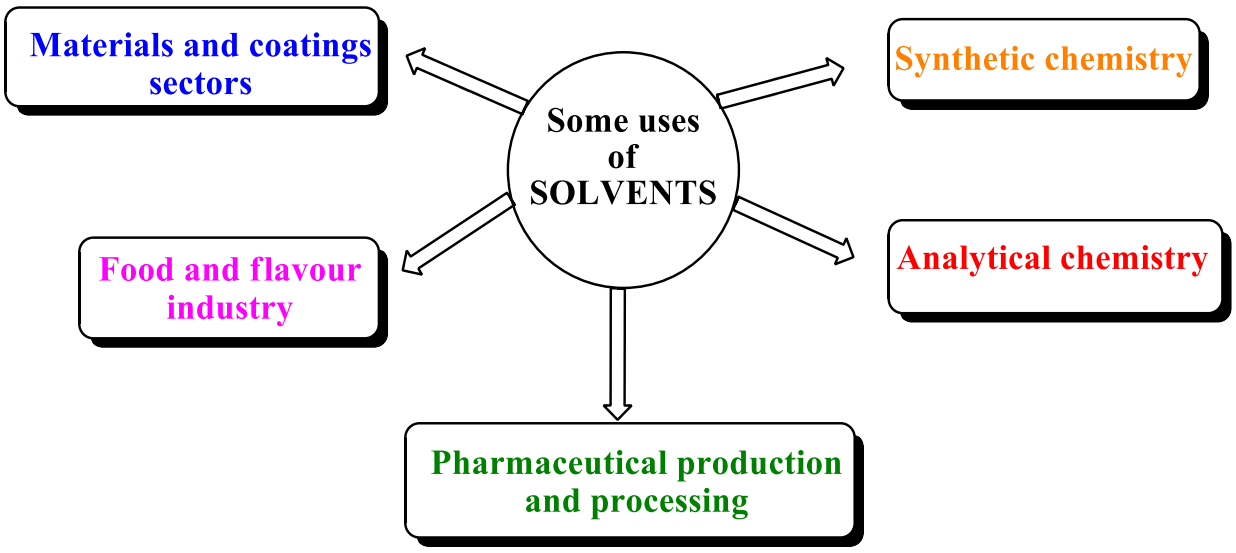


Figure 2.4 - Some applications of solvents.

The use of solvent-free systems or the use of alternative solvents such as water, supercritical fluids (SCF), ionic liquids and, more recently, liquid polymers, are some examples of these new "greener" alternatives.[36] Some properties of a few volatile organic solvents and possible alternatives are presented in Table 2.1.[36]

Table 2.1 - Properties of some volatile organic solvents, and some possible alternatives.[36]

Solvent	*Boiling point (°C)*	*Flash point (°C)*	*TLV-TWA[a] (ppm)*	*Hazards*	*Green ?*
Methanol	64	12	200	Toxic, flammable	Can be renewable
Ethanol	78	16	1000	Irritant, flammable	Can be renewable
Isopropanol	96	15	400	Irritant, flammable	
1-Butanol	117	12	100	Harmful, flammable	
Ethyl acetate	76	-2	400	Harmful, flammable	
Ethyl lactate	154	46	Not yet establised	Irritant, flammable	renewable
THF	65	-17	200	Irritant, flammable	
2-MeTHF	80	-11	Not yet establised	Irritant, flammable	renewable
2-Butanone	80	-3	200	Irritant, flammable	
Dichloromethane	40	none	100	Toxic, harmful, suspected carcinogen	
Chloroform	61	none	10	Possible carcinogen	
Toluene	110	4	50	Irritant, tetratogen, flammable	
Hexane	68	-26	50	Irritant, reproductive hazard, flammable	
Heptane	98	-4	400	Irritant, flammable	
Water	100	None	Not aplicable		Renewable, non-flammable
Carbon dioxide	Not aplicable	None	5000	Compressed gas	Renewable, non-flammable
PEG-1000	Not aplicable	None	Not aplicable		Non-toxic, non-volatile
[Bmim] [PF_6]	Not aplicable	None	Not yet establised		Non-volatile

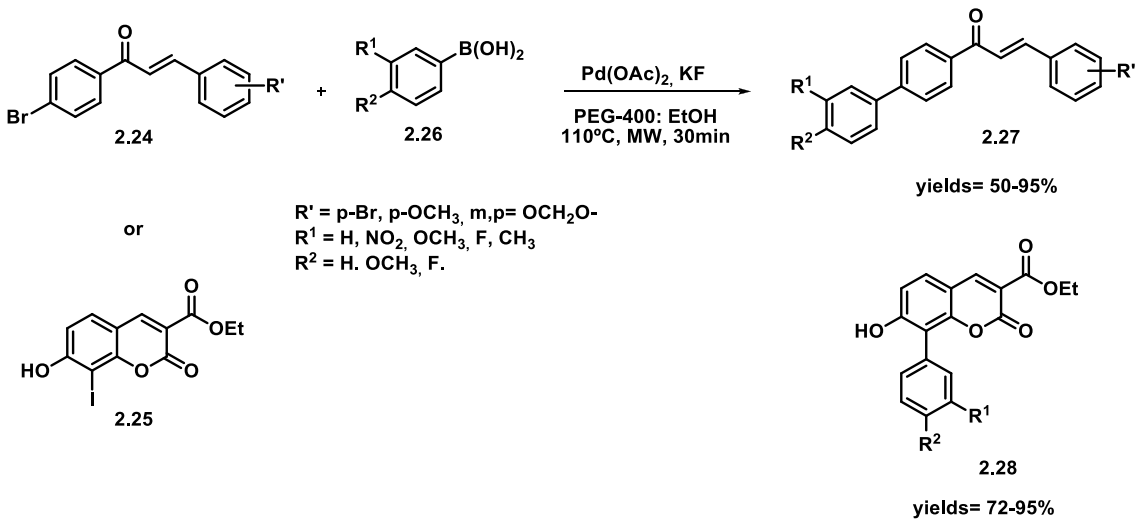
[a] TLV-TWA: threshold limit value-time weighted average in vapour.

2.1.3.1 PEG as solvent

Polyethylene glycols (PEGs) are well-known polymeric compounds with ample industrial and medical applications. PEGs are easily soluble in most polar and non-polar solvents and insoluble in aliphatic hydrocarbons and supercritical CO_2. In that way, a very attractive aspect of these compounds is their possible applications as solvents in organic reactions. [37] PEGs are relatively inexpensive and significantly less dangerous than other organic solvents and besides that, are stable under ambient conditions and do not release volatile organic compounds (VOCs) due to their low vapor pressure. They also present good stability in acidic and basic media and are suitable reaction media for oxidation/reduction transformations. [38]

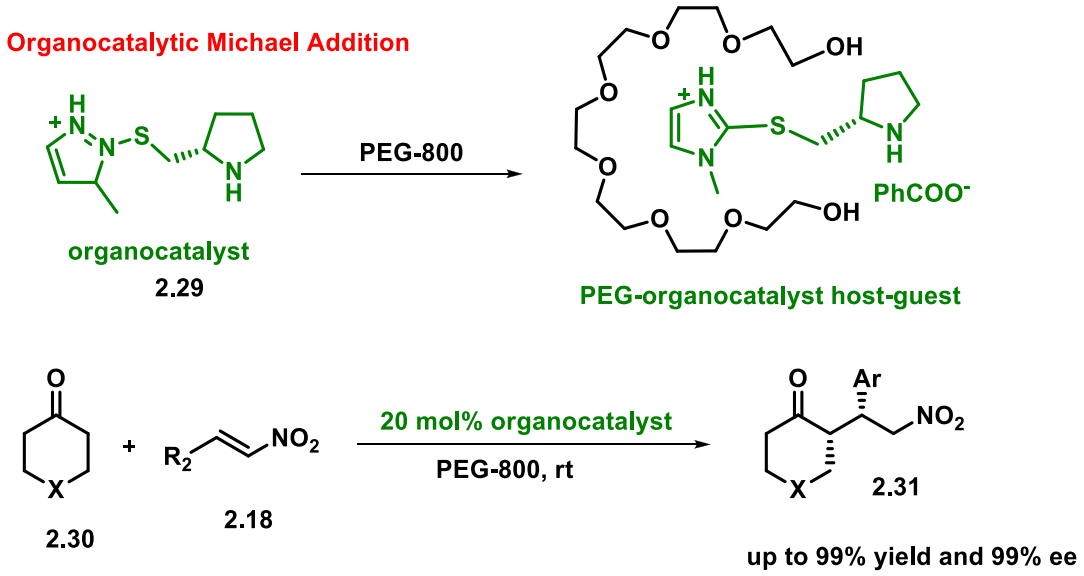
PEG has been reported as reaction medium for various organic processes such as (N, O and S)-arylations, allylation, multicomponent reactions, oxidation, cycloaddition, polymerizations, N-alkynylation, Michael addition, asymmetric hydrogenation and asymmetric Sharpless dihydroxylation (Scheme 2.5).[39]

In 2012, our group reported an eco-friendly approach for the synthesis of Suzuki coupling reaction of chalcones (2.24) and coumarins (2.25) with arylboronic acids (2.26), using 10 mol% $Pd(OAc)_2$ as catalyst, KF as base and a mixture of PEG-400:EtOH as a solvent system under microwave irradiation. The biphenyl chalcones and coumarins was obtained with good yields ranging of 50 to 95% (Scheme 2.6).[39]



Scheme 2.6 – Suzuki couplings using PEG as solvent.

Organocatalytic processes have also been reported using PEG as solvents.[40] Xu and co-workes described the asymmetric Michael addition of ketones (2.30) to nitroalkenes (2.18) carried out in PEG using pyrrolidinyl-thioimidazolium salts (2.29) as catalyst to give products (2.31) in up to 97% yield and 99% enantioselectivity. Moreover, the authors also described the ESI mass spectrometric detection for the first time, providing evidence of the presence of the PEG–organocatalyst host–guest complex (Scheme 2.7).[41]



Scheme 2.7 – PEG as solvents in organocatalytic Michael addition.

2.1.4 GABA and its derivatives

γ-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter of the mammalian central nervous system (CNS). The derangements of GABA-ergic system are responsible for the arising and development of many mental disorders such as epilepsy, Huntington's and Parkinson's diseases, anxiety, and pain. Lamentably, GABA (2.32) itself is inefficient for therapeutic purposes due to its hydrophilic behavior, which prevents its penetration through the blood–brain barrier. Therefore, GABA lipophilic derivatives are frequently used for the treatment of CNS disorders, such as Baclofen (2.35), Rolipram, Pregabalin (2.33), and Phenibut (2.34) and have found wide application. Enantiomers of these chiral medications exhibit quite different levels of activity; thus, efficient methods for their enantioselective preparation are desirable, (Figure 2.5).[42]

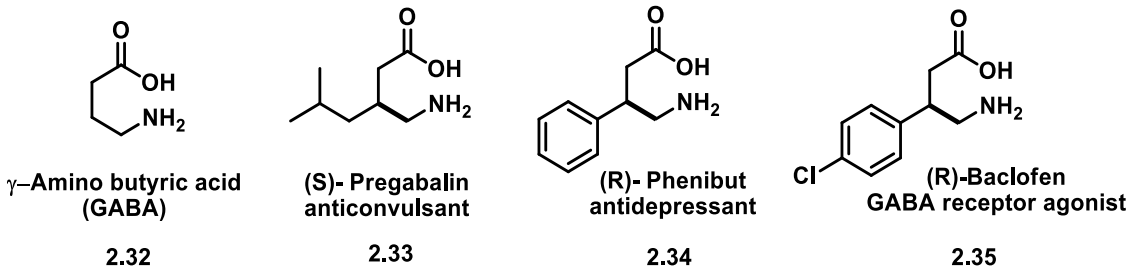


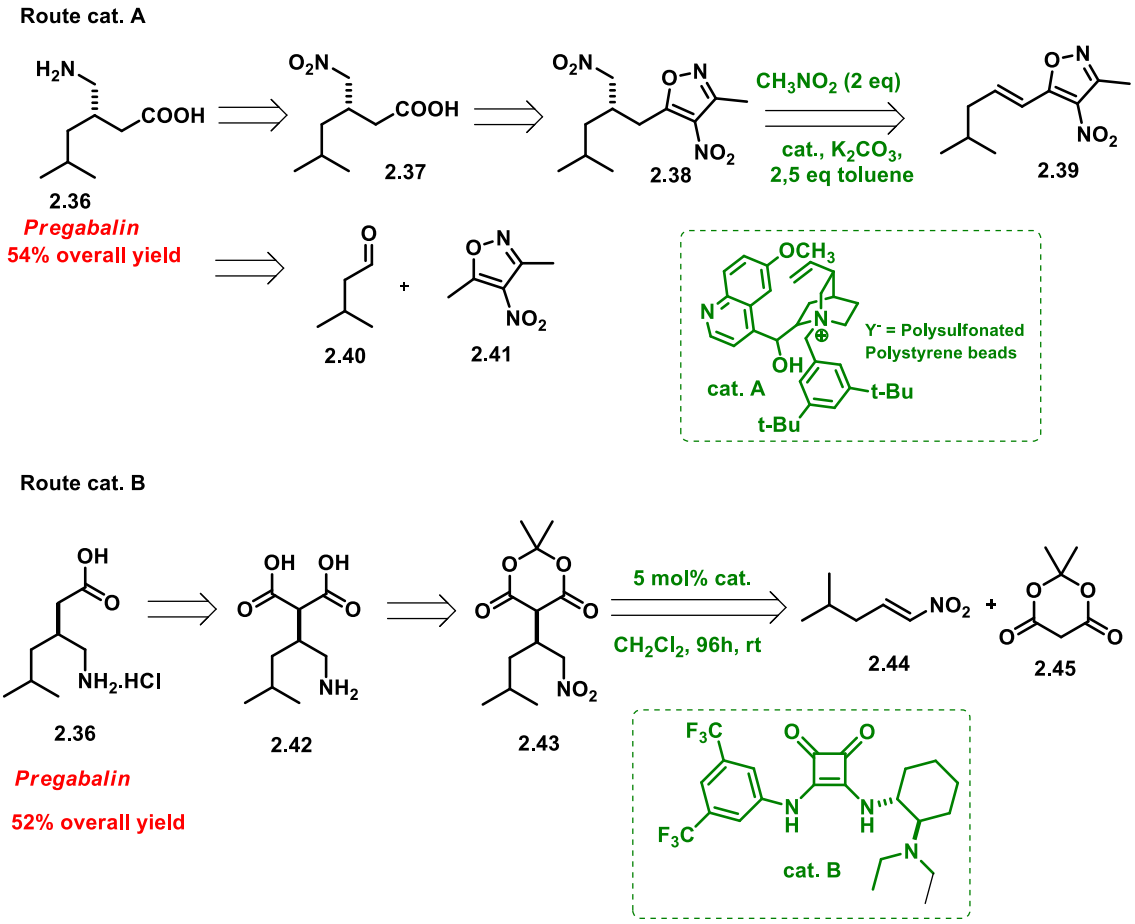
Figure 2.5 - GABA and its derivatives.

(S)-Pregabalin (2.33) is currently produced by the originator (Pfizer), which has developed a new process in which the asymmetric step was generated by an enzymatic approach.[43] However, the majority of known technologies to afford (S)-Pregabalin is based in diastereoisomeric crystallization of Pregabalin racemate, which limits the theoretical yield of the (S)-product at 50%. Recently, Harad and co-workes developed a method to racemise (R)-pregabalin in order to recycle the unwished isomer.[44] In addition, (S)- Pregabalin has been also described by other methodologies, *eg.* bioenzymatic steps, diastereoselective synthesis from natural biomass (D-mannitol), organocatalysis, and flow chemistry.

In 2015, Moccia and co-workes reported a new process for the synthesis of (S)-pregabalin using organocatalysis. The route consists of six steps, being the key step one reaction of (2.39) and nitromethane, under the catalysis of a recyclable polymer bound phase transfer (cat. A), which afforded the intermediate (2.38) with 65% yield, er: 99.95: 0.05. Then, after Sarti-Fantoni reaction (2.37) and final reduction of nitro group afforded the (S)-pregabalin in overall 54% yield. (Scheme 2.8 – top). [45]

In 2011, Šebesta and co-workes developed one useful methodology using chiral squaramide organocatalysts (cat. B) for catalyzing the Michael addition between Meldrum´s acid (2.45) and an aliphatic nitroalkene (2.44). This afforded the product (2.43) whith 83% yield and e.r. 97:3. Then, after reduction of nitro group/opening of Meldrum acid (2.42)

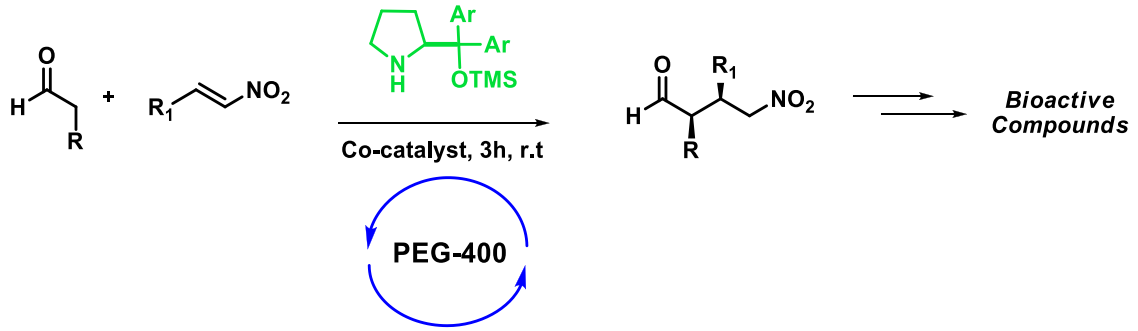
and decarboxylation, gave the pregabalin hydrochloride salt (2.36) in overall 52% yield over three steps, (Scheme 2.8- bellow).[46]



Scheme 2.8 – Selected organocatalytic alternatives to synthesis of (S)-Pregabalin.

2.2 Objetives

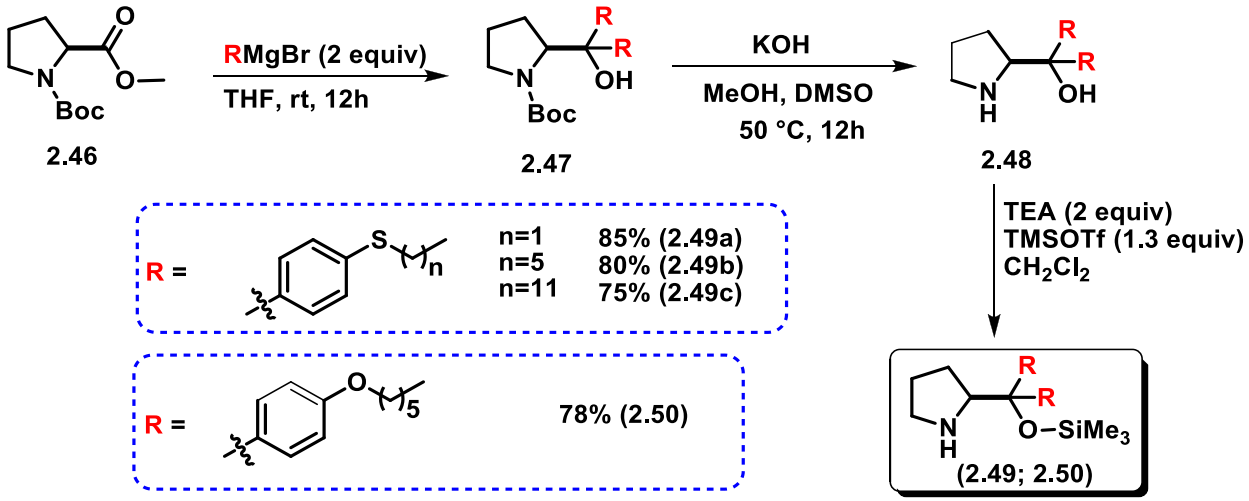
Motivated by the 12 principles of green chemistry, especially in what regards catalysis and safer solvents, beyond the lack of studies using alternative solvents. The aim of this chapter is to study the application of PEG-400 as a recyclable reaction medium in the asymmetric Michael addition of aldehydes to trans-β-nitrostyrenes using the organocatalysts developded by our group. Besides that, another objective is the formal synthesis of some GABA derivatives such as Pregabalin, Bacoflen and Phenibut.



2.3 Results and Discussion

2.3.1 Synthesis of organocatalysts (2.49 and 2.50)

The organocatalysts were synthesized via a procedure described previously by our group, (Scheme 2.9).[47] These catalysts were made available by the Grignard reaction between the ester proline derivative (2.46) with the correspondent magnesium halides to get an amino alcohol (2.47). Then, (2.47) suffered deprotection of BOC group (2.48) followed the hydroxy protection with TMS to afford the desired four organocatalysts (2.49 and 2.50) with overall yield in the range of 75 to 85%.

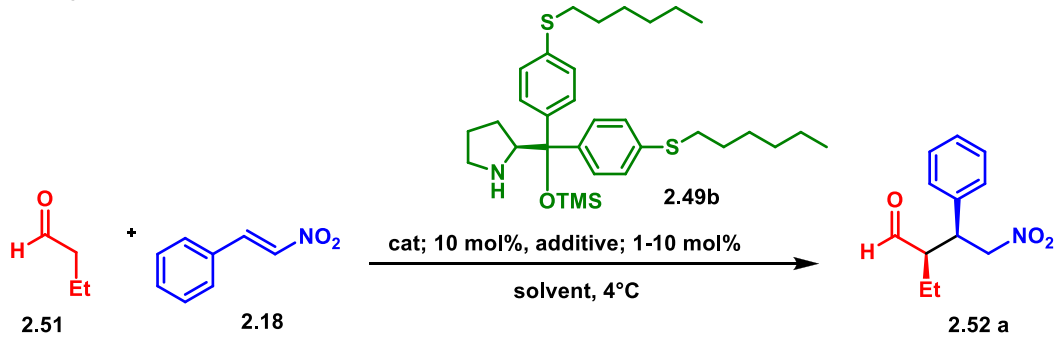


Scheme 2.9 - Synthesis of organocatalyst **48** and **49**.

2.3.2 Evaluation of the catalytic activity of the aminocatalysts in the asymmetric Michael addition

With the organocatalysts in hands, the Michael addition of butyraldehyde (2.51) to trans-β-nitrostyrene (2.18) and the organocatalyst (2.49b) was chosen as the model reaction to study the feasibility of our organocatalytic system in different solvents, (Table 2.2).

Table 2.2 - Optimization studies of Michael addition of butyraldehyde to nitrostyrene.



Entry	Solvent	Additive	Time (h)	Yield (%)[b]	*dr* [c]	*ee* (%)[d]
1	EtOH	Benzoic acid	48	68	64:36	94
2	H_2O	Benzoic acid	48	46	60:40	94
3	Glycerol	Benzoic acid	48	57	60:40	95
4	Toluene	Benzoic acid	48	92	67:33	97
5	Diethylene Glycol	Benzoic acid	2	96	88:12	97
6	**PEG-400**	**Benzoic acid**	**2**	**99**	**80:20**	**97**
7[e]	PEG-400	Benzoic acid	1	92	65:35	95
8	PEG-400	4-Nitrophenol	5	93	84:16	95
9	PEG-400	*L*-Tartaric acid	3	85	78:22	96
10	PEG-400	*L*- Malic acid	2	92	84:16	96
11	PEG-400	CSA	24	-	-	-
12[f]	PEG-400	CSA	3	89	77:23	94
13	PEG-400	4-Nitrobenzoic acid	2	98	77:23	96
14	PEG-400	------	11	84	90:10	96

[a] Unless otherwise specified, all reactions were performed using *trans-β*-nitrostyrene (0.3 mmol), butylraldehyde (0.6 mmol), additive (10 mol %) and organocatalyst (10 mol %) in environmentally begin solvent (0.15 mL) at 4ºC. **[b]** Isolated yield. **[c]**Determined by ^{1}H NMR. **[d]** Determined by chiral-phase HPLC analysis for *syn*- product. [e] The reaction was carried out at rt. [f] 1 mol% of additive was used.

As showed in Table 2.2, when the reactions were carried out in EtOH, water or glycerol, the desired products were obtained with moderate chemical yields and diastereoseletivities, but with high enantioselectivities (Table 2.2, entries 1, 2 and 3).

When toluene is used, an increment on the chemical yield was observed, with no variation in the diastereo- and enantioselectivity (Table 2.2, entry 4). Moreover, diethylene glycol provided the product after only 2h, with higher yield and stereoselectivities than those evaluated before.

These results have prompted us to evaluate a greener, non-volatile and recoverable solvent such as PEG-400 (Table 2.2, entry 6). To our delight, the desired product (2.52a) was smoothly obtained within 2 h in quantitative yield and excellent enantioselectivity (Table 2.2, entry 6 *vs* 5). Thus, we further optimized the protocol, varing others parameters.

Moreover, a set of co-catalysts was also evaluated. In doing so, when the reactions were performed in the presence of 10 mol% of 4-nitrophenol, L-tartaric acid or L-maleic acid (Table 2.2, entries 8 - 10), a slight decrease on the reaction yield and on the stereoselectivities were noted. Changing the additive for 10 mol% camphorsulfonic acid (CSA) led to a complete degradation of the product (Table 2.2, entry 11). On the other hand, decreasing the loading of CSA to 1 mol %, the formation of the Michael adduct is achieved in lower yield (89%), maintaining good stereoselectivities (Table 2.2, entry 12). Compared to benzoic acid, the accomplishment of the reaction with 4-nitrobenzoic acid did not affect significantly the yield and stereoselectivities, (Table 2.2, entry 13) thus indicating that among all tested additives, benzoic acid provides optimal yield, ee and dr. As expected, in absence of co-catalyst, the reaction yield has dropped to 84%, maintaining good selectivity (Table 2.2, entry 14).

In this sense, after optimized both solvent and additive, we turned our attention to study of the load of organocatalyst and additive in the reaction (Chart 2.1).

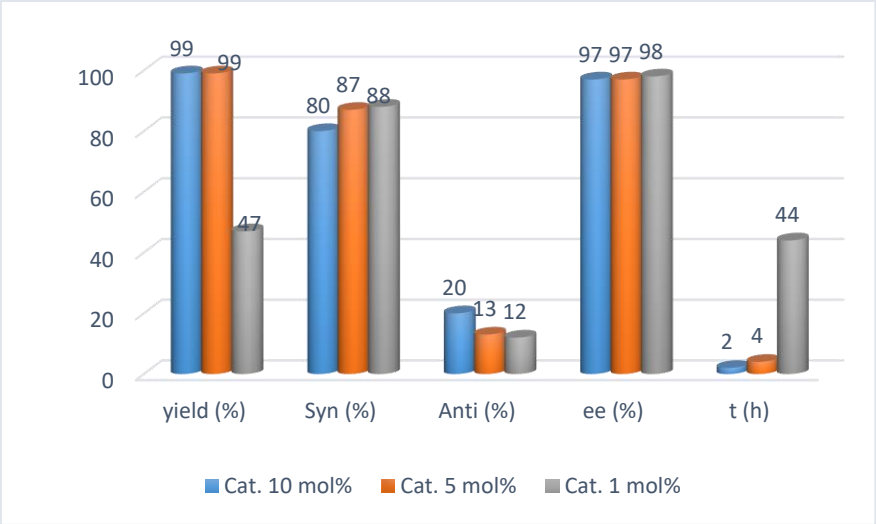
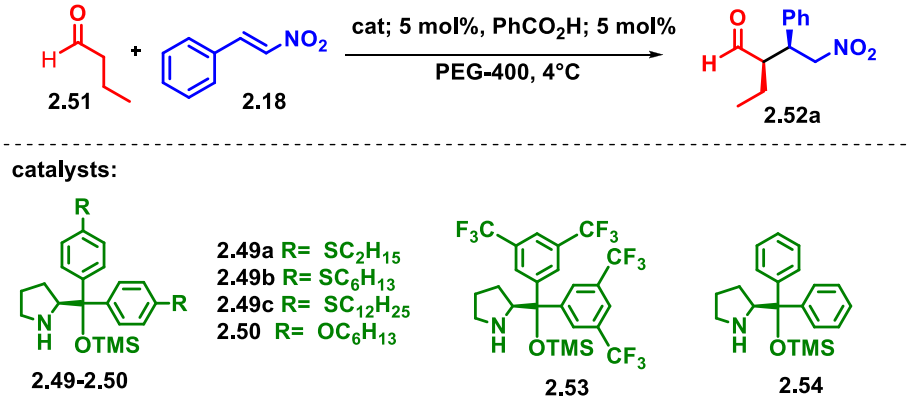


Chart 2.1 - Optimization of catalyst loading.

When the amount of organocatalyst and additive was lowered to 5 mol%, the product was obtained in quantitative yield with excellent enantioselectivity and a better diastereoisomeric ratio, but in a longer reaction time. Unfortunately, decreasing the catalytic loading from 5 to 1 mol% produced significantly losses of yield (47%), albeit without substantial changes in the dr and ee (Chart 2.1).

The next step was the investigation of the architecture of diarylprolinol silyl ether based organocatalysts, in order to increase the reactivity and selectivity of the catalytic system (Table 2.3).

Table 2.3 - Optimization of the reaction conditions: Catalyst Screening[a]



Entry	Cat.	[mol L^{-1}]	Time (h)	Yield [b] (%)	*ee* [c] (%)	dr[d]
1	2.49b	2	4	99	97	87:13
2	2.49a	2	19	99	97	90:10
3	2.49c	2	19	52	98	91:09
4	2.50	2	4	98	95	86:14
5	2.53	2	19	16	97	93:07
6	2.54	2	19	62	97	72:28
7	2.49b	-	2	67	97	91:09
8	2.49b	0.6	19	99	97	92:08
9	2.49b	0.3	19	73	96	89:11

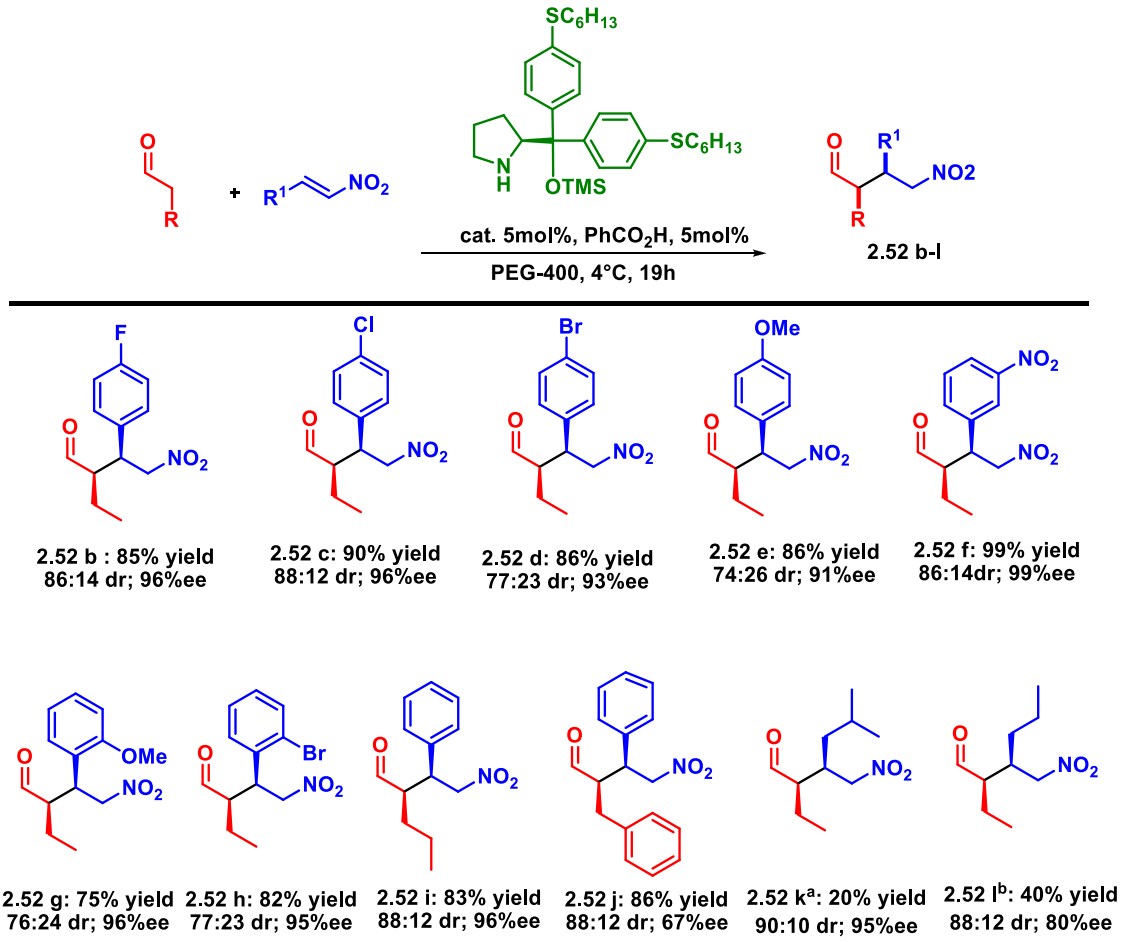
[a] Unless otherwise specified, all reactions were performed using trans-*β*-nitrostyrene (0.3 mmol), butylraldehyde (0.6 mmol), benzoic acid (0.015 mmol-5 mol %) and organocatalyst (0.015 mmol – 5 mol %) in PEG 400 (0.15 mL- 2 mol.L^{-1}). [b] Isolated yield. [c]The ee values were determined by chiral HPLC. [d]The dr values were determined by chiral HPLC and NMR of the crude mixture.

All evaluated organocatalysts were able to perform the Michael addition under environmentally benign reaction media, although the reaction outcome varied as a function of the alkyl side-chain length. In this way, when the length of the hydrophobic alkyl chain was an ethyl group (2.49a), the desired Michael adduct was obtained with slightly decreased yield along with a longer reaction time (Table 2.3, entry 1). Increasing the alkyl chain to dodecyl (2.49c) led to a great drop in the chemical efficiency of product formation. However, the degree of stereocontrol remained high (Table 2.3, entry

3). Similar yield, ee and dr were obtained using an oxygen-based analogue of the organocatalyst (2.50) within 4 h (Table 2.3, entries 1 *vs* 4). The commercial available catalyst (2.53) and (2.54) were also studied under our reaction conditions. Notwithstanding catalysts (2.53) and (2.54) proved to be less effective even when the reaction time was extended, reaching the desired Michael adduct in only 16% and 62% yields, respectively (Table 2.3, entry 5 and 6).

In order to conclude the optimization studies using this catalytic system, the reaction was carried out in different concentrations. In solvent-free conditions, the product was obtained in a lower yield with high diastereomeric ratio (Table 2.3, entry 7). Furthermore, diluting the reaction media to 0.6 M (Table 2.3, entry 8), despite of the longer time (19h), the reaction performed with excellent selectivities (92:8 dr and 97% ee) and these results indicate that no further improvements in yield or selectivity were observed for lower concentrations.

In that way, with the optimized reaction conditions in hands (Table 2.3, entry 8), we explored the scope of the Michael addition (Scheme 2.10).



* Unless otherwise specified, all reactions were performed using nitroolefins (0.3 mmol), aldehydes (0.6 mmol),benzoic acid (0.015 mmol- 5 mol%) and the organocatalyst (0.015 mmol- 5mol%) in PEG-400 (0.5 mL-0.6 mol.L-1) [a] the reaction time was 70h, [b] the reaction time was 64h.

Scheme 2.10 - Reactions of differentes aldehydes and nitroolefins in the organocatalytic Michael reaction.

Firstly, a variety of nitroolefins was evaluated to establish the generality of the asymmetric catalytic system.

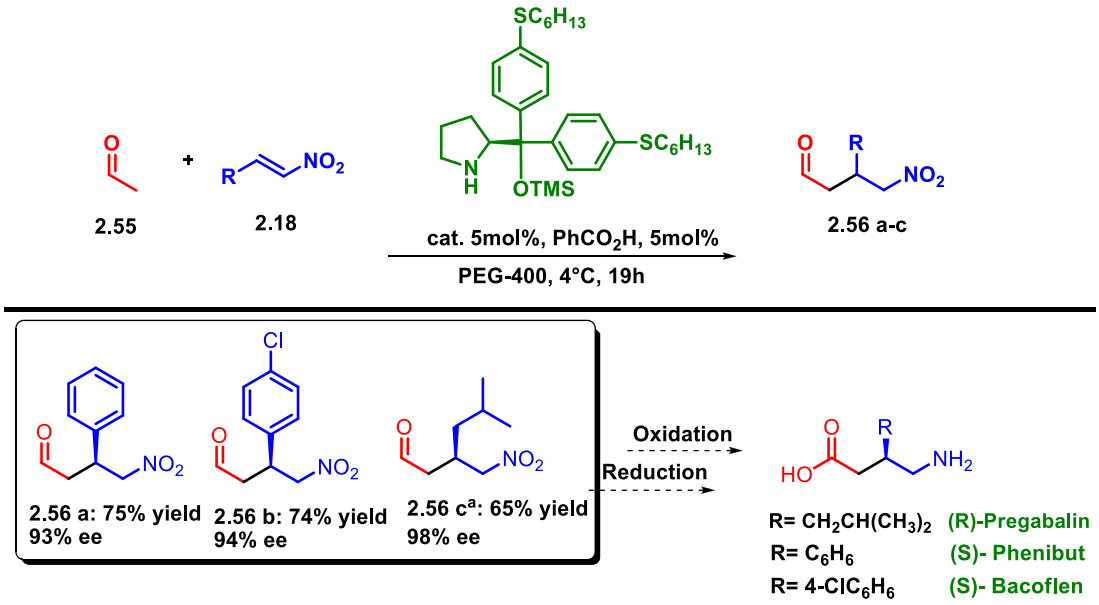
As depicted in Scheme 2.10, nitrostyrenes bearing *β*-aryl substituents with either electron-donating (e.g. methoxy) or electron-withdrawing groups (e.g. chloro, bromo, fluoro, and nitro) are almost equally tolerated, thus giving the desired Michael adducts in excellent chemical yield with good diastereomeric ratios and ee values within the range of 91-99% (2.52 b-h).

Even *β*-alkyl-substituted nitroolefins participated in this catalytic system to give the desired adduct with good dr as well as ee, albeit in modest chemical yield, (2.52k) and (2.52l). When valeraldehyde was used as donor, the reaction proceeded very efficiently, affording the corresponding product (2.52i) in 83%, with high levels of stereoselectivities. A sterically hindered aldehyde provoked a decrease on the enantioselectivity, keeping good yield and dr (2.52j). Furthermore, aliphatic nitroolefins reacted in a Michel fashion with excellent enantioselectivities, however the chemical yield of the product was low when compared to the other substrates (products 2.52k and 2.52l).

The Michael addition involving acetaldehyde has emerged as a versatile yet challenging transformation in asymmetric catalysis.[48] However, examples including it as donor are scarcely described, which might be explained by the fact that acetaldehyde is very reactive and volatile. For these reasons, it needs to be carefully manipulated, and its reactions normally involve the use of inert atmosphere and high catalyst loadings to deliver the desired product with acceptable yields.

The nitroaldehyde products are versatile synthetic intermediates that can be easily transformed into γ-aminobutyric acid derivatives (GABAs), which are very important inhibitors of the neurotransmission in the brain.

Gratifyingly, when the optimized reaction conditions with minor modifications were applied to acetaldehyde with β-nitrostryrene, *p*-chloro-nitrostyrene and β-alkyl-substituted nitroolefins, these reactions proceeded smoothly, leading to the desired products in 60-75% yields, with excellent enantiomeric excesses (2.56 a-c) (Scheme 2.11).



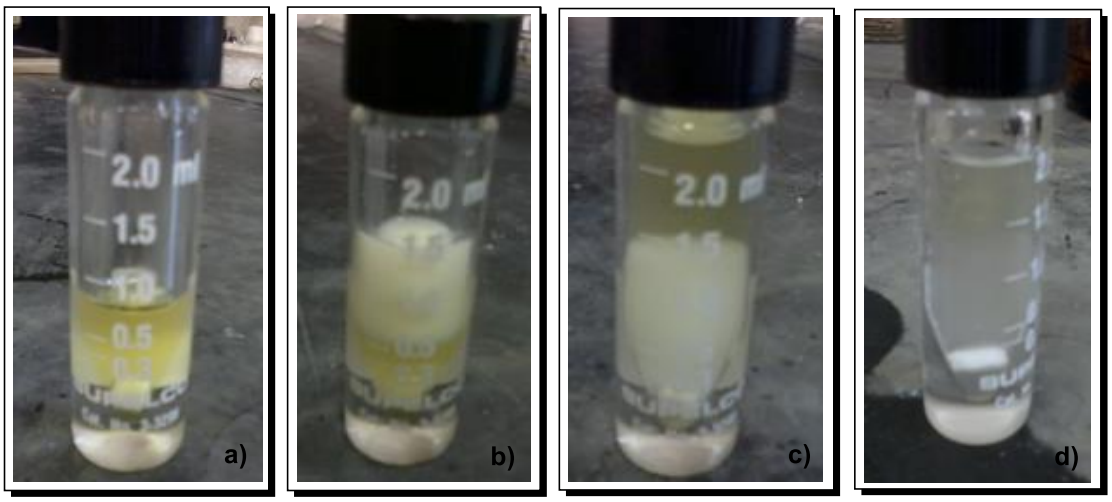
* Unless otherwise specified, all reactions were performed using nitroolefins (0.3 mmol), acetaldehyde (3 mmol), benzoic acid (0.015 mmol- 5 mol%) and the organocatalyst (0.015 mmol- 5mol%) in PEG-400 (0.5 mL-0.6 mol.L-1). [a] the reaction time was 53h.

Scheme 2.11 - Formal synthesis of GABA derivatives.

Those excellent results can be explained by the use of PEG-400 (green and recoverable solvent), which might play an important role in the retention of the acetaldehyde in solution.

2.3.3 Recyclability of ionic liquids

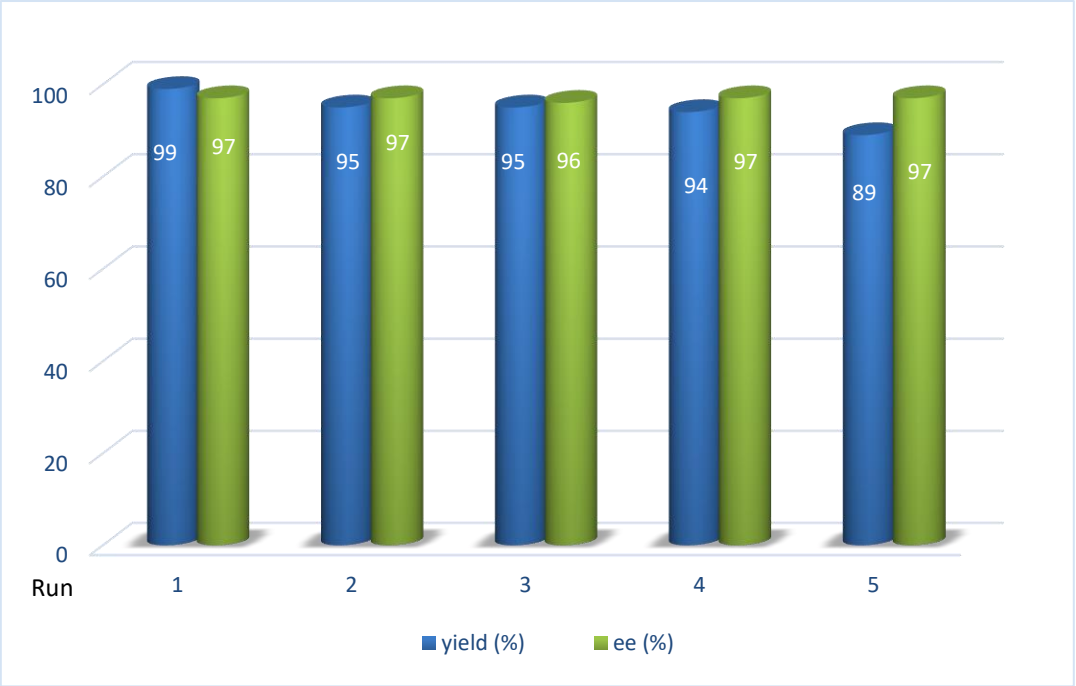
The recyclability of the solvent in the catalytic system was also studied for the reaction of trans-*β*-nitrostyrene and n-butyraldehyde, (Figure 2.6).



a) Reaction mixture at the end time, b) 0.25 mL of water was added – emulsion appears, c) extraction with ether, d) the emulsion disappears – with total recovery of PEG.

Figure 2.6 - PEG recovering.

In order to accomplish that, a set of experiments was performed to explore whether PEG could be reused for further reactions (Chart 2.2). So, after completion of the reaction, PEG was recovered and subjected to another run, affording the product in almost same yield, dr and ee. Four additions runs were performed affording the product in excellent yields, dr and ee.



* Unless otherwise specified, all reactions were performed using nitrostyrene (0.3 mmol), butiraldehyde (0.6 mmol), benzoic acid (0.015 mmol- 5 mol%) and the organocatalyst (0.015 mmol- 5mol%) in PEG-400 (0.5 mL-0.6 mol.L-1).

Chart 2.2 - Recyclability of PEG for the conjugate addition

2.4 Conclusion and outlook

In conclusion, a simple experimental procedure was presented for Michael addition of linear aldehydes to nitroolefins combined with the ease of recovery and reuse of the reaction medium, PEG-400. Furthermore, intermediates of the GABA derivatives were also synthesized in good yields and enantioselectivity.

In the future, it would be interesting to develop a procedure in which the catalyst is immobilized in a PEG resin, what would allow the recyclability, not only of the solvent, but also of the catalyst in this reaction.

Chapter 3

3 Chapter 3

The present chapter is the result of a research stay in the group of Prof. Karl Anker Jørgensen. In a collaboration between Aarhus University- Denmark and the Federal University of São Carlos through the Ph.D program abroad (PSDE-CAPES).

Herein will be discussed an novel organocatalytic asymmetric cascade process, *via* 1,6- Friedel-Crafts/ 1,4- Oxa-Michael reaction sequence of hyroxyarenes to 2,4-Dienals for the synthesis of chiral chromans. Thus, this chapter is organized in a short introduction about one-pot strategies, remote organocatalytic functionalization and chromans, followed by the chapter objectives, results and discussion and final remarks. Introduction

3.1.1 Organocatalytic One-Pot reactions

The one-pot synthesis is defined as multiple chemical transformations, which are carried out sequentially in single reaction vessel without intermediary purification. This approach is an alternative to classical "stop-and-go" synthesis.[49] This concept observes two crucial issues in currently organic chemistry: efficiency and environmentally friendly processes. Thus, turning the process environmental friendly because it decreases the chemical waste, saves time, and simplifies practical aspects (Figure 3.1).[50]

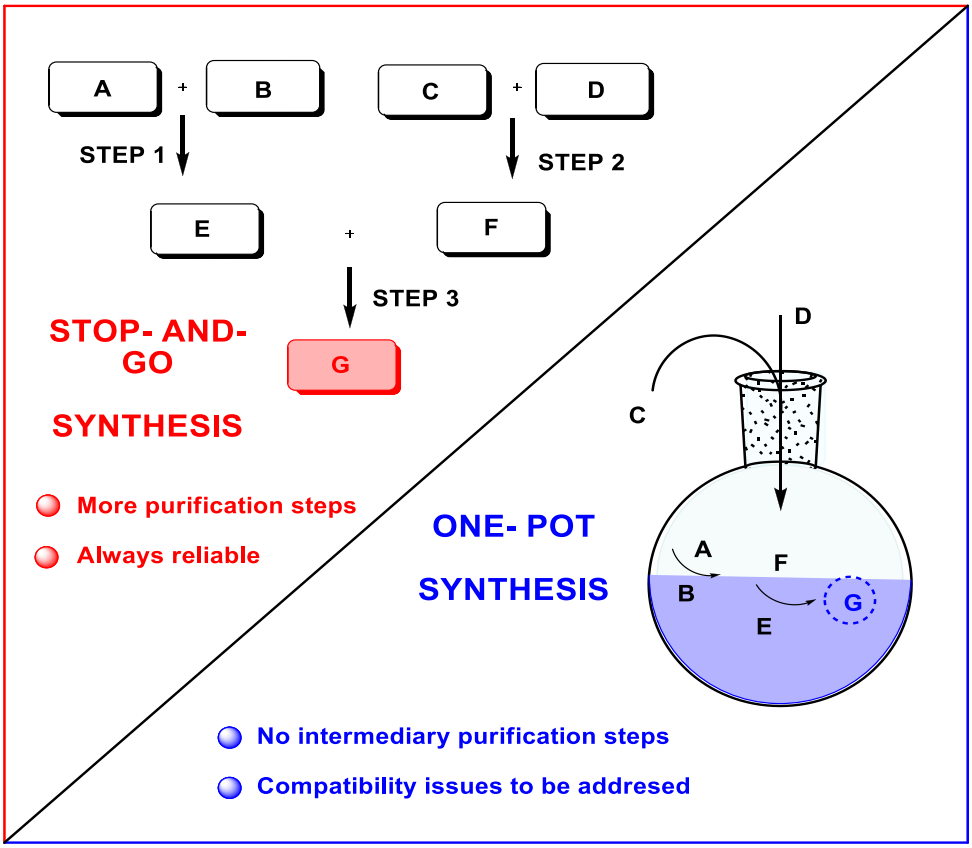


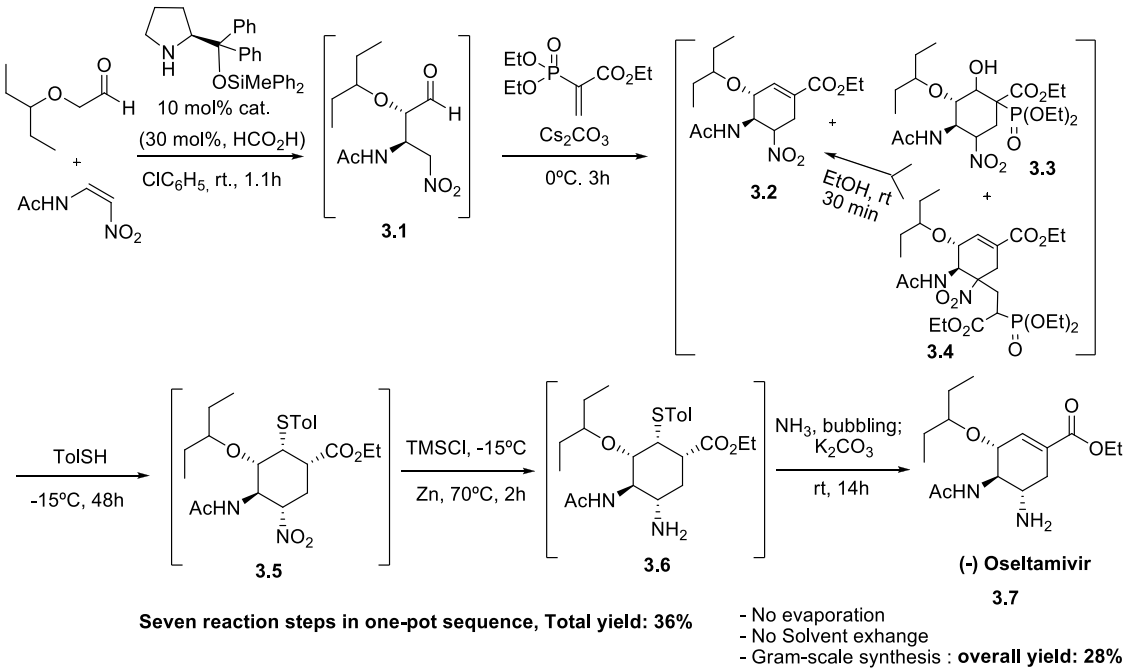
Figure 3.1 - “Stop-and-go” *versus* “one-pot synthesis”.

In the literature, it is possible to find several terminologies for reactions carried out within the one-pot concept, which include: “domino reaction”, “cascade reaction”, and “tandem reaction”. However, researchers differ in the definitions of each of them. For example, among other scientists, K.C.Nicolaou described that these descriptions are relatively interchangeable,[51] but Tietze point out the usage of “domino reaction” instead of “cascade reaction” or “tandem reaction”, and explains that a domino reaction is a process involving two or more bond-forming transformations (commonly C–C bonds), that occurs under the same reaction conditions without adding additional reagents or catalysts, being that subsequent reactions are consequence of the functionality formed in the previous step. [52]

Although all these differences regarding the nomenclatures of one-pot reactions- this, has a much broad meaning than a cascade, domino or tandem reaction. The concept of a one-pot synthesis includes all such reaction types as well as the multi-step strategies and work-up procedures or quenching events that are adopted in a single vessel.[50]

In addition, the well-known characteristics of Organocatalysis as among others the robustness and easy to handle. Besides its wide variety with differents activation models, permits their use as one efficient synthetic tool in one-pot approach.[53]

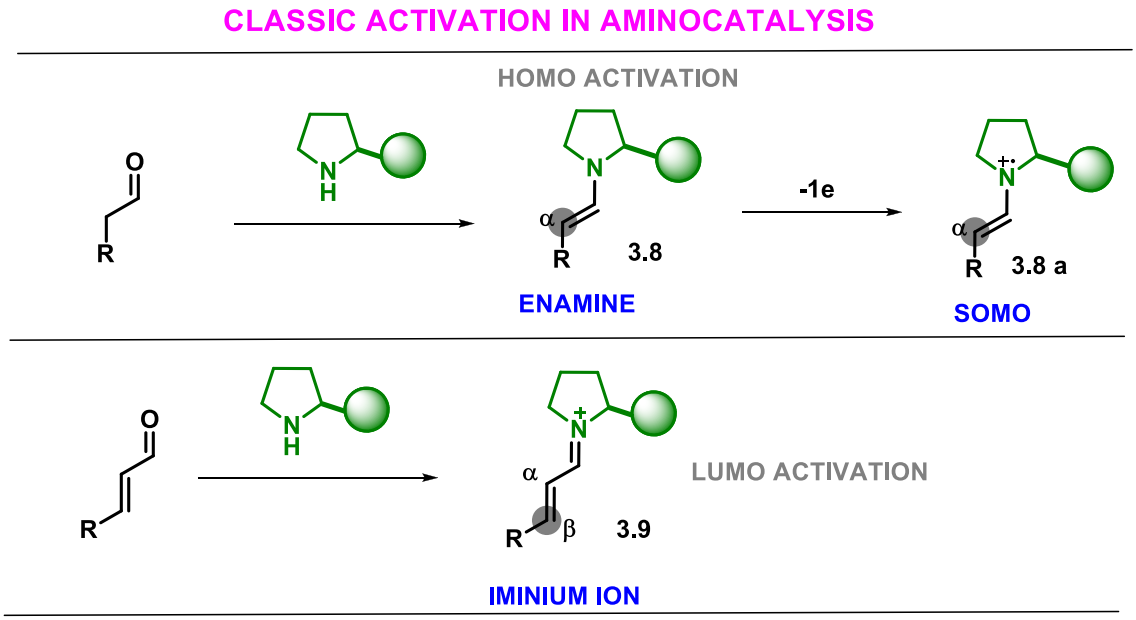
One important example of organocatalytic domino processes was developed by Hayashi and co-workers, in this exciting report the authors described the one-pot sequential synthesis of (-)-Oseltamivir (3.7), which is one of the most effective anti-influenza drugs. The synthesis was made without evaporation or solvent exchange during the entire protocol in 36% yield over seven reactions in 40mg scale, and 28% overall yield in the 1.5g scale, (Scheme 3.1).[54]



Scheme 3.1 - One-pot total synthesis of (-) Oseltamivir.

3.1.2 Remote functionalization

Asymmetric aminocatalysis has been extensively used as reliable synthetic platform for generating stereogenic centers at the α and β positions of carbonyl compounds with very high efficiency. By enamine, previous discussed in chapter 2, (3.8) or SOMO (3.8a) in α-position and iminium ion (3.9) in β-position, (Scheme 3.2). However, chemists have expanding their frontiers targeting stereocentes in remote positions of conjugated carbonyl compounds, (Scheme 3.3).[55, 56]

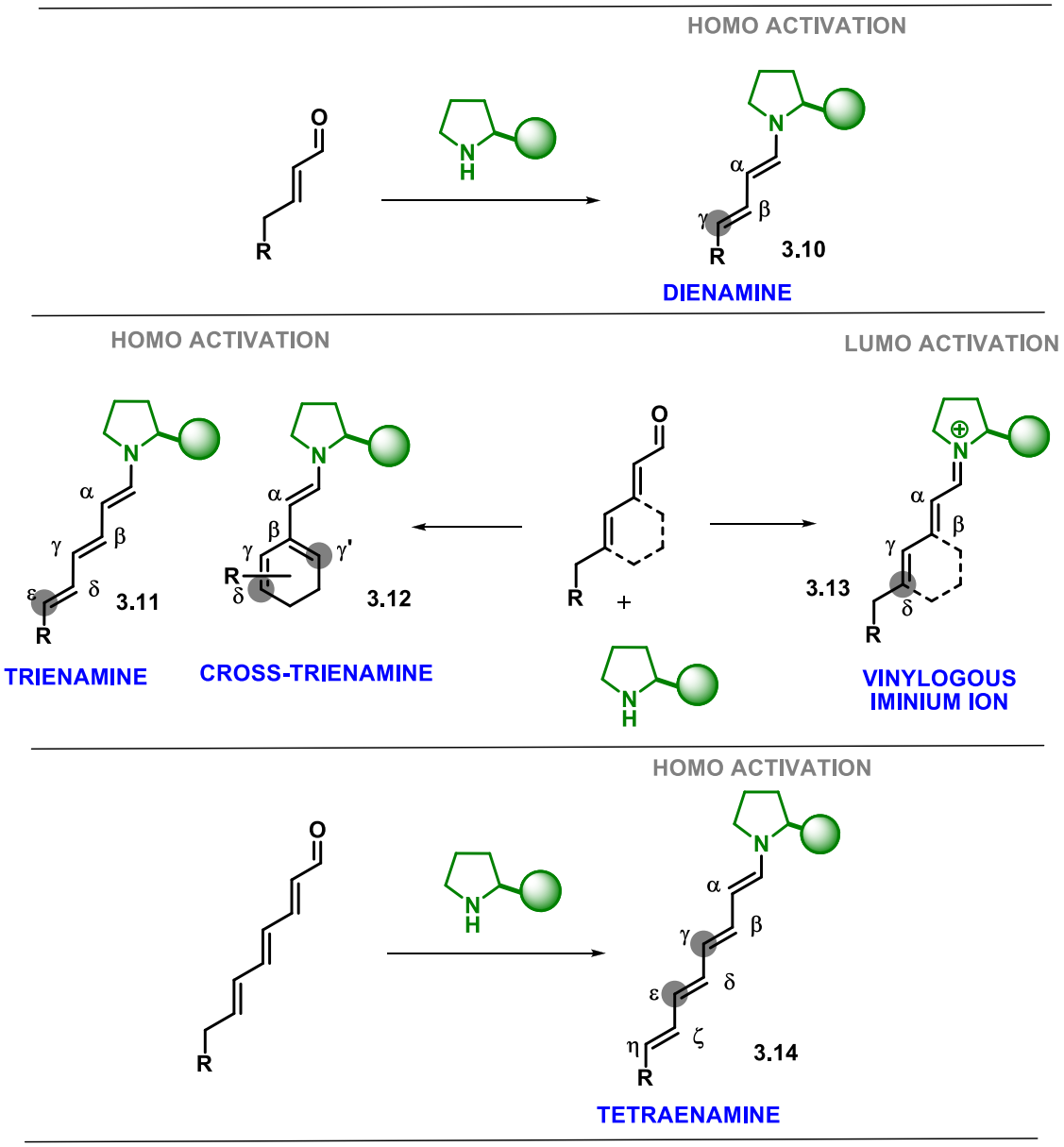


Scheme 3.2 Classic activation in aminocatalysis.

This expansion of the borders to remote positions of carbonyl compounds is a great challenge, due to the distance of the chirality relay and the rigidity of the molecule. Thus, the effective transmission of stereochemical information in good stereocontrol will clearly become more challenging.[58]

Therefore, the application of aminocatalysis for the activation of unsaturated carbonyl compounds have been suffering tremendous

development in their methodologies, with formation of new stereogenic centers located at five (for γ-functionalizations) to seven (for ε-functionalizations) bonds away from the stereo differentiating element of the aminocatalyst. These were possible by a unique property of π-systems where the electron density and reactivity is extended along conjugated bonds, which was proposed 81 years ago by Fuson as Vinylogy. [57] Based in this interesting behavior of vinylogous reactivity, it has been demonstrated in different systems such: dienamine (3.10), trienamine (3.11), cross-trienamine (3.12) vinylogous iminium ion (3.13), and more recently tetra enamine (3.14) activation as modern strategies for the asymmetric functionalization of carbonyl compounds, (Scheme 3.3).[26]



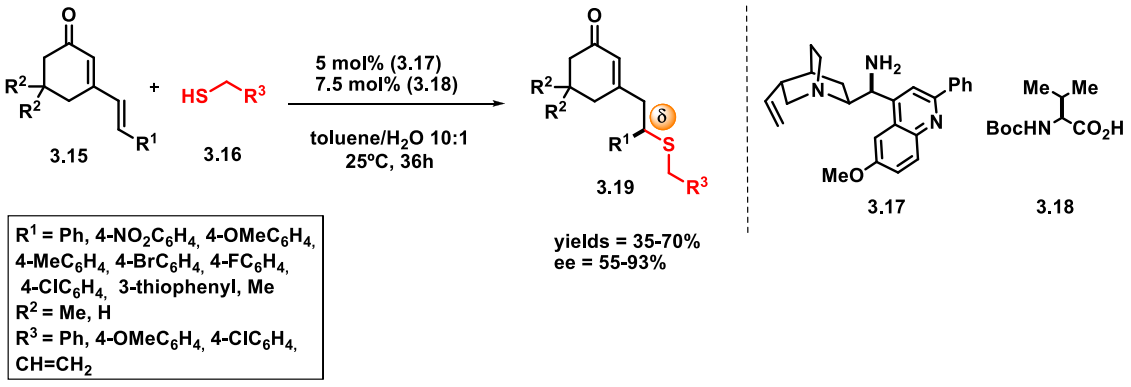
Scheme 3.3 - Classification of aminocatalysis based on the reactive intermediates.

3.1.2.1 Vinylogous iminium activation

The inherent challenge of one transmission of the LUMO-lowering effect within the extended π-system of unsaturated carbonyls is among others find a aminocatalyst that could ensure configurational control

and π-facial discrimination of the covalent extended iminium ion intermediate, in order to enforce high levels of enantioselectivity.[57] In addition, the regiochemistry issues is one tremendous challenge such as the favoring of 1.6 - addition instead of 1.4- or 1.2 –adducts.[58]

The pioneer study using vinylogous iminium ion strategy was described by Melchiorre and co-workers in 2012, where the highly δ-selective addition of sulphur nucleophiles (3.16) to cyclic enones (3.15) leads the mercaptoenones (3.19). The catalytic system used was a combination of a modified cinchona alkaloid (3.17) and Boc-protected valine (3.18) allowing the reaction to proceed with high enantioselectivities, up to 93% ee and good yields up to 70%, (Scheme 3.4).[59] In this case of 1,6-addition of thiols to the cyclic dienones, the steric hindrance of the β-substituent in (3.15) provided a fundamental control for securing δ-site selectivity by suppressing the competitive 1,4-addition.

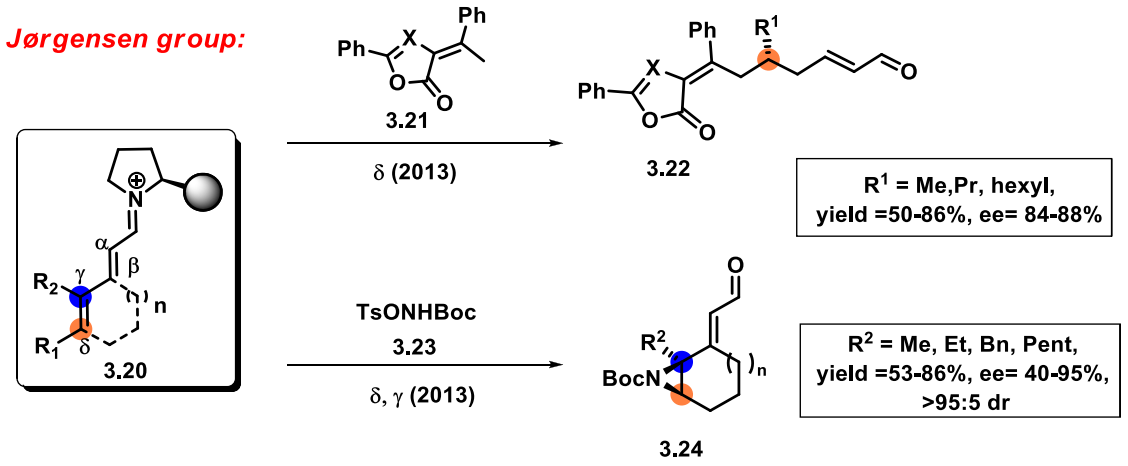


Scheme 3.4 - Enantioselective 1,6-addition of thiols to dienones through vinylogous iminium ion activation.

In 2013, Jørgensen group reported the vinylogous iminium ion without the β-position blocked by one bulky group, containing three electrophilic sites. This, substrate underwent the addition of olefinic azlactones (3.21) with complete regioselectivity surprisingly in the δ-

position of iminium ion, leading functionalized products (3.22) with 50-86% yield and 84–88% ee, (Scheme 3.5, top).[60]

Soon after, the same group reported a second application of vinylogous iminium ion intermediates. In this case, remote aziridination of cyclic 2,4-dienals was developed, the reaction of dienals (3.20) with a protected hydroxylamine containing a leaving group on the nitrogen atom (3.23), led to the products (3.24) with 53–86% yield and 40–95% ee. (Scheme 3.5, below). [61]

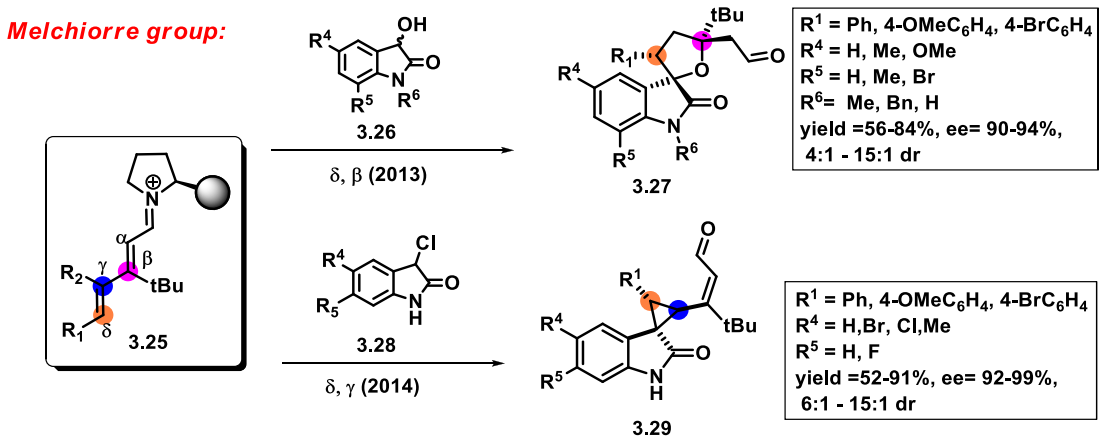


Scheme 3.5 - Selected examples of vinylogous iminum catalysis described by Jørgensen group.

The Melchiorre group also explored the vinylogous iminium activation using aldehydes (3.25). They applied a nucleophile with both a nucleophilic carbon atom and a nucleophilic oxygen atom (3.26), which added at 1,4-position followed the initial 1,6- addition in cascade mode. Thus, δ, β-functionalization of the aldehyde was achieved, obtaining the products (3.27) in 56–84% yield and 90–94% ee, (Scheme 3.6, top).[62]

In addition, a recently collaboration between our research group and Melchiorre group, resulted also in example of vinylogous cascade strategy. The treating of chlorooxindole (3.28) with dienal (3.25) led the

construction of spirooxindolic cyclopropane derivatives (3.29), with 52-91% yield and 92-99% ee (Scheme 3.6, below).[63]



Scheme 3.6 - Selected examples of vinylogous iminum catalysis described by Melchiore group.

3.1.3 Chromans

3.1.3.1 Biologic Activity

Chromans are an important class of heterocycles often found in nature, which most of them exhibit useful biological activity.[64]

Here, we chose a selection of examples contained the chroman core, (Figure 3.2), such as, Centchroman (3.30), which is one of the selective estrogen receptors, mostly used in oral contraceptive pills. It is further an effective drug for dysfunctional uterine bleeding and breast cancer. Bitucarpin A (3.31) shows potent antibacterial and anticlastogenic activity. Carpanone (3.32) complex natural product and its analogues have shown promising activity as antihypertensive, antimalarial, antibacterial and hepatoprotective properties. Epiconicol (3.33) displays cytotoxic activities versus P388, A549, HT29, and CV1 cells, Catechin (3.34) it is an agent antitumor and NCS 381582 (3.35) a synthetic compound, podophyllotoxin

analogue, used as antimitotic agent. Also, a synthetic compound worn as Dopamine D_2 partial agonist (3.36). Lastly, Cromakalim (3.37), which is a potassium channel opening (vasodilator) and used in the treatment of hypertension.[66]

Thus, due the importance of polysubstituted chiral chromans, the development of new asymmetric strategies for their synthesis has become an active field of study.[65]

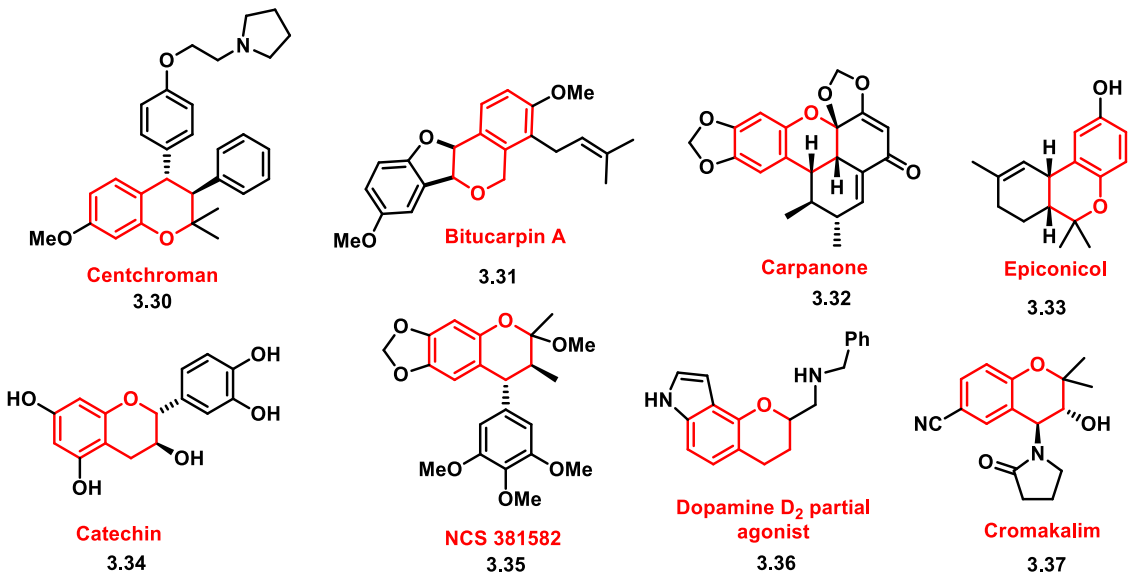
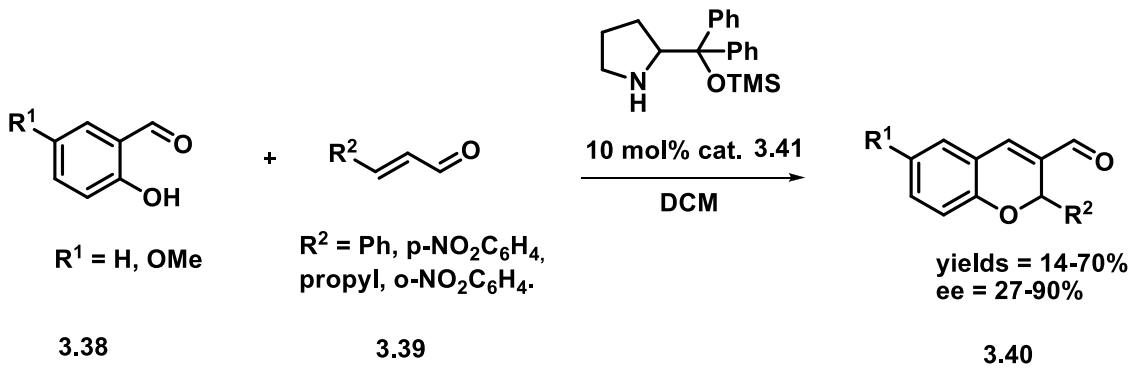


Figure 3.2 - Structures containing a chiral chroman.

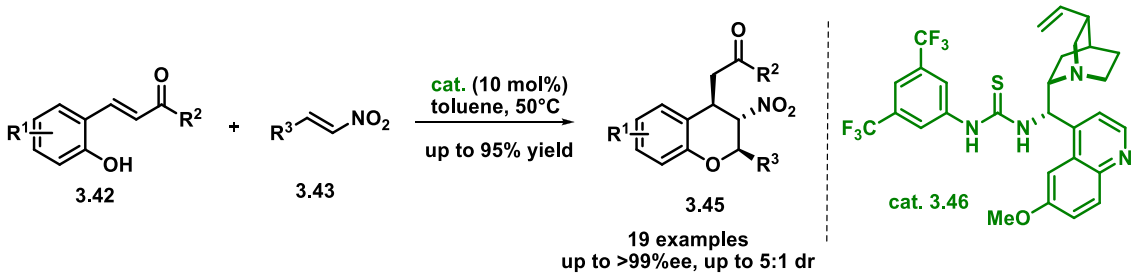
3.1.3.2 Synthesis of chroman core

Arvidsson and co-workers in 2006, using salicylaldehyde (3.38), cinnamaldehyde (3.39) and diaylprolinol as catalyst (3.41) published the first organocatalytic enantioselective synthesis of a chromene framework whith moderates yields and good ee (Scheme 3.7).[66] After this seminal work, great attention and efforts has been made for several scientific groups to the synthesis of chiral chroman derivatives, particularly via an organocatalytic domino approach.



Scheme 3.7 -Organocatalytic synthesis of chiral benzopyrans

Singh and co-workers reported in 2015 an enantioselective synthesis of chiral chroman derivatives (3.45) whith (3.42) and (3.43) via an oxa-Michael-Michael cascade reaction employing a bifunctional thiourea organocatalyst (3.46), leading the products (3.45) with great enantioselectivity (up to >99%), yields and diastereoselectivities (Sheme 3.8).[67]

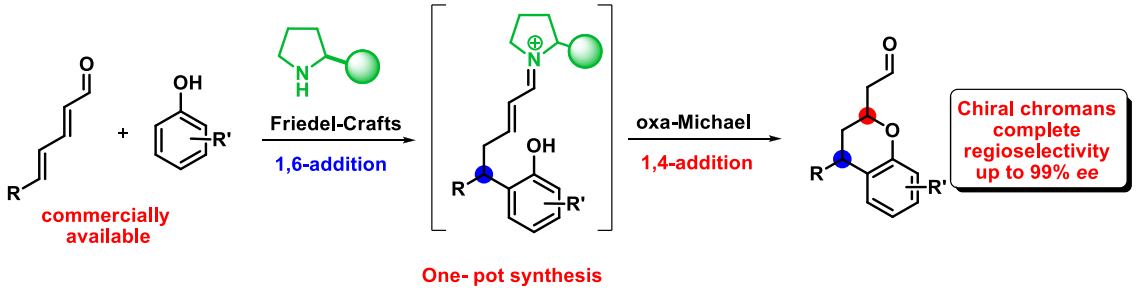


Scheme 3.8 -Enantioselective organocatalytic synthesis of chroman core.

3.2 Objetives

Motivated by well know properties of chiral chroman derivatives and the open-field of remote activation via aminocatalysis, we envisioned to investigate the feasibility of a novel organocatalytic asymmetric cascade reaction between hydroxyarenes and 2,4-dienals through vinylogous iminium-ion remote activation.

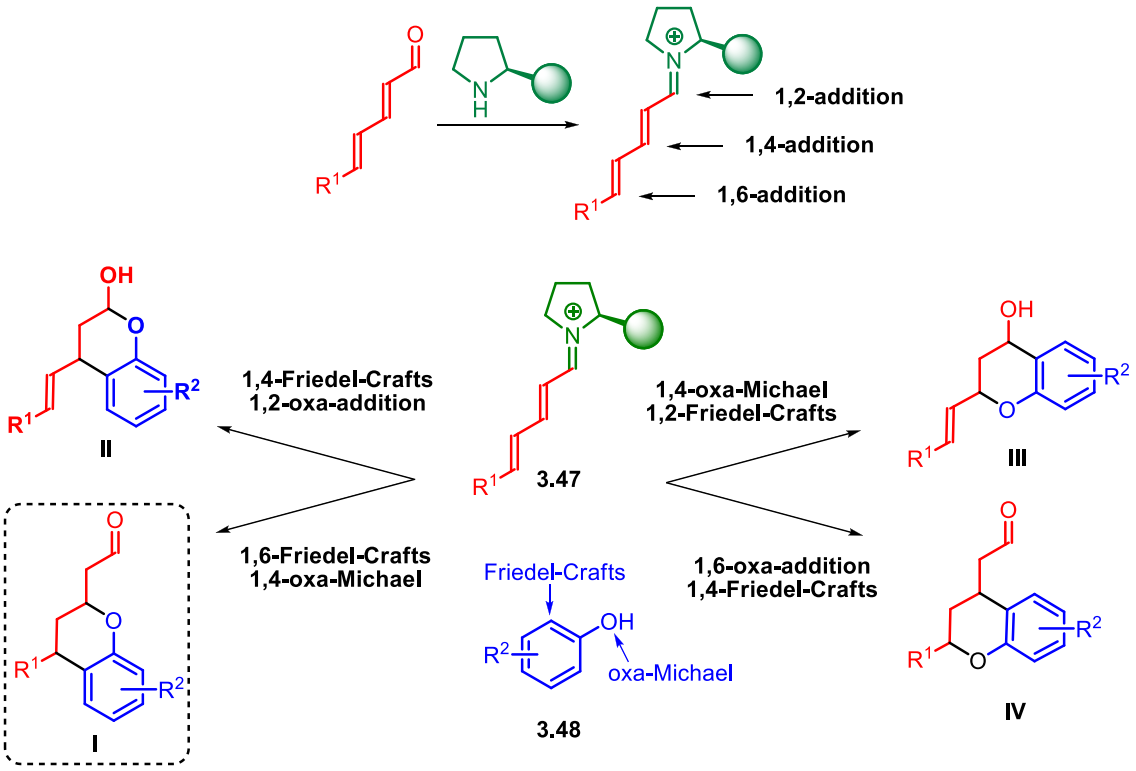
The main aim of this chapter is to develop a one-pot cascade 1,6-Friedel-Crafts/ 1,4-Oxa-Michael reaction pathway for the synthesis of chiral chromans. Moreover, the manipulation of such scaffold into more complex molecules is also our goal.



3.3 Results and Discussion

3.3.1 Theoretical aspects - *Regioselectivity issue*

Before starting the presentation of the chapter results, it is important to point out some theoretical aspects of this reaction system. First, we should mention the challenge of regioselectivity. Because, both substrates of choice, hydroxyarenes (3.47) and vinylogous iminium ion (3.48) have multiple reactive sites. The four possibilities of reaction paths and the corresponding products are show in the Scheme 3.9.



Scheme 3.9- Four Different Regioselective Approaches of Hydroxyarenes to the Vinylogous Iminium-Ion.

In addition, the stereoselectivity control is another important challenge that must be taken in to consideration, as the initial new stereocenter is formed at the 6-position of the aldehyde, which means a

distance of six bonds from the chiral center to the binding point where the organocatalyst is.

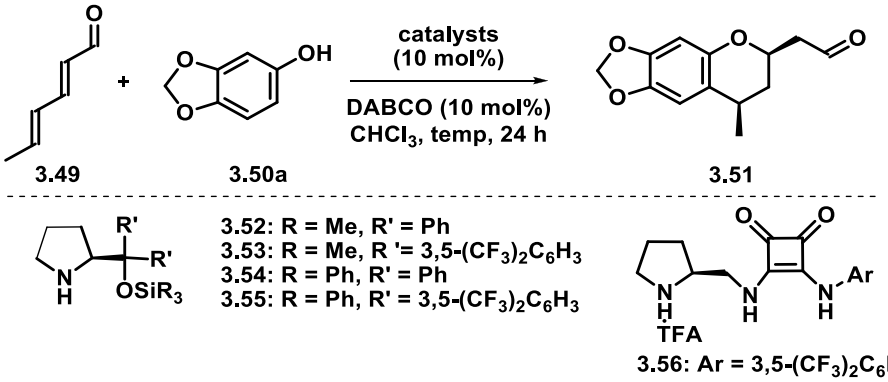
Thus, to our surprise, we observed just one product out of several possibilities, being to the best of our knowledge, the first report of an asymmetric Friedel-Crafts reaction[67]of hydroxyarenes with aliphatic and aromatic 2,4-dienals, followed by a ring-closing oxa-Michael reaction[68] in a 1,6-1,4 addition sequence, (Scheme 3.9, I).

Furthermore, it is worth mentioning that no substituents on the 2,4-dienal are needed to ensure complete remote selectivity in the first step, which represents one advantage over the previous studies. [64, 65, 66,69, 73] Those, except for one single example using aliphatic dienals,[63] count on sterically blocking the 4-position in order to suppress the competing 1,4-addition.

3.3.2 Evaluation of organocatalytic cascade process

We started our studies of the 1,6-Friedel-Crafts/1,4-oxa-Michael cascade reaction by carrying out the reaction between *E*,*E*-2,4-hexadienal (3.49) and sesamol (3.50a), (Table 3.1). The reaction was performed in the presence of 10 mol% of the TMS-protected diphenylprolinol catalyst (3.52) and 10 mol% of DABCO in $CHCl_3$ at room temperature, giving only one product (3.51) corresponding to the 1,6-Friedel-Crafts, followed by an 1,4-oxa-Michael reaction, with 87% conversion and poor stereocontrol, 1:1.2 dr, 34% ee, (Table 3.1, Entry 1).

Table 3.1 - Organocatalytic Asymmetric 1,6-1,4-Friedel-Crafts-oxa-Michael Cascade Reaction - Screening Results[a]



entry	3.49:3.50a	Cat.	solvent	T (°C)	conv.[b] (%)	dr[c]	ee[d] (%)
1	3:1	3.52	$CHCl_3$	rt	87	1:1.2	34
2	3:1	3.53	$CHCl_3$	rt	41	2.7:1	87
3	3:1	3.54	$CHCl_3$	rt	15	1.2:1	63
4	3:1	3.55	$CHCl_3$	rt	40	6.0:1	98
5	3:1	3.56	$CHCl_3$	rt	-	-	-
6	3:1	3.55	$CHCl_3$	40	49	4.5:1	97
7	3:1	3.55	CH_2Cl_2	40	50	3.1:1	93
8	3:1	3.55	MTBE	40	-	-	-
9	3:1	3.55	Toluene	40	19	1.6:1	69
10	1:2	3.55	$CHCl_3$	rt	83	3.3:1	93

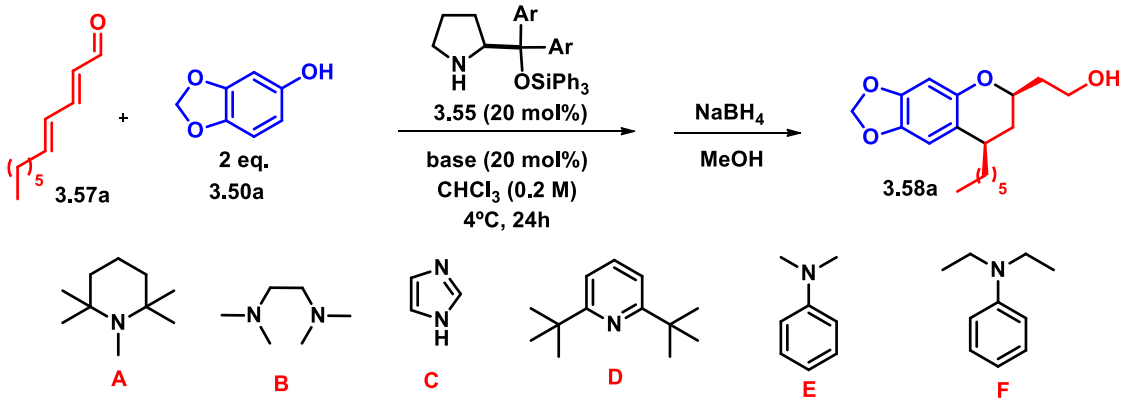
[a]Reactions were performed on a 0.1 mmol scale. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Enantiomeric excess was determined by UPC[2].

Then, we initiated the screening of a series of catalysts in order to obtain better results, and as shown in the Table 3.1 the catalyst (3.55), possessing both CF_3-disubstituted aryl groups and a triphenylsilyl-protection group, led to improvements in both enantio- and diastereoselectivity as compared to others organocatalysts (Table 3.1, entry 4). The H-bond directing catalyst (3.56) was unable to catalyze the reaction (Table 3.1, entry 5). The reaction also showed to be very solvent dependent; while an increase

in temperature to 40 ºC resulted in decreased stereoselectivity and did not improve the conversion (Table 3.1, entries 6-9).

However, when we changed the proportion of substrates, using 1 equivalent (eq.) of aldehyde (3.49) and 2 eq. of sesamol (3.50a), was observed an raising of conversion, a slight decreased of ee and a considerable decrease of dr, as compared to initial condition, (Table 3.1, entry 10 *vs* 4). This result combined with others results from early screenings, encouraged us to screening the base, keeping this proportion 1:2 aldehyde/sesamol. In addition, was also observed during the screenings that a longer alkyl chain in the aldehyde substrate resulted in improved diastereoselectivity, therefore *trans*,*trans*-2,4-undecadienal (3.57a) was applied in following screenings. (Table 3.2).

Table 3.2 - Screening of base additives[a]

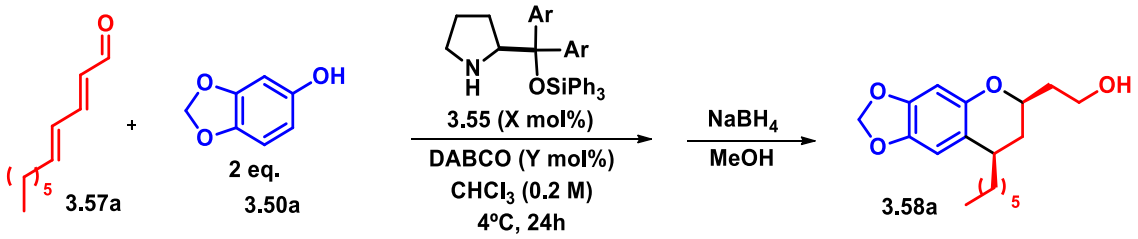


entry	base	conv. (%)[b]	dr[c]	ee[d]
1	DBU	46	1.3:1	-
2	A	43	1:1.5	-
3	Et_3N	54	1:1.7	-
4	DIPEA	47	1:1.3	-
5	B	54	1:3.0	-
6	DABCO	60	1:4.6	97
7	C	29	1:1.7	-
8	D	32	1:1.0	-
9	pyridine	75	1:2.0	75
10[e]	pyridine	61	1:2.3	89
11	E	80	1:1.5	-
12	F	39	1:1.0	-
13	Quinine	60	1:1.1	-
14	Quinidine	60	1:3.4	-

[a] Reactions were performed on a 0.1 mmol scale.[b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess was determined by UPC^2. [e] 50 mol% of the base was applied.

Unfortunately, as shown in table 3.2, all bases tested didn't improve the early results using DABCO. The next step was the investigation of the of DABCO and catalyst (3.55) loading, (Table 3.3).

Table 3.3 - Screening of the catalyst and DABCO loadings[a]

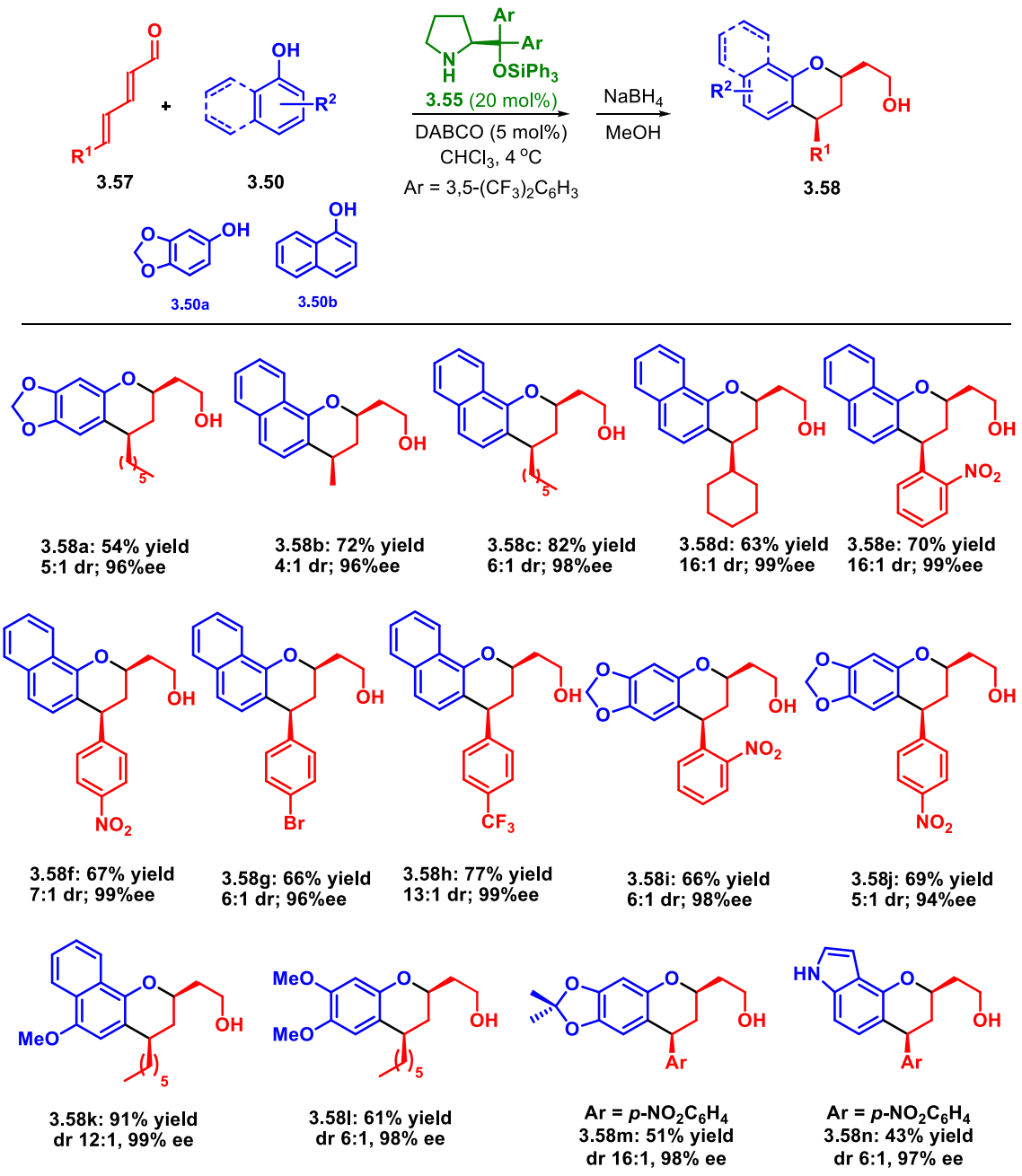


entry	catalyst (mol%)	DABCO (mol%)	conv. (%)[b]	dr[c]	ee[d] (%)
1	20	50	35	1:7.3	-
2	20	20	60	1:4.6	97
3	20	10	62	1:4.7	96
4	20	5	78	1:4.7	94
5	20	2	85	1:2.0	97
6	10	20	40	1:6.7	99
7	10	10	47	1:6.0	96
8	10	5	52	1:5.8	95
9	10	2	68	1:2.7	-
10	5	5	39	1:11	95
11	5	2	49	1:3.2	93

[a] Reactions were performed on a 0.1 mmol scale.[b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess was determined by UPC[2].

We could observe a tendency for the results shown in Table 3.3. The decreasing amount of the DABCO results in a raising of product conversion (3.58a) in all levels of catalyst loading. Thus, we determine the optimal reaction condition as 1:2 (3.57a)/ (3.50a) using 20 mol% catalyst (3.55), 5 mol% DABCO in chloroform at 4ºC, (Table 3.3, entry 4).

The scope of the organocatalytic asymmetric cascade reaction was then explored for various 2,4-dienals (3.57) reacting with hydroxyarenes (3.50) in the presence of (3.55) as the catalyst (Scheme 3.10).



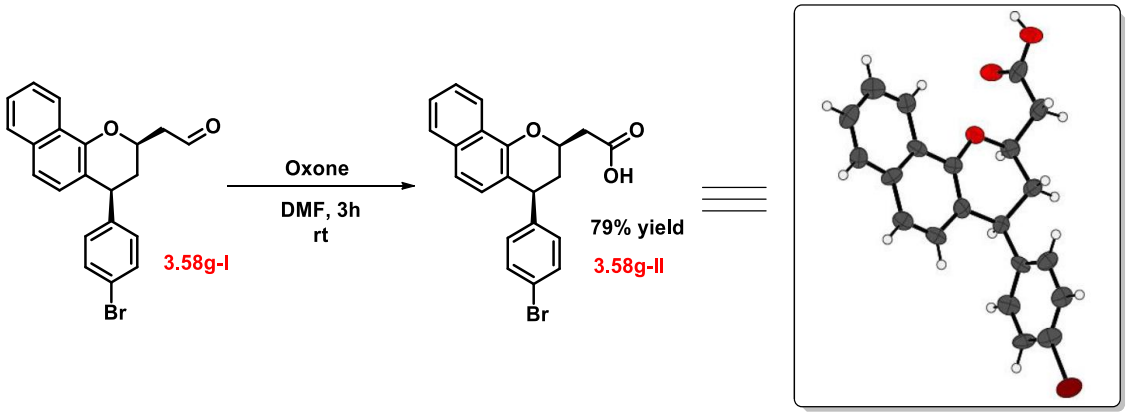
Scheme 3.10 - Reactions of different aldehydes and nucleophiles in the organocatalytic asymmetric 1,6-Friedel-Crafts/1,4-oxa-Michael cascade reaction.

The results shown in Scheme 3.10 demonstrated the methodological feasibility facing an expressed selection of aldehydes and hydroxyarenes. As depicted in Scheme 3.10, both aliphatic and aromatic 2,4-dienals react easily in the 1,6-Friedel-Crafts-/1,4-oxa-Michael cascade reaction with 1-naphthol and the chiral chromans are achieved in 54-82% yield, with excellent enantioselectivity 94-99% ee, and a diastereomeric ratio

ranging from 4:1 to 16:1 (Scheme 3.10, 3.58b-3.58i). The highest enantioselectivity and diastereoselectivity (16:1 dr and 99% ee) are accessed for both cyclohexyl substituted 2,4-dienal (3.58d) and o-NO_2 phenyl substituted 2,4-dienal (3.58e). The reaction for several 2,4-dienals proceeds also with the same excellent enantioselectivity for the nucleophile sesamol (3.50a), however the diastereoselectivity is slightly lower compared to the results obtained for 1-naphthol (3.50b), (Scheme 3.10 - 3.58a, 3.58i and 3.58j).

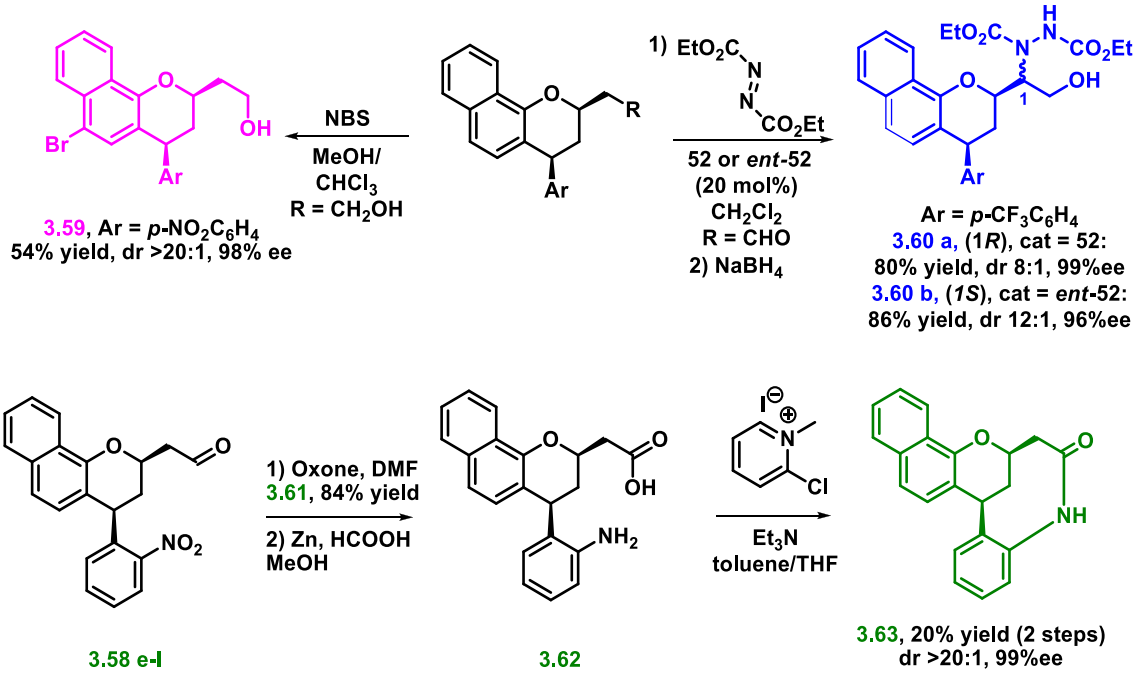
In addition, employing a more nucleophilic hydroxyarene, such as 4-methoxy-1-naphthol, pointing to an increase in both yield, diastereo- and enantioselectivities for chroman (3.58k) in comparison to 1-naphthol (3.58c). The increase in stereoselectivity should be due to the more steric-demanding nucleophile having a methoxy-substituent, instead of a hydrogen atom. An analogous increase in stereoselectivity was also observed for the dimethyl-substituted sesamol (3.58m). 3,4-Dimethoxy phenol also reacts smoothly and chroman synthesis (3.58l) is achieved in good yield and diastereoselectivity, in 98% ee. An attractive nucleophile is the one derived from indole, that provides chroman (3.58n) with similar results.

The absolute configuration of the chiral chromans obtained was unambiguously assigned by X-ray analysis of the carboxylic acid derivative of (3.58g-I). This acid was easily obtained by oxidation using Oxone in DMF as solvent, affording the product (3.58g-II) with 79% yield (Scheme 3.11). The single crystal was obtained by slow vapor diffusion between a solution of (3.58g-II) in CH_2Cl_2 and pentane.



Scheme 3.11 - Oxidation reaction of (3.58g-I) and X-ray analysis of carboxylic acid corresponding (3.58g-II).

Furthermore, the chiral chromans were used in three interesting transformations, such as selective bromination (3.59), organocatalytic alpha-amination (3.60) and one macrolactamization (3.63), (Scheme 3.12).



Scheme 3.12 - Transformation of chiral chromans.

It was observed during the study that hydroxyarenes having electron-withdrawing substituents as 4-Bromo-1-naphthol or phenol are not

reactive under the optimized reaction conditions. However, optically active chromans, in which the hydroxyarene is substituted with a bromine, can be easily obtained by bromination of (3.58f) affording (3.59) in 54% yield, >20:1 dr and 98% ee (Scheme 3.12, top left).

The chroman aldehydes can also be selectively manipulated in the α-position of the aldehyde just adding a further step to the cascade sequence. However, this requires a less sterically-hindered catalyst (3.53) and employing both enantiomers of (3.53) gives access to both diastereomeric forms of the α-aminated aldehydes (3.60a and 3.60b) in good yield and great stereoselectivity (Scheme 3.12, top right).

Besides, a macrocyclic lactam chroman core structure was synthesized (3.60) by oxidation of aldehyde moiety (3.58e-I) leading the acid (3.61), followed reduction of nitro group affording the (3.62), which suffered the lactamazation affording the desired macrocyclic lactam with high diastereo- and enantioselectivity, and 20% yield after two steps (Scheme 3.12, bottom).

3.4 Conclusion and outlook

In conclusion, the first asymmetric organocatalytic 1,6-1,4-Friedel-Crafts-oxa-Michael cascade by reaction of hydroxyarenes with 2,4-dienals for the construction of chromans is described.

The reaction proved to be a general methodology giving optically active chromans with excellent regio- and stereoselectivities in high yields and 94-99% ee.

The robustness of the reaction concept developed was demonstrated with a series of transformations, including the formation of an optically active macrocyclic lactam. Moreover, computational and experimental studies revealed a reaction sequence, involving a number of

intermediates, driven by thermodynamic control of the Friedel-Crafts reaction step.

Chapter 4

4 Chapter 4

In this last chapter, the preliminary results on formal [3+3] cycloaddition of azomethine imine with isocyanide is described, using two differents methodologies: a) the non-covalent organocatalysis; b) a merging organocatalysis with Lewis acid catalysis.

The chapter starts with a briefl description of some basic aspects of the reaction in study, which involves a formal [3+3] cycloaddition, cooperative catalysis, as well as the importance of triazine compounds. Afterwards, the results and discussion will be presented, followed by conclusions and perspectives.

.

4.1 Introduction

4.1.1 [3+3]-Cycloaddition

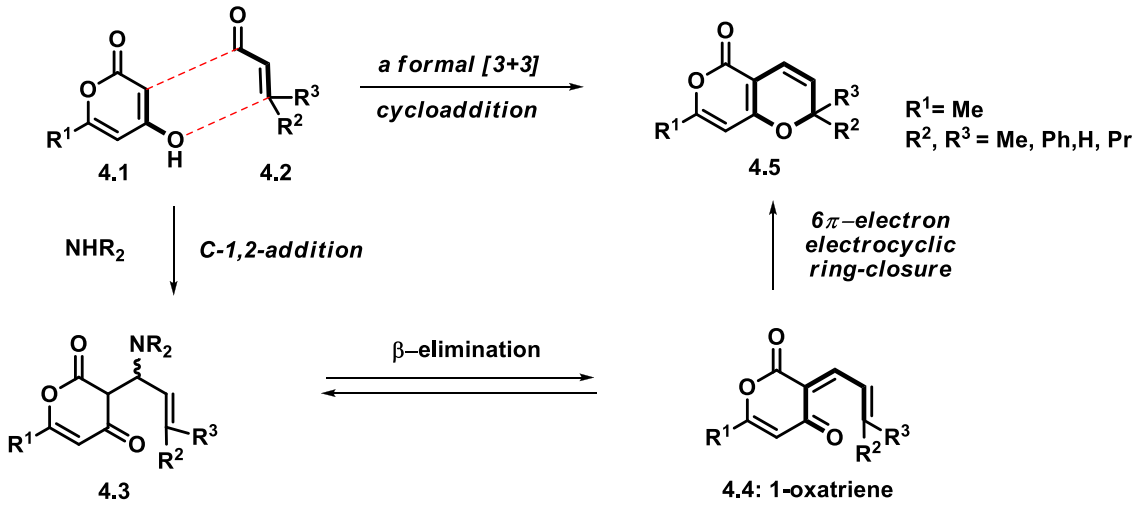
Cycloaddition and annulation reactions are amidst the most effective and powerful methods for building up complexity in organic synthesis due their capacity to provide multiple bond creation with regio- and stereochemical control. [70]

Theses reactions are extremely versatile, mainly because of the numerous combinations of two unsaturated structural units, for example the six-membered rings are formally accessible either by [5+1]-, [4+2]-, [2+2+2]-, or [3+3]-cycloadditions. Among these possibilities, the concerted [4+2]-cycloaddition, the so-called Diels-Alder reaction, is the the most famous and commonly applied.[71]

The [3+3]–cycloaddition, or more correctly termed “formal [3 +3] cycloaddition’’, it is one stepwise process, between two fragments with

complementary reactivity. This reaction provides advantages on the synthesis of a wide range of heterocyclic compounds and for that reason, has been receiving considerable attention recently.[72]

In 1944, Link discovery this annulation reaction working with the 4-hydroxycoumarins. However, just in 1980s, with the studies of Moreno-Manãs, which this annulation regained attention. Mechanistically, this reaction pathway proceeds through the route shown in Scheme 4.1. Firstly a 1,2-addition occurs of 6- alkyl- or 6-aryl-4-hydroxy-2-pyrones (4.1) to the iminium salt generated in situ from α, β-unsaturated aldehydes (4.2) and a secondary amine. Then, the β-elimination gives 1-oxatriene intermediates (4.4), which it is a Knoevenagel type condensation, and the route ends with a 6π- electron electrocyclic ring-closure of (4.4) to lead the 2*H*-pyrans (4.5).[76,73]

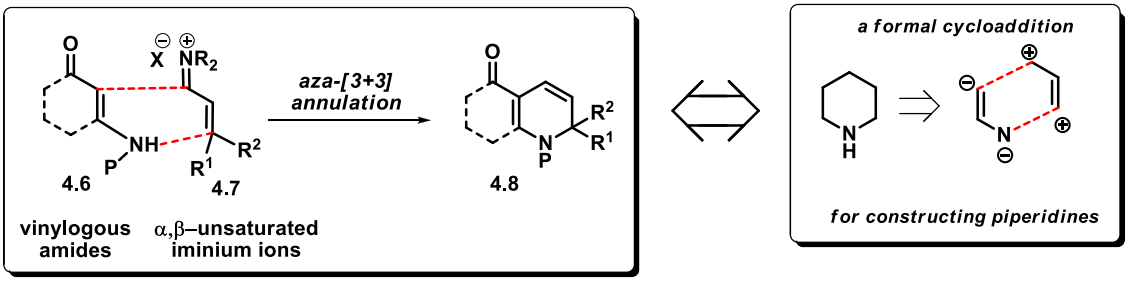


Scheme 4.1 – The formal [3+3] cycloaddition.

Therefore, the final result of annulation is two σ-bonds and a new stereocenter adjacent to the heterocyclic oxygen atom, thus composing a tandem anionic/pericyclic ring-closure sequence. This can be called formally an equivalente of a [3+3] cycloaddition in which the three carbon atoms of aldehyde (4.2) have been added to the two carbon atoms and one

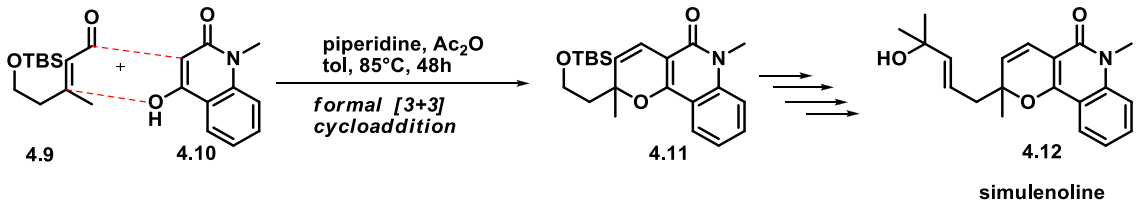
oxygen atom of pyrone (4.1). The term [3+3] cycloaddition was addapted from seminal Seebach's work describing a Stork-type carbo-[3+3] annulation reaction between nitroalkenes and enamines.[78,79,74]

The *aza*-[3+3] annulation or formal cycloaddition strategy for constructing heterocycles, have been also described. This annulation involves the same reaction pathway of the oxygen-version, with a Knoevenagel-type condensation, followed by a 6π-electron electrocyclic ring-closure, by reaction of vinylogous amides (4.6) as equivalentes of pyrones (4.1) and iminium ions (4.7), (Scheme 4.2).[78]



Scheme 4.2- The Aza [3+3] Annulation

The formal [3+3] cycloaddition has been used in the synthesis of naturally occurring alkaloids, *e.g* pyranoquinoline alkaloid Simulenoline, a potent inhibitors of platelet aggregation. The route is shown in Scheme 4.3, the key step is the formal cycloaddition between the α, β-unsaturated aldehyde (4.9) with 4-hydroxy-2-quinolone (4.10) under standard conditions to afford the tricyclic pyran (4.11), which after removal of the TBS group, Dess-Martin oxidation of the intermediate alcohol to aldehyde, Wittig olefination and final addition of excess MeLi to this enone afforded the natural product Simulenoline (4.12) in 40% overall yield.[75]

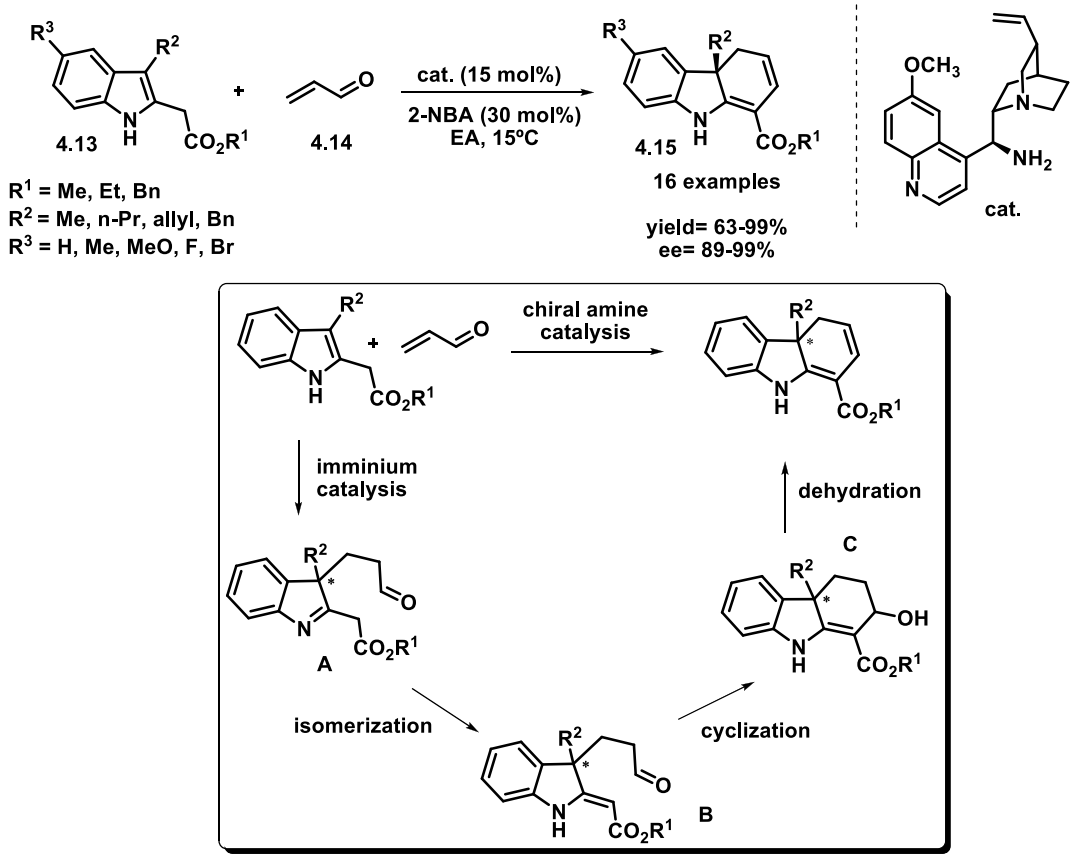


Scheme 4.3 – Total synthesis of Simulenoline

The formal [3+ 3] cycloaddition suffered rapid development of its synthetic methodology, since 1980s-1990s. Currently, the substrates were beyond the iminium ions and pyrones, besides being used catalytic methods, as organocatalysis or transition metal catalysis.[77]

4.1.1.1 Organocatalytic [3+3] cycloaddition

In 2013, Wu and co-workers described one formal [3+3]-organocatalytic cascade route for the asymmetric preparation of tricyclic hydrocarbazoles (4.15) in good to excellent yields and excellent enantioselectivites. The authors envisioned that the 2,3-disubstituted indole (4.13) shall acts as a nucleophile in the conjugate addition to acrolein (4.14) leading to an alternative and asymmetric route to hydrocarbazoles (4.15). The proposed mechanism is outlined in Scheme 4.4.

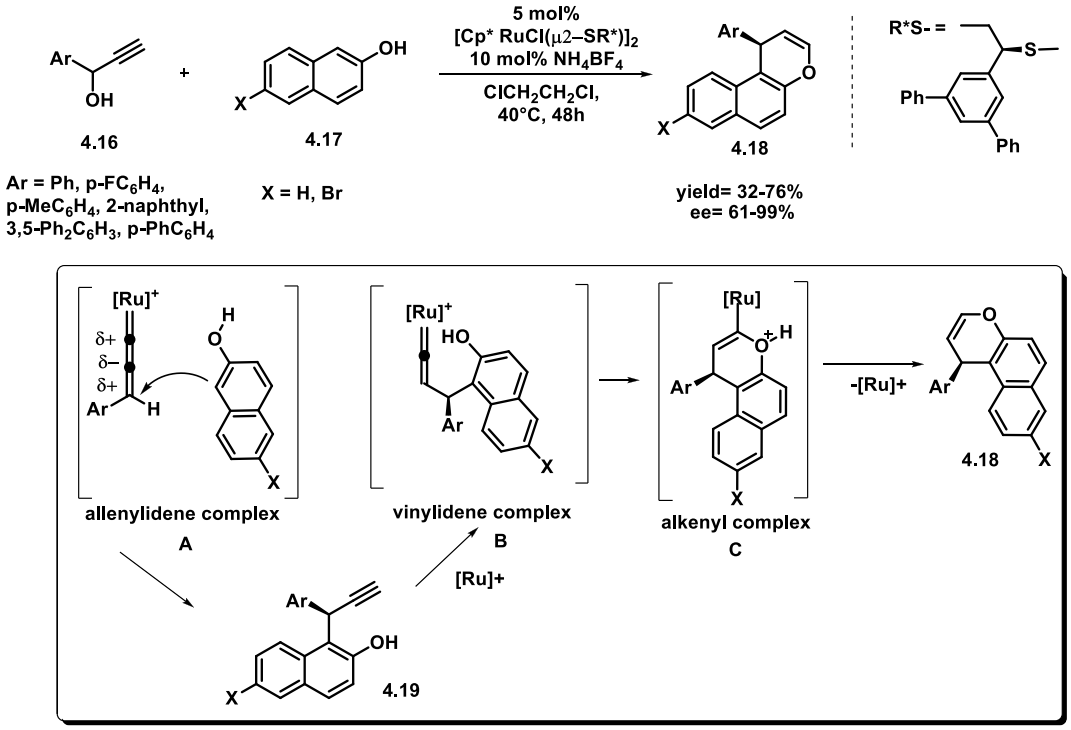


Scheme 4.4 -Asymmetric organocatalytic formal [3+3] cycloaddition of indoles derivatives with acrolein to obtain hydrocarbazoles.

The first step is the reaction of an indole derivative with acrolein by an imminium intermediate formed previously through activation of the enal with the catalyst, giving the indolenine intermediate (A) after release of the catalyst. The intermediate (A) undergoes isomerization, leading to the enamino-ester (B) that, after an intramolecular cyclization (C) and following dehydration, leads to the functionalized hydrocarbazole (4.15), (Scheme 4.4).[76]

4.1.1.2 Metal catalysis [3+3] cycloaddition

In 2010, Nishibayashi and co-workers developed a novel method for the preparation of chiral naphthopyrans through ruthenium-catalyzed enantioselective [3+3]-cycloaddition of propargylic (4.16) alcohols with 2-naphthols (4.17) affording the corresponding naphthopyran derivatives (4.18) in moderate to good yields with a high enantioselectivity, (Scheme 4.5).[83]



Scheme 4.5 - Ruthenium-catalyzed enantioselective [3+3] cycloaddition of propargylic alcohols with 2-naphthols affording naphthopyran derivatives.

The cycloaddition route proceeds via a stepwise reaction pathway. The propargylation of 2-naphtol (4.17) is followed by cyclization of the produced propargylated naphtol (4.19). This cyclization into the corresponding cycloaddition product (4.18) occurred without loss of optical purity at the propargylic position of (4.19). The propargylation occurs *via*

ruthenium-allenylidene complex (A) as a key intermediate, and the cyclization of (4.19) to product (4.18) may occur *via* ruthenium-vinylidene (B) and the corresponding alkenyl complex (C), (Scheme 4.5).[77]

4.1.2 Merging Metal catalysis and Organocatalysis

The fusion of transition metal catalysis and organocatalysis is a new and exciting research area, which has attracted increasing attention of the scientific community. The combination of these two catalytic models allows the development of new transformations, and can further improve the reactivity, efficiency and stereocontrol of existing chemical transformations.[78]

The combination of organo- and transition metal catalysis is much more than just mixing two different catalysts. The organo-/transition metal catalyst combinations can be classified based on their mode of activation, the general classification is shown in Figure 4.1.[84]

The first type of activation is the cooperative catalysis, where the two catalysts are directly involved in the same catalytic cycle, working cooperatively to lead to the desired product. Contrasting with cooperative catalysis, the second type of catalysis is called synergistic catalysis, where both the organocatalyst and the transition metal catalyst activate simultaneously the substrates A and B in two directly coupled catalytic cycles, in order to afford the product. The last type of catalysis is also known as sequential or relay catalysis, which requires both the organocatalyst and the transition metal catalyst to perform two distinct catalytic cycles for the consecutive reactions. Therefore, the substrates (A and B) first react to create an intermediate (INT I) in the first catalytic cycle, which can either be the organocatalytic cycle or the transition metal catalytic cycle. Afterwards, this

intermediate is converted to the final product (P) by another independent catalyst (Figure 4.1).[84]

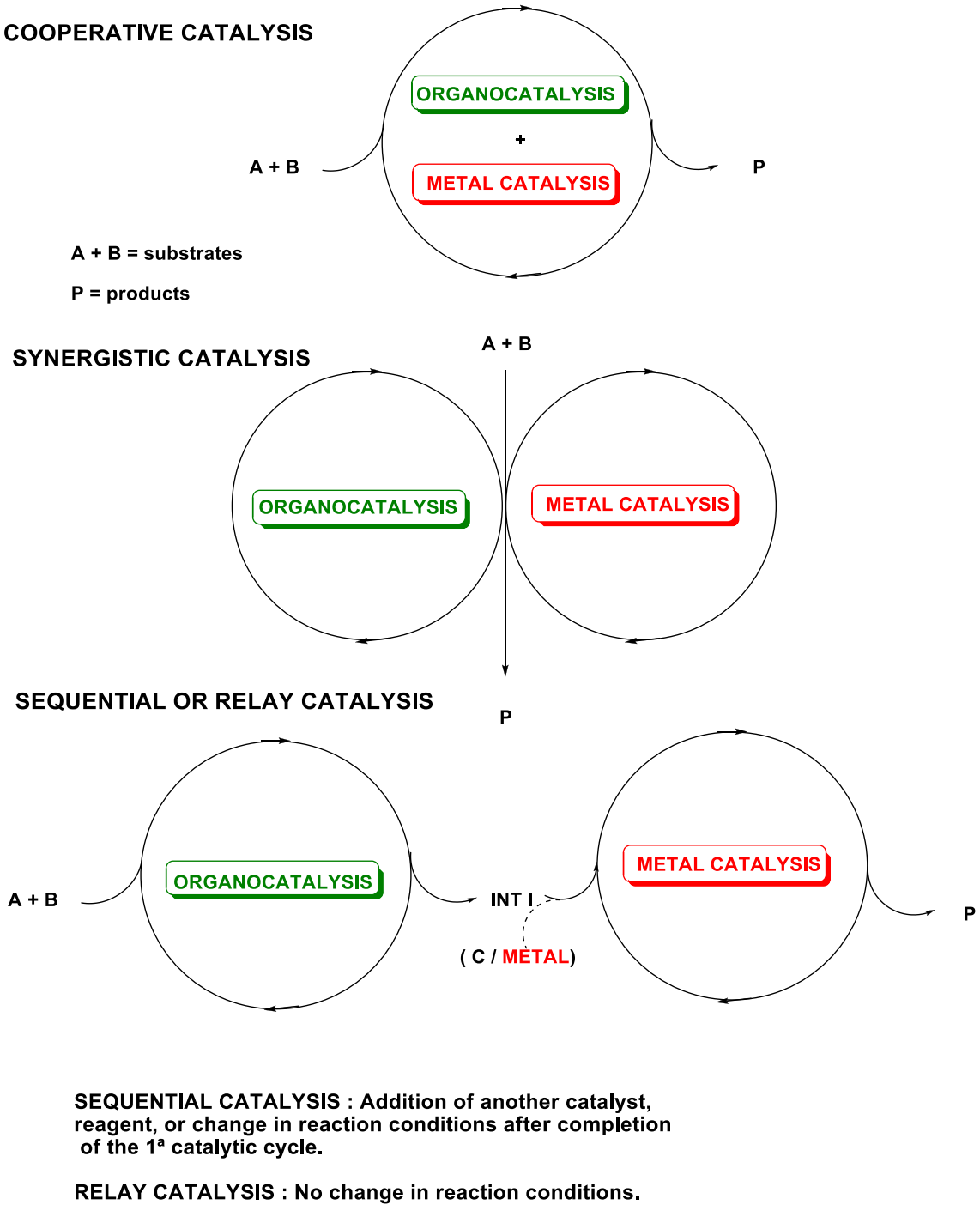


Figure 4.1 - Taxonomy of combining organo- and transition metal catalysis.

Despite the evident advantages of fusing organocatalysis and metal catalysis, there are some challenges facing this approach. The crucial challenge is to ensure affinity of catalysts, substrates, intermediates and solvents throughout the full reaction sequence. The trick to overcome this challenge is the careful selection of appropriate catalyst combinations. [84]

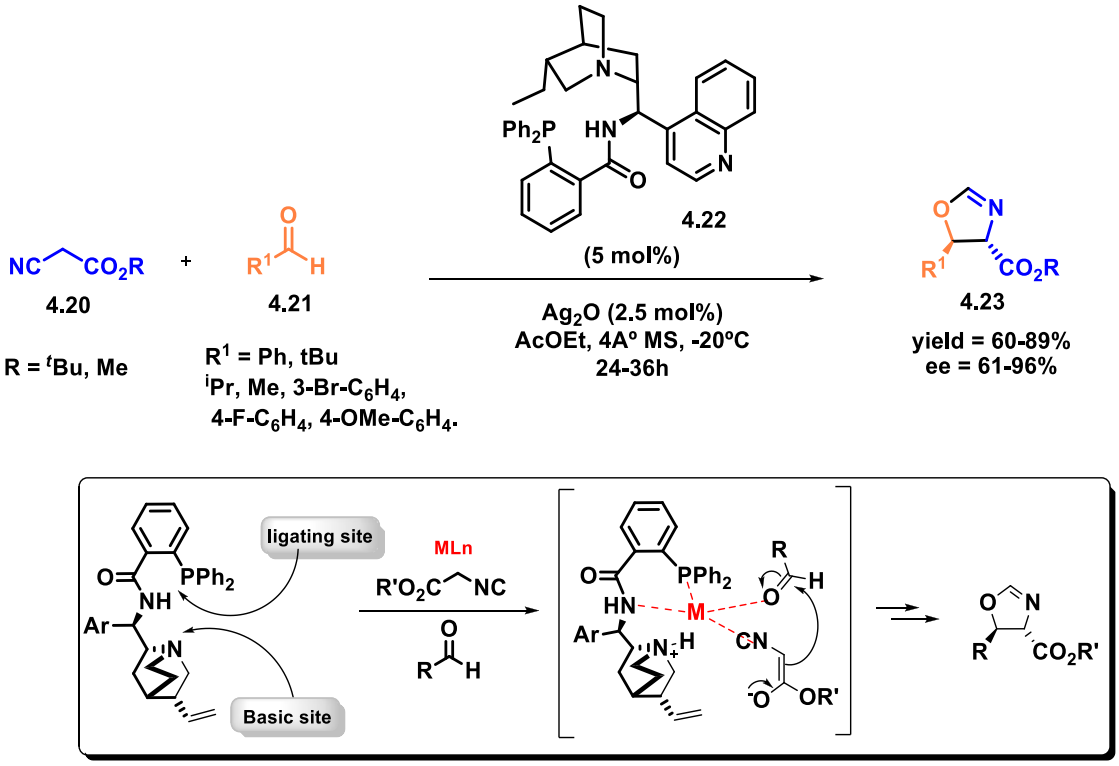
Transition metal catalysts have been merged with the following variety of organocatalysts: (a) aminocatalysts including primary and secondary amines; (b) Brønsted acid catalysts, especially phosphoric acids based on the chiral BINOL scaffold; (c) hydrogen-bonding catalysts such as thioureas; (d) Brønsted base catalysts; (e) Lewis base (nucleophilic) catalysts; (f) chiral phase transfer catalysts; and (g) N-heterocyclic carbene catalysts. With respect to transition metals, the following metals have been employed in the combined organo- and transition metal catalysis: Pd, Rh, Ru, Cu, Ni, Zn, Fe, Ir, Co, Mn, Ti, Y, In, Nb, Au, Ag, Pt, V. [84]

4.1.2.1 Cooperative catalysis

The field of cooperative catalysis, inspired by observations of enzymatic activation, is a growing research area. More specifically, cinchona derived scaffolds in combination with a broad range of metal ions and complexes have been highlighted. This fusion has led to the development of unprecedented transformations in terms of reactivity and stereocontrol.[79]

In 2011, Dixon and co-workers reported a new class of chiral amino-phosphine precatalysts derived from 9-amino (9-deoxy) epi-cinchona alkaloids (4.22) that, in combination with an appropriate transition metal ion, can perform as effective cooperative Brønsted base/Lewis acid catalysts. Furthermore, the authors applied this concept to aldol reaction of isocyanoacetate (4.20) with aldehydes (4.21) in the presence of Ag(I) salts leading to product (4.23) with moderate to good yields 60-89% and *ee* up to

96%. They suggested that the acidity of the R-C-H of isocyanoacetates could be raised after complexation with a properly "soft" transition metal ion (complex). This would permit deprotonation by the bridgehead nitrogen, affording the bound and activated nucleophilic component poised for reaction with Lewis acid activated aldehydes, (Scheme 4.6). [80]



Scheme 4.6 - Aldol reaction of isocyanoacetates with aldehydes using cooperative catalysis.

4.1.3 Triazines

The field of heterocyclic chemistry is vital to biology and medicine, consisting of a large group of organic molecules showing a wide range of biological activities, which is a basis for life and society. The larger number of pharmaceutical products that mimic natural products with biological activity are heterocyclic molecules. [81]

Triazines are six membered heterocyclic compounds containing three nitrogen atoms in its structure with general formula of $C_3H_3N_3$. The three isomers of triazine are distiguished by the positions of their nitrogen atoms, and are named 1,2,3-triazine (A), 1,2,4-triazine (B) and 1,3,5-triazine (C) (Figure 4.2). [88]

In particular, 1,2,4-triazine and its derivatives have been found to display a variety of biological applications such as antifungal, anti-HIV, anticancer, anti-inflammatory, analgesic, antihypertensive, cardiotonic, neuroleptic, nootropic, antihistaminergic, tuberculostatic, antiviral, anti-protozoal, estrogen receptor modulators, antimalarial, cyclin-dependent kinase inhibitors, antimicrobial and antiparasitic.[88]

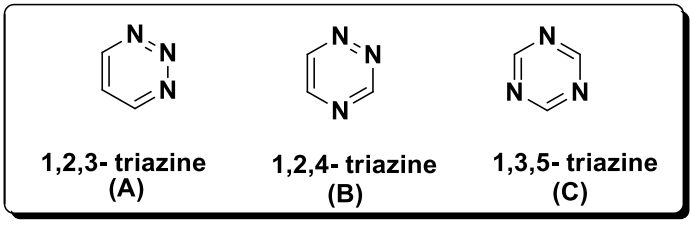


Figure 4.2 - Triazine compounds

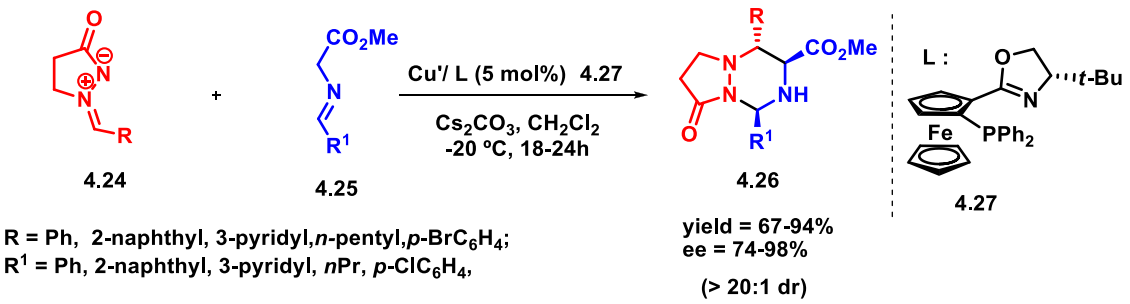
Regarding the field of their biological applications paired with their chemical potential, it is of huge importance the design and synthesis of triazines and their derivatives.

In fact, the synthesis of 1,2,4-triazine is already well documented in the literature, however, the asymmetric version of its derivatives is an open field of research.[82]

4.1.3.1 Asymmetric Synthesis of triazines derivatives

In 2013, Wang and co-workers reported the first copper(I)-catalyzed cross-1,3-Dipolar Cycloaddition (DC) between pyrazolidinium

ylides (4.24) and *in situ* formed azomethine ylides (4.25) to give highly substituted 1,2,4-triazine frameworks (4.26) employing the CuI/tBu-Phosferrox complex (4.27) as the catalyst. The products were obtained with moderate to good yields 67-94%, exclusive diastereoselectivity and excellent enantioselectivity 74-98% (Scheme 4.7).[83]

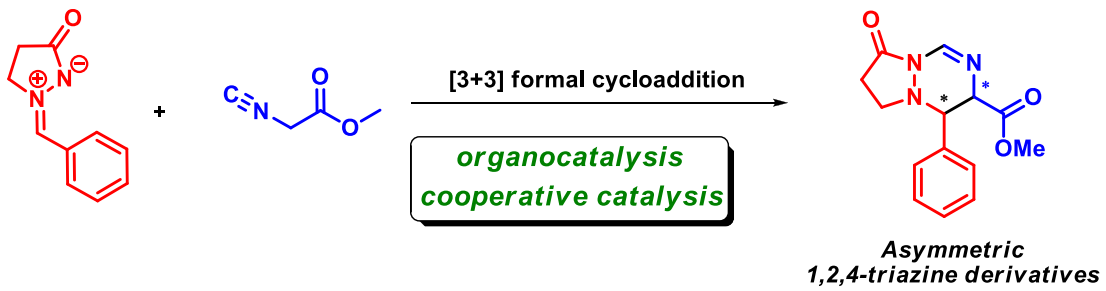


Scheme 4.7 - Synthesis of chiral 1,2,4-triazine frameworks.

4.2 Objectives

Encouraged by the broad spectrum of biological activities of 1,2,4-triazine derivatives and the open field of its asymmetric synthesis, we envisioned the synthesis of 1,2,4-triazine frameworks through a formal [3+3] cycloaddition, using asymmetric organocatalysis as synthetic tool.

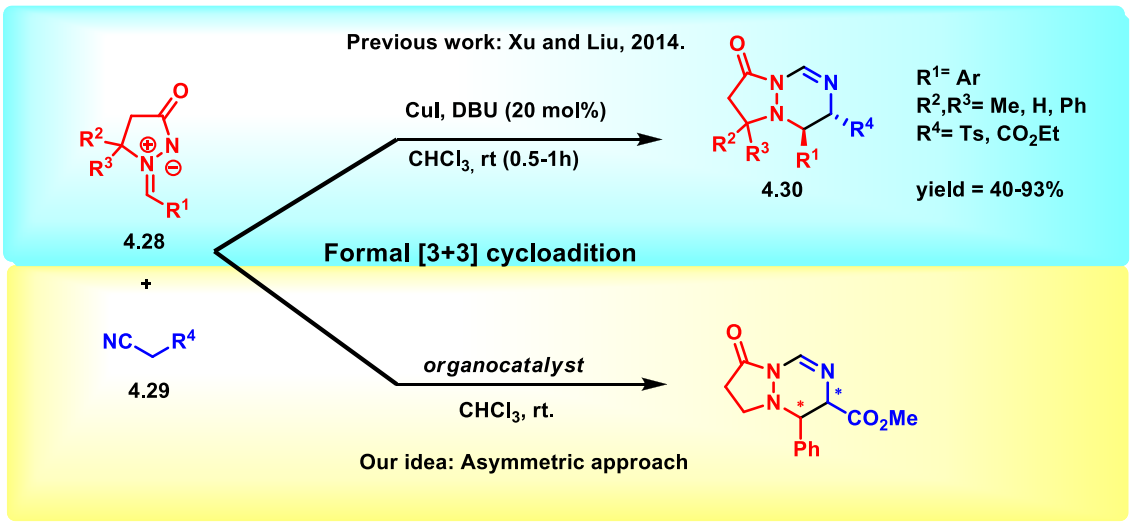
Thus, the main aim of the work reported in this chapter is to develop a new asymmetric methodology for the synthesis of 1,2,4-triazine derivatives by the reaction of α-acidic isocyanides with 1,3-dipolar azomethine imines using organocatalysis or cooperative organocatalysis/metal catalysis.



4.3 Results and Discussion

4.3.1 Initial Idea

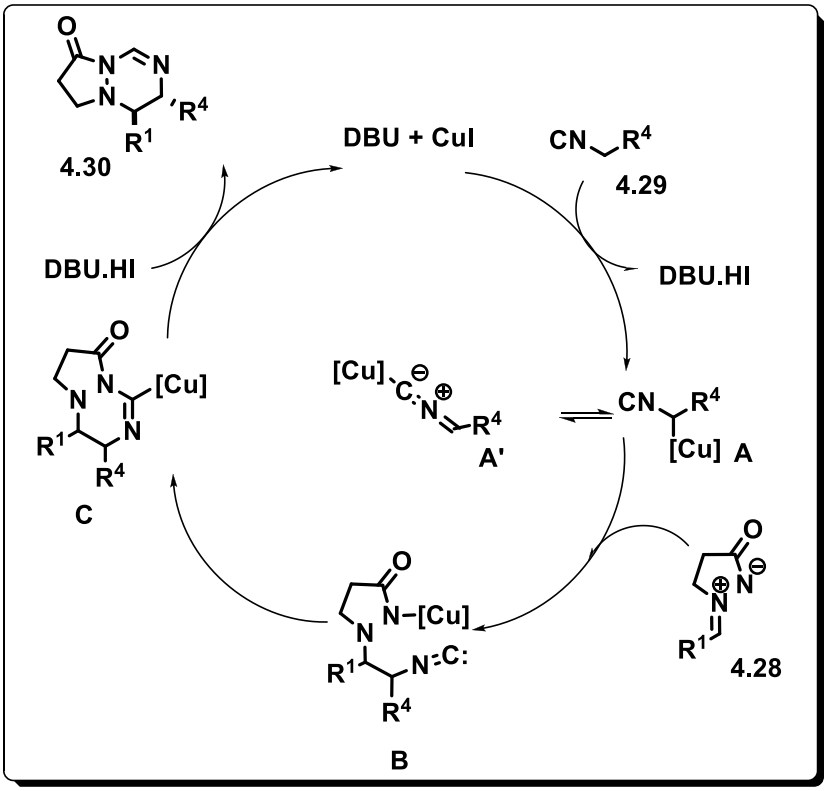
In 2014, Xu and Liu described a new formal [3+3]-cross-cycloaddition reaction of α-acidic isocyanides (4.31) with 1,3-dipolar azomethine imines (4.30) in the presence of a catalytic amount of copper salt (Scheme 4.8-top). [84] Inspired by this transformation, we envisioned to develop the enantioselective version of this approach using organocatalysis and Silver chemistry (Scheme 4.8- bottom).



Scheme 4.8 - Metal-catalyzed and organocatalytic reactions of α-acidic isocyanides with 1,3-dipolar azomethine imines.

The proposed reaction mechanism by Xu and Liu for this transformationis shown in Scheme 4.9. The reaction began with the formation of α-cuprioisocyanide (A) or its tautomer (A′) from isocyanoacetate (4.29) in the presence of CuI and DBU. Then, the nucleophilic addition of α-cuprioisocyanide (A) on the azomethine imine (4.28) occurs to form intermediate (B). Insertion of isonitrile into the N−Cu bond give rise to imidoyl−copper intermediate (C) which, after protonation

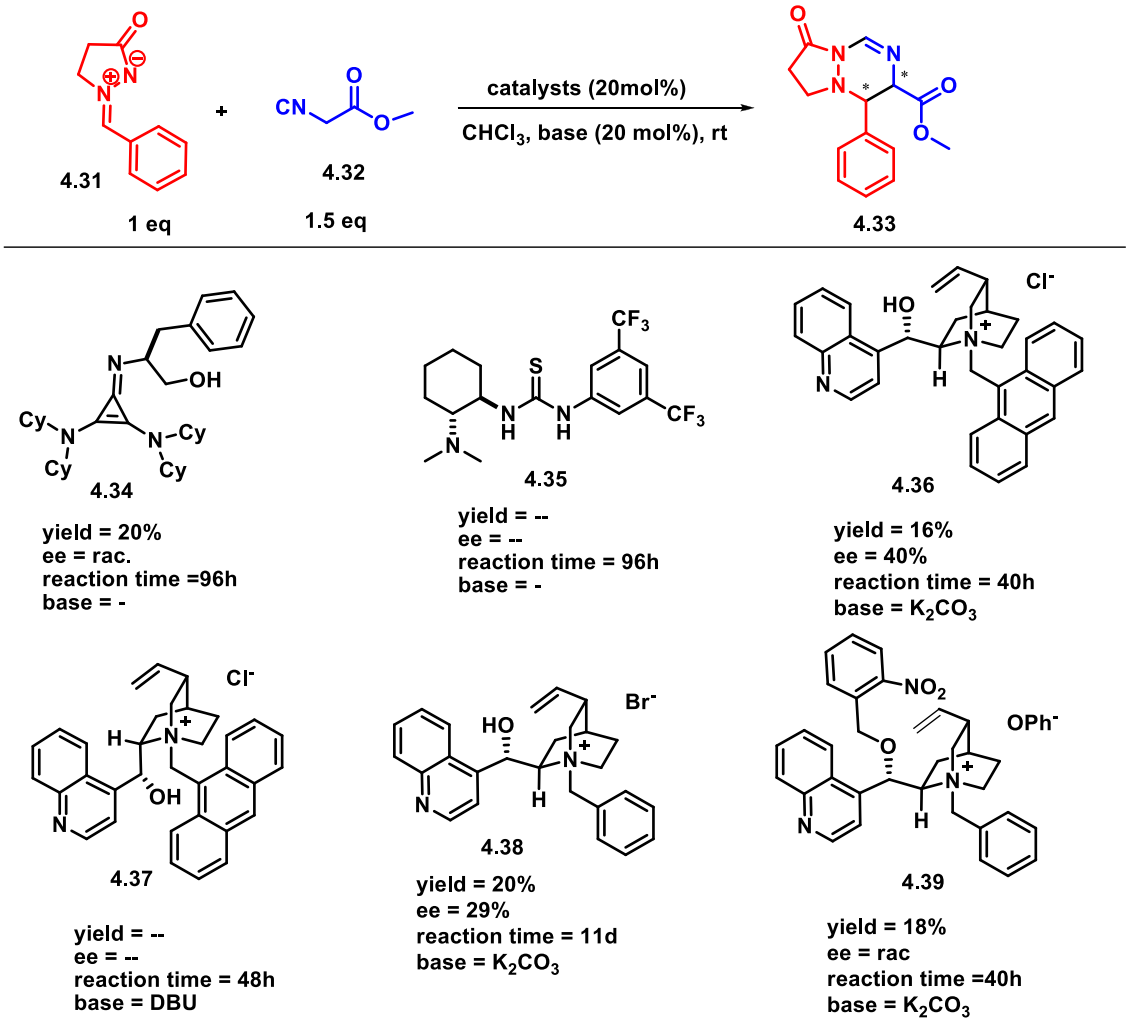
lead to 1,2,4-triazine (4.30) with regeneration of the catalysts, CuI and DBU, for the next catalytic cycle (Scheme 4.9).



Scheme 4.9 - Mechanism of [3+3] cycloaddition proposed by Xu and Liu.[96]

4.3.2 Optimization studies

We started our studies of formal [3+3] cycloaddition by screening of catalytic activity. In the model reaction was employed the (Z)-2-benzylidene-5-oxopyrazolidin-2-ium-1-ide (4.31) and methyl isocyanoacetate (4.34) in $CHCl_3$ as solvent at room temperature (Scheme 4.10).



[a] Reactions were performed on a 0.1 mmol scale, Enantiomeric excess was determined by UPC[2] and Yields of isolated products.

Scheme 4.10 - Optimization studies: Screening of catalysts.[a]

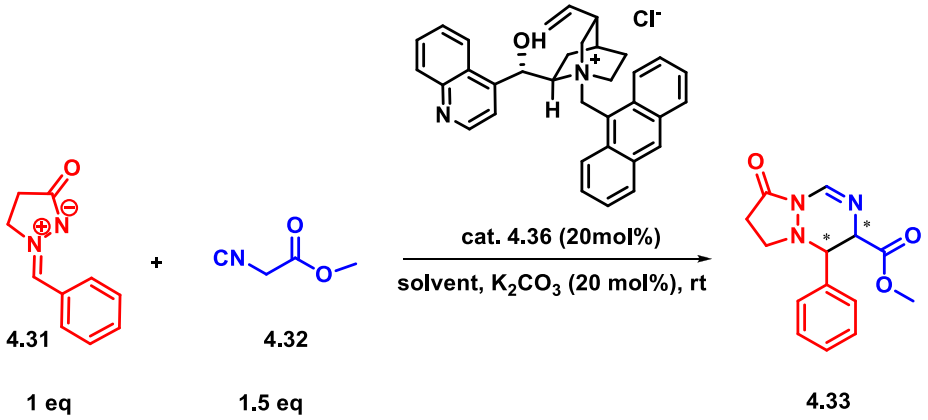
Based on the reaction pathway, in the first set of experiments, we evaluated the reactivity of isonitrile enolization by a chiral catalyst with basic behavior, and therefore avoiding the use of aditional base.

Unfortunately, the chiral base (4.36) and the bifunctional catalyst containing one tertiary amine (4.37) were unable to catalyze the reaction, (Scheme 4.11). Then, the next step was to modify the organocatalysts class. Inspired by the seminal studies of alkylations using phase transfer catalysis (PTC),[85,86] we decided to apply chiral quarternary ammonium salts to our reaction system, (Scheme 4.11 – 4.38 to 4.41).

In that way, the organocatalyst (4.36) showed the better catalytic activity amongst the other phase transfer catalysts, delivering the desired product in 16% of chemical yield and 40% *ee* after 40h, at room temperature and using K_2CO_3 as base. In addition, the formal [3+3] cycloaddition demonstrated to be highly diastereoselective, which are in agreement with the previous reported by Xu and Liu.

Encouraged by this result, we then turned our attention to the solvent screening, employing 20 mol% of catalyst (4.36) and K_2CO_3 (20 mol%) at room temperature, the results obtained are presented in the table below, (Table 4.1).

Table 4.1 - Optimization studies: Solvents screening to catalyst 4.36.

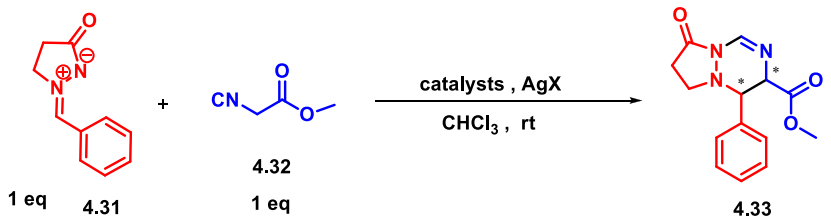


Entry [a]	Solvent	Yield (%)	*ee* (%)
1	$CHCl_3$	16	40
2	DCM	6	8
3	THF	4	6
4	Toluene[b]	7	4

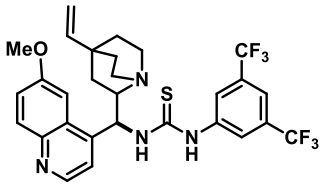
[a] Reactions were performed on a 0.1 mmol scale, Enantiomeric excess were determined by UPC^2.Yields of isolated products. [b] Cs_2CO_3 was used as base.

From this results, it was clear that the yield and enantioselectivity did not improve when the solvent was changed either to DCM, THF or toluene, (Table 4.1).

Thus, after the negative results of table 4.1, we returned to the literature and looking back our initial inspiration, which used Lewis acid catalysis. We decided to try merging organocatalysis with Silver catalysis in our model reaction, (Scheme 4.11). The different conditions presented in the Scheme 4.11 were based in previous studies, which used cooperative catalysis in similar reaction system.



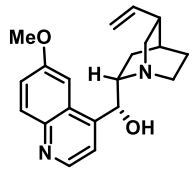
A



(10 mol %) 4.40

yield =51%
ee = racemic
reaction time = 36h
AgX = $AgNO_3$ (5 mol%)

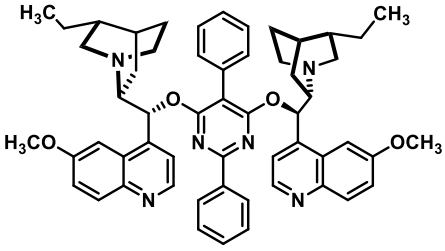
B



(20 mol%) 4.41

yield = 59%
ee = racemic
reaction time = 18h
AgX = $AgNO_3$ (10 mol%)

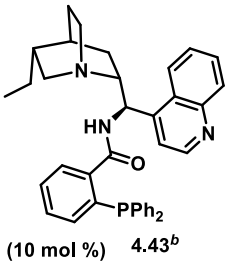
C



(10 mol % -$[DHQ]_2PYR$) 4.42

yield = 35%
ee = racemic
reaction time = 48h
AgX = Ag_2O (2.5 mol%)

D



(10 mol %) 4.43[b]

yield = 69%
ee = 42%
reaction time = 48h
AgX = Ag_2O (2.5 mol%)

[a] Reactions were performed on a 0.1 mmol scale, enantiomeric excess were determined by UPC[2].Yields of isolated products.[b] The reaction was performed at -20°C using AcOEt as solvent.

Scheme 4.11 - Optimization studies: Screening of catalyst system in cooperative catalysis.[a]

Initially, the catalytst system A that consist of silver nitrate (5 mol%) and quinine derived-thiourea catalyst (4.40, 10 mol%) was examined

in chloroform at room temperature. The 1,2,4 triazine derivative was obtained with 51% yield in 36 hours, however the product was racemic. In addition, also was tried quinidine alkaloid (4.41) merging with silver nitrate, leading the product with 59% yield after 18 hours. But, unfortunately provided the racemic 1,2,4 triazine derivative as the catalyst system A, (Scheme 4.11, system A and B).

Thus, we changed to the Lewis acid to Ag_2O in order to obtain better results. When, we tested the catalyst system C, with $[DHQ]_2PYR$ (4.42) in combination with Silver Oxide, this provided the product (4.33) with 35% yield in 48h, and racemic as well the catalyst system A and B, (Scheme 4.11).

Therefore, we changed one more time the reaction conditions. In the catalyst system D, were used the amino-phosphine quinidine derivative (4.43) and Ag_2O at -20°C using AcOEt as solvent. The product (4.3) was obtained with 69% yield after 48 hours, and with 42% ee, (Scheme 4.11).

Taking a general look in the Scheme 4.11, it clear emerged that all the catalyst systems (A-D) tested improved the chemical yield of the transformation when compared with previous results using only organocatalysis. However, regarding the enantiomeric excess only the catalyst system D presented the product (4.33) with 42% ee.

Thereby, the catalyst system D provided the 1,2,4 triazine derivative (4.33) with the better results so far.

The product has been properly characterized by NMR analysis. In the ^1H NMR, the doublet at 8.13 ppm with J = 2.5 Hz corresponds to the hydrogen (**1**). In the aromatic region, more precisely with a chemical shift of 7.41-7.38 ppm integrate to 3 hydrogens refers to signals (**3**) and in the region of 7.37-7.35 integrate to 2 hydrogens corresponds to signals (**2**). The doublet of doublets in 4.40 ppm with J = 8.6, 2.6 Hz corresponds to the hydrogen (**4**)

and the doublet at 3.67 ppm J = 8.6 Hz refers to hydrogen (**5**). The singlet at 3.57 ppm integrates to 3 hydrogens correspond to the methyl group (**6**). The multiplet in the region at 3.33-3.24 ppm corresponds to hydrogen (**7**). The multiplet signal in the region at 2.73-2.62 ppm integrates to 2 hydrogens, corresponding to CH_2 group (**8**) and in the region at 2.57-2.48 ppm appears the multiplet corresponding the hydrogen (**9**), (Figure 4.3).

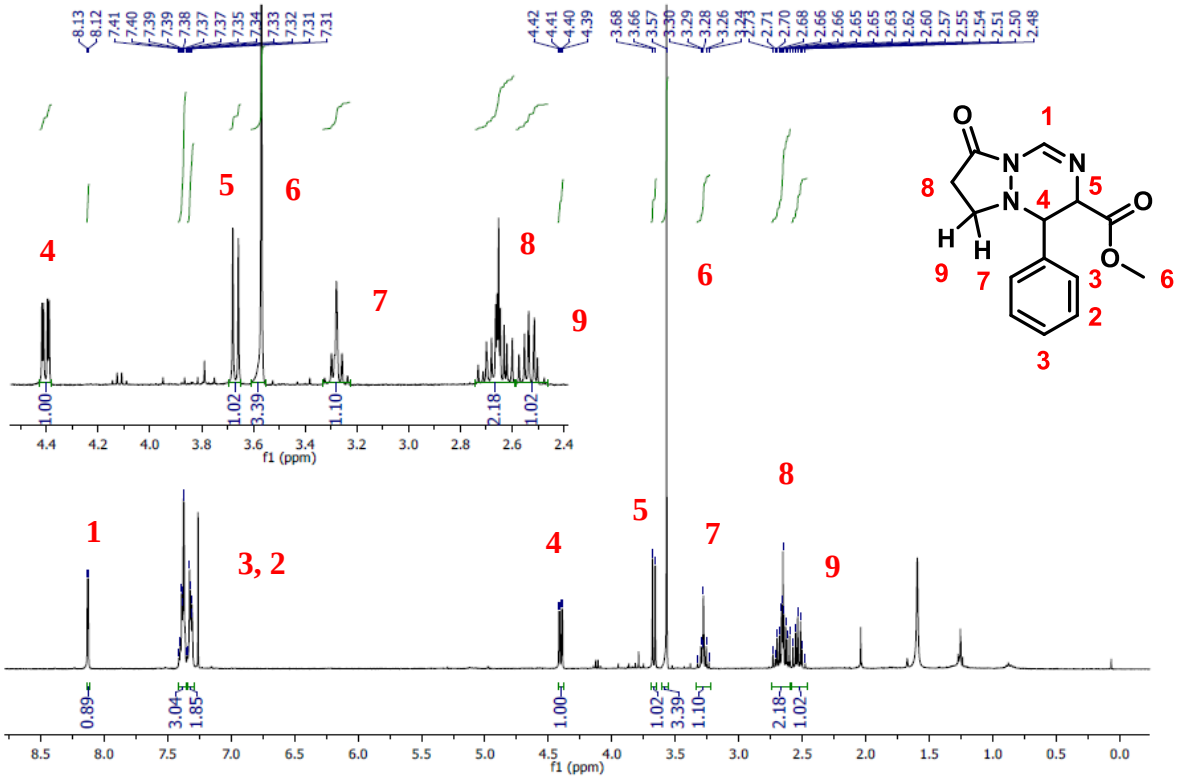


Figure 4.3 - 400 MHz ^{1}H NMR spectra in $CDCl_3$ of compound (4.33). Zoom range between 2.4- 4.5 ppm.

The ^{13}C NMR spectra of (4.33) is shown in Figure 4.4. The 12 observed signals correspond to the carbons of the product, showing the following chemical shifts: ^{13}CNMR δ: 170.0, 167.0, 137.0, 135.0, 129.3, 129.21, 128.4, 67.3, 66.6, 52.4, 50.4 and 30.6 ppm.

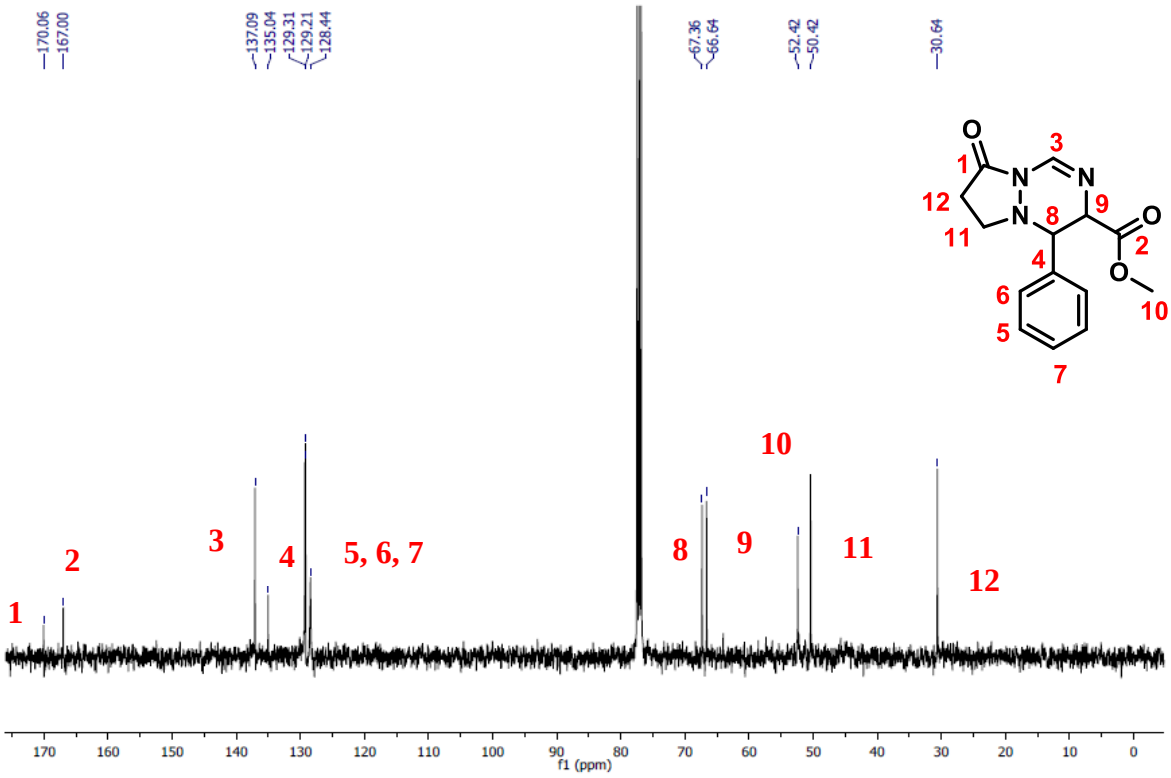
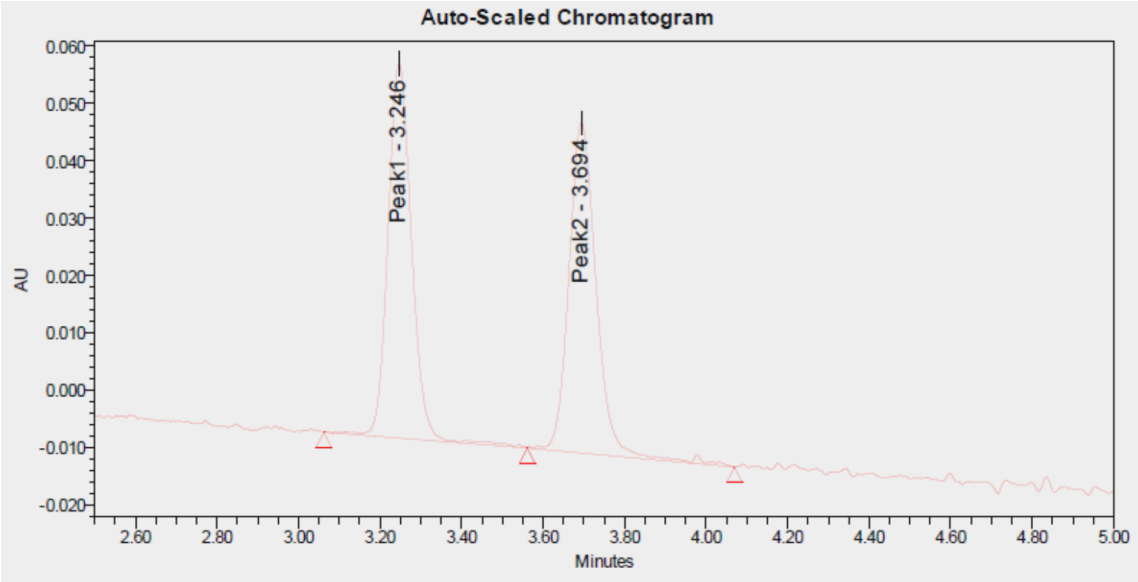


Figure 4.4 - 400 MHz ^{13}C NMR spectrum in $CDCl_3$ of compound (4.33).

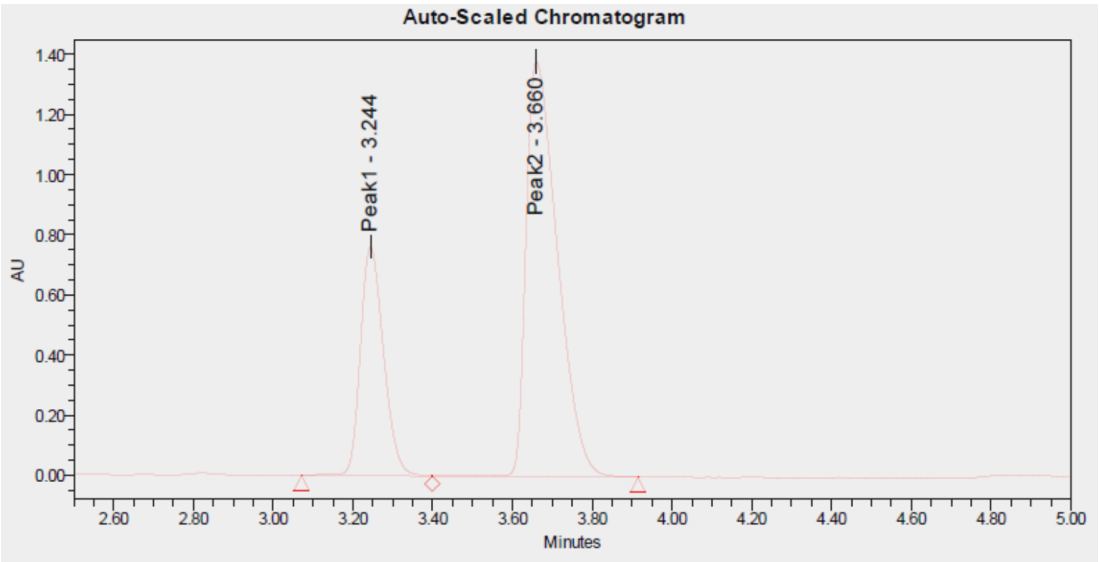
The enantiomeric excess of the product (4.33) was determined by comparison with the corresponding racemic standard, by Ultraperformance convergence chromatography (UPC^2) using Waters ACQUITY UPC^2 Trefoil CEL2 as chiral stationary phase, (Figures 4.6 and 4.7).



Processed Channel: PDA 275.0 nm

	Peak Name	Processed Channel	Retention Time (min)	Area	% Area	Height
1	Peak1	PDA 275.0 nm	3.246	263774	49.48	65351
2	Peak2	PDA 275.0 nm	3.694	269341	50.52	57602

Figure 4.5 - Chromatogram of racemic (4.33).



Processed Channel: PDA MaxPlot (190.0 nm to 800.0 nm)

	Peak Name	Processed Channel	Retention Time (min)	Area	% Area	Height
1	Peak1	PDA MaxPlot (190.0 nm to 800.0 nm)	3.244	3083626	28.95	761821
2	Peak2	PDA MaxPlot (190.0 nm to 800.0 nm)	3.660	7566420	71.05	1380326

Figure 4.6 - Chromatogram asymmetrical (4.33).

4.4 Partial conclusions and perspectives

Although we are in the initial step of this project, it is already possible to foresee some perspectives on it. We have demonstrated that by cooperative catalysis using catalyst system (D) it was possible to achieve 1,2,4-triazines in good yield and moderate enantioselectivity. However, the screening of other parameters, as solvents, temperature, concentration and analogues of catalyst (4.43) are still crucial for the search of the optimal reaction conditions for this transformation.

Experimental Section

5 Experimental Section

5.1 Experimental section of chapter 1

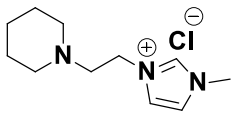
5.1.1 General Remarks:

For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. All solvents were used as purchased unless otherwise noted. Purification of products was carried out by flash chromatography (FC) on silica gel. Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were obtained using deuterated solvents ($CDCl_3$ and DMSO-d_6) in a Bruker Avance III spectrometer running at 400MHz for ^{1}H, 100 MHz for ^{13}C. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard. ^{1}H and ^{13}C NMR spectral data of the compounds are identical to those reported.

5.1.2 Synthesis of the Ionic Liquids:

The ionic liquids were synthesized according to the procedures described in the literature.[22,23]

Compound 1.35 = 1-methyl-3-(2-(piperidin-1-yl)ethyl)-1H-imidazol-3-ium-chloride.[22]

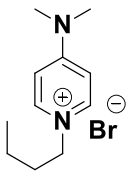


In a two neck 100 mL round-bottomed flask equipped with reflux condenser and magnetic stirrer, N-methyl imidazole (1.025 g, 12.5 mmol), 1-(2-chloroethyl)piperidine hydrochloride (1.84 g, 10 mmol) and absolute ethanol (10 mL) were added. The mixture was refluxed for 24 h. After the reaction,

the solvent was removed under vacuum, the residue was washed with dichloromethane and dried at 70 ˚C under vacuum. The white solid was dissolved in the mixture of ethanol (5 mL) and water (5 mL), and neutralized by NaOH (0.4 g, 10 mmol). After removal of solvents, the product was extracted with dichloromethane, dried at 70˚C under vacuum for 10 h. Pale yellow oily liquid was obtained in 90% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.52-1.37 (m, 6 H), 2.53-2.59 (m, 4 H), 2.90-2.94 (m, 2 H), 3.86 (s, 3 H), 4.42-4.47 (m, 2 H), 7.76 (s, 1 H), 7.86 (s, 1H), 9.41 (s, 1H) ppm**.**
^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.1, 24.4, 35.7, 45.0, 53.2, 56.5, 122.5, 123.2, 137.0 ppm.

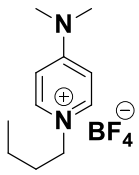
Compound 1.36: 1-butyl-4-(dimethylamino)pyridinium bromide.[23]



A mixture of 4-dimethylaminopyridine (5 mmol) and butyl bromide (6 mmol) and MeCN (10 mL) was allowed to stir 24 h at 70 ^{0}C. The resulting mixture was then evaporated affording the yellow crystals. The resulting crystalline mass was washed twice with ether (20 mL) and, after vacuum drying, a pale yellow crystals were obtained in 95% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (t, J = 7.3 Hz, 3 H), 1.27-1.16 (m, 2 H), 1.76-1.68 (m, 2 H), 3.17 (s, 6 H), 4.17 (t, J = 7.3 Hz, 2 H), 7.03 (d, J = 7.8 Hz, 2 H), 8.34 (d, J = 7.7 Hz, 2 H) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.3, 18.7, 32.3, 39.7, 56.3 (2C), 107.7, 142.0, 155.8 ppm.

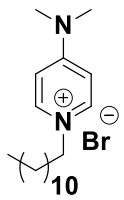
Compound 1.37: 1-butyl-4-(dimethylamino)pyridinium tetrafluoroborate.[23]



A mixture of 1-butyl-4-(dimethylamino)pyridinium bromide (5 mmol), sodium tetrafluoroborate (6 mmol) and distilled water (1 mL) was vigorously stirred for 60 min. The lower aqueous phase was separated and discarded and, to the remaining liquid, dichloromethane (20 mL) was added. The organic phase was separated and solvent evaporation afforded the desired 1-butyl-3-methylimidazolium tetrafluoroborate in quantitative yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (t, J = 7.3 Hz, 3 H), 1.27-1.16 (m, 2 H), 1.76-1.68 (m, 2 H), 3.17 (s, 6 H), 4.17 (t, J = 7.3 Hz, 2 H), 7.03 (d, J = 7.8 Hz, 2 H), 8.34 (d, J = 7.7 Hz, 2 H) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.3, 18.7, 32.3, 39.7, 56.3 (2C), 107.7, 142.0, 155.8 ppm.

Compound 1.38: 4-(dimethylamino)-1-dodecylpyridinium bromide.[23]

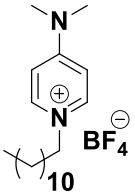


A mixture of 4-dimethylaminopyridine (5 mmol) and dodecyl bromide (6 mmol) and MeCN (10 mL) was allowed to stir 24 h at 70 ^{0}C. The resulting mixture was then evaporated affording the yellow crystals. The resulting crystalline mass was washed twice with ether (20 mL) and, after vacuum drying, pale yellow crystals was obtained in 99% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.83 (t, J = 7.25 Hz, 3 H), 1.30-1.13 (m, 18 H), 1.78-1.69 (m, 2 H), 3.17 (s, 6 H), 4.16 (t, J = 7,2 Hz, 2H), 7.03 (d, J = 7,6 Hz, 2H), 8.33 (d, J = 7.8 Hz, 2H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 25.4, 28.4, 28.7, 28.8, 28.9, 29.0 (2C), 31.3, 39.7, 56.6, 107.6, 142.0, 155.8 ppm.

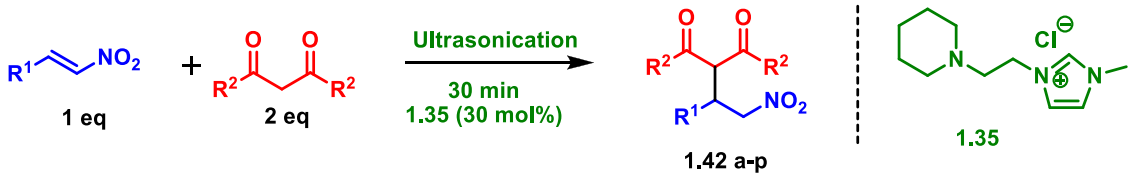
Compound 1.39: 4-(dimethylamino)-1-dodecylpyridinium tetrafluoroborate.[23]



A mixture of 4-(dimethylamino)-1-dodecylpyridinium bromide (5 mmol), sodium tetrafluoroborate (6 mmol) and distilled water (1 mL) was vigorously stirred for 60 min. The lower aqueous phase was separated and discarded and, to the remaining liquid, dichloromethane (20 mL) was added. The organic phase was separated and solvent evaporation afforded the desired 4-(dimethylamino)-1-dodecylpyridinium tetrafluoroborate in 100% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.83 (t, J = 7.25 Hz, 3 H), 1.30-1.13 (m, 18 H), 1.78-1.69 (m, 2 H), 3.17 (s, 6 H), 4.16 (t, J = 7,2 Hz, 2H), 7.03 (d, J = 7,6 Hz, 2H), 8.33 (d, J = 7.8 Hz, 2H) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 25.4, 28.4, 28.7, 28.8, 28.9, 29.0 (2C), 31.3, 39.7, 56.6, 107.6, 142.0, 155.8 ppm.

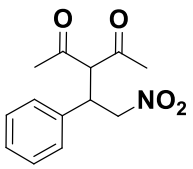
5.1.3 General Procedure for the Synthesis of Michael Adduct



In a vial, ionic liquid (0,075 mmol, 30 mol%), trans-β-nitrostyrene (0.25 mmol) and 1,3-dicarbonyl compound (0.5 mmol) was added and the reaction mixture was allowed under ultrasonication for 30

min. After completion of the reaction (monitored by TLC), the reaction mixture was washed with Et_2O (3x 10 mL) and dried over Na_2SO_4. The crude was purified by silica column chromatography affording the corresponding pure Michael adducts. The NMR data's of products were in accordance with literature.[85]

Compound 1.42a: 3-(2-nitro-1-phenylethyl)pentane-2,4-dione.



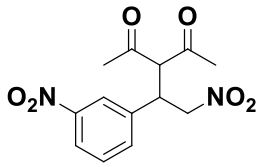
Following the general procedure, the product was isolated by FC on silica in 98% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.94 (s, 3 H), 2.28 (s, 3 H), 4.24-4.27 (m, 1 H), 4.37 (d, *J* = 10.8 Hz, 1 H), 4.63-4.65 (m, 2 H), 7.18-7.20 (m, 2 H), 7.28-7.33 (m, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.6, 30.4, 42.8, 70.6, 78.1, 128.0, 128.5, 129.3, 136.0, 201.1, 201.8 ppm.

Melting point = 53-54 ºC

Compound 1.42b: 3-(2-nitro-1-(3-nitrophenyl)ethyl)pentane-2,4-dione.

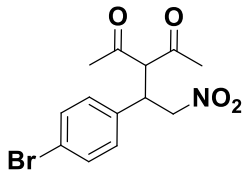


Following the general procedure, the product was isolated by FC on silica in 51% yield as a orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.06 (s, 3 H), 2.35 (s, 3 H), 4.39-4.43 (m, 2 H), 4.68-4.71 (m, 2 H), 7.55-7.58 (m, 2 H), 8.11-8.19 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.1, 30.6, 42.2, 70.1, 72.5, 122.7, 123.6, 130.4, 134.5, 138.5, 148.6, 200.0, 200.8 ppm.

Compound 1.42c: 3-(1-(4-bromophenyl)-2-nitroethyl)pentane-2,4-dione.



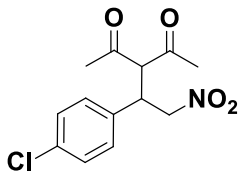
Following the general procedure, the product was isolated by FC on silica in 71% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.98 (s, 3 H), 2.30 (s, 3 H), 4.21-4.25 (m, 1 H), 4.33 (d, *J* = 10.7 Hz, 1 H), 4.58-4.62 (m, 2 H), 7.08 (dd, *J* = 8.3; 1.7 Hz, 2 H), 7.47 (dd, *J* = 8.5; 1.9 Hz, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.7, 30.4, 42.1, 70.4, 77.8, 122.7, 129.6, 132.5, 135.1, 200.5, 201.4 ppm.

Melting point = 93-95 ºC.

Compound 1.42d: 3-(1-(4-chlorophenyl)-2-nitroethyl)pentane-2,4-dione.



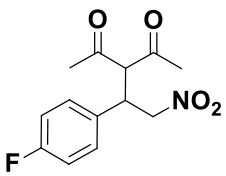
Following the general procedure, the product was isolated by FC on silica in 74% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.98 (s, 3 H), 2.30 (s, 3 H), 4.23-4.26 (m, 1 H), 4.34 (d, *J* = 10.7 Hz, 1 H), 4.59-4.65 (m, 2 H), 7.14 (dd, *J* = 8,3; 1.8 Hz, 2 H), 7.31 (dd, *J* =8,5; 1.9 Hz, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.6, 30.4, 42.1, 70.5, 77.9, 129.3, 129.6, 134.5, 134.6, 200.6, 201.4 ppm.

Melting point = 119-121 ºC.

Compound 1.42e: 3-(1-(4-fluorophenyl)-2-nitroethyl)pentane-2,4-dione.



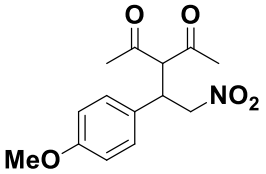
Following the general procedure, the product was isolated by FC on silica in 99% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.97 (s, 3 H), 2.30 (s, 3 H), 4.24-4.27 (m, 1 H), 4.33 (d, *J* = 10.8 Hz, 1 H), 4.60-4.62 (m, 2 H), 7.01-7.05 (m, 2 H), 7.16-7.20 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.6, 30.4, 42.0, 70.7, 78.1, 116.3, 116.5, 129.6, 129.7, 131.7, 163.7, 200.7, 201.5 ppm.

Melting point = 99-103 ºC.

Compound 1.42f: 3-(1-(4-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione.



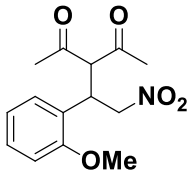
Following the general procedure, the product was isolated by FC on silica in 99% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.94 (s, 3H), 2.29 (s, 3 H), 3.77 (s, 3 H), 4.18-4.22 (m, 1 H), 4.33 (d, *J* = 10,9 Hz, 1 H), 4.58-4.60 (m, 2 H), 6.84 (d, *J* = 8,7 Hz, 2 H), 7.10 (d, *J* = 8,7 Hz, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.4, 30.3, 42.1, 55.2, 70.9, 78.4, 114.7, 127.6, 129.0, 159.5, 201.1, 201.9 ppm.

Melting point = 116-118 ºC.

Compound 1.42g: 3-(1-(2-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione.

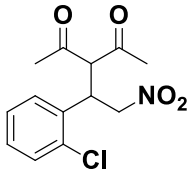


Following the general procedure, the product was isolated by FC on silica in 83% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.94 (s, 3 H), 2.28 (s, 3 H), 3.88 (s, 3 H), 4.49-4.56 (m, 1 H), 4.59-4.62 (m, 2 H), 4.78 (dd, *J* = 12.0, 7.5 Hz, 1 H), 6.88-6.91 (m, 2 H), 7.08 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.25-7.29 (m, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.7, 30.4, 38.9, 55.4, 69.1, 76.6, 111.2, 121.2, 123.5, 129.8, 130.2, 157.0, 201.6, 202.3 ppm.

Compound 1.42h: 3-(1-(2-chlorophenyl)-2-nitroethyl)pentane-2,4-dione.



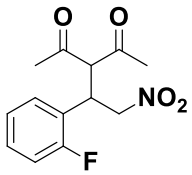
Following the general procedure, the product was isolated by FC on silica in 99% yield as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.04 (s, 3 H), 2.30 (s, 3 H), 4.61 (d, *J* = 9.8 Hz, 1 H), 4.66 (dd, *J* = 12.4, 3.9 Hz, 1 H), 4.72-4.77 (m, 1 H), 4.84 (dd, *J* = 12.2, 6.5 Hz, 1 H), 7.14-7.17 (m, 1 H), 7.24-7.27 (m, 2 H), 7.42-7.45 (m, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.4, 30.9, 38.8, 69.0, 76.2, 127.6, 128.99, 129.0, 129.7, 130.6, 133.4, 133.7, 200.8, 201.9 ppm.

Melting point = 119-124 ºC.

Compound 1.42i: 3-(1-(2-fluorophenyl)-2-nitroethyl)pentane-2,4-dione.



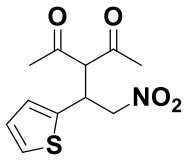
Following the general procedure, the product was isolated by FC on silica in 71% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.02 (s, 3 H), 2.30 (s, 3 H), 4.47-4.49 (m, 2 H), 4.62-4.65 (m, 1 H), 4.71-4.73 (m, 1 H), 7.08-7.10 (m, 2 H), 7.12-7.17 (m, 1 H), 7.26-7.33 (m, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.2, 30.4, 37.9, 69.0, 76.5, 116.4, 122.8, 124.9, 130.4, 130.5, 161.9, 200.7, 201.4 ppm.

Melting point = 101-104 ºC.

Compound 1.42j: 3-(2-nitro-1-(thiophen-2-yl)ethyl)pentane-2,4-dione.



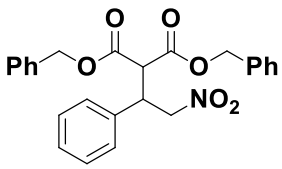
Following the general procedure, the product was isolated by FC on silica in 61% yield as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3 H), 2.30 (s, 3 H), 4.40 (d, *J* = 9.99 Hz, 1 H), 4.53-4.57 (m, 1 H), 4.67 (d, *J* = 6.05 Hz, 2 H), 6.89-6.94 (m, 2 H), 7.24 (dd, *J* = 5.1 Hz, 1.25 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.7, 30.6, 38.2, 71.1, 78.5, 125.7, 127.0, 127.4, 138.5, 200.7, 201.5 ppm.

Melting point = 67-68 ºC.

Compound 1.42k: Dibenzyl 2-(2-nitro-1-phenylethyl) malonate.



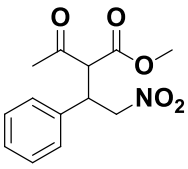
Following the general procedure, the product was isolated by FC on silica in 92% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (d, *J* = 9.2 Hz, 1 H), 4.22-4.28 (m, 1 H), 4.83-4.85 (m, 2 H), 4.90-4.98 (m, 2 H), 5.12-5.19 (m, 2 H), 7.07-7.09 (m, 2 H), 7.14-7.19 (m, 2 H), 7.26-7.33 (m, 11 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.9, 55.0, 67.6, 67.8, 77.4, 127.9, 128.3, 128.36, 128.4, 128.5, 128.6, 128.7, 129.0, 134.6, 134.7, 136.0, 166.6, 167.1 ppm.

Melting point = 72-73 ºC.

Compound 1.42l: Methyl 2-acetyl-4-nitro-3-phenylbutanoate.



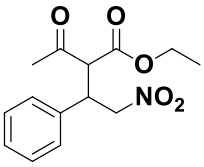
Following the general procedure, the product was isolated by FC on silica in 83% yield as a white solid. The (1.42l) showed 1:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.04 (s, 3 H), 2.29 (s, 3 H), 3.52 (s, 3 H), 3.77 (s, 3 H), 4.05 (d, *J* = 9.9 Hz, 1 H), 4.14 (d, *J* = 9.6 Hz, 1 H), 4.20-4.24 (m, 2 H), 4.77 (d, *J* = 6,4 Hz, 2 H), 4.81-4.84 (m, 2 H), 7.19-7.21 (m, 4 H), 7.29-7.32 (m, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.3, 30.4, 42.3, 42.6, 52.8, 53.0, 61.4, 61.8, 77.7, 77.8, 127.8, 127.9, 128.3, 128.4, 129.0, 129.2, 136.3, 136.4, 167.4, 168.0, 200.3, 201.2 ppm.

Melting point = 92-106 ºC.

Compound 1.42m: Ethyl 2-acetyl-4-nitro-3-phenylbutanoate.



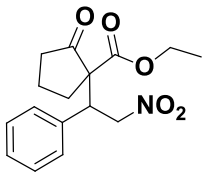
Following the general procedure, the product was isolated by FC on silica in 80% yield as a white solid. The (1.42m) showed 1:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.0 (t, *J* = 7.1 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 2.05 (s, 3 H), 2.30 (s, 3 H), 3.96 (q, *J* = 7.1 Hz, 2 H), 4.03 (d, *J* =10 Hz, 1 H), 4.12 (d, *J* = 10.2 Hz, 1 H), 4.21-4.24 (m, 4 H), 4.75 (d, *J* = 6.4 Hz, 2 H), 4.82–4.85 (m, 2 H), 7.20 (d, *J* = 7.2 Hz, 4 H), 7.28-7.32 (m, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 14.0, 30.1, 30.3, 42.3, 42.5, 61.7, 62.0 (2C) , 62.2, 77.8, 77.9, 127.9, 128.0, 128.3, 128.4, 129.0, 129.2, 136.4, 136.5, 166.9, 167.5, 200.3, 201.2 ppm.

Melting point = 71-74 ºC.

Compound 1.42n: Ethyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate.

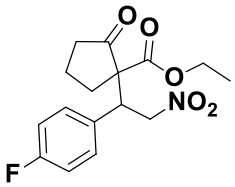


Following the general procedure, the product was isolated by FC on silica in 62 % yield as a colorless oil. The (1.42n) showed dr = 8:2, being the NMR data were described to major diastereomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, *J* = 7.6 Hz, 3 H), 1.90-2.04 (m, 4 H), 2.33-2.38 (m, 2 H), 4.08 (dd, *J* = 11.2, 3.7 Hz, 1 H), 4.20-4.23 (m, 2 H), 5.01 (dd, *J* = 13.9, 11.0 Hz, 1 H), 5.18 (dd, *J* = 13.2, 3.9 Hz; 1 H), 7.24-7.33 (m, 5 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 19.4, 31.2, 37.9, 46.2, 62.4, 62.8, 76.5, 128.3, 128.8, 129.3, 135.4, 169.4, 212.4 ppm.

Compound 1.42o: Ethyl1-(1-(4-fluorophenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate.

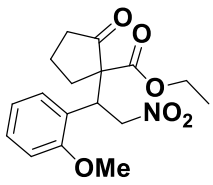


Following the general procedure, the product was isolated by FC on silica in 99 % yield as colourless oil. The (1.42o) showed dr = 7:3, being the NMR data were described to major diastereomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, *J* = 7.3 Hz, 3 H), 1.86-1.95 (m, 4 H), 2.35-2.38 (m, 2 H), 4.06 (dd, *J* =11.2; 3.7 Hz, 1 H), 4.20 (dd, *J* = 7.0; 1.6 Hz, 2 H), 4.97 (dd, *J* = 13.5; 11.5 Hz, 1 H), 5.14 (dd, *J* = 13.5; 3.7 Hz, 1 H), 6.98-7.02 (m, 2 H), 7.25-7.29 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 19.3, 31.4, 37.8, 45.5, 62.3, 62.4, 115.7, 115.9, 116.1, 130.8, 131.2, 161.3, 163.7, 169.3, 212.2 ppm.

Compound 1.42p: Ethyl 1-(1-(2-methoxyphenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate.



Following the general procedure, the product was isolated by FC on silica in 89 % yield as colourless oil. The (1.42p) showed dr = 7:3, being the NMR data were described to major diastereomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, *J* = 7.4 Hz, 3 H), 1.88-1.92 (m, 4 H), 2.31-2.40 (m, 2 H), 3.81 (s, 3 H), 4.20 (q, *J* = 7.2 Hz ,2 H), 4.35 (dd, *J* = 10.8; 3.7 Hz, 1 H), 5.12 (dd, *J* = 14.4; 10.3 Hz, 1 H), 5.39 (dd, *J* = 13.6; 3.7 Hz, 1 H), 6.86-6.91 (m, 2 H), 7.23-7.29 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 19.1, 32.4, 33.6, 37.8, 55.6, 61.8, 62.3, 76.4, 111.2, 121.1, 124.7, 129.3, 129.5, 157.7, 169.2, 213.1 ppm.

5.2 Experimental section of chapter 2

5.2.1 General remarks

^{1}H and ^{13}C NMR spectra were recorded on in a Bruker Avance III spectrometer running at 400MHz for ^{1}H, 100 MHz for ^{13}C. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard. All NMR spectra were obtained with $CDCl_3$.

HPLC chromatograms of Michael adduct were obtained on a Shimadzu apparatus, LC-20AT Pump, SPD-M20A UV-Vis Detector, CBM-20A System Controller, using a Chiralcel OD-H (4,6 mmØ x 250 mmL, particle size 5 µm), Chiralpak AD-H (4,6 mmØ x 250 mmL, particle size 5 µm), Chiralcel AS-H (4,6 mmØ x 250 mmL, particle size 5 µm) and Chiralpak IC (2,1 mmØ x 150 mmL, particle size 5 µm).

Optical rotations were measured with a Schmidt + Haensch Polartronic H Polarimeter, at 589 nm, 23 °C. Using a 1 mL cell with a 1 dm path length and reported as follows: $[\alpha]_D^{23}$(c in g per mL of solvent).All the compounds synthesized in the manuscript are known componds. Their relative and absolute configurations of the products were determined by comparison with the known ^{1}H and ^{13}C NMR, chiral HPLC analysis, and optical rotation values.

All solvents were used as purchased unless otherwise noted. Purification of products was carried out by column chromatography performed on Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with KMnO4 solution.

5.2.2 General procedure for Michael Addition:

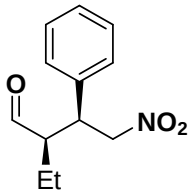
The aldehyde (0.6 mmol), nitroolefin (0.3 mmol) and the benzoic acid (0.015 mmol) were added to a solution of the catalyst (0.015 mmol) in PEG-400 (0.5 mL). The reaction mixture was stirred for 19 h and then was directly purified by flash column chromatography on silica gel using n-hexane/EtOAc as the eluent. The enantiomeric excess was determined by chiral-stationary-phase HPLC analysis through comparison with the authentic racemic material. Assignment of the stereoisomers was performed by comparison with literature data. [86]

5.2.3 General procedure for PEG-400 recyclability experiments

After complete the reaction time, 0.25 mL of water was added to the PEG mixture (an emulsion appears) and the mixture PEG-aqueous solution were extracted sequentially with 1 mL of Ether for three times until light yellow color in PEG-aqueous solution disappear. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using n-hexane/EtOAc as eluent. The PEG-aqueous solutions was concentrated under reduced pressure until the water was removed and the result PEG recovered was dried in high vacuum pump and further add the Michael reagents and run a new reaction in the solvent recycled.

5.2.4 Characterization of conjugate addition products

Compound 2.52a: (2R,3S)-2-ethyl-4-nitro-3-phenylbutanal



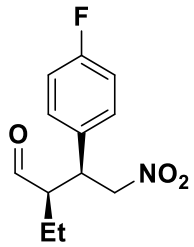
Analytical data for major diastereoisomer were in agreement with the published data

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.72, 9.49 (2xd, *J* = 2.6 Hz, 1H; CHO), 7.36- 7.29 (m, 3H; Ph), 7.19- 7.17 (m, 2H; Ph), 4.72 (dd, *J* = 5.0 Hz, 12.7 Hz, 1H; CH_2NO_2), 4.63 (dd, *J* = 9.6 Hz, 12.7 Hz, 1H, CH_2NO_2), 3.79 (td, *J* = 5.0 Hz, 9.8 Hz, 1H; CHPh), 2.71- 2.65 (m, 1H; CHCHO), 1.54- 1.47 (m, 2H; CH_2CH_3), 0.83 (t, *J* = 0.83 Hz, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 203.2, 136.8, 129.1, 128.1, 128.0, 78.5, 55.0, 42.7, 20.4, 10.7 ppm.

$[\alpha]_D^{25}$ = +25.21 (*c* 0.0046 g. mL^{-1}, MeOH)

Compound 2.52b: (2R,3S)-2-ethyl-3-(4-fluorophenyl)-4-nitrobutanal.



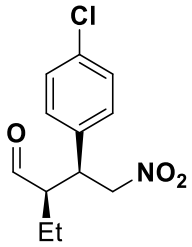
Analytical data for major diastereoisomer were in agreement with the published data

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.74-9.51 (2xd, *J* = 2.4 Hz, 1H; CHO), 7.20- 7.17 (m, 2H; Ph), 7.08- 7.02 (m, 2H; Ph), 4.74 (dd, *J* = 4.8 Hz, 12.7 Hz, 1H; CH_2NO_2), 4.61 (dd, *J* = 9.9 Hz, 12.7 Hz, 1H; CH_2NO_2), 3.84- 3.78 (m, 1H; CHPh), 2.71- 2.65 (m, 1H; CHCHO), 1.58–1.44 (m, 2H; CH_2CH_3), 0.86 (t, *J* = 7.5 Hz, 3H; CH_3) ppm;

^{13}C NMR (100 MHz, CDCl3, 25°C) δ = 203.0, 163.7, 132.7, 129.8, 129.7, 116.4, 116.2, 78.7, 55.0, 42.7, 20.4, 10.7ppm.

$[\alpha]_D^{25}$ = +9.75 (*c* 0.0041 g. mL^{-1}, MeOH)

Compound 2.52c: (2R,3S)-3-(4-chlorophenyl)-2-ethyl-4-nitrobutanal.



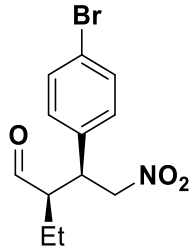
Analytical data for major diastereoisomer were in agreement with the published data.

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.74, 9.51 (2xd, *J* = 2.8 Hz, 1H; CHO), 7.36-7.28 (m, 2H; Ph), 7.16-7.14 (m, 2H; Ph), 4.73 (dd, *J* = 4.8 Hz, 12.8 Hz, 1H; CH_2NO_2), 4.63 (dd, *J* = 9.9 Hz, 12.8 Hz, 1H; CH_2NO_2), 3.80 (dt, *J* = 4.8 Hz, 10.0 Hz, 1H; CHPh), 2.72- 2.66 (m, 1H; CHCHO), 1.57- 1.47 (m, 2H; CH_2CH_3), 0.86 (t, *J* = 7.5 Hz, 3H; CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 202.8, 135.5, 134.2, 129.8, 129.5, 54.8, 42.2, 20.5, 10.7 ppm.

$[\alpha]_D^{25}$ = +7.5 (*c* 0.0020 g. mL^{-1}, MeOH)

Compound 2.52d: (2R,3S)-3-(4-bromophenyl)-2-ethyl-4-nitrobutanal.



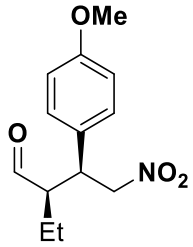
Analytical data for major diastereoisomer were in agreement with the published data.

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ =9.79, 9.49 (2xd, *J* = 2.3 Hz, 1H, CHO), 7.49- 7.45 (m, 2H, Ph), 7.07 (d, *J* = 8.3 Hz, 2H, Ph), 4.81-4.70 (m, 1H, CH_2NO_2), 4.62- 4.57 (m, 1H, CH_2NO_2), 3.80- 3.74 (m, 1H, CHPh), 2.70- 2.64 (m, 1H, CHCHO), 1.55-1.44 (m, 2H, CH_2CH_3), 0.84 (t, *J* = 7.5 Hz, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 202.8, 136.0, 132.5, 129.8, 122.3, 78.4, 54.8, 42.2, 20.5, 10.7 ppm.

$[\alpha]_D^{25}$ = +0.61 (*c* 0.0065 g. mL^{-1}, MeOH)

Compound 2.52e: (2R,3S)-2-ethyl-3-(4-methoxyphenyl)-4-nitrobutanal.



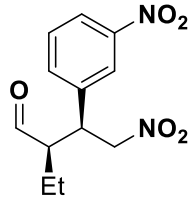
Analytical data for major diastereoisomer were in agreement with the published data.

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.71, 9.47 (2xd, *J* = 2.6 Hz, 1H, CHO), 7.09 (d, *J* = 8.6 Hz, 2H, Ph), 6.88- 6.83 (m, 2H, Ph), 4.69 (dd, *J* = 4.9 Hz, 12.5 Hz, 1H, CH_2NO_2), 4.61- 4.55 (m, 1H, CH_2NO_2), 3.79 (s, 3H, OMe), 3.75- 3.71 (m, 1H, CHPh), 2.66-2.60 (m, 1H, CHCHO), 1.56- 1.45 (m, 2H, CH_2CH_3), 0.83 (t, *J* = 7.5 Hz, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 203.5, 159.4, 129.4, 129.2, 114.6, 78.9, 55.4, 55.3, 42.2, 20.5, 10.8 ppm.

$[\alpha]_D^{25}$ = +2.29 (*c* 0.0061 g. mL^{-1}, MeOH)

Compound 2.52f: (2R,3S)-2-ethyl-4-nitro-3-(3-nitrophenyl)butanal.



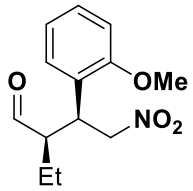
Analytical data for major diastereoisomer were in agreement with the published data

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.68, 9.48 (2xd, *J* = 2.8 Hz, 1H; CHO), 8.12-8.04 (m, 2H; Ph), 7.56-7.47 (m, 2H; Ph), 4.74 (dd, *J* = 4.8 Hz, 12.8 Hz, 1H; CH_2NO_2), 4.63 (dd, *J* = 9.9 Hz, 12.8 Hz, 1H; CH_2NO_2), 3.89 (dt, *J* = 4.8 Hz, 10.0 Hz, 1H; CHPh), 2.77-2.71 (m, 1H; CHCHO), 1.57-1.38 (m, 2H; CH_2CH_3), 0.80 (t, *J* = 7.5 Hz, 3H; CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 202.2, 148.8, 139.5, 134.6, 130.3, 123.4, 123.0, 78.0, 54.4, 42.2, 20.5, 10.5 ppm,

$[\alpha]_D^{25}$ = -1.90 (*c* 0.0042 g. mL^{-1}, MeOH)

Compound 2.52g: (2R,3S)-2-ethyl-3-(2-methoxyphenyl)-4-nitrobutanal.



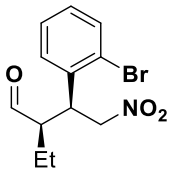
Analytical data for major diastereoisomer were in agreement with the published data.

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.70, 9.41 (2xd, *J* = 2.6 Hz, 1H, CHO), 7.29-7.25 (m, 1H, Ph), 7.11-7.09 (m, 1H, Ph), 6.93-6.87 (m, 2H, Ph), 4.87- 4.78 (m, 1H, CH_2NO_2), 4.67-4.64 (m, 1H, CH_2NO_2), 4.05- 3.99 (m, 1H, CHPh), 3.84 (s, 3H, OCH_3Ph), 2.96-2.90 (m, 1H, CHCHO), 1.49-1.45 (m, 2H, CH_2CH_3), 0.81 (t, *J* = 7.5 Hz, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 203.8, 157.6, 130.6, 129.4, 124.6, 121.1, 111.3, 55.5, 53.6, 39.5, 20.6, 10.9 ppm.

$[\alpha]_D^{25}$ = +11.72 (*c* 0.00435 g. mL^{-1}, MeOH)

Compound 2.52h: (2R,3S)-3-(2-bromophenyl)-2-ethyl-4-nitrobutanal.



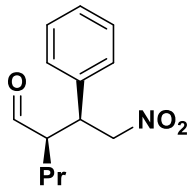
Analytical data for major diastereoisomer were in agreement with the published data.

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.74, 9.60 (2xd, *J* = 2.4 Hz, 1H, CHO), 7.61 (dd, *J* = 1.1 Hz, 8 Hz, 1H, Ph), 7.34- 7.30 (m, 1H, Ph), 7.21-7.15 (m, 2H, Ph), 4.89- 4.83 (m, 1 H,CH_2NO_2), 4.67 (dd, *J* = 4.6 Hz, 13 Hz, 1H, CH_2NO_2), 4.40- 4.31 (m, 1H, CHPh), 2.97- 2.91 (m, 1H, CHCHO), 1.67- 1.59 (m, 2H, CH_2CH_3), 0.88 (t, *J* = 0.9 Hz, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 202.9, 136.2, 134.1, 129.8, 129.6, 128.1, 76.3, 54.4, 41.4, 20.6, 11.1 ppm.

$[\alpha]_D^{25}$ = +2.98 (*c* 0.0057 g. mL^{-1}, MeOH)

Compound 2.52i: (R)-2-((S)-2-nitro-1-phenylethyl)pentanal.



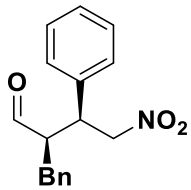
Analytical data for major diastereoisomer were in agreement with the published data

^{1}H NMR (400 MHz,CDCl3, 25°C) δ = 9.63, 9.40 (2xd, *J* = 2.4 Hz, 1H; CHO), 7.29-7.19 (m, 3H; Ph), 7.11- 7.09 (m, 2H; Ph), 4.60 (dd, *J* = 7.4 Hz, 11.7 Hz, 2H; CH_2NO_2), 3.71 (dt, *J* = 4.8 Hz, 10.0 Hz, 1H; CHPh), 2.66-2.60 (m, 1H; CHCHO), 1.58–1.06 (m, 6H; 3xCH_2), 0.73 (t, *J* = 7.5 Hz, 3H; CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 203.4, 136.9, 129.2, 128.12, 78.6, 53.9, 43.4, 29.6, 19.8, 14.0 ppm.

[α]$_D^{25}$ = +23.94 (*c* 0.005075 g. mL^{-1}, MeOH)

Compound 2.52j: (2R,3S)-2-benzyl-4-nitro-3-phenylbutanal



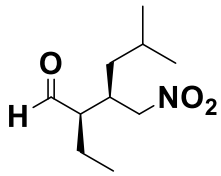
Analytical data for major diastereoisomer were in agreement with the published data

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.61, 9.46 (2xd, *J* = 2.3 Hz, 1H; CHO), 7.31-7.10 (m, 9H; Ph), 6.93-6.95 (m, 1H; Ph), 4.62 (dd, *J* = 2.6 Hz, 7.3 Hz, 2H; CH_2NO_2), 3.77- 3.71 (m, 1H; CHPh), 3.05-2.91 (m, 1H); 2.79-2.59 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 203.1, 137.3, 136.8, 129.4, 128.9, 128.6, 128.4, 128.2, 127.1, 78.4, 55.4, 43.6, 34.4 ppm.

[α]$_D^{25}$ = -8.80 (*c* 0.0042 g. mL^{-1}, MeOH)

Compound 2.52k: (2R,3R)-2-ethyl-5-methyl-3-(nitromethyl)hexanal.



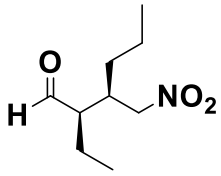
Analytical data for major diastereoisomer were in agreement with the published data

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.72, 9.61 (2xd, *J* = 1.8 Hz, 1H; CHO), 4.49- 4.40 (m, 2H, CH_2NO_2), 2.76- 2.70 (m, 1H; CH_2CH_3), 2.46- 2.33 (m, 1H, CH_2CH_3), 1.84- 1.76 (m, 1H, CHCHO), 1.63- 1.52 (m, 1H, $CH(CH_3)_2$), 1.52- 1.46 (m, 1H, $CHCH_2CH(CH_3)_2$), 1.29- 1.18 (m, 2H, $CH_2CH(CH_3)_2$), 1.03- 0.99 (m, 3H, CH_3), 0.92- 0.90 (m, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 203.1, 77.1, 54.1, 38.3, 34.7, 25.2, 22.7, 22.1, 18.6, 12.2 ppm.

$[\alpha]_D^{23}$ = -9.37 (*c* 0.0061 g. mL^{-1}, MeOH)

Compound 2.52l: (2R,3R)-2-ethyl-3-(nitromethyl)hexanal



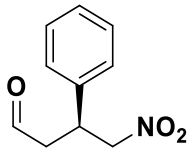
Analytical data for major diastereoisomer were in agreement with the published data

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.71, 9.62 (2xd, *J* = 1.7 Hz, 1H; CHO), 4.45 (qd, *J* = 6.6 Hz, 12.5 Hz, 2H, CH_2NO_2), 2.69- 2.64 (m, 1H; CH_2CH_3), 2.44- 2.40 (m, 1H, CH_2CH_3), 1.82- 1.74 (m, 1H, CHCHO), 1.55- 1.51 (m, 1H, $CH(CH_2)_2CH_3$), 1.40- 1.35 (m, 4H, $(CH_2)_2CH_3$), 1.03- 1.00 (m, 3H, CH_3), 0.95- 0.90 (m, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 200.4, 77.2, 53.9, 36.8, 31.3, 19.9, 18.6, 13.8, 11.9ppm.

$[\alpha]_D^{23}$ = -2.5 (*c* 0.00326 g. mL^{-1}, MeOH)

Compound 2.56a: (S)-4-nitro-3-phenylbutanal.



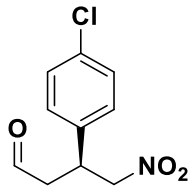
Prepared from acetaldehyde (3 mmol) and trans-β-nitrosyterene (0.3 mmol) according the general procedure.

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.62 (s, 1H; CHO), 7.29- 7.21 (m, 3H; Ph), 7.17-7.15 (m, 2H; Ph), 4.57 (qd, *J* = 7.4 Hz, 12.5 Hz; 2H,CH_2NO_2), 4.0 (p, *J* = 7.2 Hz, 1H; CHPh), 2.93- 2.82 (m, 2H; CH_2CHO) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 198.8, 138.2, 129.2, 128.1, 127.4, 79.4, 46.4, 37.9 ppm.

$[\alpha]_D^{25}$ = -0.85 (*c* 0.0047 g. mL^{-1}, MeOH)

Compound 2.56b: (S)-3-(4-chlorophenyl)-4-nitrobutanal.



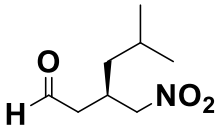
Prepared from acetaldehyde (3 mmol) and trans-β-nitrosyterene (0.3 mmol) according the general procedure.

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.70 (s, 1H; CHO), 7.34-7.30 (m, 2H; Ph), 7.19-7.16 (m, 2H; Ph), 4.70-4.65 (m, 1H; CH_2NO_2), 4.59 (dd, *J* = 7.9 Hz, 12.6 Hz, 1H; CH_2NO_2), 4.10-4.02 (m, 1H; CHPh), 2.94 (dd, *J* = 0.7 Hz, 7.1 Hz, 2H; CH_2CHO) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 198.5, 136.8, 134.2, 129.5, 128.9, 79.2, 46.4, 37.4 ppm.

$[\alpha]_D^{25}$ = -8.67 (*c* 0.0128 g. mL^{-1}, MeOH)

Compound 2.56c: (R)-5-methyl-3-(nitromethyl)hexanal



Prepared from acetaldehyde (3 mmol) and trans-β-nitrosyterene (0.3 mmol) according the general procedure.

^{1}H NMR (400 MHz,$CDCl_3$, 25°C) δ = 9.79 (s, 1H, CHO), 4.49- 4.40 (m, 2H, CH_2NO_2), 2.81- 2.75 (m, 1H, $CHCH_2CH(CH_3)_2$, 2.63 (ddd, *J* = 6.2 Hz, 18.4 Hz, 24.1 Hz, 2H, CH_2CHO), 1.67- 1.61 (m, 1H, $CH(CH_3)_2$), 1.28 (td, *J* = 2.3 Hz, 7.2 Hz, 2H, $CH_2CH(CH_3)_2$) 0.93 (dd, *J* = 6.5 Hz, 12.2 Hz, 6H, $(CH_3)_2$) ppm;

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ = 199.9, 78.5, 45.5, 40.7, 29.9, 25.1, 22.3 ppm.

$[\alpha]_D^{23}$ = -15.38 (*c* 0.0195 g. mL^{-1}, MeOH)

5.3 Experimental section of chapter 3

5.3.1 General methods

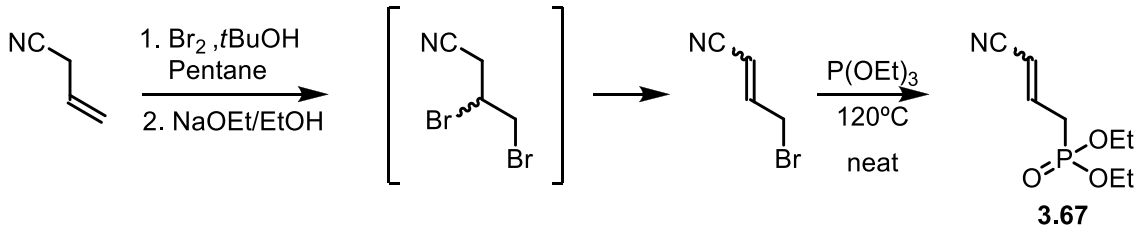
NMR spectra were acquired on a Bruker AVANCE III HD spectrometer running at 400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F and 162 MHz for ^{31}P. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). Chemical shifts (δ) for ^{19}F NMR are reported in ppm relative to $CFCl_3$ as external reference and for ^{31}P NMR relative to H_3PO_4 as external reference. The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal; dd, double doublet; ddd, double double doublet; dt, double triplet. ^{13}C spectra were acquired in broad band decoupled mode. For characterization of isomeric mixtures * denotes minor isomer, # denotes overlap of signals of both isomers, whereas no sign denotes signal of major isomer. The number of protons given in parenthesis is the sum over both isomers. Mass spectra were recorded on a Bruker Maxis Impact mass spectrometer using electronspray (ES^+) ionization (referenced to the mass of the charged species). Dry solvents were obtained from a MBraun MB SPS-800 solvent purification system. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by UV radiation, $KMnO_4$ or *p*-anisaldehyde stains. For flash chromatography (FC) silica gel (Silica gel 60, 230- 400 mesh, Sigma-Aldrich) or Iatrobeads 6RS-8060 were used. Optical rotations were measured on a PerkinElmer 241 polarimeter, $[\alpha]_D$ values are given in $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$; concentration c in g $(100\ mL)^{-1}$. The diastereomeric ratio (dr) of products was evaluated by ^{1}H NMR analysis of the crude mixture. The enantiomeric excess (*ee*) of products was determined

by Ultraperformance Convergence Chromatography (Waters ACQUITY UPC^2) using Daicel Chiralpak IA, IB, IC, and ID columns as chiral stationary phases.

Racemates for UPC^2 analysis were made applying a mixture of both enantiomers of the catalyst. In these reactions, the dr was poor and in some cases the diastereoisomers could not be well separated by FC. Therefore, the diastereoisomeric mixture was characterized by means of chiral stationary phase UPC^2 in which all four peaks were present; the correct correspondence of the peaks was confirmed by the juxtaposition of the UV spectra, recorded by the PDA detector of the UPC^2 system. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.

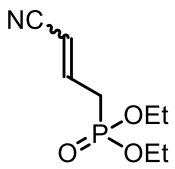
5.3.2 Synthesis of (*E*,*E*)-2,4-dienals (3.68 c-g)

5.3.2.1 Synthesis of (E,E)-2,4-dienal (3.68c)



3.67

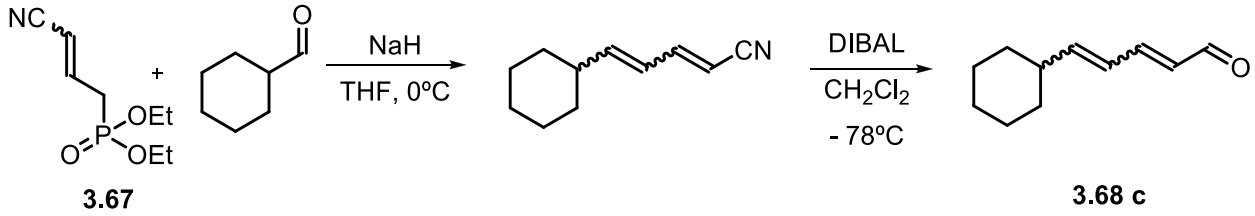
Compound 3.67: Diethyl (3-cyanoallyl)phosphonate.[87]



To a solution of allylcyanide (20.0 g, 0.3 mol, 1.0 eq) in pentane (130 mL) at 0 ºC, a solution of Br_2 (15.3 mL, 0.3 mol, 1.0 eq) in *t*BuOH (30 mL) was added. The mixture was stirred at room temperature for 30 min, then NaOEt (111.3 mL, 0.3 mol, 1.0 eq, 21% in EtOH) was added dropwise. The obtained suspension was filtered over celite and the filtrate concentrated. The crude product was used in the next step

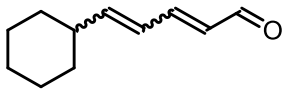
without further purification. Triethyl phosphite (42.0 mL, 240 mmol, 0.8 eq,) was added to the crude product and the mixture was stirred at 120 ºC for 3 h. Product **3.67** was isolated by FC on silica (EtOAc/pentane 50:50) and obtained as an orange oil in 79% yield over 2 steps with a *E*/*Z*-ratio of 1.2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (dq, *J* = 15.6, 7.7 Hz, 1H), 6.58-6.48* (m, 1H), 5.54-5.45$^{\#}$ (m, 2H), 4.21-4.04$^{\#}$ (m, 8H), 2.98* (dd, *J* = 23.3, 8.1 Hz, 2H), 2.75 (dd, *J* = 23.1, 7.7 Hz, 2H), 1.36-1.30$^{\#}$ (m, 12H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (d, *J* = 11.5 Hz), 144.0* (d, *J* = 11.1 Hz), 116.5 (d, *J* = 4.5 Hz), 115.1* (d, *J* = 4.9 Hz), 104.0 (d, *J* = 15.0 Hz), 103.2* (d, *J* = 14.4 Hz), 62.6 (d, *J* = 2.5 Hz, 2C), 62.5* (d, *J* = 2.6 Hz, 2C), 32.7 (d, *J* = 139.4 Hz), 30.5* (d, *J* = 138.1 Hz), 16.4 (d, *J* = 3.5 Hz, 2C), 16.3* (d, *J* = 3.6 Hz, 2C).
^{31}P NMR (162 MHz, $CDCl_3$) δ 22.53, 22.40*.
HRMS calculated for: $[C_8H_{14}NO_3P+H]^+$ 204.0790; found: 204.0786.



3.67 **3.68 c**

Compound 3.68c: 5-Cyclohexylpenta-2,4-dienal.



Cyanophosphonate **3.67** (2.23 g, 11 mmol, 1.1 eq) was added dropwise to a suspension of NaH (520 mg, 13 mmol, 1.3 eq, 60% in mineral oil) in dry THF (50 mL) at 0 ºC under N_2 atmosphere, and the mixture was stirred for 10 min. Cyclohexanecarboxaldehyde (1.21 mL, 10 mmol, 1.0 eq) was then added dropwise during 5 min. The system was allowed to warm up to room

temperature and stirred for 2.5 h. Upon completion of the reaction, sat. aq. NH_4Cl (10 mL) was added dropwise. The system was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

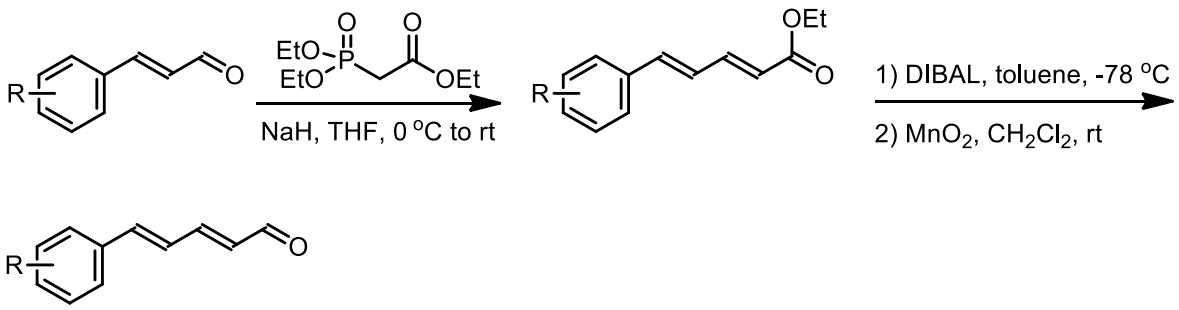
The crude product of the previous step was diluted in dry CH_2Cl_2 (50 mL) and cooled to -78 ºC under N_2 atmosphere. DIBAL (13.0 mL, 13 mmol, 1.3 eq, 1.0 M in CH_2Cl_2) was added dropwise and the system stirred at -78 ºC for 2.5 h. Upon completion of the reaction, EtOAc (10 mL) was added dropwise, and the system was let to warm up to room temperature. Sat. aq. Rochelle salt (100 mL) was added dropwise. The suspension was stirred vigorously for 5 h to give a biphasic system and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was isolated by FC on silica using (EtOAc/pentane 10:90 to 20:80). The product was obtained in 62% yield over 2 steps as a mixture of isomers (*E*/*E* : *Z*/*E* : *E*/*Z* 12:3:2) as a yellow oil. In the ^{1}H NMR description below, $*^1$ and $*^2$ represents the two minor isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17$*^2$ (d, *J* = 8.0 Hz, 1H), 9.62$*^1$ (d, *J* = 8.2 Hz, 1H), 9.53 (d, *J* = 8.0 Hz, 1H), 7.51-7.40$*^2$ (m, 1H), 7.08 (dd, *J* = 15.2, 10.0 Hz, 1H), 7.02-6.86$*^{1+2}$ (m, 2H), 6.34-6.02$^{\#}$ (m, 6H), 5.89-5.74$*^{1+2}$ (m, 2H), 2.65-2.55$*^2$ (d, *J* = 10.3 Hz, 1H), 2.20-2.08$^{\#}$ (s, 2H), 1.79-1.61$^{\#}$ (m, 15H), 1.37-1.11$^{\#}$ (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 153.4, 152.6, 130.1, 126.1, 41.3, 32.1 (2C), 25.9, 25.7 (2C).

HRMS calculated for: $[C_{11}H_{16}O+H]^+$ 165.1274; found: 165.1274.

5.3.2.2 Synthesis of aromatic (E,E)-2,4-dienals 3.68 d-g.[88]



1d-g

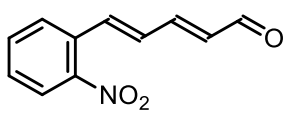
Triethylphosphonoacetate (1.1 mL, 5.5 mmol, 1.1 eq) was added dropwise to a stirred suspension of NaH (220 mg, 5.5 mmol, 1.1 eq, 60% oil dispersion) in dry THF (10 mL) at 0 °C under Ar atmosphere. The mixture was stirred for 1 h before a solution of the (*E*)-cinnamaldehyde (5.0 mmol, 1.0 eq) in THF (5 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred until completion, monitored by TLC. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and the aqueous phase extracted with Et_2O (3 x 10 mL). The combined organic phase was washed with water (20 mL), brine (3 x 20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification.

DIBAL (15.0 mL, 15.0 mmol, 3 eq, 1.0 M in toluene) was added dropwise to a stirred solution of the diene ester in dry toluene (35 mL) under Ar atmosphere at -78 °C. The reaction was stirred for 15 min before it was quenched by carefully adding water (5 mL). The mixture was allowed to warm to room temperature before it was poured into a suspension of $NaHCO_3$ (18 g) and $MgSO_4$ (18 g) in EtOAc (180 mL). After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step without further purification.

The alcohol was dissolved in dry CH_2Cl_2 (180 mL) and activated MnO_2 (4.78 g, 55 mmol, 11 eq) was added. After stirring

vigorously for 1.5 h the solid was filtered off, washing with EtOAc, and the solvent removed under reduced pressure. The crude product was purified by FC.

Compound 3.68d: (2*E*,4*E*)-5-(2-Nitrophenyl)penta-2,4-dienal.



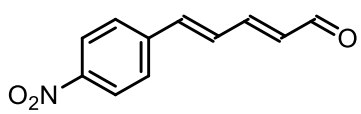
Following the general procedure the aldehyde **3.68d** was isolated by FC on silica (EtOAc/pentane 20:80 to 50:50) in 77% yield over 3 steps as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.59-7.47 (m, 2H), 7.32 (dd, *J* = 15.3, 10.9 Hz, 1H), 6.96 (dd, *J* = 15.4, 10.9 Hz, 1H), 6.33 (dd, *J* = 15.3, 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 150.5, 148.1, 136.4, 133.5, 133.4, 131.2, 130.8, 129.7, 128.5, 125.0.

HRMS calculated for: $[C_{11}H_9NO_3+H]^+$ 204.0655; found: 204.0652.

Compound 3.68e: (2*E*,4*E*)-5-(4-Nitrophenyl)penta-2,4-dienal.



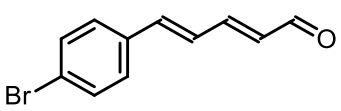
Following the general procedure (10 mmol scale) the aldehyde **3.68e** was isolated by FC on silica (EtOAc/pentane 5:95 to 35:65) in 63% yield over 3 steps as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 7.8 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.33-7.23 (m, 1H), 7.17-7.03 (m, 2H), 6.37 (dd, *J* = 15.2, 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 150.0, 147.9, 141.7, 139.0, 133.7, 130.2, 127.9 (2C), 124.3 (2C).

HRMS calculated for: $[C_{11}H_9NO_3+H]^+$ 204.0655; found: 204.0657.

Compound 3.68f: (2*E*,4*E*)-5-(4-Bromophenyl)penta-2,4-dienal.



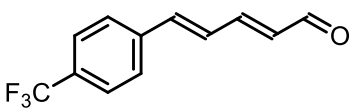
Applying 4-bromobenzaldehyde as starting material in the general procedure (5 mmol scale) and repeating the procedure without the purification after the third step, **3.68f** was isolated by FC on silica (EtOAc/pentane 5:95 to 8:92) in 26% yield over 6 steps as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.28-7.20 (m, 1H), 7.04 -6.90 (m, 2H), 6.29 (dd, *J* = 15.2, 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 151.4, 140.8, 134.5, 132.1 (2C), 132.1, 128.9 (2C), 126.8, 123.8.

HRMS calculated for: $[C_{11}H_9BrO+H]^+$ 236.9910; found: 236.9910.

Compound 3.68g: (2*E*,4*E*)-5-(4-(Trifluoromethyl)phenyl)penta-2,4-dienal.



Applying 4-(trifluoromethyl)benzaldehyde as starting material in the general procedure (5 mmol scale) and repeating the procedure without the purification after the third step, **3.68g** was isolated by FC on silica (EtOAc/pentane 20:80) in 26% yield over 6 steps as a pale yellow solid.

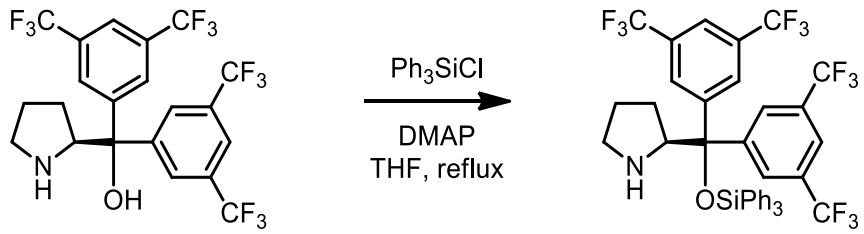
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 7.9 Hz, 1H), 7.62 (q, *J* = 8.4 Hz, 4H), 7.32-7.27 (m, 1H), 7.13- 6.99 (m, 2H), 6.33 (dd, *J* = 15.3, 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 150.8, 140.2, 138.9, 132.8, 131.0 (q, *J* = 32.8 Hz), 128.4, 127.6 (2C), 125.9 (q, *J* = 3.8 Hz, 2C), 123.9 (q, *J* = 272.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75.

HRMS calculated for: $[C_{12}H_9F_3O+H]^+$ 227.0678; found: 227.0678.

5.3.3 Synthesis of the catalyst 3.55



3d

Compound 3.55:

(*S*)- 2(Bis(3,5bis(trifluoromethyl)phenyl)((triphenylsilyl)oxy)methyl) Pyrrolidine.

(*S*)-α,α-Bis(3,5-dimethylphenyl)-2-pyrrolidinemethanol (1.05 g, 2.0 mmol, 1.0 eq), chlorotriphenylsilane (0.885 g, 3.0 mmol, 1.5 eq), and 4-dimethylaminopyridine (0.489 g, 4.0 mmol, 2.0 eq) were suspended in dry THF (4 mL) under Ar atmosphere and the mixture was refluxed overnight. The reaction was quenched with water (2 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 4 mL). The combined organic phase was dried over $MgSO_4$. After removal of the solvent the catalyst **3.55** was isolated by FC on silica (EtOAc/pentane 2:98) in 80% yield as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 2H), 7.76 (s, 1H), 7.66 (s, 1H), 7.56 (s, 2H), 7.50-7.33 (m, 12H), 7.33-7.22 (m, 3H), 4.13 (t, *J* = 7.1 Hz, 1H), 2.86-2.72 (m, 1H), 2.37-2.25 (m, 1H), 1.77-1.69 (m, 1H), 1.64-1.56 (m, 1H), 1.47-1.36 (m, 1H), 1.04-0.94 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 145.6, 135.1 (6C), 134.3 (3C), 131.2 (q, *J* = 33.9 Hz, 2C), 130.7 (q, *J* = 33.6 Hz, 2C), 130.1 (3C), 129.0 (q, *J* = 2.9 Hz, 2C) 128.6 (q, *J* = 2.8 Hz, 2C), 127.9 (6C), 123.3 (q, *J* = 273.1 Hz, 2C), 123.0 (q, *J* = 273.3 Hz, 2C) 121.8 (q, *J* = 3.8 Hz), 121.6 (q, *J* = 3.7 Hz), 83.9, 64.4, 47.0, 28.2, 25.5.

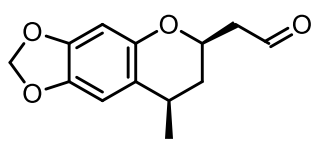
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.78, -62.80.

HRMS calculated for: $[C_{39}H_{29}F_{12}NOSi+H]^+$ 784.1900; found: 784.1910.

5.3.4 The asymmetric 1,6-1,4-addition cascade of hydroxyarenes to 2,4-dienals

5.3.4.1 Optimization

Compound 3.51: 2-((6*R*,8*R*)-8-Methyl-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-yl)acetaldehyde.



The product **3.51** was isolated by FC on Iatrobeads (EtOAc/pentane 2:98 to 7:93) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90* (s, 1H), 9.88 (s, 1H), 6.68 (s, 1H), 6.55* (s, 1H), 6.32# (s, 2H), 5.86# (s, 4H), 4.60-4.52* (m, 1H), 4.53-4.44 (m, 1H), 3.05-2.92 (m, 1H), 2.91-2.74# (m, 3H), 2.73-2.58# (m, 2H), 2.05 (dd, *J* = 13.2, 5.7 Hz, 1H), 1.93-1.85* (m, 1H), 1.73* (d, *J* = 13.4 Hz, 1H), 1.54-1.44 (m, 1H), 1.31* (d, *J* = 7.3 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4*, 200.4, 148.8, 148.2*, 146.5*, 146.3, 141.8, 141.7*, 118.7*, 118.6, 107.8*, 106.1, 100.9, 100.8*, 98.5*, 98.5, 71.2, 67.0*, 49.2, 49.0*, 37.4, 34.5*, 29.4, 28.2*, 24.1*, 20.7.

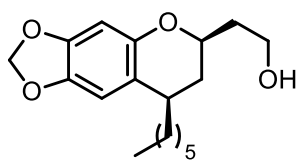
HRMS calculated for: $[C_{13}H_{14}O_4+H]^+$ 235.0965; found: 235.0965.

It was observed that a longer alkyl chain in the aldehyde substrate resulted in improved diastereoselectivity, therefore (*E*,*E*)-2,4-undecadienal was applied in further screenings. The resulting aldehyde product was reduced directly in the crude mixture before isolation.

5.3.5 General procedure for the organocatalytic synthesis of 5a-n

A glass vial (4 mL) equipped with a magnetic stirring bar was charged with catalyst **3.55** (15.7 mg, 0.02 mmol, 0.2 eq), nucleophile (0.2 mmol, 2.0 eq.) and $CHCl_3$ (0.45 mL). A solution of DABCO in $CHCl_3$ (50 µL, 0.1 M, 0.005 mmol, 0.05 eq) was added. The mixture was stirred for 10 min at 4 °C, before the aldehyde (0.1 mmol, 1.0 eq) was added in one portion. The resulting mixture was stirred at 4 °C until completion. MeOH (0.5 mL) and $NaBH_4$ (7.6 mg, 0.2 mmol, 2.0 eq) were added. The mixture was stirred at room temperature for 1 h before it was diluted with CH_2Cl_2 (0.5 mL) and quenched with sat. aq. NH_4Cl (0.5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic phase was dried over $MgSO_4$ and concentrated.

Compound 3.58a: 2-((6*R*,8*R*)-8-Hexyl-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-yl)etanol.



Following the general procedure (reaction time 2 d) the product **3.58a** was isolated by FC on silica (EtOAc/pentane 10:90) in 54% yield as a colorless solid.

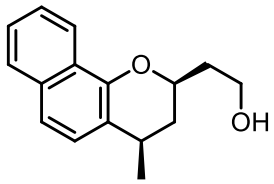
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.54* (s, 1H), 6.33$^{\#}$ (s, 2H), 5.86$^{\#}$ (dd, *J* = 4.2, 1.4 Hz, 4H), 4.21* (ddd, *J* = 12.8, 8.7, 3.9 Hz, 1H), 4.15-4.06 (m, 1H), 3.96-3.83$^{\#}$ (m, 4H), 2.91-2.80 (m, 1H), 2.66-2.58* (m, 1H), 2.08-1.97$^{\#}$ (m, 2H), 1.96-1.74$^{\#}$ (m, 6H), 1.55-1.18$^{\#}$ (m, 20H), 0.89$^{\#}$ (t, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 146.0, 141.8, 118,3, 106.3, 100.8, 98.6, 75.3, 60.4, 38.2, 35.5, 34.6, 34.2, 31.8, 29.5, 26.1, 22.6, 14.1.

HRMS calculated for: $[C_{18}H_{26}O_4+H]^+$ 307.1904; found: 307.1903.

The **ee** was determined by UPC^2 using a Chiralpak ID-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (2%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 6.8 min, τ_{minor} = 7.5 min (96% ee). **[α]$^{20}_{D}$** = -86.2 (c = 0.5, CH_2Cl_2).

Compound 3.58b: 2-((2*R*,4*R*)-4-Methyl-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)etanol.



Following the general procedure (reaction time 6 d) the product **3.58b** was isolated by FC on silica (EtOAc/pentane 10:90 to 20:80) in 72% yield as a dark orange oil.

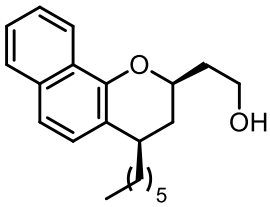
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.06$^{\#}$ (m, 2H), 7.78-7.71$^{\#}$ (m, 2H), 7.48-7.41$^{\#}$ (m, 4H), 7.41-7.34$^{\#}$ (m, 4H), 4.49-4.34$^{\#}$ (m, 2H), 4.14-3.98$^{\#}$ (m, 4H), 3.25-3.13 (m, 1H), 3.10-3.02*(m, 1H), 2.19-2.00$^{\#}$ (m, 6H), 1.96-1.63$^{\#}$ (m, 4H), 1.39$^{\#}$ (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 133.0, 127.4, 125.7, 125.3, 125.2, 124.9, 121.4, 120.9, 119.9, 74.5, 60.1, 38.3, 37.9, 29.6, 20.7.

HRMS calculated for: $[C_{16}H_{18}O_2+H]^+$ 243.1380; found: 243.1383.

The **ee** was determined by UPC^2 using a Chiralpak IB-3 column [10% iPrOH, isocratic, 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 4.6 min, τ_{minor} = 6.1 min (96% ee). **[α]$^{20}_{D}$** = -85.1 (c = 0.6, CH_2Cl_2).

Compound 3.58c: 2-((2*R*,4*R*)-4-Hexyl-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)etanol.



Following the general procedure (reaction time 2.5 d) the product **3.58c** was isolated by FC on silica (EtOAc/pentane 5:95 to 10:90) in 82% yield as a brown oil.

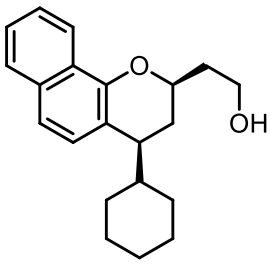
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.10[#] (m, 2H), 7.77-7.71[#] (m, 2H), 7.46-7.40[#] (m, 4H), 7.40-7.34[#] (m, 4H), 4.44* (ddd, *J* = 12.5, 8.6, 3.7 Hz, 1H), 4.37-4.26 (m, 1H), 4.14-3.97[#] (m, 4H), 3.17-3.05 (m, 1H), 2.88-2.81* (m, 1H), 2.22-1.98[#] (m, 8H), 1.67[#] (dt, *J* = 13.3, 11.4 Hz, 4H), 1.56-1.47[#] (m, 2H), 1.43-1.23[#] (m, 16H), 0.92-0.87[#] (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 132.9, 127.3, 125.7, 125.3, 125.3, 125.1, 121.4, 120.2, 119.9, 74.6, 60.1, 38.5, 35.1, 34.7, 34.3, 31.8, 29.6, 26.3, 22.7, 14.1.

HRMS calculated for: $[C_{21}H_{28}O_2+H]^+$ 313.2162; found: 313.2166.

The **ee** was determined by UPC[2] using a Chiralpak IB-3 column [1% MeOH (0.5 min), then gradient from 1% to 40% (10%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 3.4 min, τ_{minor} = 3.7 min (98% ee). **$[\alpha]^{20}_D$** = -52.9 (c = 0.7, CH_2Cl_2).

Compound 3.58d: 2-((2*R*,4*S*)-4-Cyclohexyl-3,4-dihydro-2*H*-benzo[*h*]chromen-2yl)ethanol.



Following the general procedure (reaction time 2 d) the product **3.58d** was isolated by FC on silica (EtOAc/pentane 10:90 to 15:85) in 63% yield as a yellow oil.

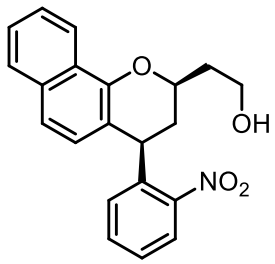
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.10[#] (m, 2H), 7.78-7.70[#] (m, 2H), 7.47-7.41[#] (m, 4H), 7.40-7.34 (m, 4H), 4.56-4.47* (m, 1H), 4.27 (t, *J* = 9.2 Hz, 1H), 4.13-3.95[#] (m, 4H), 3.18-3.10 (m, 1H), 2.68-2.62* (m, 1H), 2.19-1.90[#] (m, 8H), 1.90-1.53[#] (m, 10H), 1.45-1.27[#] (m, 4H), 1.27-1.08[#] (m, 8H), 0.97-0.84[#] (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 132.8, 127.3, 125.7, 125.3, 125.2, 125.1, 121.4, 120.1, 119.2, 74.9, 60.2, 40.8, 39.6, 38.6, 31.5, 29.5, 27.2, 26.7, 26.6, 25.8.

HRMS calculated for: $[C_{21}H_{26}O_2+H]^+$ 311.2006; found: 311.2010.

The **ee** was determined by UPC[2] using a Chiralpak IC-3 column [1% MeOH (0.5 min), then gradient from 1% to 40% (5%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 6.5 min, τ_{minor} = 7.7 min (99% ee). **$[\alpha]^{20}_D$** = -54.4 (c = 0.5, CH_2Cl_2).

Compound 3.58e: 2-((2R,4S)-4-(2-Nitrophenyl)-3,4-dihydro-2H-benzo[h]chromen-2 yl)ethanol.



Following the general procedure (reaction time 5 d) the product **3.58e** was isolated by FC on silica (EtOAc/pentane 15:85 to 20:80) in 70% yield (major diastereomer) as a pale brown foam.

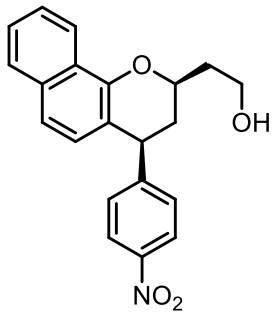
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.13 (m, 1H), 7.86 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.76-7.70 (m, 1H), 7.54-7.41 (m, 3H), 7.39-7.35 (m, 1H), 7.27 (d, *J* = 4.4 Hz, 1H), 7.11 (d, *J* = 7.0 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 4.95 (dd, *J* = 11.4, 6.5 Hz, 1H), 4.55-4.46 (m, 1H), 4.15-4.02 (m, 2H), 2.66 (dd, *J* = 12.9, 7.0 Hz, 1H), 2.21-1.98 (m, 3H), 1.85 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 150.7, 139.9, 133.3, 132.9, 130.8, 127.5, 127.4, 127.1, 126.4, 125.7, 125.0, 123.9, 121.5, 120.4, 118.0, 74.4, 59.8, 38.4, 38.1, 37.5.

HRMS calculated for: $[C_{21}H_{19}NO_4+H]^+$ 350.1387; found: 350.1388.

The **ee** was determined by UPC^2 using a Chiralpak IC-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (10%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 4.5 min, τ_{minor} = 4.9 min (99% ee). **$[\alpha]^{20}_D$** = +130.6 (c = 1.0, CH_2Cl_2).

Compound 3.58f: 2-((2*R*,4*S*)-4-(4-Nitrophenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)etanol.



Following the general procedure (reaction time 6 d) the product **3.58f** was isolated by FC on silica (EtOAc/pentane 10:90 to 40:60) in 67% yield as a brown foam.

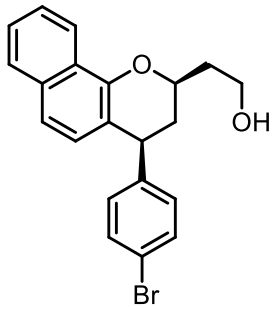
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.14 (m, 3H), 7.76-7.74 (m, 1H), 7.53-7.45 (m, 2H), 7.37-7.34 (m, 2H), 7.27 (d, *J* = 9.4 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 4.57-4.45 (m, 2H), 4.15-4.09 (m, 1H), 4.08-4.01 (m, 1H), 2.40 (dd, *J* = 12.0, 6.4 Hz, 1H), 2.22-2.13 (m, 1H), 2.12-1.98 (m, 2H), 1.77 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 150.3, 146.9, 133.4, 129.3 (2C), 127.5, 126.8, 126.4, 125.7, 125.0, 124.0 (2C), 121.5, 120.3, 117.5, 74.0, 59.6, 42.9, 38.9, 38.2.

HRMS calculated for: $[C_{21}H_{19}NO_4+H]^+$ 350.1387; found: 350.1389.

The **ee** was determined by UPC^2 using a Chiralpak ID-3 column [1% MeOH (0.5 min), then gradient from 1% to 40% (5%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 8.2 min, τ_{minor} = 8.7 min (99% ee). **$[\alpha]^{20}_D$** = +91.2 (c = 1.0, CH_2Cl_2).

Compound 3.58g: 2-((2*R*,4*S*)-4-(4-Bromophenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)ethanol.



Following the general procedure (reaction time 6 d) the product **3.58g** was isolated by FC on silica (EtOAc/pentane 5:95 to 20:80) in 66% yield (major diastereomer) as a colorless solid.

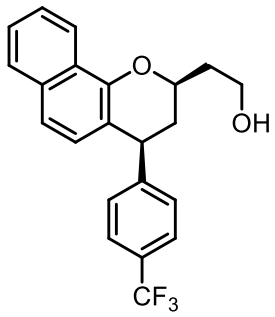
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.52-7.40 (m, 4H), 7.25 (d, *J* = 6.4 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 1H), 4.54-4.48 (m, 1H), 4.34 (dd, *J* = 11.8, 6.4 Hz, 1H), 4.41-4.00 (m, 2H), 2.34 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.20-1.97 (m, 3H), 1.84 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 144.1, 133.3, 131.8 (2C), 130.2 (2C), 127.5, 127.1, 126.2, 125.5, 124.9, 121.5, 120.4, 120.0, 118.5, 74.3, 59.8, 42.5, 38.9, 38.2.

HRMS calculated for: $[C_{21}H_{19}BrO_2+Na]^+$ 405.0461; found: 405.0468.

The **ee** was determined by UPC^2 using a Chiralpak IA-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (5%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 8.0 min, τ_{minor} = 8.5 min (96% ee). **$[\alpha]^{20}_D$** = +71.2 (c = 1.0, CH_2Cl_2).

Compound 3.58h: 2-((2*R*,4*S*)-4-(4-(Trifluoromethyl)phenyl)-3,4-dihydro-2*H* benzo[*h*]chromen-2-yl)ethanol.



Following the general procedure (reaction time 1.5 d) the product **3.58h** was isolated by FC on silica (EtOAc/pentane 20:80) in 77% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.53-7.44 (m, 3H), 7.33-7.27 (m, 2H), 6.77 (d, *J* = 8.6 Hz,

1H), 4.53 (t, *J* = 8.8 Hz, 1H), 4.45 (dd, *J* = 11.7, 6.3 Hz, 1H), 4.08 (d, *J* = 24.3 Hz, 2H), 2.37 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.23-1.99 (m, 3H), 1.84 (s, 1H).

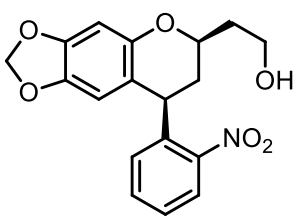
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 149.3, 133.4, 129.0 (q, *J* = 32.0 Hz), 128.9 (2C), 127.5, 127.1, 126.3, 125.6 (q, *J* = 3.6 Hz, 2C), 125.6, 125.0, 124.2 (q, J = 272.0 Hz) 121.5, 120.1, 118.2, 74.2, 59.7, 42.9, 39.0, 38.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.36.

HRMS calculated for: $[C_{22}H_{19}F_3O_2+H]^+$ 373.1410; found: 373.1413.

The **ee** was determined by UPC[2] using a Chiralpak IB-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (10%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 3.9 min, τ_{minor} = 4.3 min (99% ee). **$[\alpha]^{20}_D$** = -28.6 (c = 0.8, CH_2Cl_2).

Compound 3.58i: 2-((6*R*,8*S*)-8-(2-Nitrophenyl)-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-yl)ethanol.



Following the general procedure (reaction time 5.5 d) the product **3.58i** was isolated by FC on silica (EtOAc/pentane 10:90 to 30:70) in 66% yield as a yellow foam.

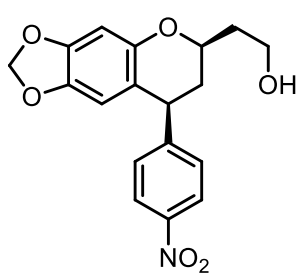
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93* (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.59-7.53* (m, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.37[#] (t, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.12* (d, *J* = 7.9 Hz, 1H), 6.44* (s, 1H), 6.40 (s, 1H), 6.24* (s, 1H), 6.06 (s, 1H), 5.88* (d, *J* = 4.7 Hz, 2H), 5.85 (d, *J* = 10.8 Hz, 2H), 4.66[#] (dd, *J* = 11.6, 6.4 Hz, 2H), 4.30-4.24 (m, 1H), 4.21-4.14* (m, 1H), 3.92[#] (t, *J* = 5.8 Hz, 4H), 2.45 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.32.2.19* (m, 1H), 2.05-1.81[#] (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 150.4, 147.0, 141.9, 139.8, 132.9, 130.7, 127.5, 123.8, 116.0, 108.2, 101.1, 98.6, 74.9, 60.0, 38.10, 37.8, 37.3.

HRMS calculated for: $[C_{18}H_{17}NO_6+H]^+$ 344.1129; found: 344.1129.

The **ee** was determined by UPC^2 using a Chiralpak ID-3 column [1% MeOH (0.5 min), then gradient from 1% to 40% (10%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 3.5 min, τ_{minor} = 3.6 min (98% ee). **$[\alpha]^{20}_D$** = +26.2 (c = 1.0, CH_2Cl_2).

Compound 3.58j: 2-((6*R*,8*S*)-8-(4-Nitrophenyl)-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-yl)ethanol.



Following the general procedure (reaction time 5.5 d) the product **3.58j** was isolated by FC on silica (EtOAc/pentane 10:90 to 30:70) in 69% yield as a pale yellow foam.

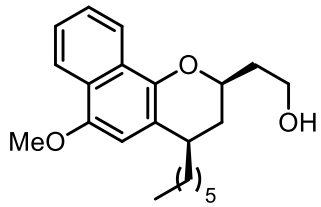
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 2H), 6.41 (s, 1H), 6.04 (s, 1H), 5.85 (d, *J* = 5.3 Hz, 2H), 4.34-4.20 (m, 2H), 3.98-3.84 (m, 2H), 2.21 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.03-1.82 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 150.0, 147.2, 146.9, 141.9, 129.2 (2C), 124.0 (2C), 115.5, 108.0, 101.1, 98.7, 74.5, 59.8, 42.8, 38.5, 37.9.

HRMS calculated for: $[C_{18}H_{17}NO_6+H]^+$ 344.1129; found: 344.1126.

The **ee** was determined by UPC^2 using a Chiralpak IA-3 column [18% i-PrOH, isocratic, 120 bar, 40 ^{o}C]; flow rate 3.0 mL/min; τ_{major} = 10.5 min, τ_{minor} = 15.0 min (94% ee). **$[\alpha]^{20}_D$** = +53.8 (c = 1.0, CH_2Cl_2).

Compound 3.58k: 2-((2*R*,4*R*)-4-Hexyl-6-methoxy-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)ethanol.



Following the general procedure (reaction time 2 d) the product **3.58k** was isolated by FC on silica (EtOAc/pentane 10:90 to 20:80) in 91% yield as a deep blue oil.

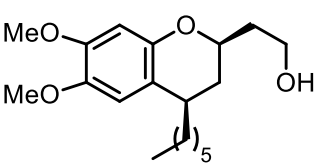
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.3, 2.0 Hz, 1H), 8.04 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.50-7.40 (m, 2H), 6.67 (s, 1H), 4.29-4.19 (m, 1H), 4.10-3.97 (m, 2H), 3.96 (s, 3H), 3.14-3.03 (m, 1H), 2.21-1.89 (m, 4H), 1.73-1.63 (m, 1H), 1.63-1.47 (m, 1H), 1.45-1.21 (m, 8H), 0.93-0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 143.7, 126.0, 125.9, 125.2, 124.9, 121.6, 121.2, 119.6, 103.1, 74.5, 60.3, 55.8, 38.4, 35.3, 35.2, 34.7, 31.9, 29.6, 26.3, 22.7, 14.6.

HRMS calculated for: $[C_{22}H_{30}O_3+H]^+$ 343.2268; found: 343.2272.

The **ee** was determined by UPC^2 using a Chiralpak IB-3 column [5% MeOH, isocratic, 120 bar, 40 ^{o}C]; flow rate 3.0 mL/min; τ_{major} = 8.0 min, τ_{minor} = 18.2 min (99% ee). **$[\alpha]^{20}_{D}$** = -68.9 (c = 0.2, CH_2Cl_2).

Compound 3.58l: 2-((2*R*,4*R*)-4-Hexyl-6,7-dimethoxychroman-2-yl)ethanol**.**



Following the general procedure (reaction time 4 d) the product **3.58l** was isolated by FC on silica (EtOAc/pentane 20:80) in 61% yield as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.57* (s, 1H), 6.36$^{\#}$ (s, 2H), 4.28-4.20* (m, 1H), 4.19-4.10 (m, 1H), 3.95-3.88$^{\#}$ (m, 4H), 3.82$^{\#}$ (d, *J* = 4

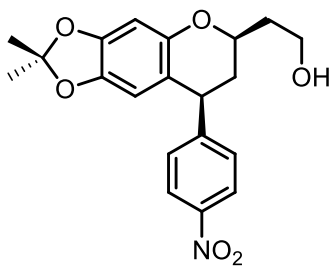
Hz, 12H), 2.94-2.83 (m, 1H), 2.69-2.61* (m, 1H), 2.20-1.78# (m, 8H), 1.63-1.21# (m, 20H), 0.89# (t, *J* = 6.5 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.1, 143.3, 117.1, 110.6, 100.8, 75.5, 60.5, 56.6, 55.8, 38.2, 35.1, 34.8, 33.8, 31.8, 29.6, 26.2, 22.6, 14.1.

HRMS calculated for: $[C_{19}H_{30}O_4+H]^+$ 323.2217; found: 323.2223.

The **ee** was determined by UPC^2 using a Chiralpak ID-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (2%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 7.9 min, τ_{minor} = 9.1 min (98% ee). **$[\alpha]^{20}_D$** = -86.0 (c = 0.6, CH_2Cl_2).

Compound 3.58m: 2-((6*R*,8*S*)-2,2-Dimethyl-8-(4-nitrophenyl)-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-yl)ethanol.



Following the general procedure (reaction time 8 d) the product **3.58m** was isolated by FC on silica (EtOAc/pentane 20:80 to 40:60) in 51% yield as a yellow solid.

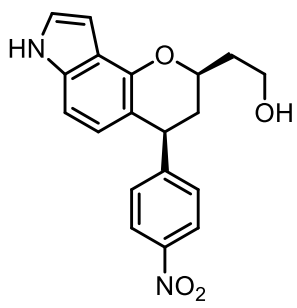
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 6.31 (s, 1H), 5.93 (s, 1H), 4.33-4.19 (m, 2H), 3.97-3.84 (m, 2H), 2.20 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.06-1.83 (m, 3H), 1.62 (s, 3H), 1.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 149.4, 147.1, 146.8, 142.0, 129.3 (2C), 124.0 (2C), 118.1, 114.8, 107.7, 98.4, 74.6, 59.9, 42.8, 38.6, 37.9, 25.7, 25.7.

HRMS calculated for: $[C_{20}H_{21}NO_6+H]^+$ 372.1442; found: 372.1444.

The **ee** was determined by UPC^2 using a Chiralpak IA-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (10%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 4.2 min, τ_{minor} = 4.7 min (98% ee). **$[\alpha]^{20}_D$** = -44.4 (c = 0.6, CH_2Cl_2).

Compound 3.58n: 2-((2*R*,4*S*)-4-(4-Nitrophenyl)-2,3,4,7-tetrahydropyrano[2,3-*e*]indol-2-yl)etanol.



Following the general procedure (reaction time 7 d, at room temperature) the product **3.58n** was isolated by FC on silica (EtOAc/pentane 20:80 to 50:50) in 43% yield as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.12 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.15 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.60 (s, 1H), 6.43 (d, *J* = 8.5 Hz, 1H), 4.55-4.43 (m, 2H), 4.07-3.97 (m, 2H), 2.31 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.17-2.06 (m, 1H), 2.06-1.97 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 148.1, 146.7, 136.1, 129.3 (2C), 123.9 (2C), 123.7, 123.3, 117.9, 113.1, 104.6, 99.5, 74.9, 60.3, 42.6, 39.2, 38.0.

HRMS calculated for: $[C_{19}H_{18}N_2O_4+H]^+$ 339.1339; found: 339.1343.

The **ee** was determined by UPC^2 using a Chiralpak IA-3 column [1% MeOH (0.5 min), then gradient from 1% to 40% (10%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 5.2 min, τ_{minor} = 5.4 min (97% ee). **$[\alpha]^{20}_D$** = -21.3 (c = 0.5, CH_2Cl_2).

5.3.6 General procedure for the organocatalytic synthesis of *ent*-3.58k on 3.0 mmol scale

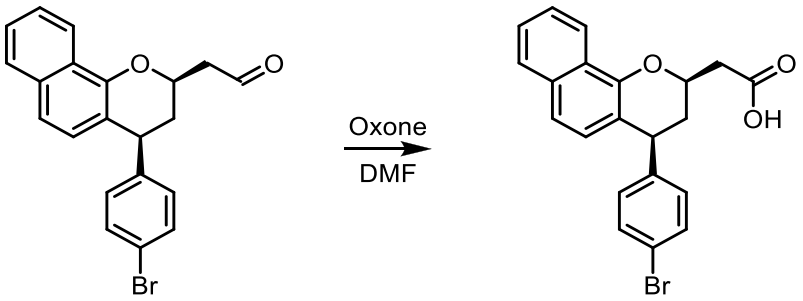
A 50 mL flask equipped with a magnetic stirring bar was charged with catalyst *ent*-**3.55** (470 mg, 0.6 mmol, 0.2 eq), 4-methoxy-1-naphthol (1.05 g, 6.0 mmol, 2.0 eq.) and $CHCl_3$ (15 mL). DABCO (16.8 mg, 0.15 mmol, 0.05 eq) was added. The mixture was stirred for 30 min at -30 °C, before the aldehyde (0.57 ml, 3.0 mmol, 1.0 eq) was added in one portion. The resulting mixture was stirred at 4 °C for 3 d. MeOH (15 mL) and $NaBH_4$ (227 mg, 0.2 mmol, 2.0 eq) were added. The mixture was stirred

at room temperature for 1 h before it was quenched with sat. aq. NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The product *ent*-**3.58k** was isolated by FC on silica (EtOAc/pentane 10:90 to 30:70) in 69% yield (0.7 g) as a blue solid.

The ee was determined by UPC[2] using a Chiralpak IB-3 column [5% MeOH, isocratic, 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 17.3 min, τ_{minor} = 8.1 min (99% ee).

5.3.7 Transformations

*5.3.7.1 Synthesis of the acid derivative of **3.58g**.*[89]



3.58g-I **3.58g-II**

Compound 3.58g-II: 2-((2*R*,4*S*)-4-(4-Bromophenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)acetic acid.

A glass vial (4 mL) equipped with a magnetic stirring bar was charged with catalyst **3.55** (15.7 mg, 0.02 mmol, 0.2 eq), 1-naphthol **3.50b** (28.8 mg, 0.2 mmol, 2.0 eq.) and $CHCl_3$ (0.45 mL). A solution of DABCO in $CHCl_3$ (50 μL, 0.1 M, 0.005 mmol, 0.05 eq) was added. The mixture was stirred for 10 min at 4 °C, before the aldehyde **3.68f** (23.6 mg, 0.1 mmol, 1.0 eq) was added in one portion. The resulting mixture was stirred at 4 °C until completion. The crude mixture was filtered thought a plug of Iatrobeads

washing with CH_2Cl_2 and the filtrate concentrated. The aldehyde **3.58g-I** was isolated by FC on Iatrobeads (EtOAc/pentane 5:95 to 20:80).

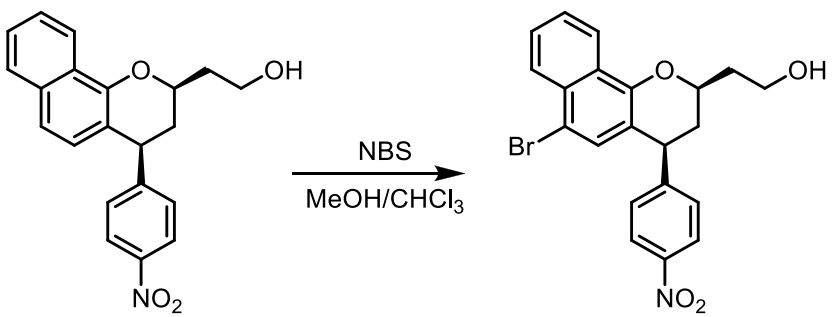
The aldehyde **3.58g-I** (38.1 mg, 0.1 mmol, 1.0 eq) was dissolved in DMF (1.0 mL). Oxone (30.8 mg, 0.1 mmol, 1.0 eq) was added in one portion and the reaction stirred for 3h. 1 M HCl (2 mL) was added and the aqueous phase extracted with EtOAc (3 x 0.5 mL). The organic phase was washed with 1 M HCl (3 x 1 mL), brine (1 mL), dried over $MgSO_4$ and concentrated. The product **3.58g-II** was isolated by FC on silica (EtOAc/pentane/formic acid 10:89.8:0.2 to 15:84.8:0.2) in 79% yield as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.16 (m, 1H), 7.74-7.71 (m, 1H), 7.47-7.43 (m, 4H), 7.27-7.25 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 4.78-4.72 (m, 1H), 4.37 (dd, *J* = 12.0, 5.9 Hz, 1H), 3.05 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.84 (dd, *J* = 15.6, 5.3 Hz, 1H), 2.45 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.03 (q, *J* = 12.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 149.8, 143.7, 133.3, 131.8 (2C), 130.2 (2C), 127.4, 126.9, 126.3, 125.6, 124.9, 121.6, 120.6, 120.3, 118.1, 72.5, 42.2, 40.4, 38.2.

HRMS calculated for: $[C_{21}H_{17}BrO_3+H]^+$ 397.0434; found: 397.0431. **$[\alpha]^{20}_D$** = +69.6 (c = 0.6, CH_2Cl_2).

*5.3.7.2 Bromination of the aromatic moiety of **3.59.***



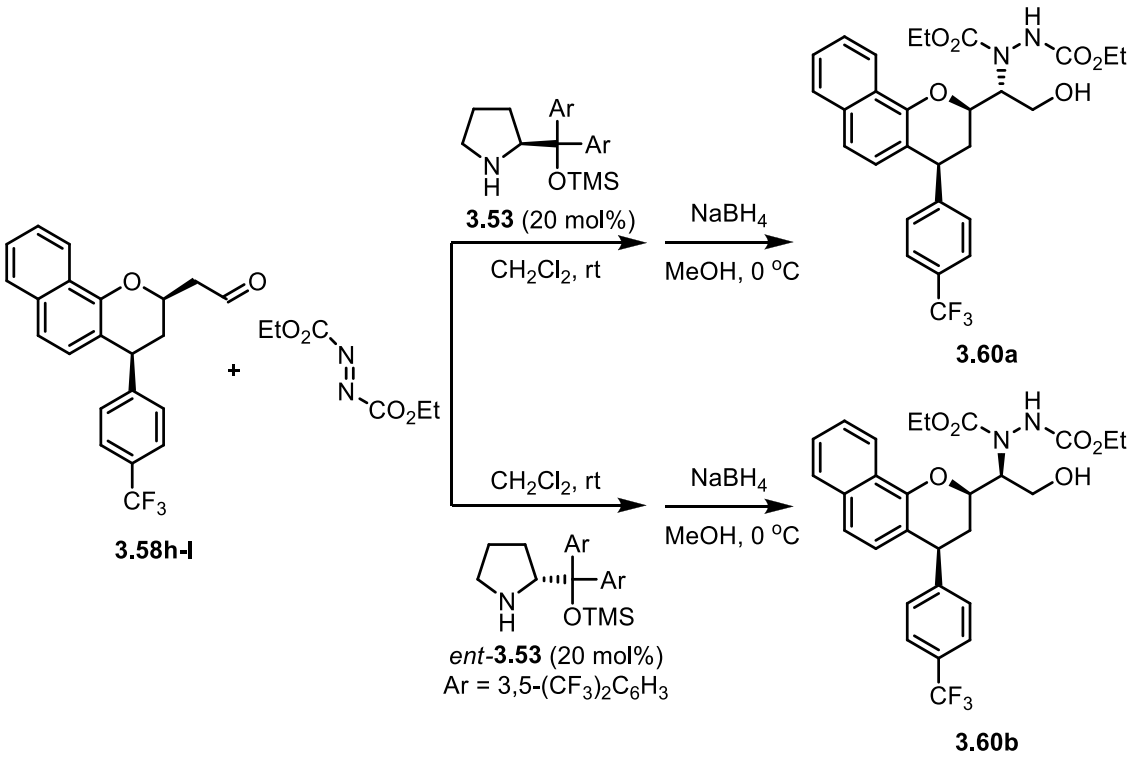
3.58f **3.59**

Compound 3.59: 2-((2*R*,4*S*)-6-Bromo-4-(4-nitrophenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)ethanol.

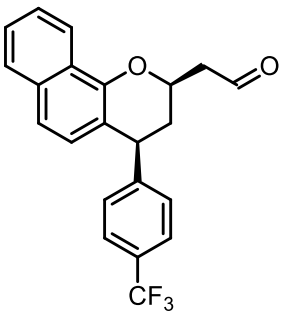
A glass vial (4 mL) equipped with a magnetic stirring bar was charged with **3.58f** (21.7 mg, 0.062 mmol, 1.0 eq) which was dissolved in MeOH/$CHCl_3$ (1:1, 0.5 ml) and cooled to 4 °C. NBS (16.7 mg, 0.093 mmol, 1.5 eq) was added in one portion and the mixture stirred for 30 min. The mixture was diluted with CH_2Cl_2 (1 mL) and 1 M NaOH (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 0.5 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The product **3.59** was isolated by FC using silica (EtOAc/pentane 10:90 to 35:65) in 54% yield as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.2 Hz, 3H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.58 (dt, *J* = 15.0, 7.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.02 (s, 1H), 4.57-4.43 (m, 2H), 4.14-4.08 (m, 1H), 4.06-3.94 (m, 1H), 2.39 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.23-2.12 (m, 1H), 2.11-1.97 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 150.2, 147.1, 131.6, 130.1, 129.3 (2C), 127.8, 127.0, 126.5, 126.3, 124.2 (2C), 122.0, 118.6, 113.5, 74.1, 59.3, 42.7, 38.6, 38.1.
HRMS calculated for: $[C_{21}H_{18}BrNO_4+H]^+$ 428.0492; found: 428.0491.
The **ee** was determined by UPC^2 using a Chiralpak IB-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (10%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 5.1 min, τ_{minor} = 5.6 min (98% ee). **$[\alpha]^{20}_D$** = +20.8 (c = 0.3, CH_2Cl_2).

5.3.7.3 Diastereoselective α-amination of the aldehyde 3.58h-I.[90]



Compound 3.58h-I: 2-((2*R*,4*S*)-4-(4-(Trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)acetaldehyde.



A glass vial (12 mL) equipped with a magnetic stirring bar was charged with catalyst **3.55** (157.0 mg, 0.2 mmol, 0.2 eq), 1-naphthol **3.50b** (228 mg, 2.0 mmol, 2.0 eq.) and $CHCl_3$ (4.5 mL). A solution of DABCO in $CHCl_3$ (0.5 mL, 0.1 M, 0.05 mmol, 0.05 eq) was added. The mixture was stirred for 10 min at 4 °C, before the aldehyde (226 mg, 1.0 mmol, 1.0 eq) was added in one portion. The resulting mixture was stirred at 4 °C until completion. The crude mixture was filtered thought a plug of Iatrobeads washing with CH_2Cl_2 and the filtrate concentrated. The aldehyde **3.58h-I** was isolated by FC on Iatrobeads (EtOAc/pentane 5:95 to 20:80) in 72% yield as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.18-8.12 (m, 1H), 7.76-7.71 (m, 1H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.50- 7.46 (m, 2H), 7.30-7-23 (m, 3H),

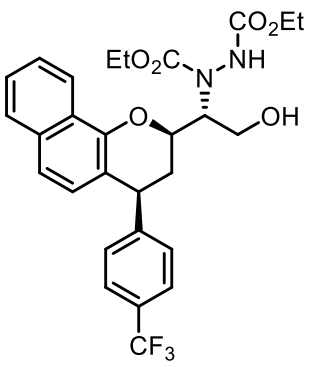
6.77 (d, *J* = 8.5 Hz, 1H), 4.91-4.83 (m, 1H), 4.49 (dd, *J* = 11.5, 6.4 Hz, 1H), 3.09 (dd, *J* = 16.9, 7.8 Hz, 1H), 2.87 (dd, *J* = 16.9, 4.8 Hz, 1H), 2.45 (dd, *J* = 13.3, 6.4 Hz, 1H), 2.11-2.00 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 149.9, 148.8, 133.4, 129.1 (q, *J* = 33.0 Hz), 128.8 (2C), 127.4, 126.9, 126.4, 125.7, 125.7 (q, *J* = 3.9 Hz, 2C), 124.9, 124.2, (q, *J* = 272.0 Hz), 121.6, 120.5, 117.8, 71.4, 49.2, 42.5, 38.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.34.

HRMS calculated for: $[C_{22}H_{17}F_3O_2+H]^+$ 371.1253; found: 371.1255. **$[\alpha]^{20}_D$** = +49.9 (c = 1.6, CH_2Cl_2).

Compound 3.60a: Diethyl 1-((*R*)-2-hydroxy-1-((2*R*,4*S*)-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2 yl)ethyl)hydrazine-1,2-dicarboxylate.



Aldehyde **3.58h-I** (37.0 mg, 0.1 mmol, 1.0 eq), diethyl diazodicarboxylate (24 µL, 0.15 mmol, 1.5 eq), and catalyst **3.53** (12.0 mg, 0.02 mmol, 1.0 eq) were dissolved in CH_2Cl_2 (100 µL) at room temperature. The reaction mixture was stirred for 2.5 h. Then it was diluted with MeOH (200 µL) and cooled to 0 °C before $NaBH_4$ (7.5 mg, 0.2 mmol, 2.0 eq) was added. The mixture was stirred at room temperature for 1 h before it was diluted with CH_2Cl_2 (2 mL) and quenched with sat. aq. NH_4Cl (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The product **3.60a** was isolated by FC on silica (EtOAc/pentane 20:80 to 33:67) in 80% yield as a white solid. In the ^{13}C NMR description below rot indicates the splitting of the signals due to rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.0 Hz, 1H), 7.74 (d, *J* = 6.9 Hz, 1H), 7.62-7.55 (m, 2H), 7.52-7.44 (m, 2H), 7.33-7.24 (m, 3H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.67 (bs, 1H), 4.47-4.14 (m, 9H), 2.44-2.28 (m, 1H), 2.12-1.97 (m, 1H), 1.40-1.20 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 (2C, rot), 149.4 (1C, rot), 148.5 (1C, rot), 133.3, 129.3 (*q*, *J* = 32.7 Hz, 1C, rot), 128.8 (2C), 127.7 (1C, rot), 126.8 (1C, rot), 126.4 (1C, rot), 126.0 (1C, rot), 125.7 (2C, rot), 124.8, 124.1 (*q*, *J* = 271.0 Hz, 1C), 121.0 (1C, rot), 120.6 (1C, rot), 118.1 (1C, rot), 73.7 (1C, rot), 63.5 (1C, rot), 62.9 (2C, rot), 59.4 (1C, rot), 42.4 (1C, rot), 35.7, 14.4 (2C, rot).

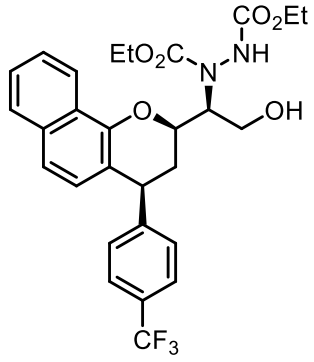
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.41.

HRMS calculated for: $[C_{28}H_{29}F_3N_2O_6+H]^+$ 547.2050; found: 547.2055.

The **ee** was determined by UPC[2] using a Chiralpak IC-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (2%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 11.2 min, τ_{minor} = 13.3 min (99% ee). **$[\alpha]^{20}_D$** = +33.4 (c = 1.8, CH_2Cl_2).

The stereochemistry of the newly introduced stereocenter was assigned by analogy comparing with previous reports on the same transformation, as catalyst control was clearly observed.[93]

Compound 3.60b: Diethyl 1-((*S*)-2-hydroxy-1-((2*R*,4*S*)-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen 2yl)ethyl)hydrazine-1,2-dicarboxylate,



Aldehyde **3.58h-I** (37.0 mg, 0.1 mmol, 1.0 eq), diethyl diazodicarboxylate (24 μL, 0.15 mmol, 1.5 eq), and catalyst *ent*-**3.53** (12.0 mg, 0.02 mmol, 1.0 eq) were dissolved in CH_2Cl_2 (100 μL) at room temperature. The reaction mixture was stirred for

2.5 h. Then it was diluted with MeOH (200 µL) and cooled to 0 °C before $NaBH_4$ (7.5 mg, 0.2 mmol, 2.0 eq) was added. The mixture was stirred at room temperature for 1 h before it was diluted with CH_2Cl_2 (2 mL) and quenched with sat. aq. NH_4Cl (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The product **3.60b** was isolated by FC on silica (EtOAc/pentane 20:80 to 33:67) in 86% yield as a white solid. In the ^{13}C NMR description below rot indicates the splitting of the signals due to rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 6.4 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.62-7.54 (m, 2H), 7.53-7.45 (m, 2H), 7.33-7.24 (m, 3H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.68 (bs, 1H), 4.47-4.11 (m, 9H), 2.44-2.24 (m, 1H), 2.15-1.95 (m, 1H), 1.40-1.19 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (2C, rot), 149.8 (1C, rot), 148.7 (1C, rot), 133.3, 129.2 (*q*, *J* = 31.8 Hz, 1C, rot), 128.9 (2C), 127.5 (1C, rot), 126.8 (1C, rot), 126.4 (1C, rot), 125.7 (3C, rot), 124.8, 124.2 (*q*, *J* = 271.7 Hz, 1C), 121.4, 120.5 (1C, rot), 118.1 (1C, rot), 74.8 (1C, rot), 63.5 (1C, rot), 63.0 (1C, rot), 62.3, 59.3 (1C, rot), 42.5 (1C, rot), 35.9, 14.4 (2C, rot).

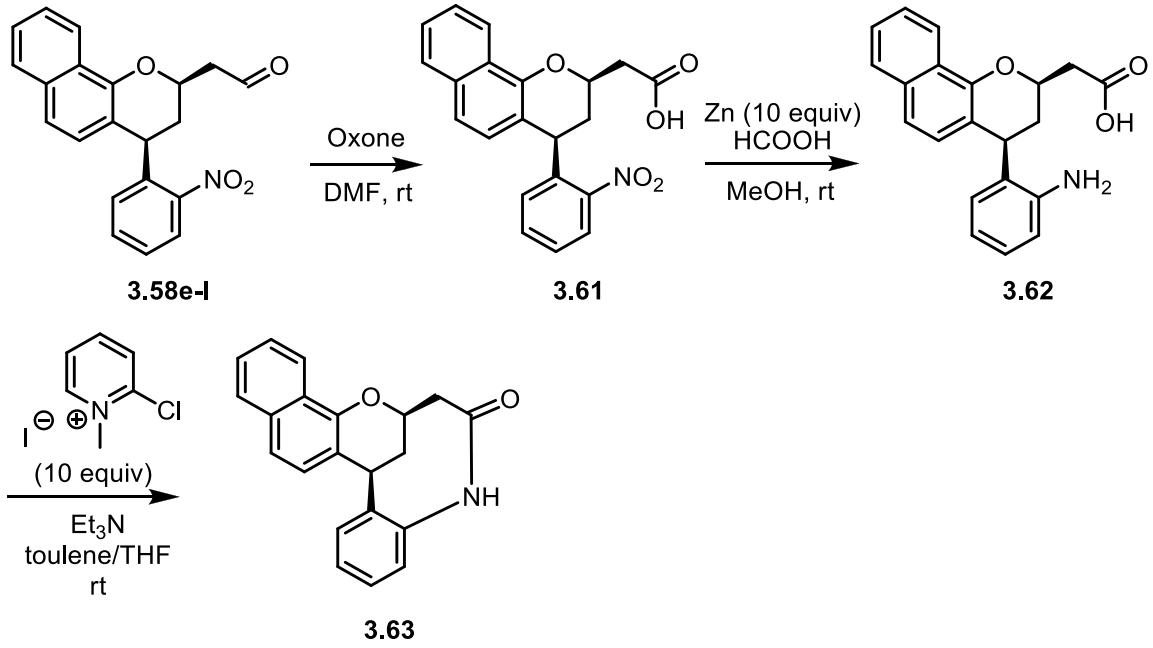
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.40.

HRMS calculated for: $[C_{28}H_{29}F_3N_2O_6+H]^+$ 547.2050; found: 547.2055.

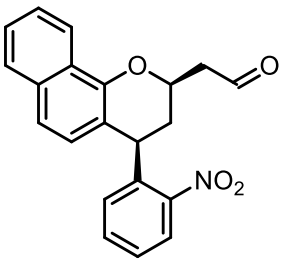
The **ee** was determined by UPC[2] using a Chiralpak IC-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (2%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 7.8 min, τ_{minor} = 8.9 min (96% ee). **$[\alpha]^{20}_D$** = +9.8 (c = 1.1, CH_2Cl_2).

The stereochemistry of the newly introduced stereocenter was assigned by analogy comparing with previous reports on the same transformation[4], as catalyst control was clearly observed.[93]

*5.3.7.4 Synthesis of macrocyclic lactam **3.63**.*



Compound 3.58e-I: 2-((2*R*,4*S*)-4-(2-Nitrophenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)acetaldehyde.



A glass vial (4 mL) equipped with a magnetic stirring bar was charged with catalyst **3.55** (15.7 mg, 0.02 mmol, 0.2 eq), 1-naphthol **3.50b**(28.8 mg, 0.2 mmol, 2.0 eq.) and $CHCl_3$ (0.45 mL). A solution of DABCO in $CHCl_3$ (50 µL, 0.1 M, 0.005 mmol, 0.05 eq) was added. The mixture was stirred for 10 min at 4 °C, before the aldehyde **3.68b** (20.3 mg, 0.1 mmol, 1.0 eq) was added in one portion. The resulting mixture was stirred at 4 °C until completion. The crude mixture was filtered thought a plug of Iatrobeads washing with CH_2Cl_2 and the filtrate concentrated. The aldehyde **3.58e-I** was isolated by FC on Iatrobeads (EtOAc/pentane 5:95 to 10:90) in 64% yield as a yellow solid.

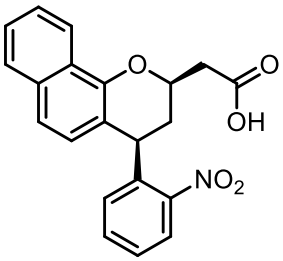
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 9.97* (s, 1H), 8.18-8.10$^{\#}$ (m, 2H), 7.99* (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.73$^{\#}$ (d, *J* = 5.3 Hz,

2H), 7.54-7.32[#] (m, 8H), 7.30-7.23[#] (m, 2H), 7.09[#] (t, *J* = 7.7 Hz, 2H), 6.88* (d, *J* = 8.6 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 4.97[#] (dd, *J* = 11.1, 6.5 Hz, 2H), 4.86-4.81 (m, 1H), 4.77-4.71* (m, 1H), 3.07-2.93[#] (m, 2H), 2.85[#] (dd, *J* = 16.5, 2.7 Hz, 2H), 2.71[#] (dd, *J* = 13.2, 6.2 Hz, 2H), 2.23* (q, *J* = 14.1 Hz, 1H), 2.03 (q, *J* = 12.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 150.6, 150.5, 139.5, 133.3, 133.0, 130.7, 127.6, 127.4, 126.9, 126.5, 125.8, 124.9, 124.0, 121.6, 120.8, 117.6, 71.5, 49.0, 37.8, 37.3.

HRMS calculated for: $[C_{21}H_{17}NO_4+Na]^+$ 370.1050; found: 370.1053. **$[\alpha]^{20}_D$** = +132.4 (c = 1.0, CH_2Cl_2).

Compound 3.61: 2-((2*R*,4*S*)-4-(2-Nitrophenyl)-3,4-dihydro-2*H*-benzo[*h*]chromen-2-yl)acetic acid.[92]



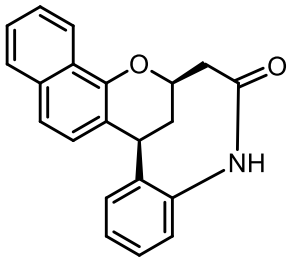
The aldehyde **3.58e-I** (69.5 mg, 0.2 mmol, 1.0 eq) was dissolved in DMF (2.0 mL). Oxone (61.5 mg, 0.1 mmol, 1.0 eq) was added in one portion and the reaction stirred for 3 h. 1 M HCl (3 mL) was added and the mixture extracted with EtOAc (3 x 1 mL). The organic phase was washed with 1 M HCl (3 x 2 mL), brine (2 mL), dried over $MgSO_4$ and concentrated. The product **3.61** was isolated by FC on silica (EtOAc/pentane/formic acid 10:89.8:0.2 to 20:79.8:0.2) in 84% yield as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 6.0 Hz, 1H), 7.50-7.43 (m, 3H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 9.1 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 4.97 (dd, *J* = 11.0, 7.0 Hz, 1H), 4.80-4.73 (m, 1H), 3.02 (dd, *J* = 15.7, 7.9 Hz, 1H), 2.88 (dd, *J* = 15.6, 4.3 Hz, 1H), 2.76 (dd, *J* = 13.0, 5.8 Hz, 1H), 2.10-2.00 (m, *J* = 23.7, 11.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 150.6, 150.6, 139.6, 133.3, 133.0, 130.8, 127.6, 127.3, 126.8, 126.4, 125.8, 125.0, 124.0, 121.7, 120.6, 117.6, 72.5, 40.5, 37.6, 37.3.

HRMS calculated for: $[C_{21}H_{17}NO_5+Na]^+$ 386.0999; found: 386.0997. **$[\alpha]^{20}_D$** = +110.8 (c = 1.0, CH_2Cl_2).

Compound 3.63: (2*R*,10*S*)-5,10-Dihydro-2*H*-2,10-methanobenzo[*f*]naphtho[2,1-*i*][1,5]oxazecin-4(3*H*)-one.[91,92]



A suspension of **3.61** (36.3 mg, 0.1 mmol, 1.0 eq) and Zn powder (65.4 mg, 1.0 mmol, 10.0 eq) in MeOH (0.2 mL) and HCOOH (50 μL) was stirred for 2 h at room temperature. The mixture was filtered through a plug of celite washing with CH_2Cl_2. The organic phase was washed with brine (3 x 2 mL), dried over $MgSO_4$, and concentrated. The amino acid product **3.62** was used without further purification.

The crude amino acid **3.62** was dissolved in THF/toluene (3:2, 17 mL) and added dropwise via a syringe pump over 15 h to a stirred solution of 2-chloro-1-methylpyridinium iodide (256 mg, 1.0 mmol, 10.0 eq) and Et_3N (279 μL, 2.0 mmol, 20.0 eq) in toluene (12 mL). The mixture was stirred for further 2 h at room temperature before it was filtered washing with toluene. The filtrate was concentrated and the product **3.63** was isolated by FC on silica (CH_2Cl_2/pentane 0:100 to 2:98) in 20% yield over 2 steps as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.55-7.42 (m, 3H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 9.5 Hz, 1H), 6.87 (t, *J* = 6.6 Hz, 2H), 6.73 (s, 1H), 5.11 (d, *J* = 9.6 Hz, 1H), 4.51 (d, *J* =

7.1 Hz, 1H), 3.14 (t, *J* = 10.9 Hz, 1H), 2.85-2.78 (m, 1H), 2.45 (d, *J* = 12.4 Hz, 1H), 2.12 (d, *J* = 14.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 148.6, 139.6, 135.1, 133.6, 132.2, 128.0, 127.4, 127.3, 126.5, 126.2 (2C), 125.8, 125.7, 121.9, 120.6, 115.6, 66.5, 38.8, 38.6, 34.4.

HRMS calculated for: $[C_{21}H_{17}NO_4+Na]^+$ 338.1151; found: 338.1152.

The **ee** was determined by UPC[2] using a Chiralpak IC-3 column [1% iPrOH (0.5 min), then gradient from 1% to 40% (10%/min), 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_{major} = 7.0 min, τ_{minor} = 6.6 min (99% ee). **$[\alpha]^{20}_D$** = +460.4 (c = 0.3, CH_2Cl_2).

5.4 Experiment experiments of chapter 4

5.4.1 General Remarks

NMR spectra were acquired on a Bruker AVANCE III spectrometer running at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 162 MHz for ^{31}P. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR).

The enantiomeric excess (*ee*) of products was determined by Ultraperformance Convergence Chromatography (Waters ACQUITY UPC^2) using Water Acquity UPC^2 Trefoil CEL 2 column as chiral stationary phase. Racemate for UPC^2 analysis was made applying a mixture of both enantiomers of the catalyst

The analytical grade solvents and commercially available reagents were used without further purification, with exception of $CHCl_3$ was dried and stored over 4Aº MS.

5.4.2 General procedere to formal [3+3] cycloaddition

5.4.2.1 General procedure for the organocatalytic synthesis of 1,2,4-triazine derivtive

A glass vial (4 mL) equipped with a magnetic stirring bar was charged with desired catalyst and base (0.02 mmol, 0.2 eq), azomethine imine (0.1 mmol, 17.5 mg, 1.0 eq.), Methyl isocyanoacetate (0. 15 mmol, 14 µL, 1.5 eq.) and solvent (1 mL). The mixture was stirred at room temperature until completion analysed by TLC. The crude mixture was purified direct by flash chromatography on silica gel using Hexane and Ethyl Acetate as eluent (7:3 Hex/Ac to 1:1 Hex/Ac) to give the product as a white solid.

5.4.2.2 Procedure for the cooperative synthesis of 1,2,4- triazine derivtive

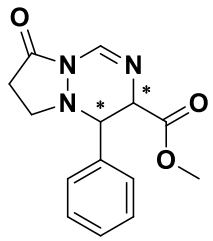
A) Using $AgNO_3$: Adapted from Escolano and coworkes.[93]

A glass vial (4 mL) equipped with a magnetic stirring bar was charged with desired catalyst (0.02 mmol, 0.2 eq), Silver Nitrate (0.01 mmol, 1.7 mg, 0.1 eq.) and Methyl isocyanoacetate (0. 15 mmol, 14 µL, 1.5 eq.) in $CHCl_3$ (1 mL). Then, to reaction solution was added the azomethine imine (0.1 mmol, 17.5 mg, 1.0 eq.). The mixture was stirred at room temperature until completion analysed by TLC. The crude mixture was purified direct by flash chromatography on silica gel using Hexane and Ethyl Acetate as eluente (7:3 Hex/Ac to1:1 Hex/Ac) to give the product as a white solid.

B) Using Ag_2O: Adapted from Dixon and coworkes.[80]

Pre-catalyst (4.43) (10 mol%) and Ag_2O (2.5 mol%) were dissolved in 1.0 mL of EtOAc in presence of powered 4Aº MS and the Azomethine imine (0.1 mmol) was added. The heterogeneous mixture was cooled at -20ºC in a fridge and stirred for 30 min. After that, the isocyanate (0.1 mmol) previously dissolved in 1.0 mL of EtOAc and cooled at -20ºC, was added. The reaction mixture was stirred at the same temperature until total consumption of the isocyanate, according with the TLC. The reaction mixture was direct purified by flash column chromatography on silica gel using Hexane and Ethyl Acetate as eluente (7:3 Hex/Ac to1:1 Hex/Ac) to give the product as a white solid.

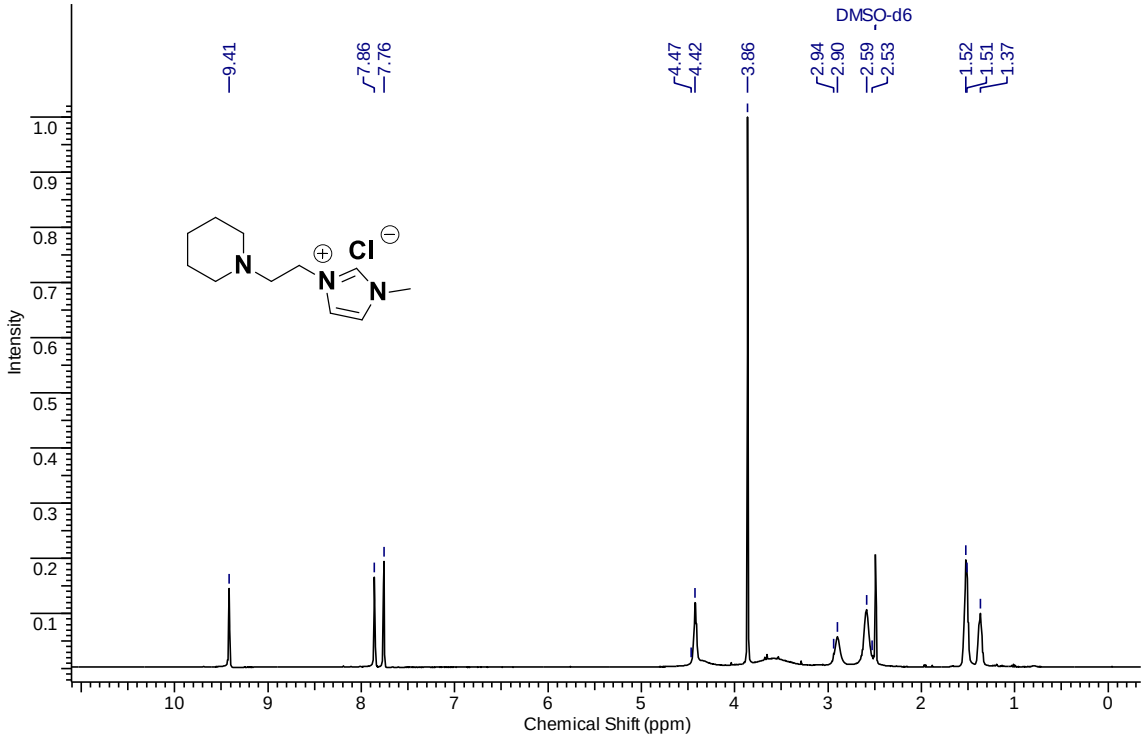
Compound 4.33: methyl 8-oxo-4-phenyl-4,6,7,8-tetrahydro-3H-pyrazolo[1,2-a][1,2,4]triazine-3-carboxylate.



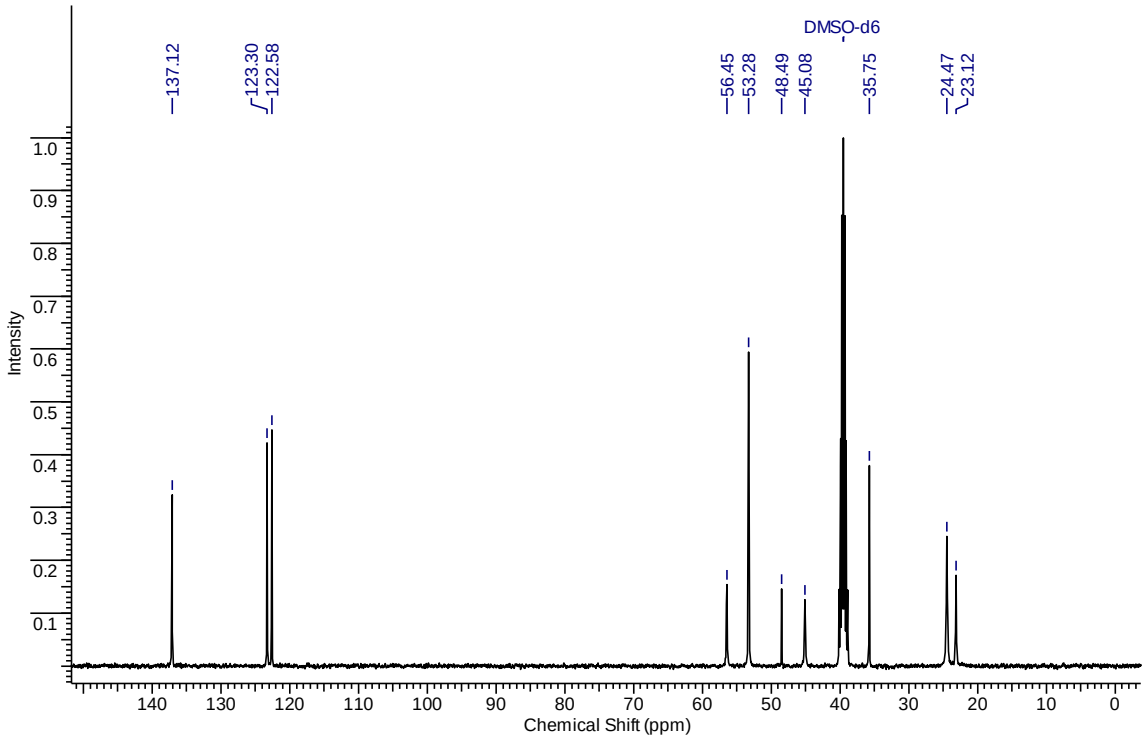
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.5 Hz, 1H), 7.41-7.38 (m, 3H), 7.37-7.35 (m, 2H), 4.40 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.67 (d, *J* = 8.6 Hz, 1H), 3.57 (s, 3H), 3.33-3.24 (m, 1H), 2.73-2.62 (m, 2H), 2.57-2.48 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 167.0, 137.0, 135.0, 129.3, 129.2, 128.4, 67.3, 66.6, 52.4, 50.4, 30.6 ppm.

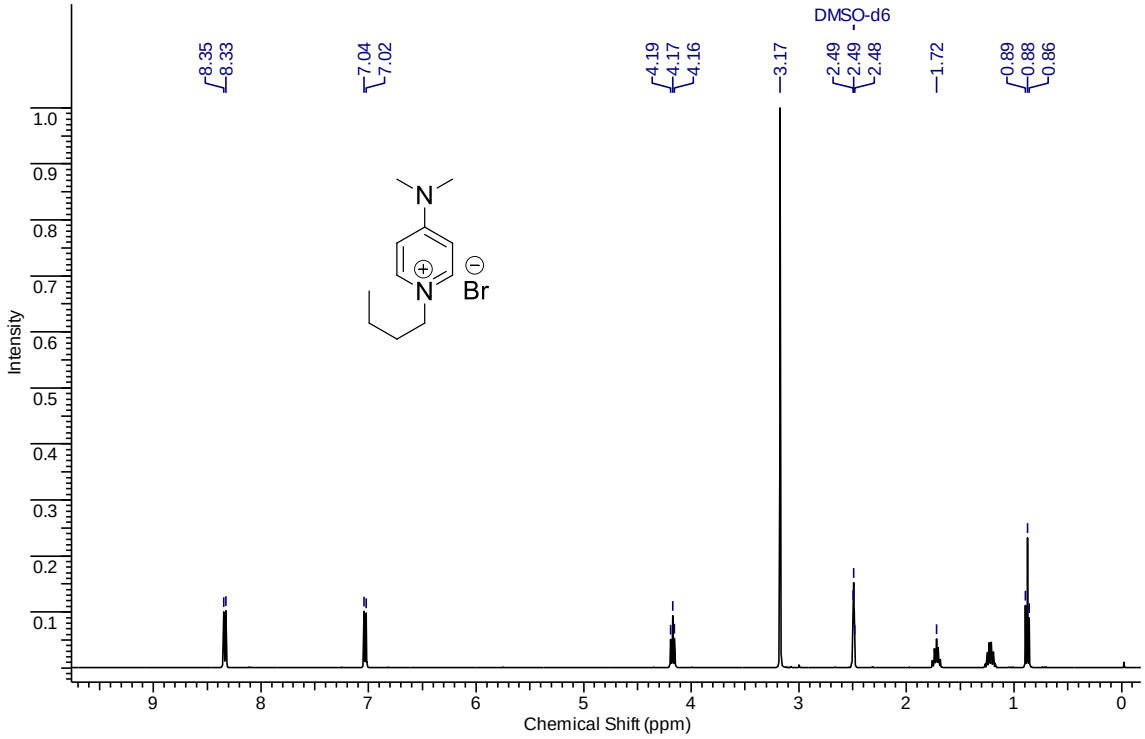
Selected figures and spectra



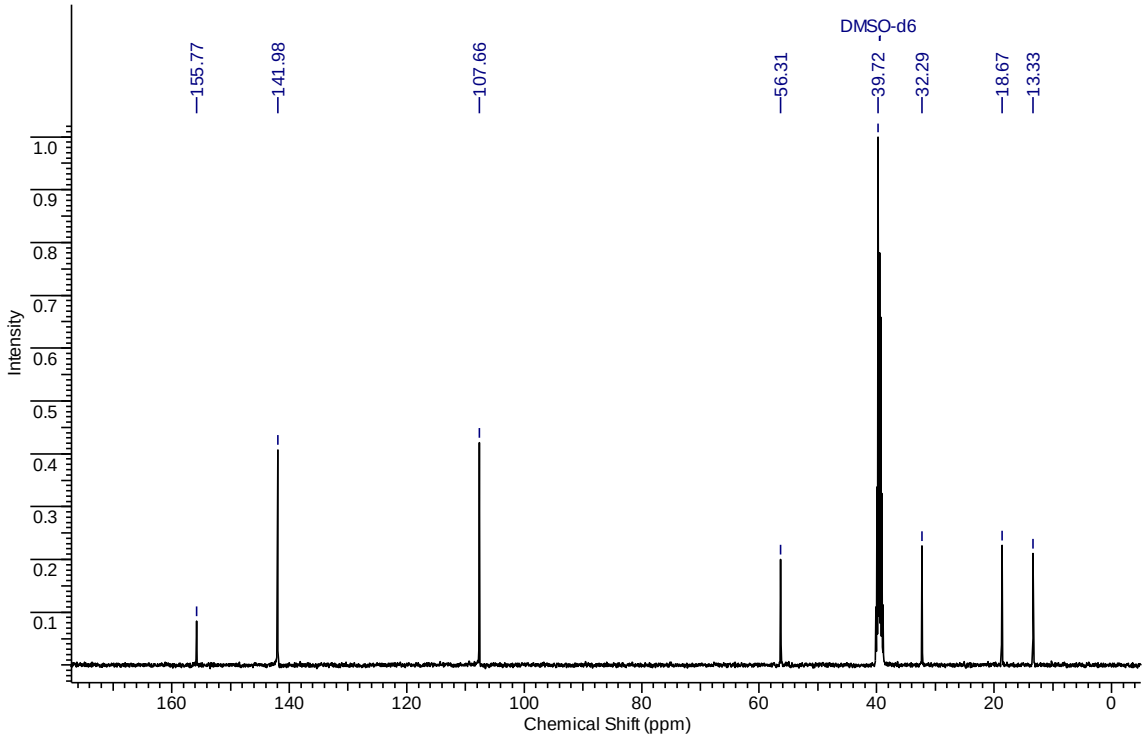
^{1}H NMR spectrum of 1.35



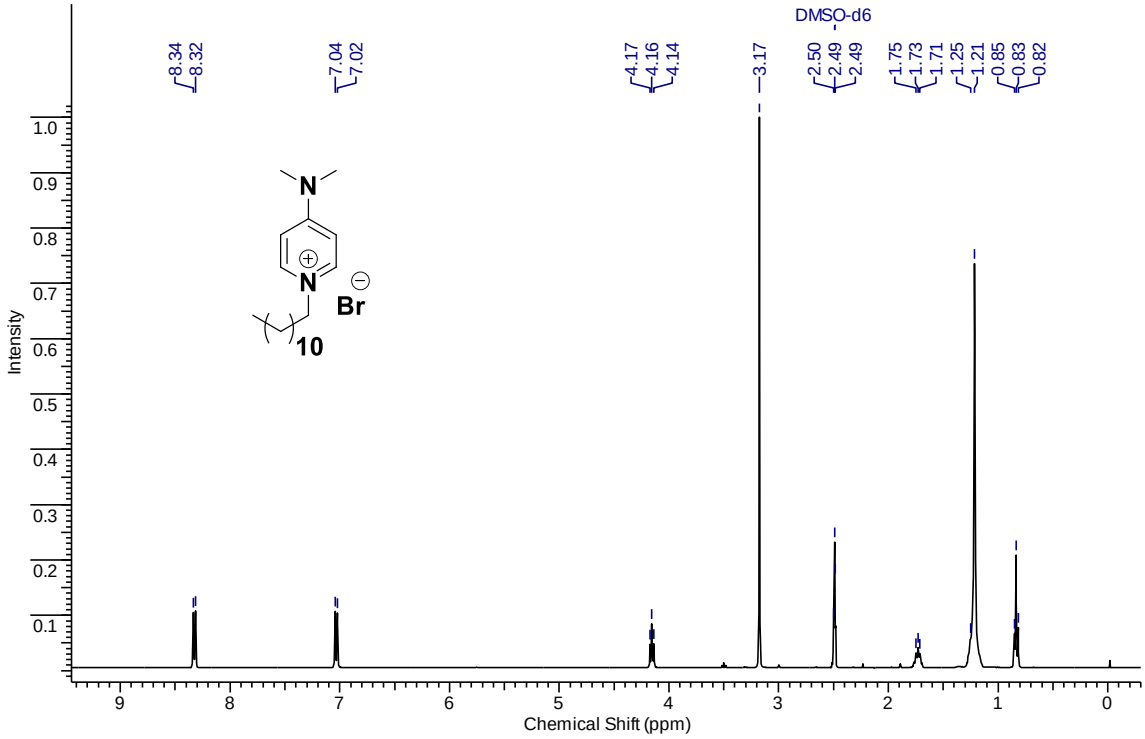
^{13}C NMR spectrum of 1.35



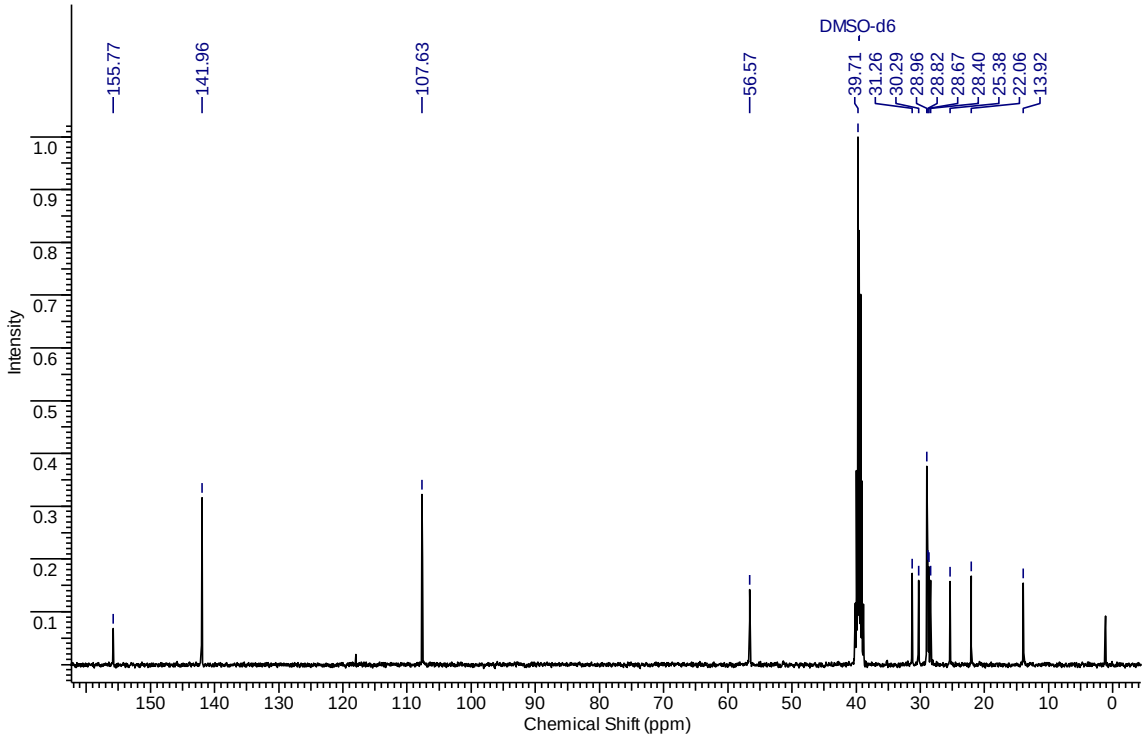
^{1}H NMR spectrum of 1.36



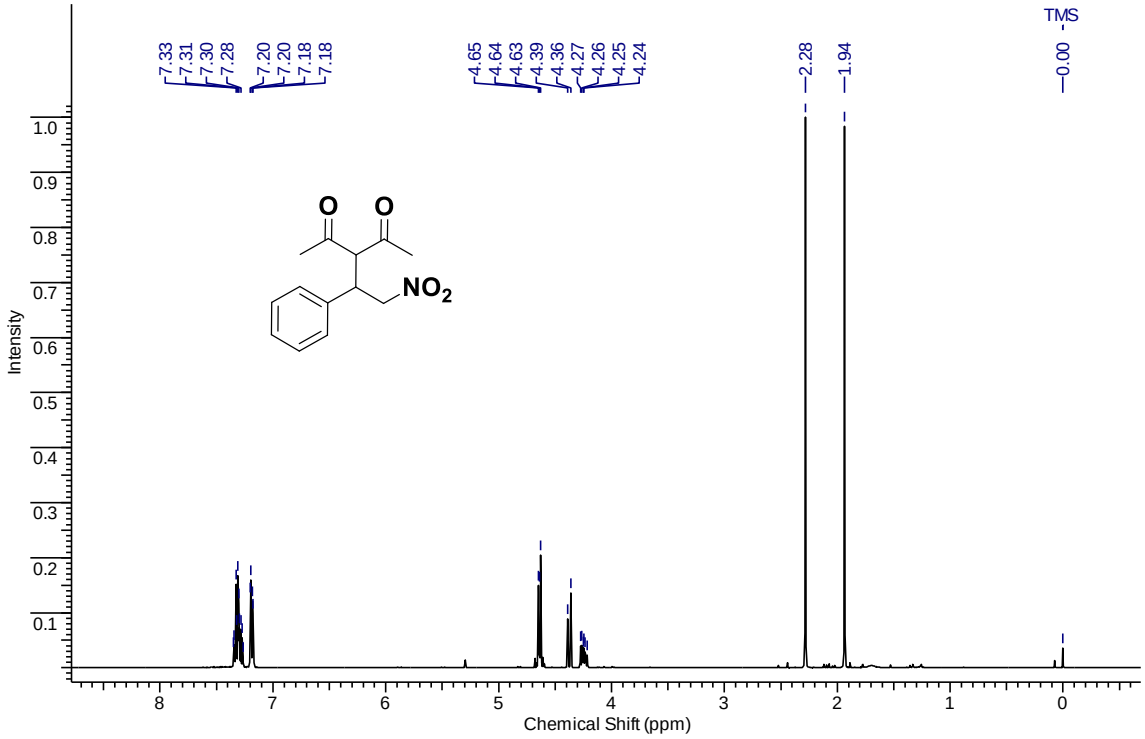
^{13}C NMR spectrum of 1.36



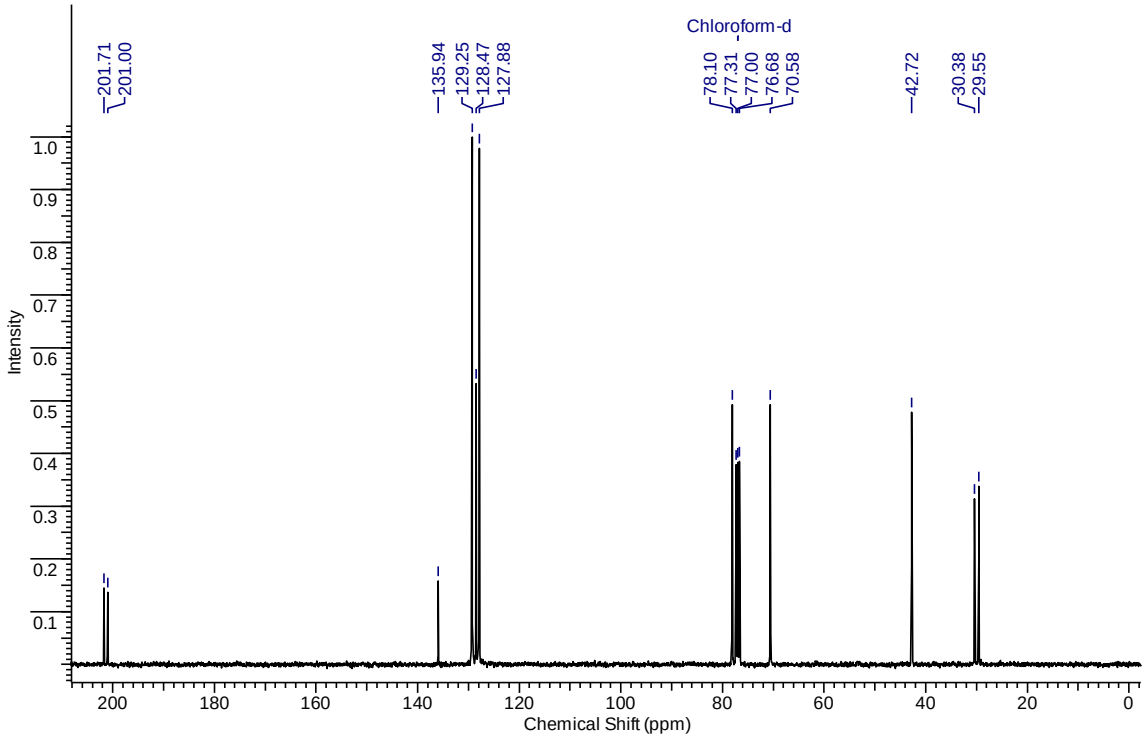
^{1}H NMR spectrum of 1.38



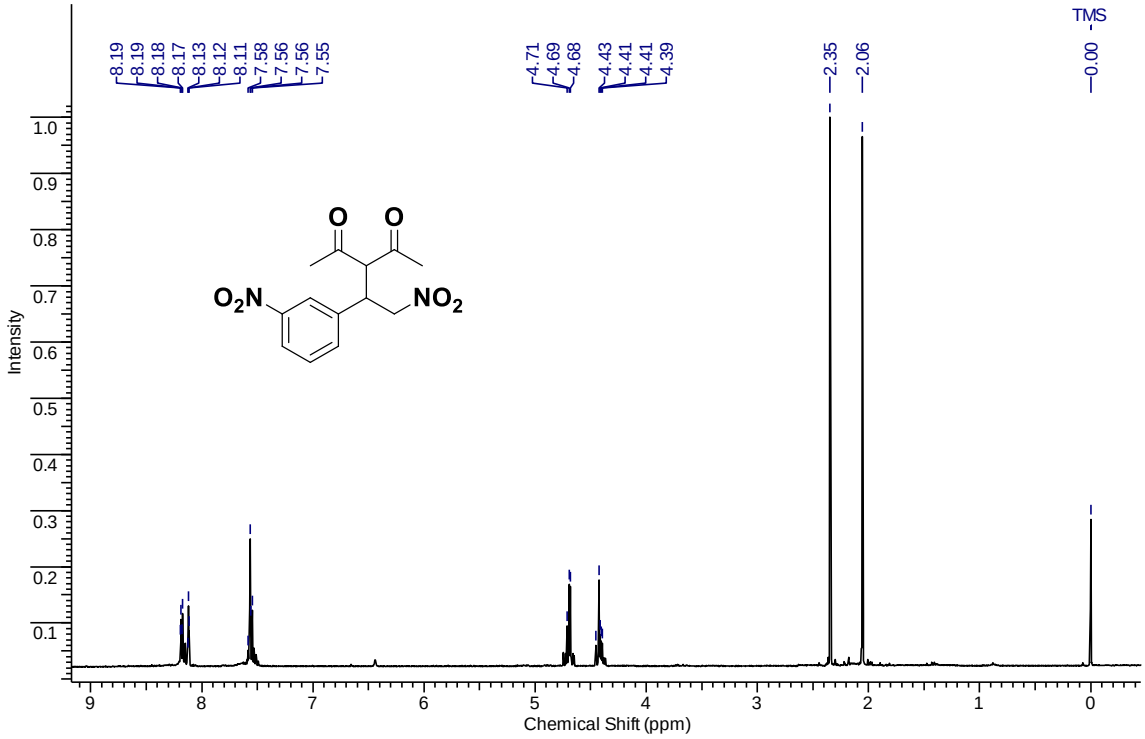
^{13}C NMR spectrum of 1.38



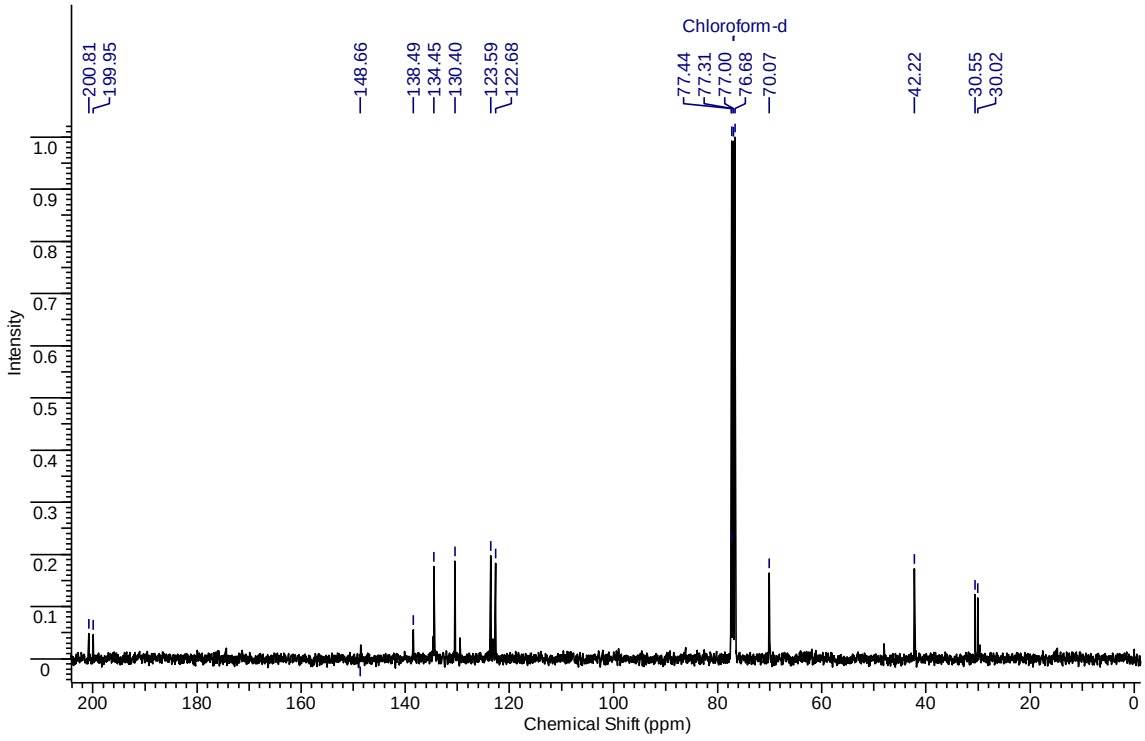
^{1}H NMR spectrum of 1.42a



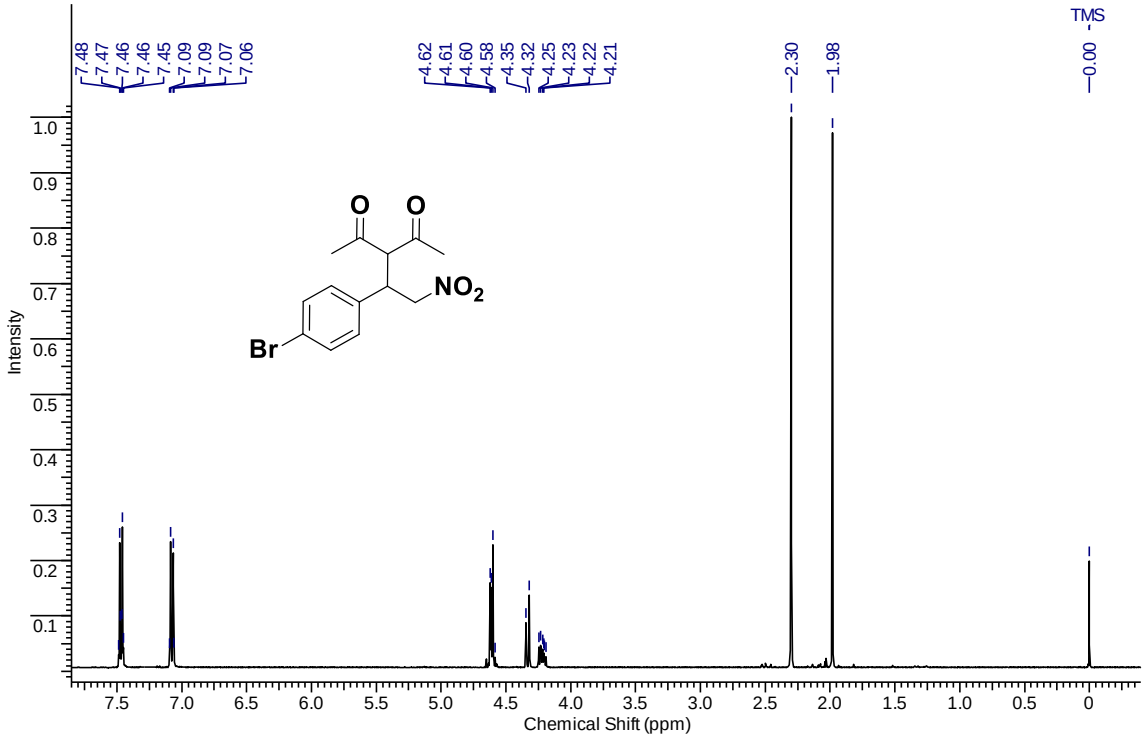
^{13}C NMR spectrum of 1.42a



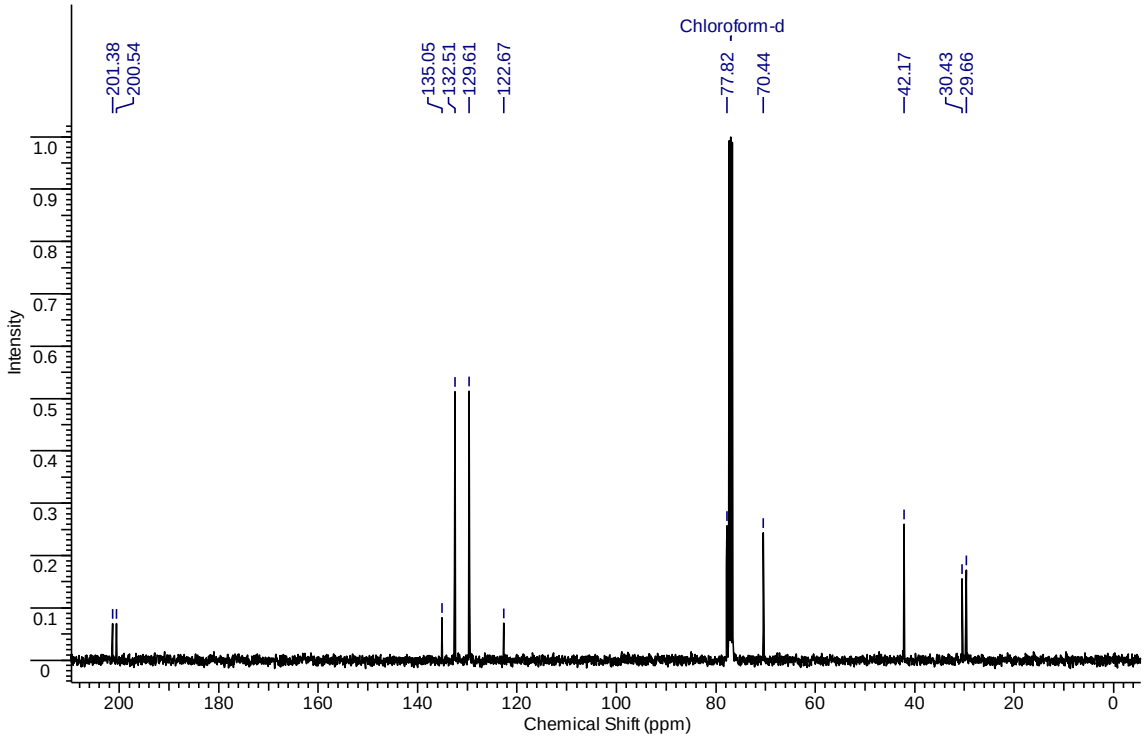
^{1}H NMR spectrum of 1.42b



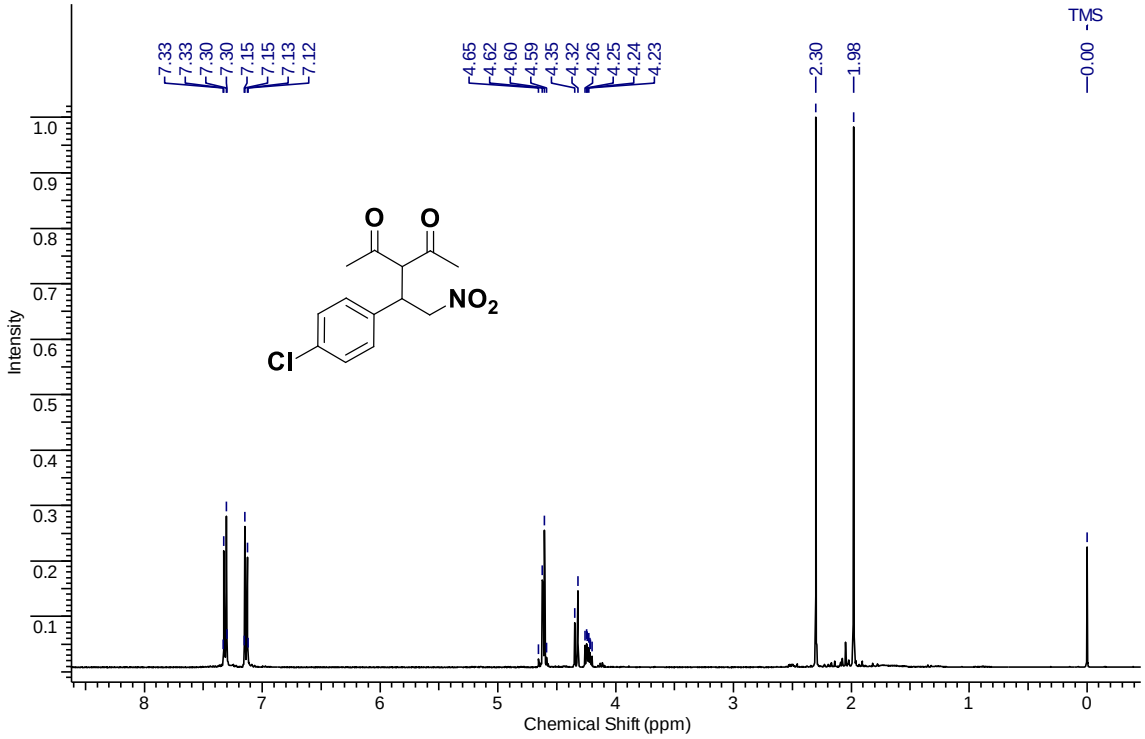
^{13}C NMR spectrum of 1.42b



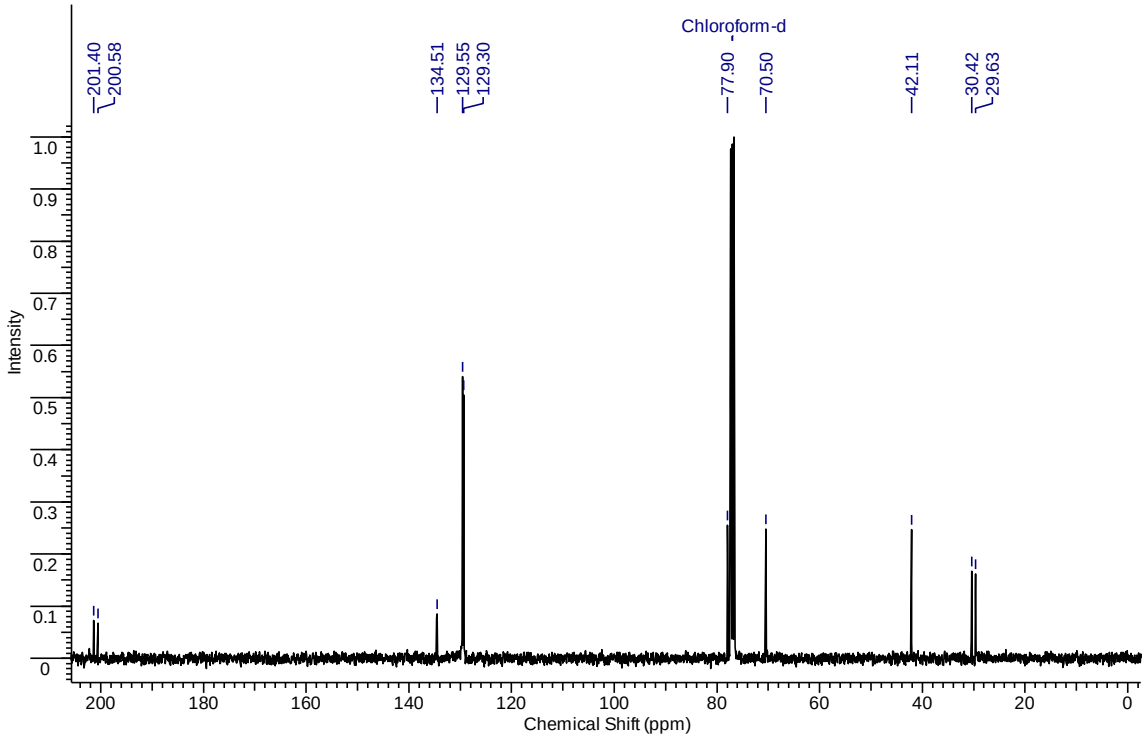
^{1}H NMR spectrum of 1.42c



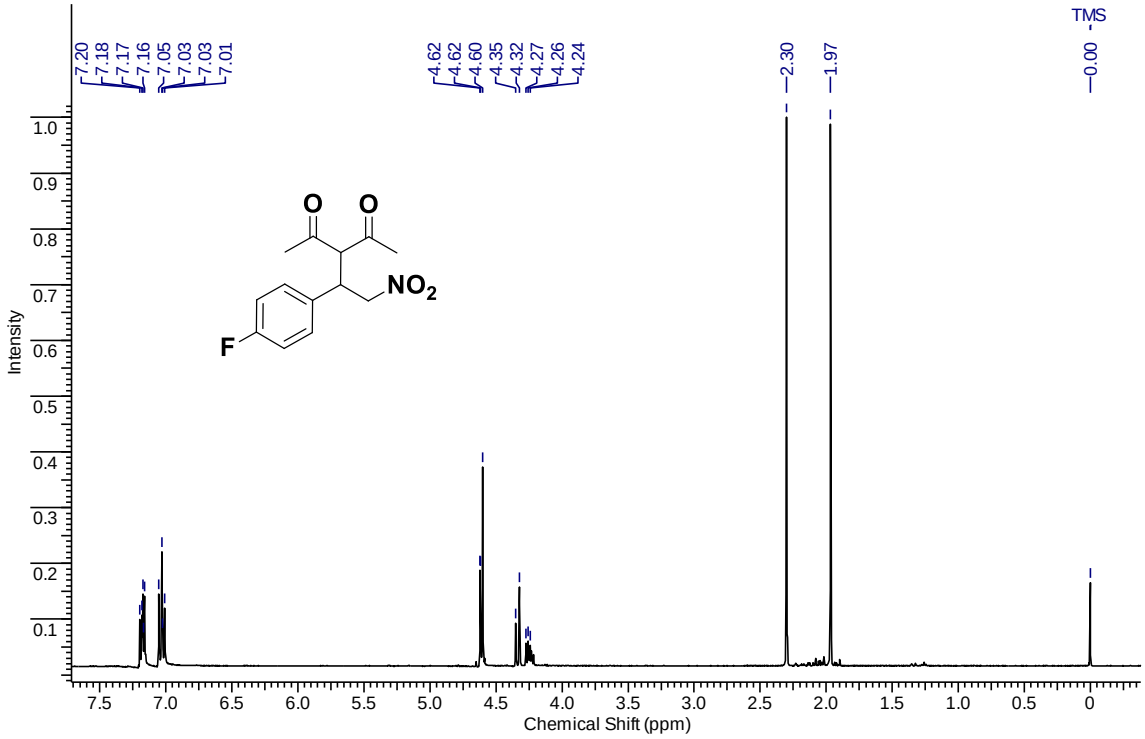
^{13}C NMR spectrum of 1.42c



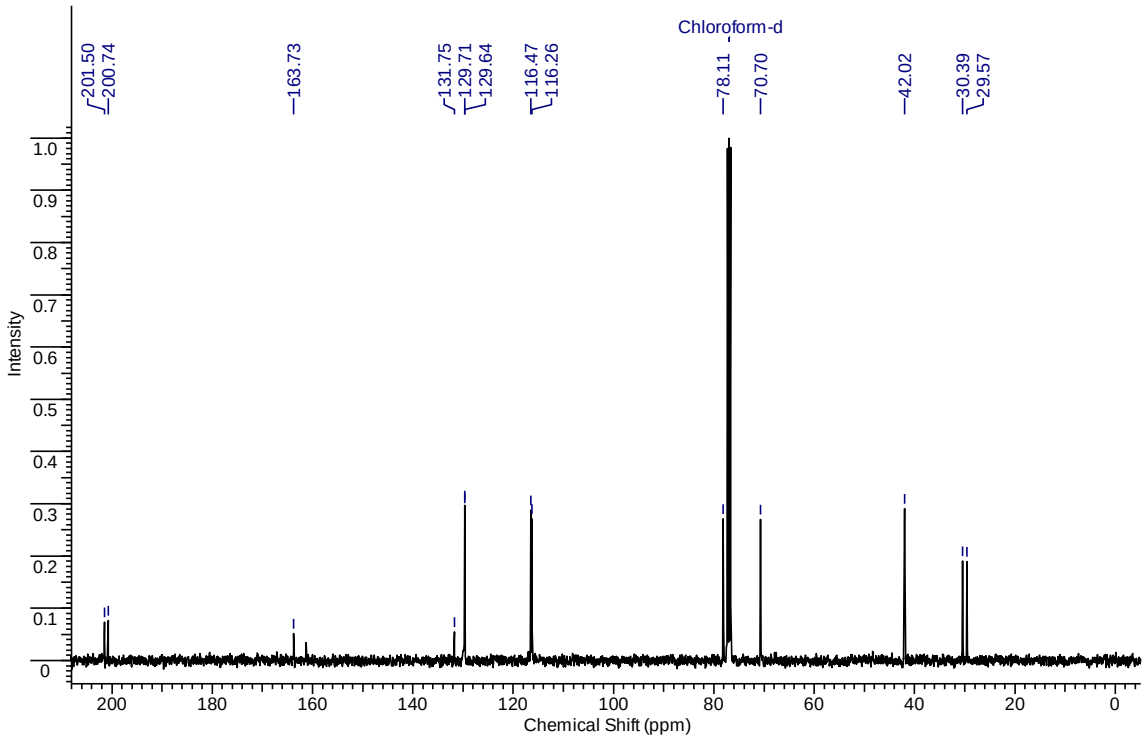
^{1}H NMR spectrum of 1.42d



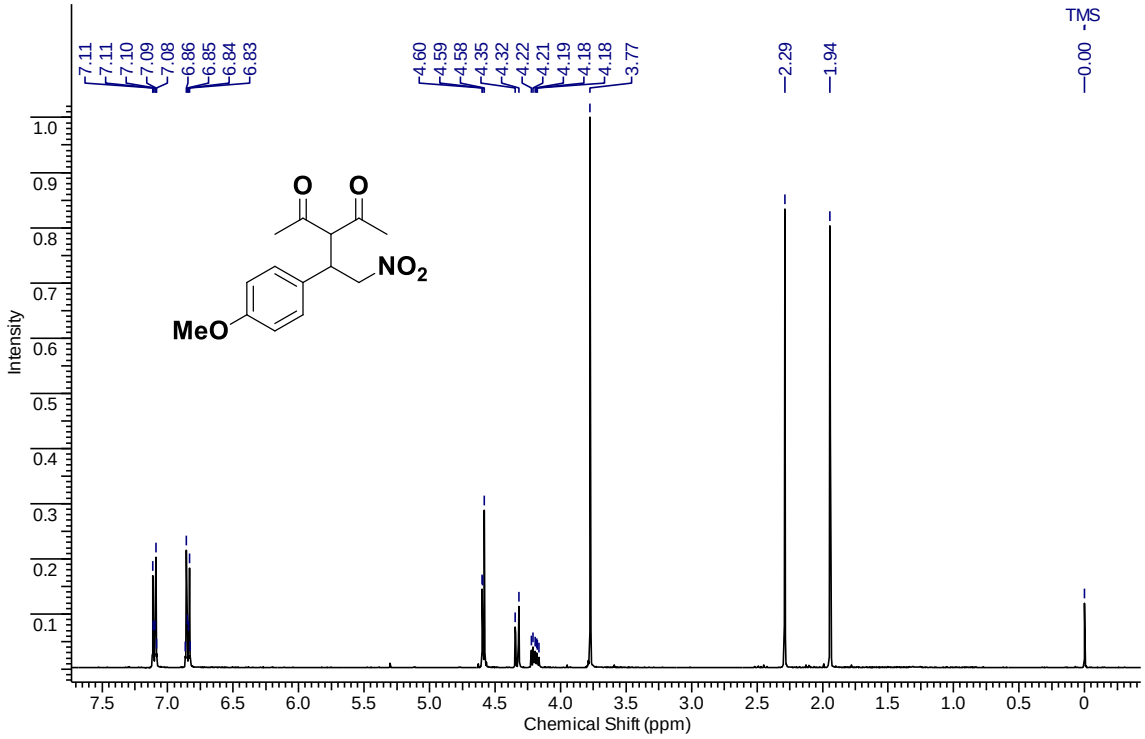
^{13}C NMR spectrum of 1.42d



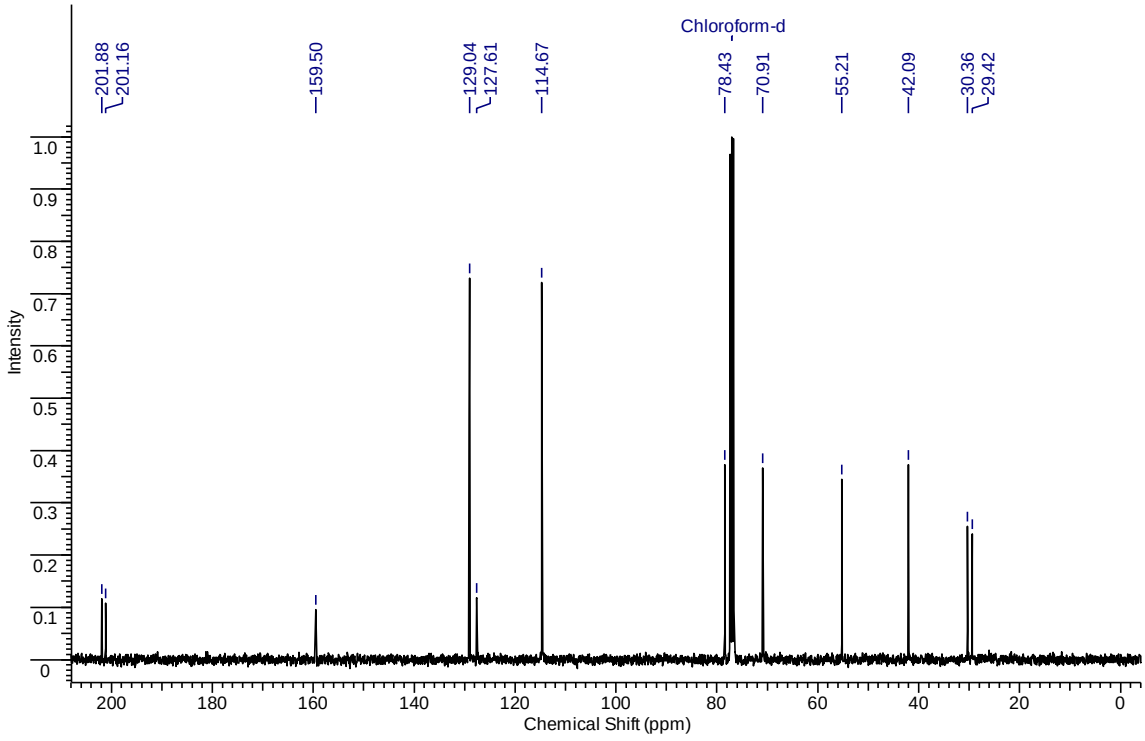
^{1}H NMR spectrum of 1.42e



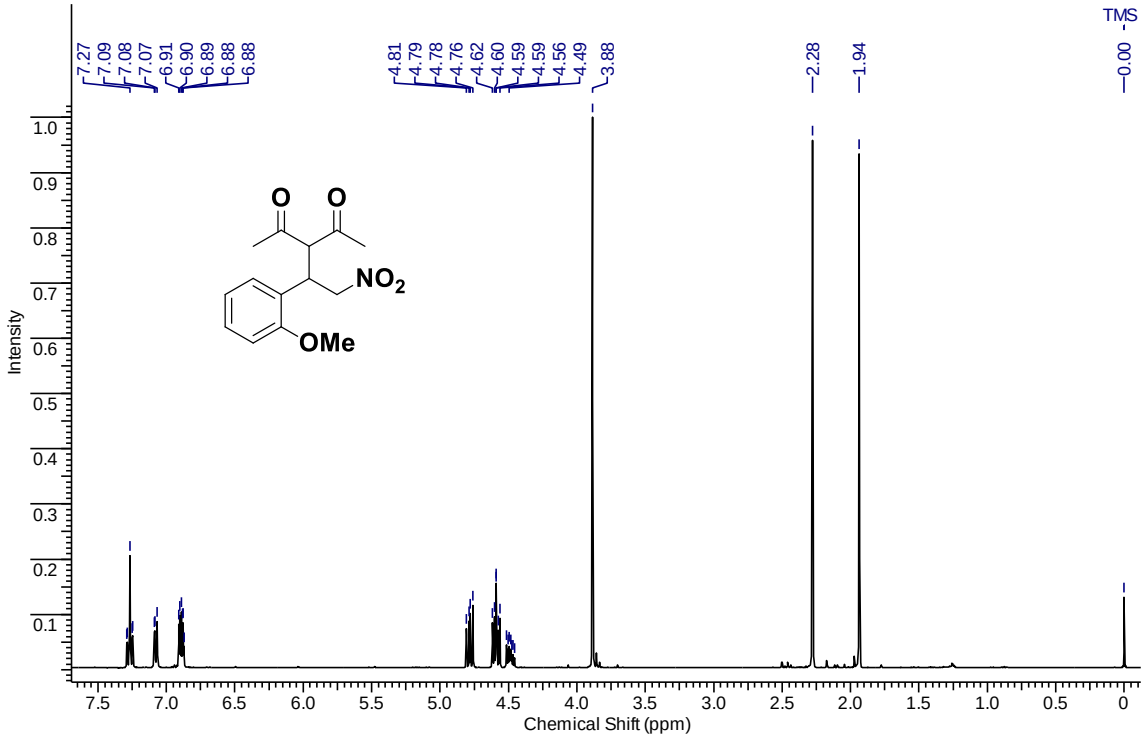
^{13}C NMR spectrum of 1.42e



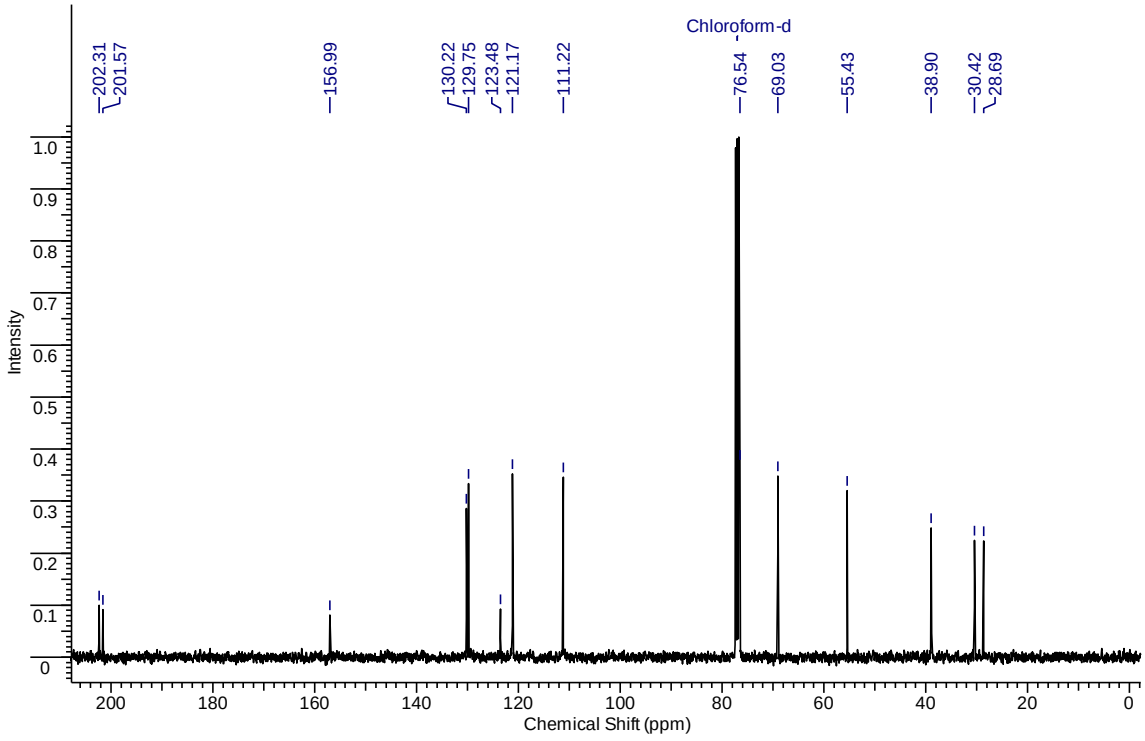
^{1}H NMR spectrum of 1.42f



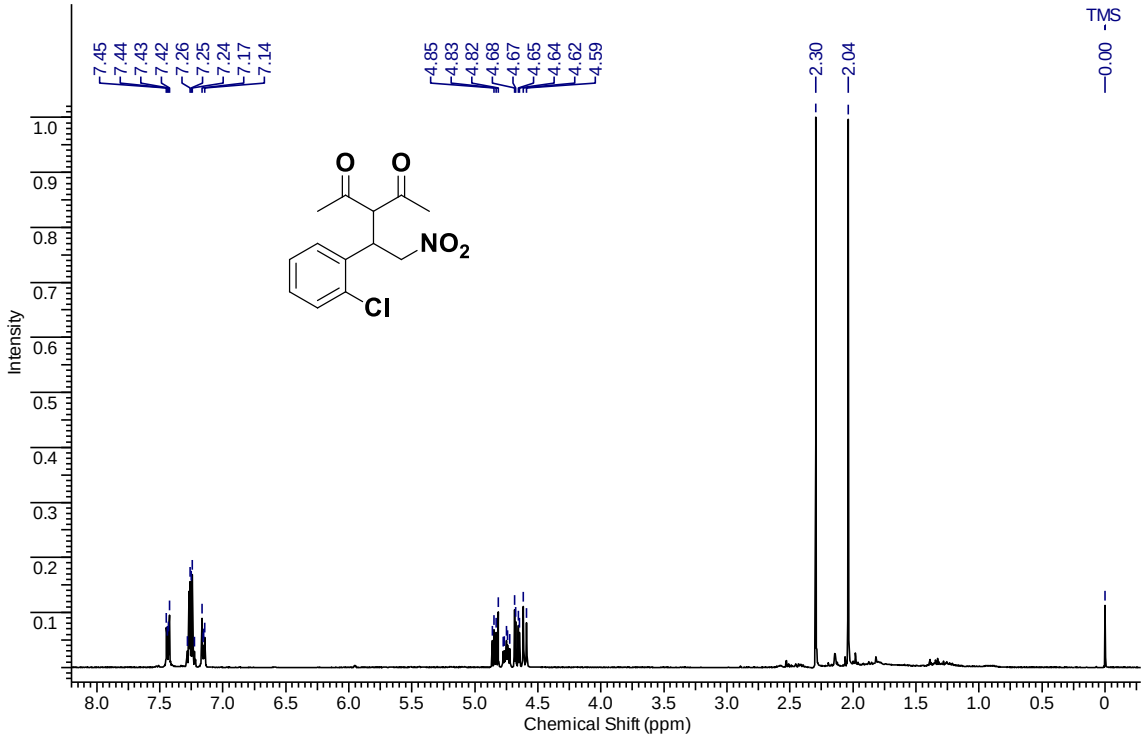
^{13}C NMR spectrum of 1.42f



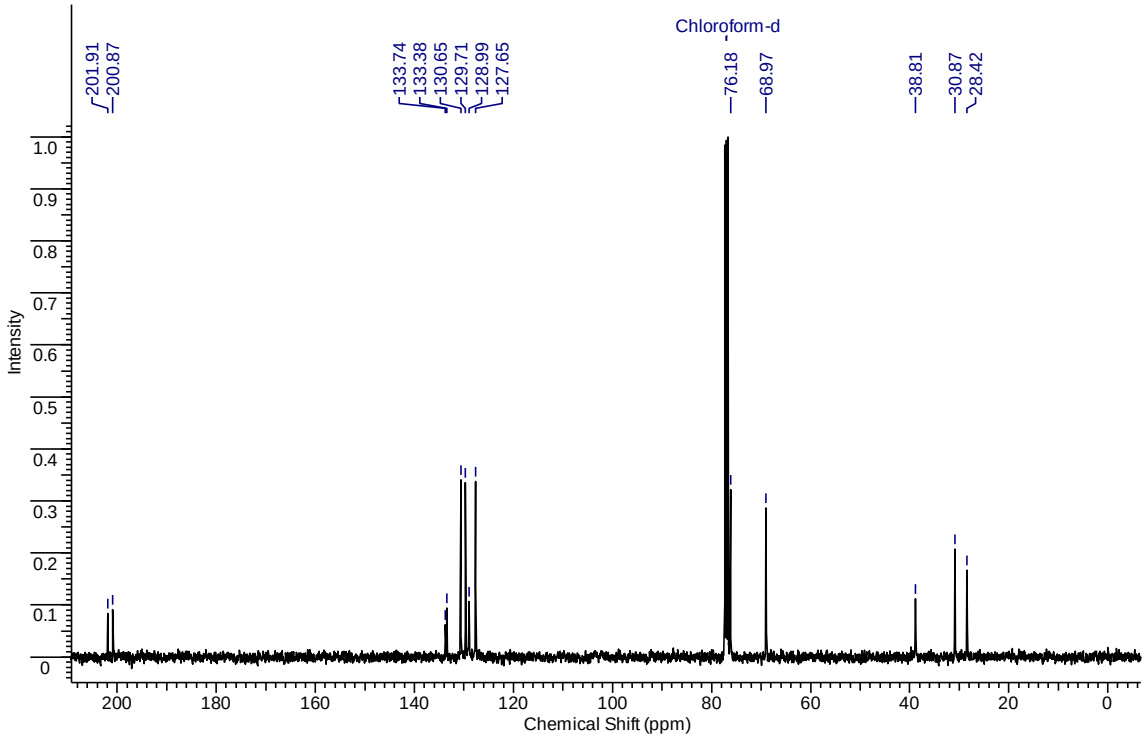
^{1}H NMR spectrum of 1.42g



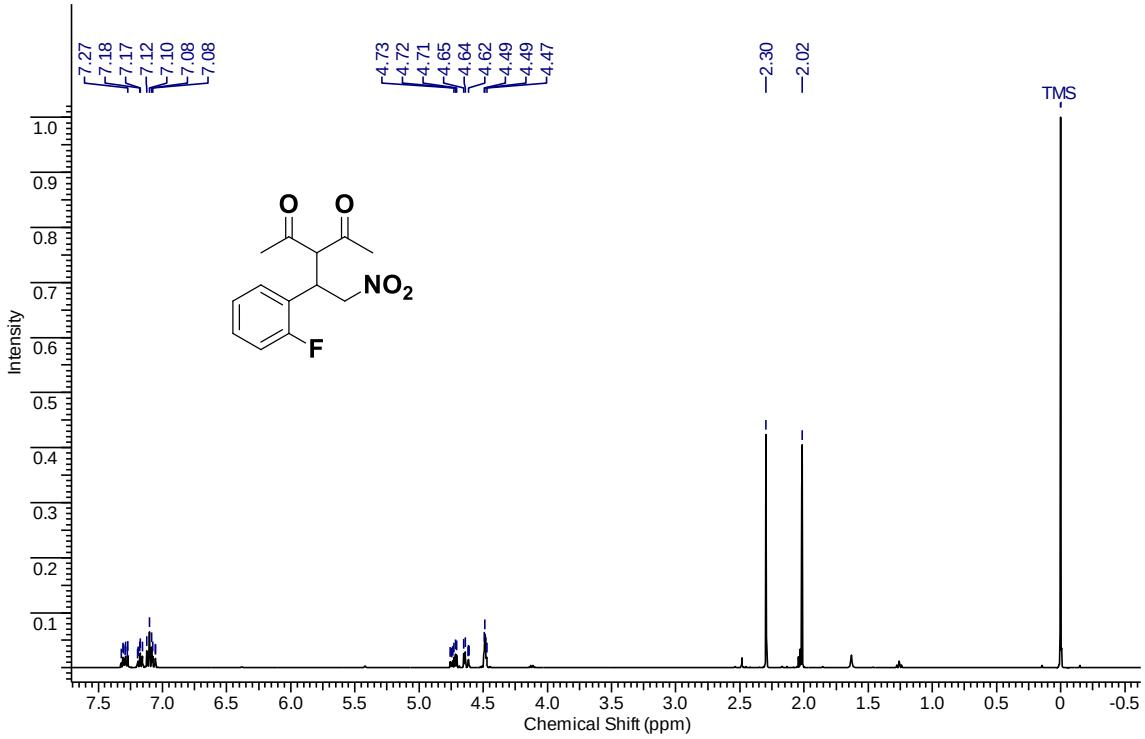
^{13}C NMR spectrum of 1.42g



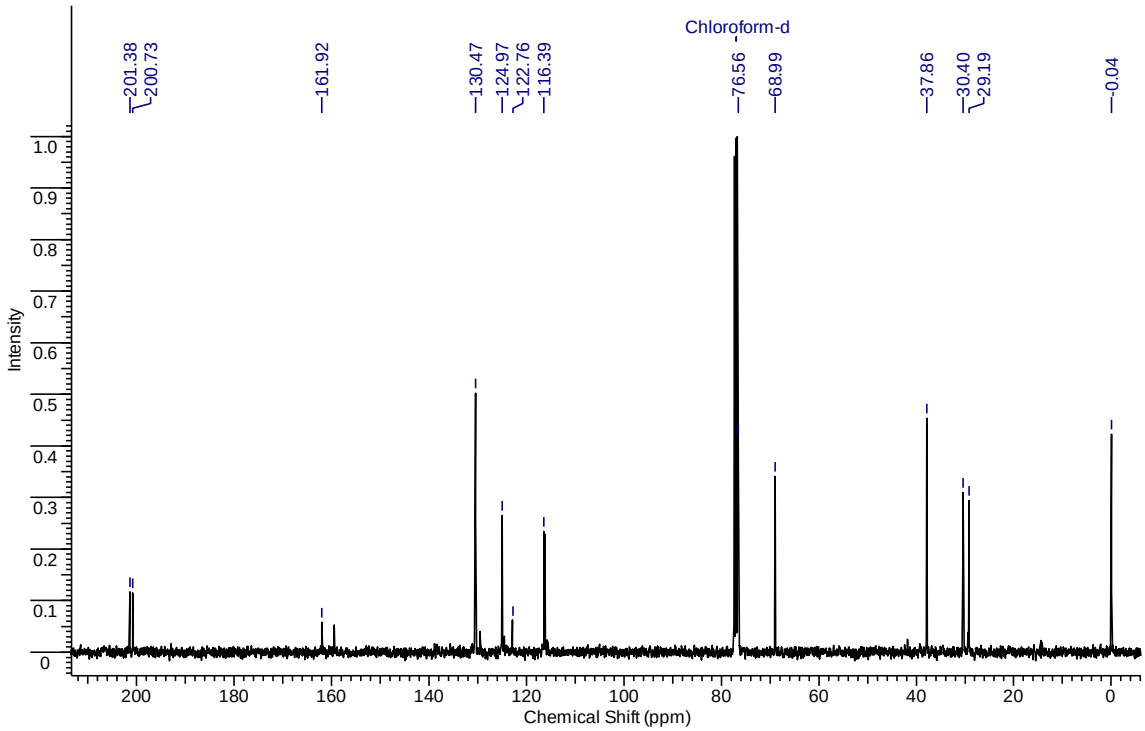
^{1}H NMR spectrum of 1.42h



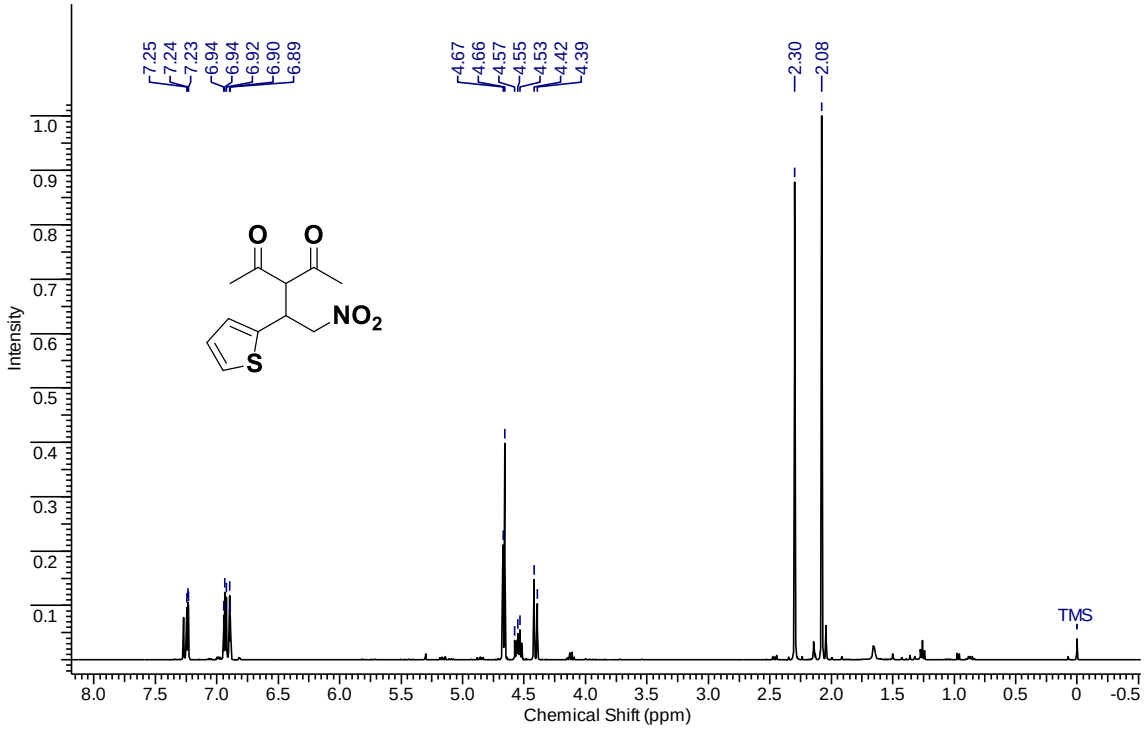
^{13}C NMR spectrum of 1.42h



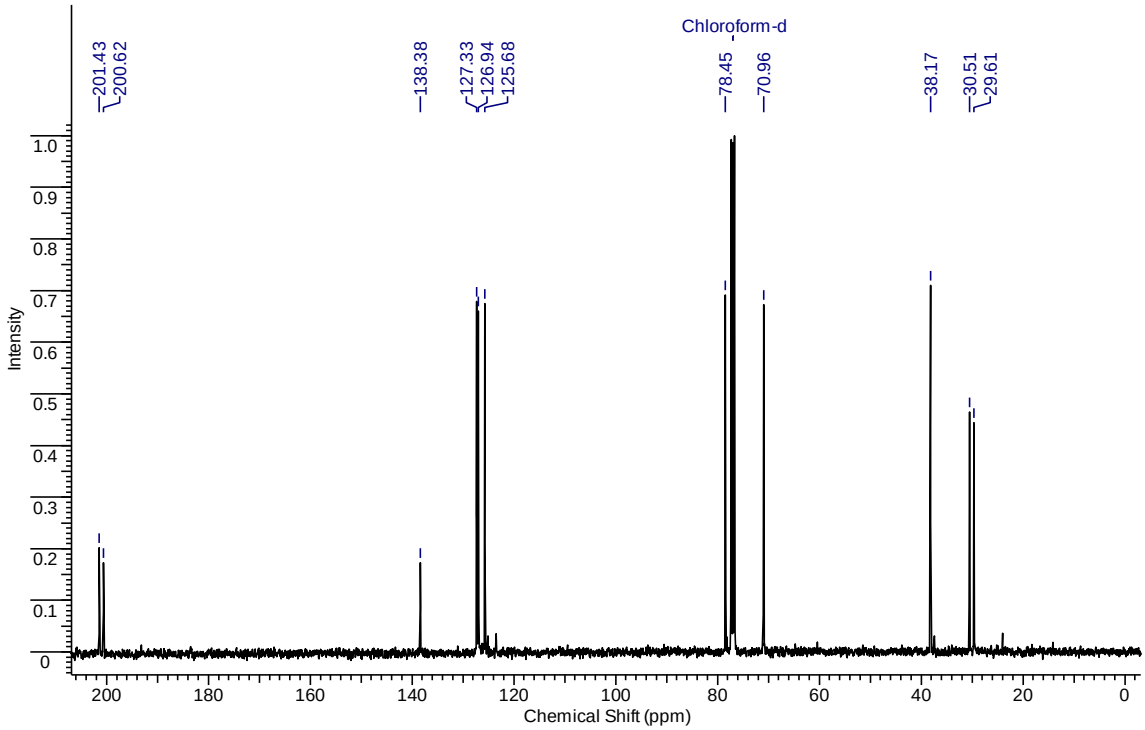
^{1}H NMR spectrum of 1.42i



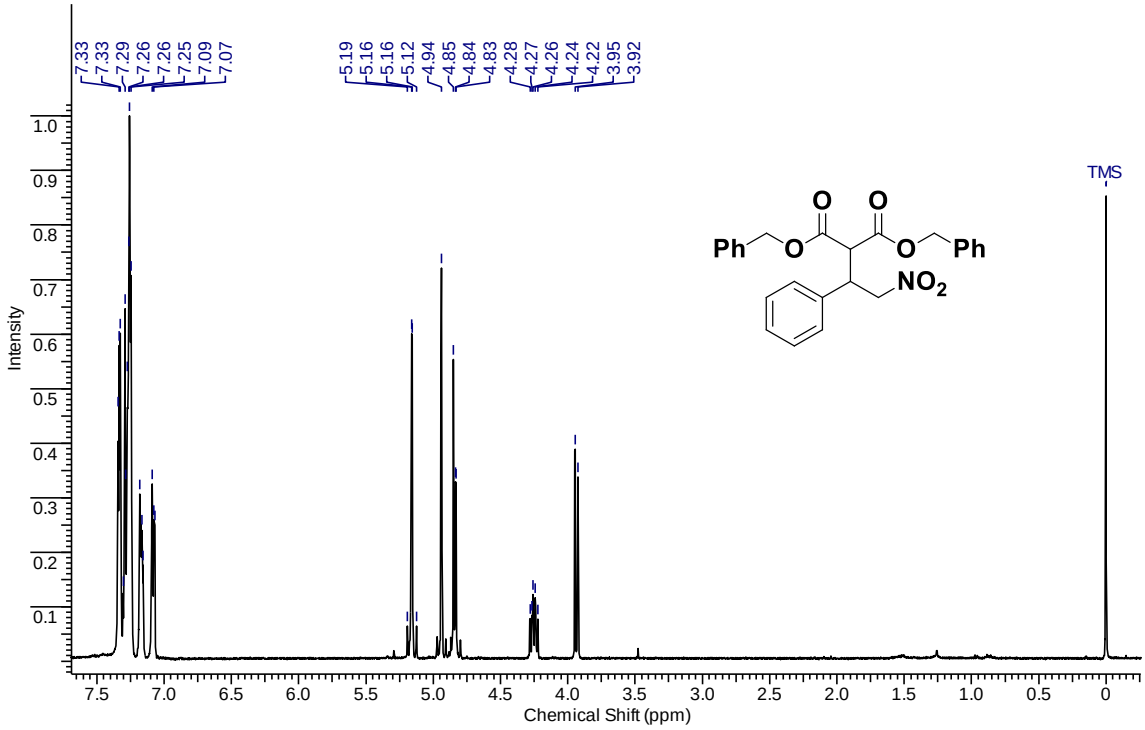
^{13}C NMR spectrum of 1.42i



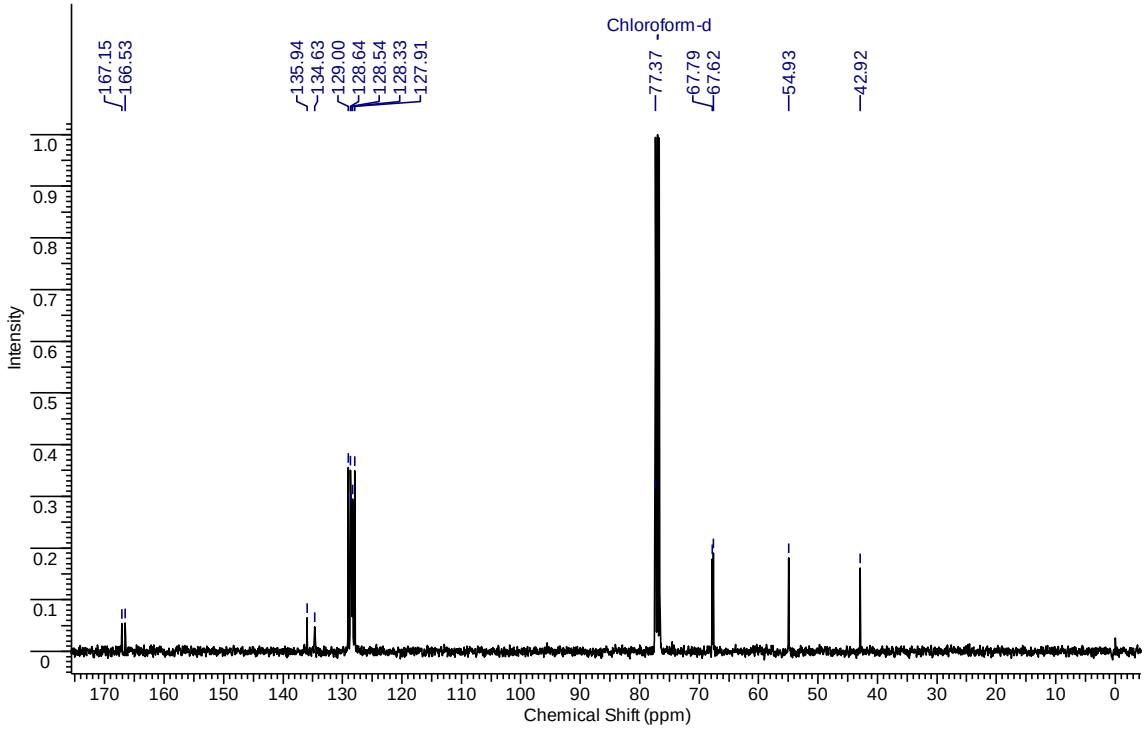
^{1}H NMR spectrum of 1.42j



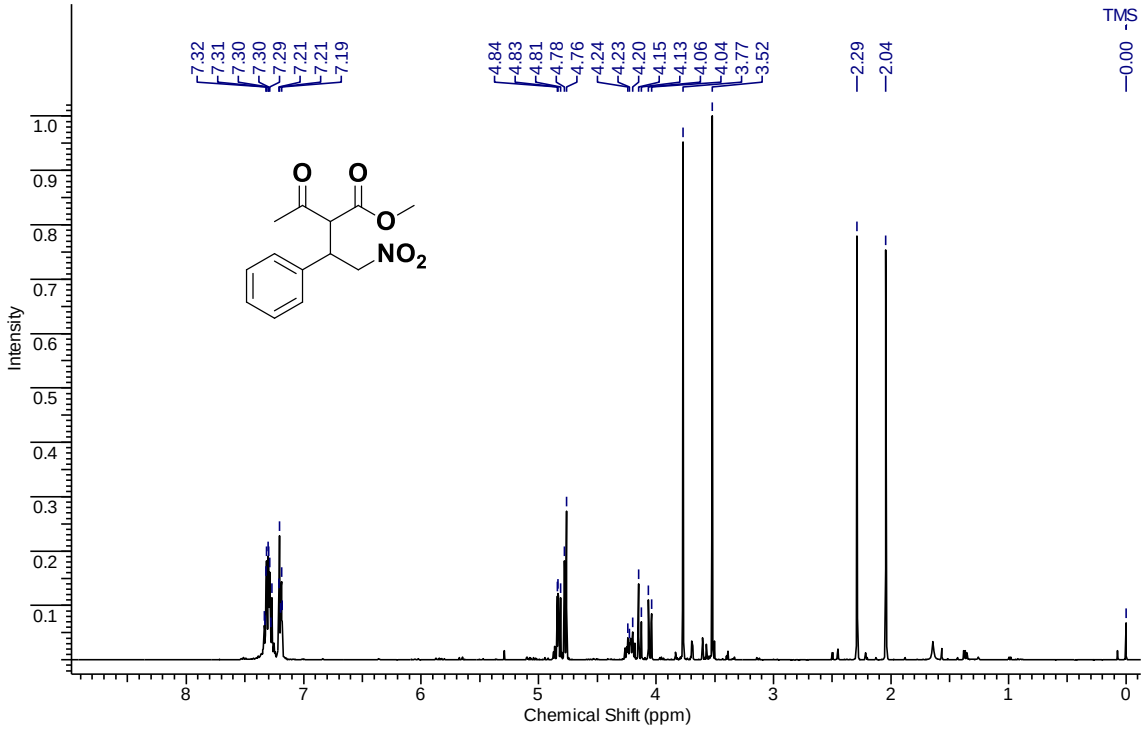
^{13}C NMR spectrum of 1.42j



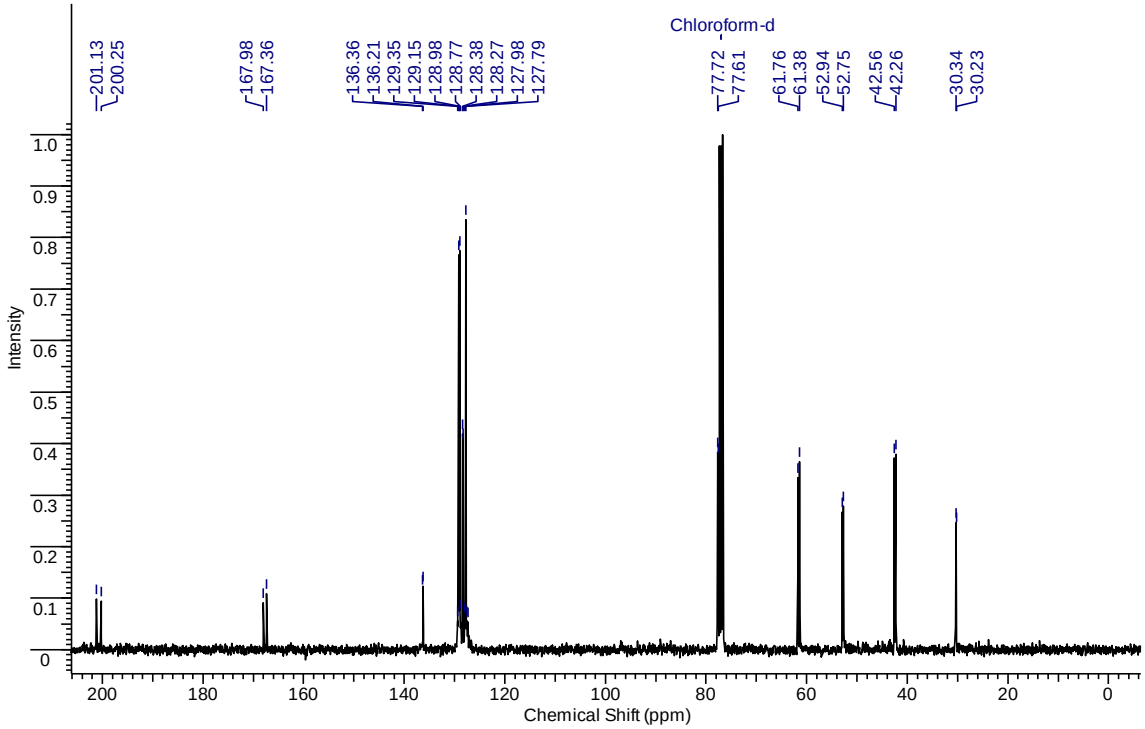
^{1}H NMR spectrum of 1.42k



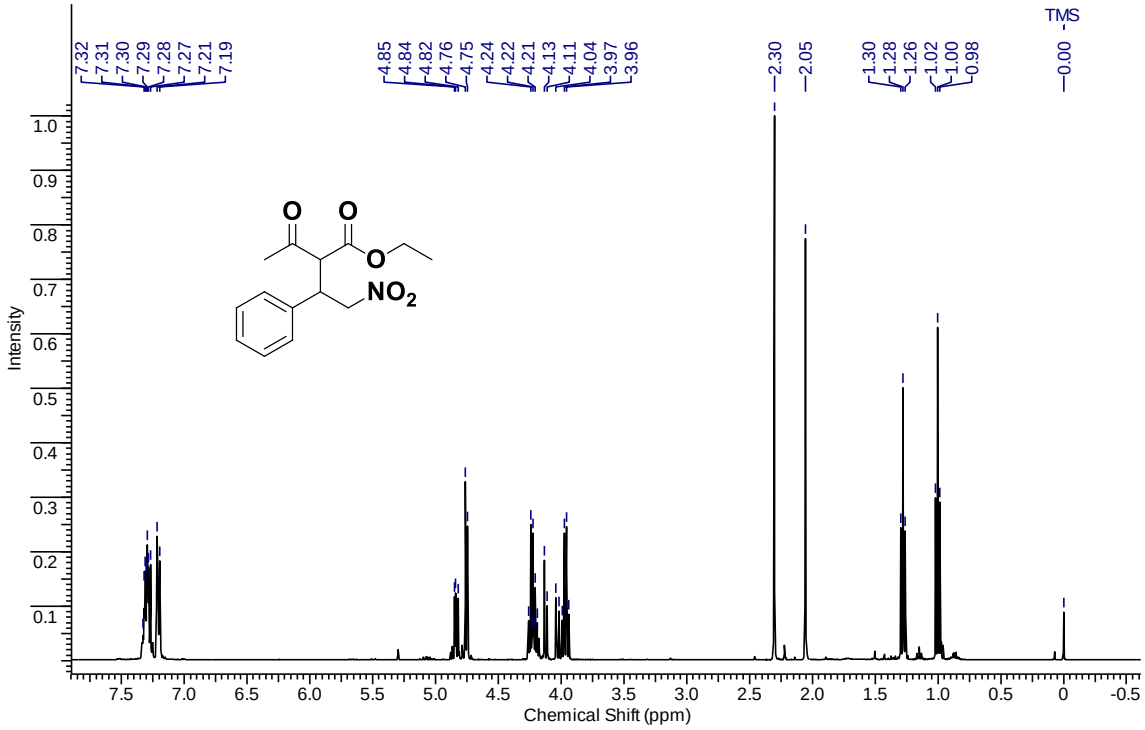
^{13}C NMR spectrum of 1.42k



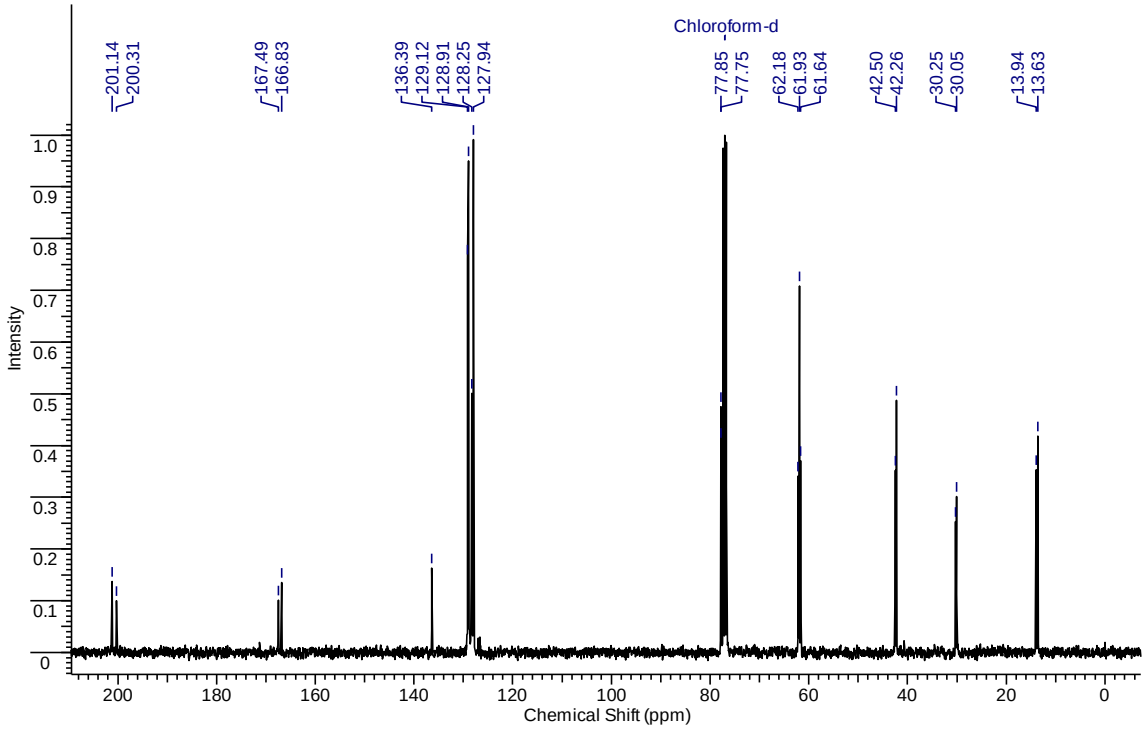
^{1}H NMR spectrum of 1.42l



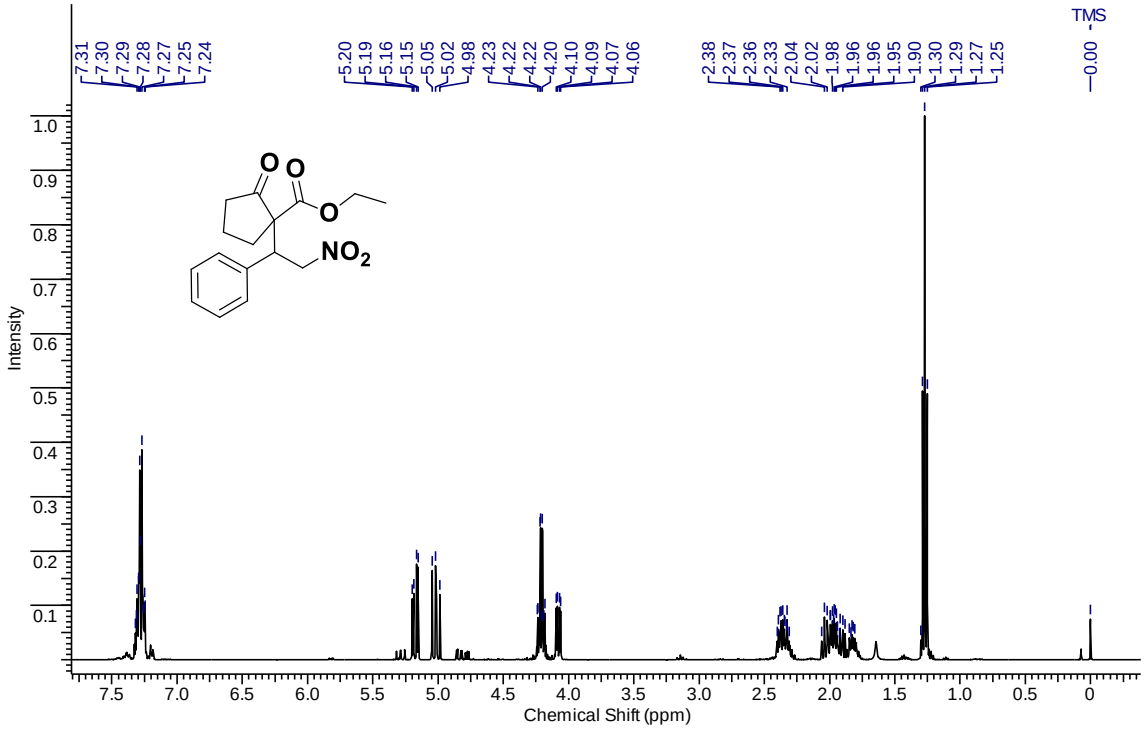
^{13}C NMR spectrum of 1.42l



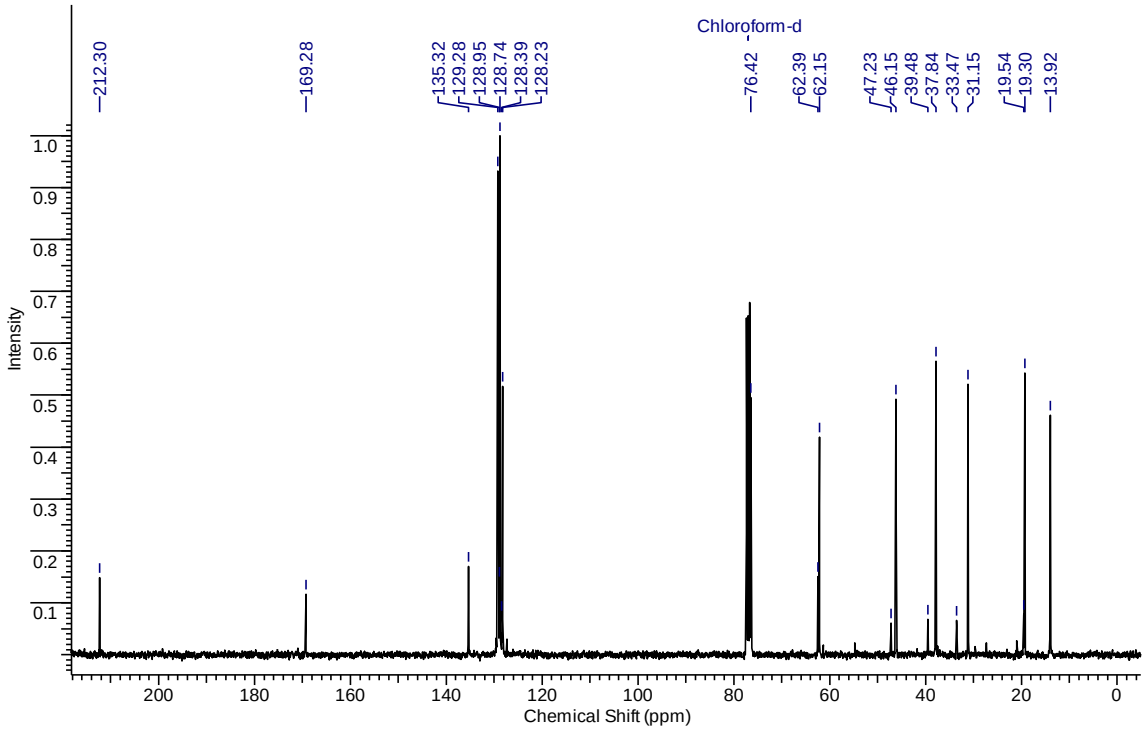
^{1}H NMR spectrum of 1.42m



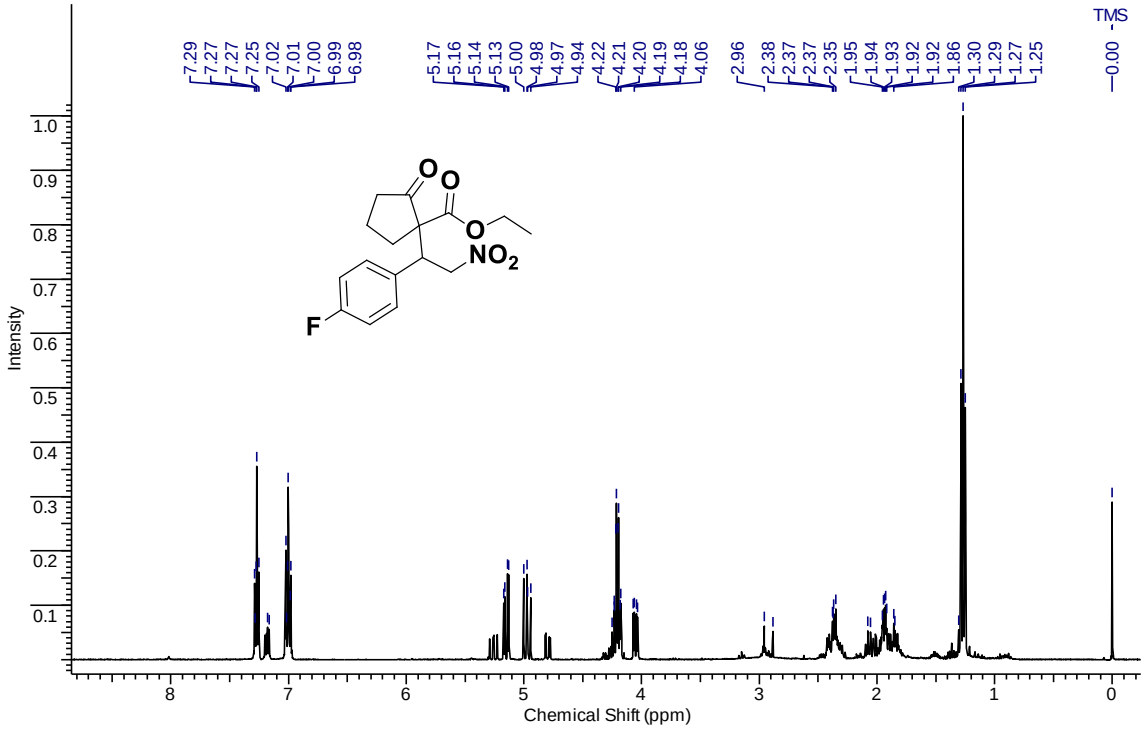
^{13}C NMR spectrum of 1.42m



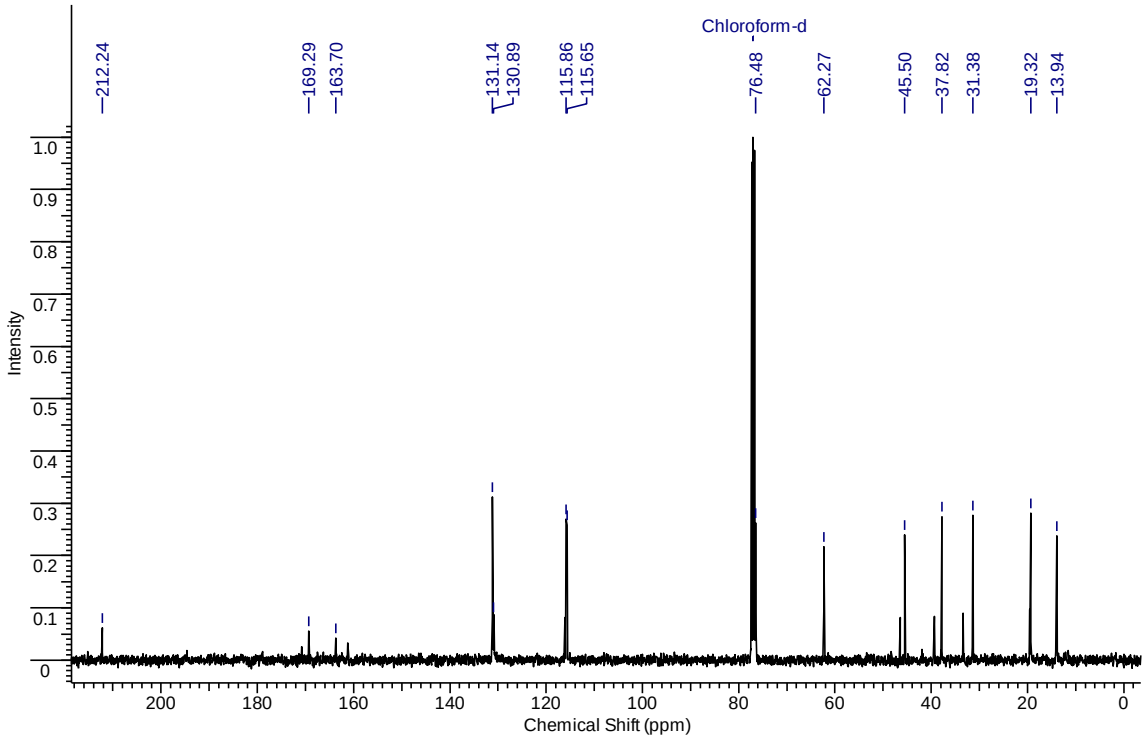
^{1}H NMR spectrum of 1.42n



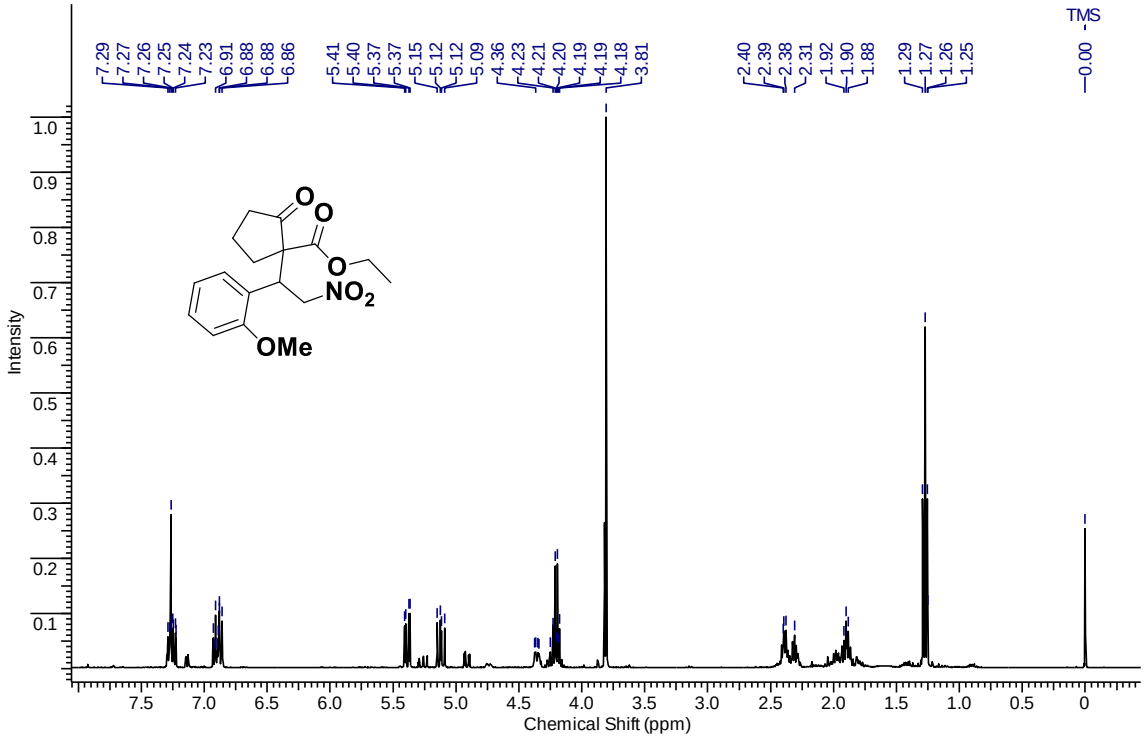
^{13}C NMR spectrum of 1.42n



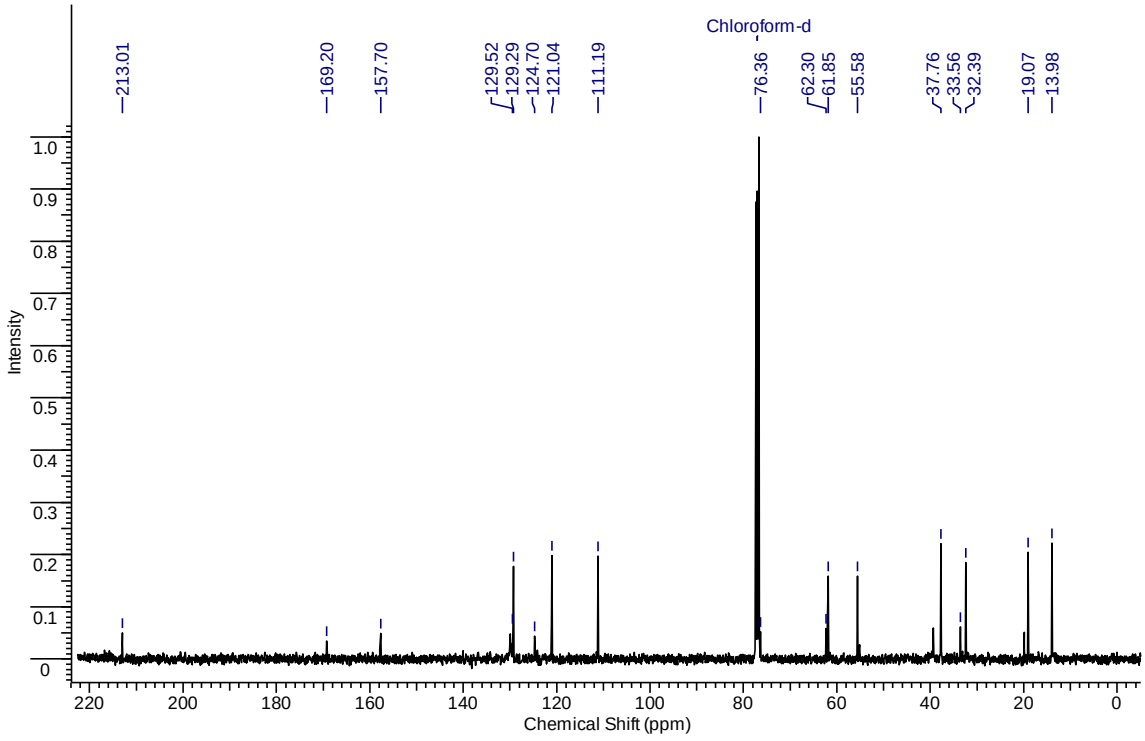
^{1}H NMR spectrum of 1.42o



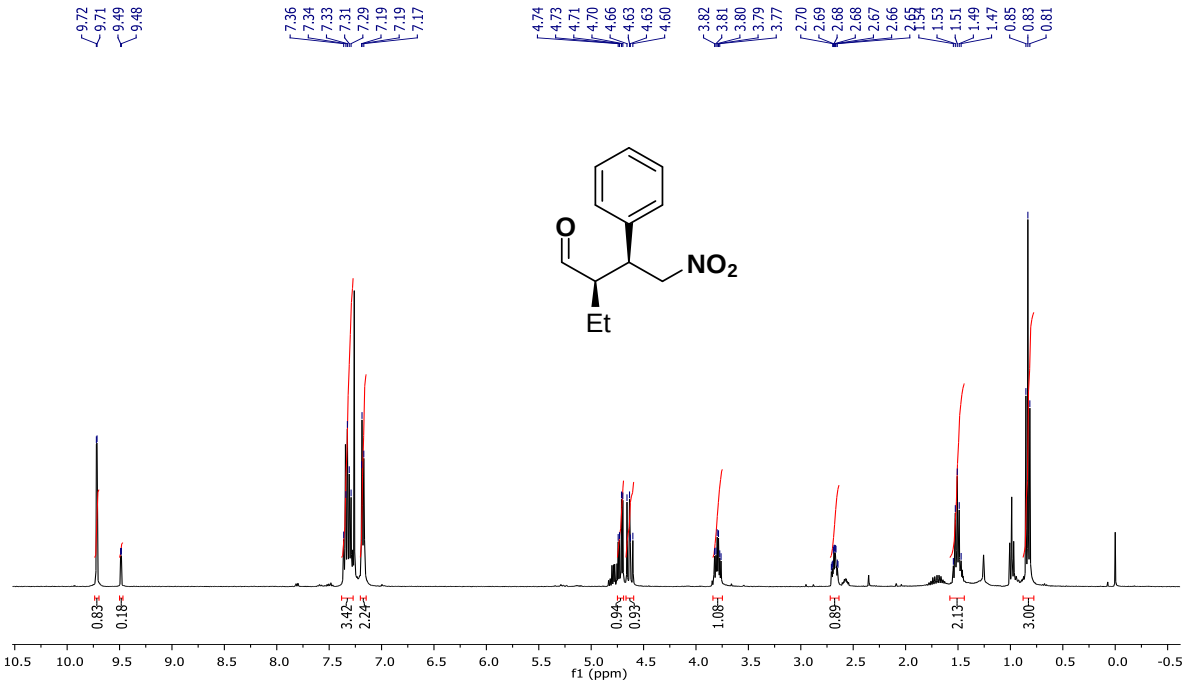
^{13}C NMR spectrum of 1.42o



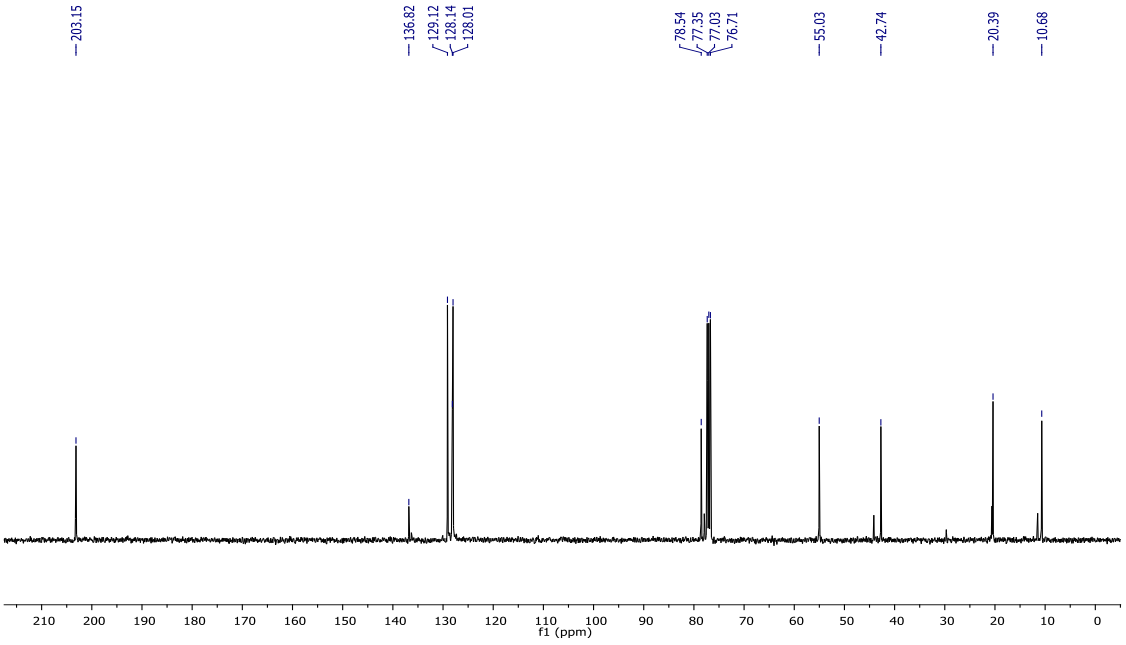
^{1}H NMR spectrum of 1.42p



^{13}C NMR spectrum of 1.42p

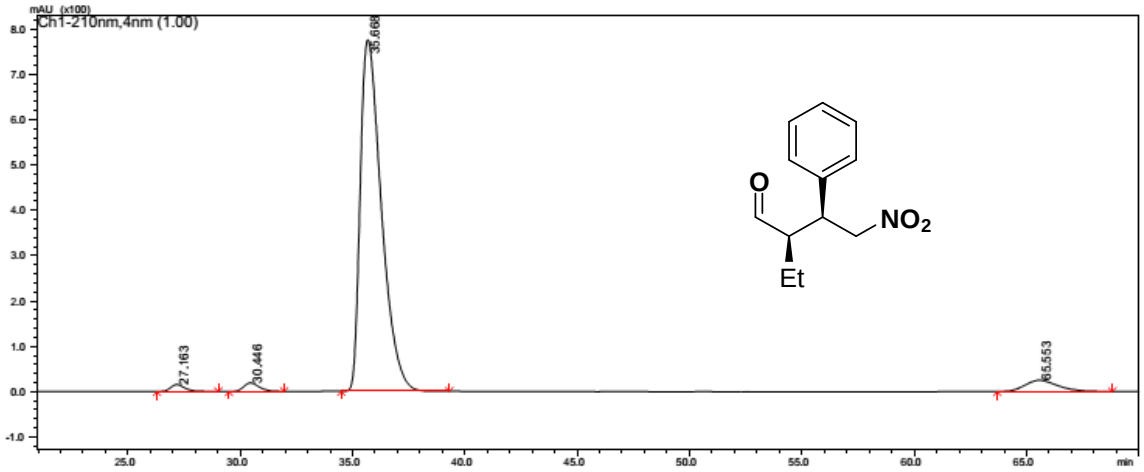


^{1}H NMR spectrum of 2.52a



^{13}C NMR spectrum of 2.52a

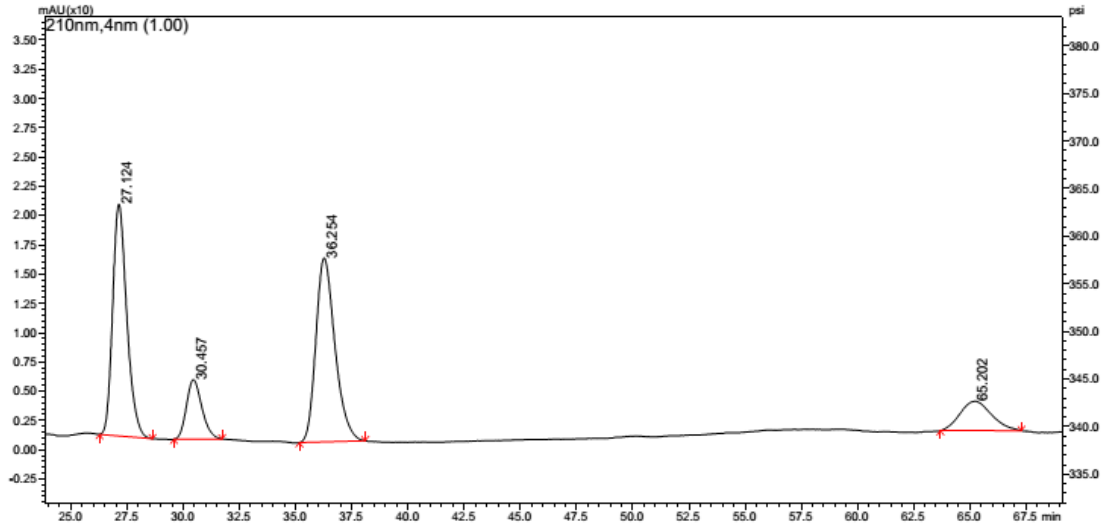
HPLC: Chiracel OD-H column (n-hexane/i-PrOH 91:09, 25ºC) at 0.9 mL/min (97% ee)



PeakTable

PDA Ch1 210nm 4nm

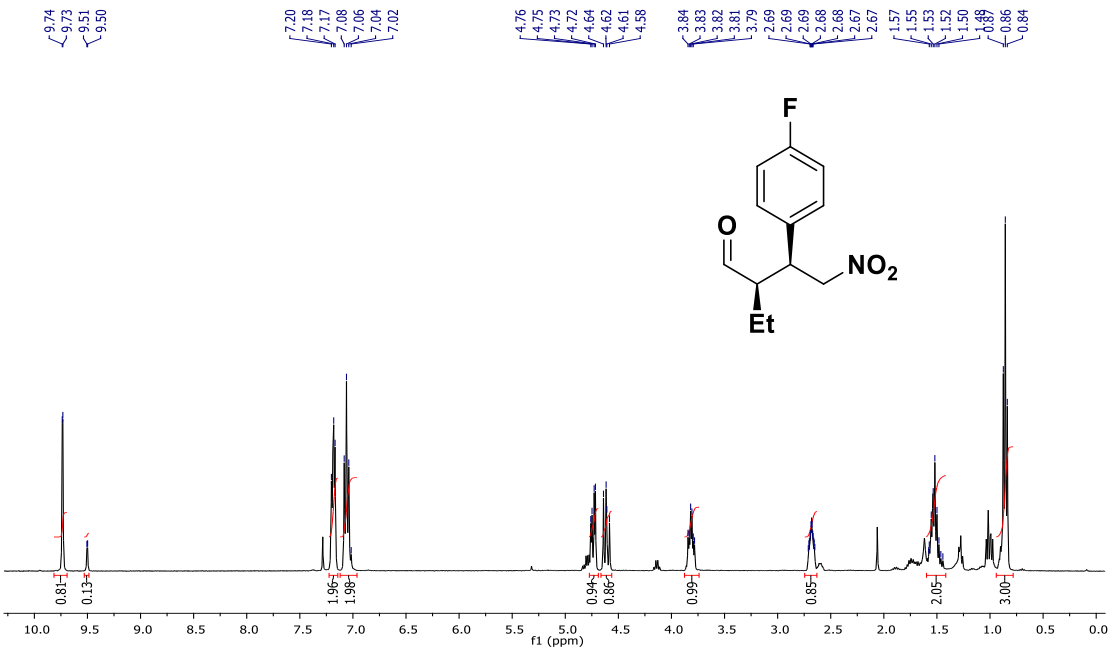
Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.163	712943	15604	1.295	1.866
2	30.446	943621	19257	1.715	2.303
3	35.668	50772270	776262	92.254	92.847
4	65.553	2606421	24945	4.736	2.984
Total		55035255	836068	100.000	100.000



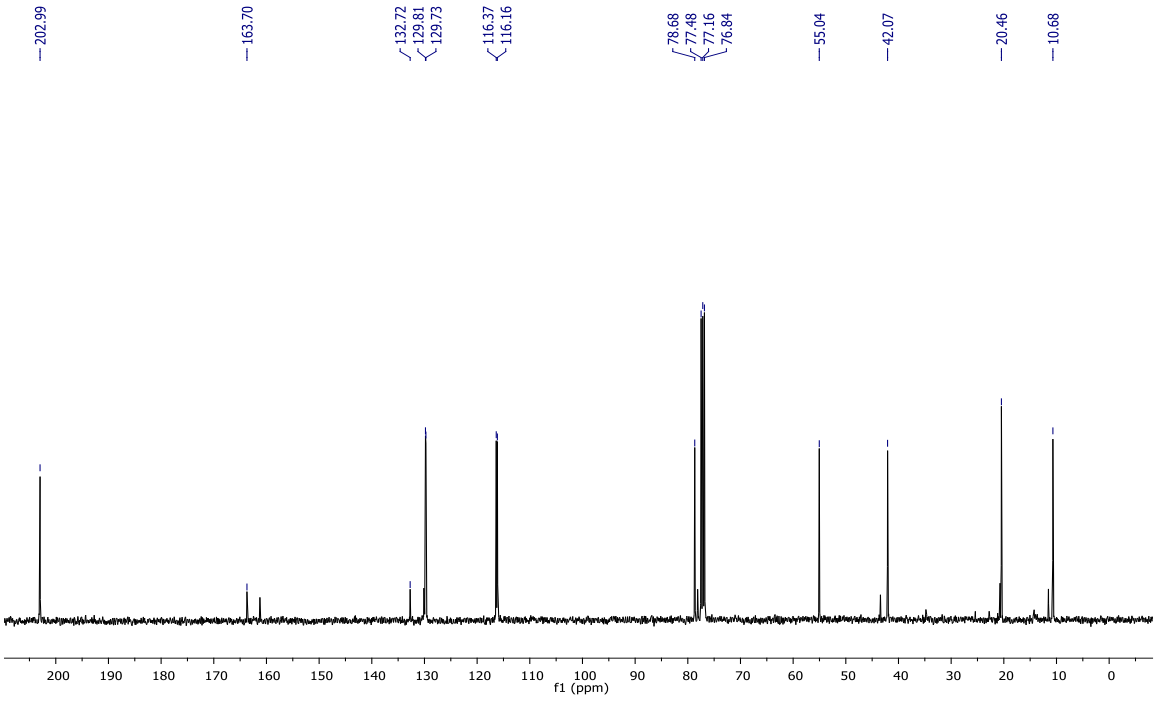
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.124	867445	19800	37.957	45.951
2	30.457	242098	5070	10.593	11.767
3	36.254	931040	15712	40.739	36.463
4	65.202	244769	2508	10.710	5.819
Total		2285353	43090	100.000	100.000

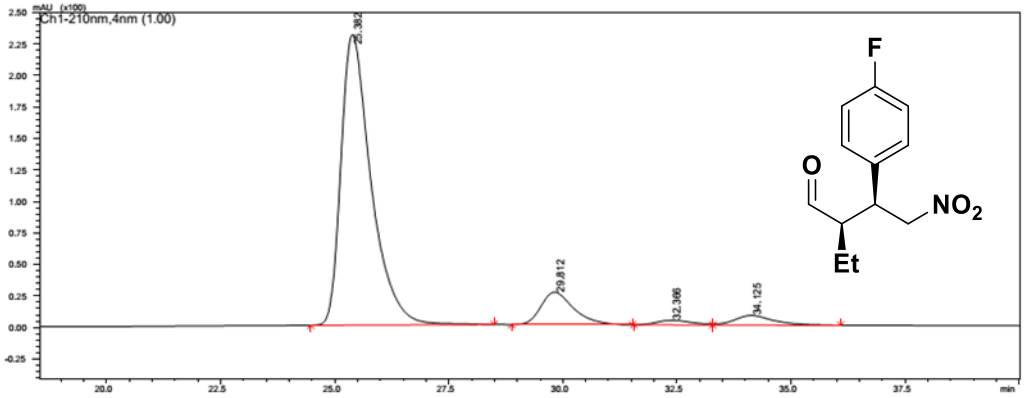


^{1}H NMR spectrum of 2.52b



^{13}C NMR spectrum of 2.52b

HPLC: Chiracel OD-H column (n-hexane/i-PrOH 95:05, 25ºC) at 1 mL/min (96% ee)



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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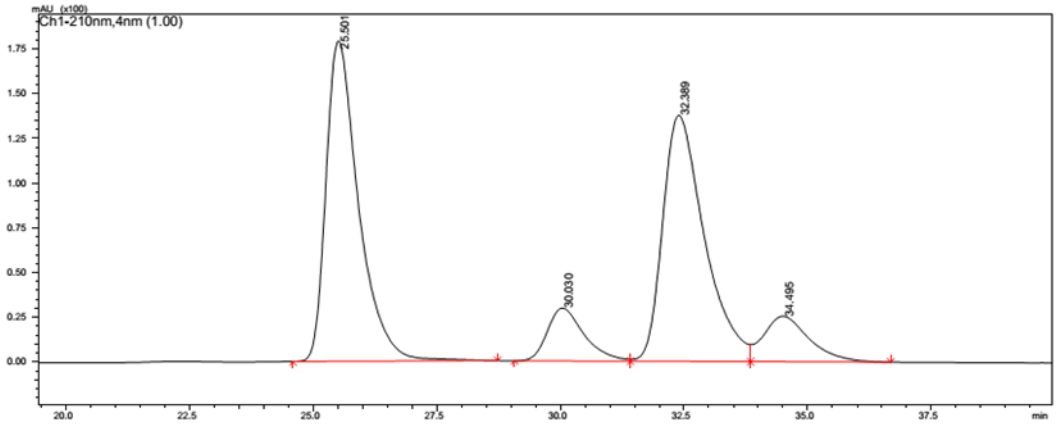
2	29.812	1289444	25764	10.312	9.632
3	32.366	189253	3620	1.513	1.353
4	34.125	454313	7595	3.633	2.839
Total		12504901	267488	100.000	100.000



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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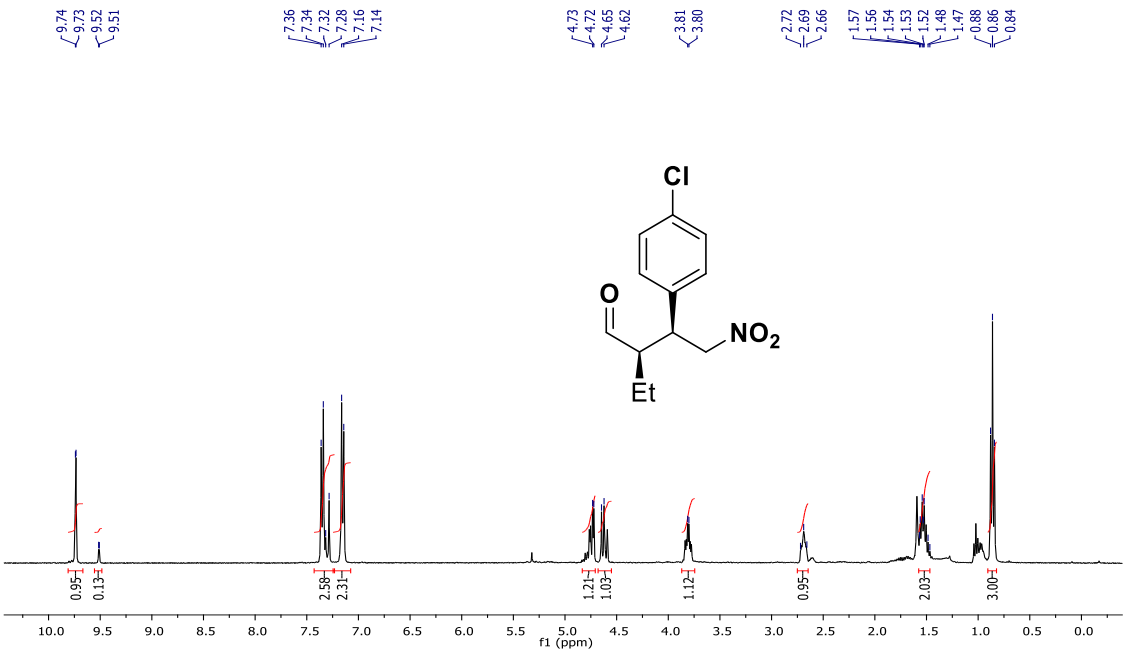
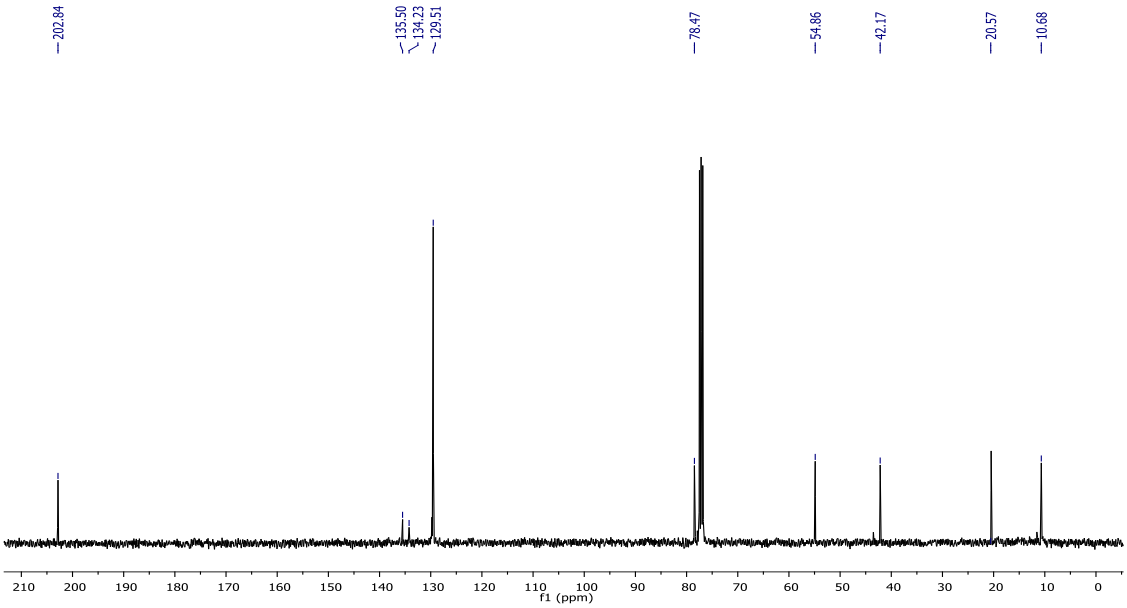
2	30.030	1520218	29493	7.827	7.941
3	32.389	8069247	137384	41.543	36.992
4	34.495	1630250	25432	8.393	6.848
Total		19423975	371387	100.000	100.000

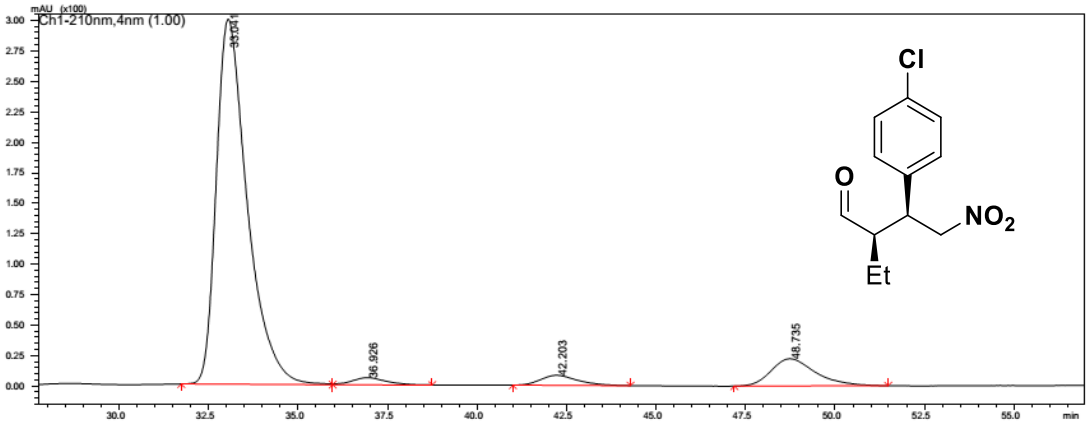


^{1}H NMR spectrum of 2.52c



^{13}C NMR spectrum of 2.52c

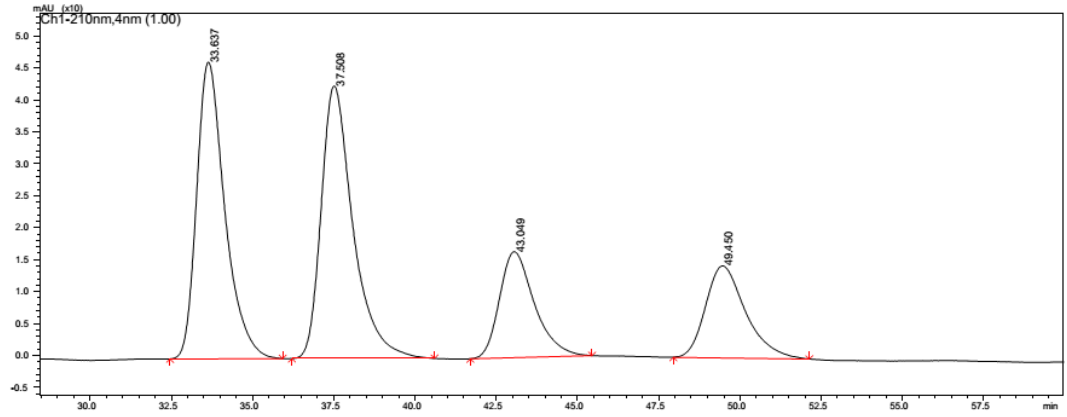
HPLC: Chiracel OD-H column (n-hexane/i-PrOH 95:5, 25ºC) at 1 mL/min (96% ee)



PeakTable

PDA Ch1 210nm 4nm

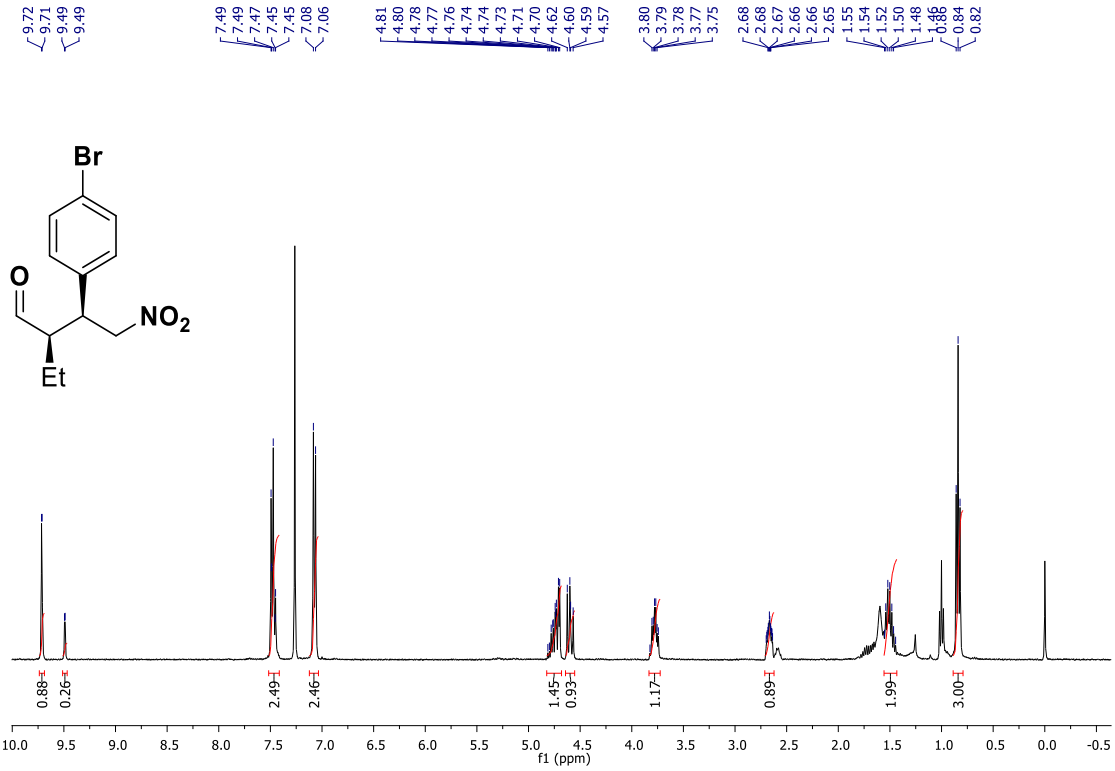
Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.041	18052281	299606	86.237	89.199
2	36.926	378705	5873	1.809	1.749
3	42.203	590311	8143	2.820	2.424
4	48.735	1912108	22265	9.134	6.629
Total		20933405	335886	100.000	100.000



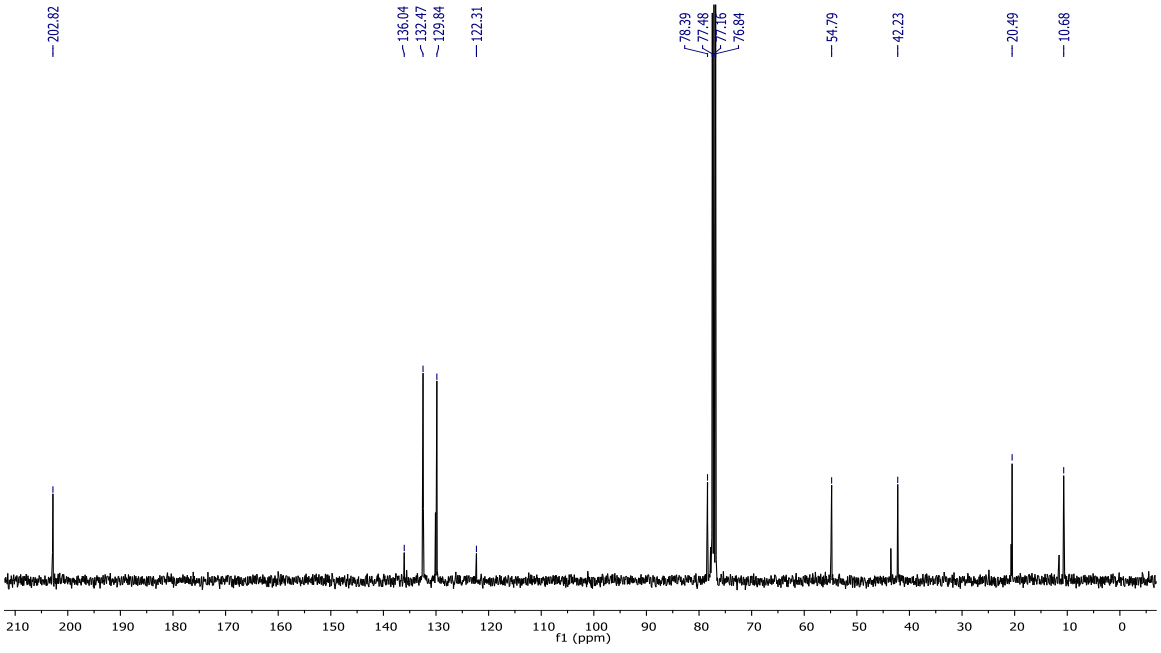
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.637	2800026	46439	34.224	38.680
2	37.508	2907345	42657	35.535	35.529
3	43.049	1236687	16551	15.115	13.786
4	49.450	1237525	14414	15.126	12.005
Total		8181582	120061	100.000	100.000

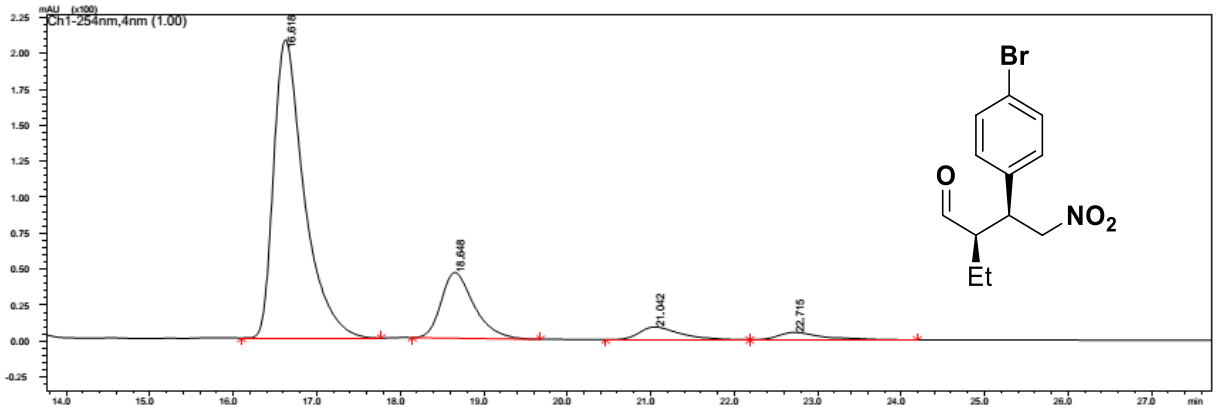


^{1}H NMR spectrum of 2.52d



^{13}C NMR spectrum of 2.52d

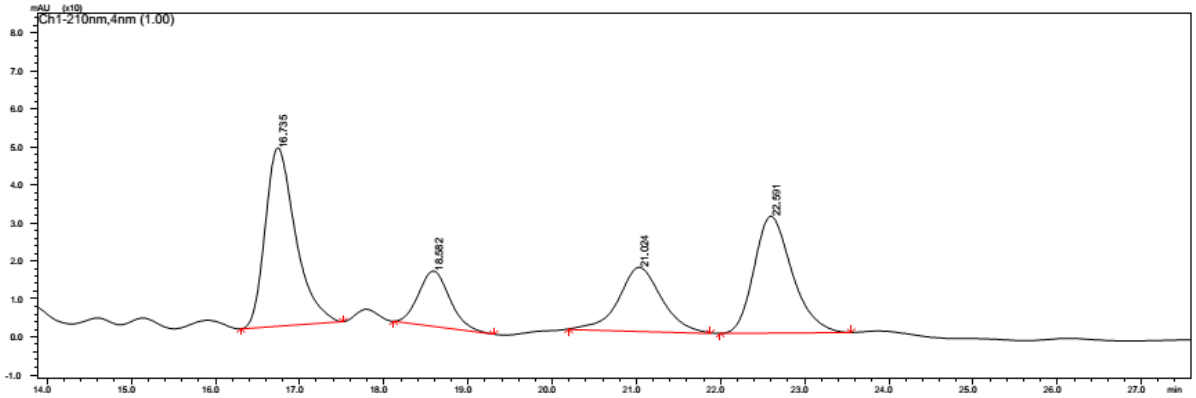
HPLC: Chiracel AD-H column (n-hexane/i-PrOH 95:05, 25ºC) at 0.8 mL/min (93% ee)



PeakTable

PDA Ch1 254nm 4nm

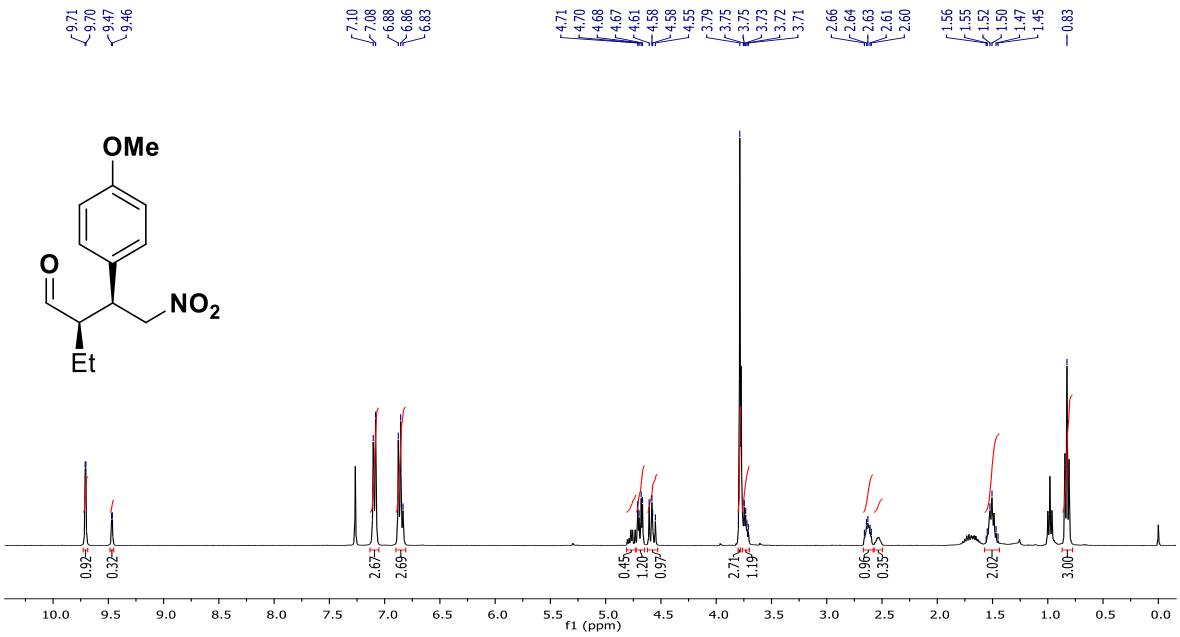
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.618	5290575	207418	74.982	77.585
2	18.648	1253711	45652	17.769	17.076
3	21.042	312597	9045	4.430	3.383
4	22.715	198871	5227	2.819	1.955
Total		7055754	267341	100.000	100.000



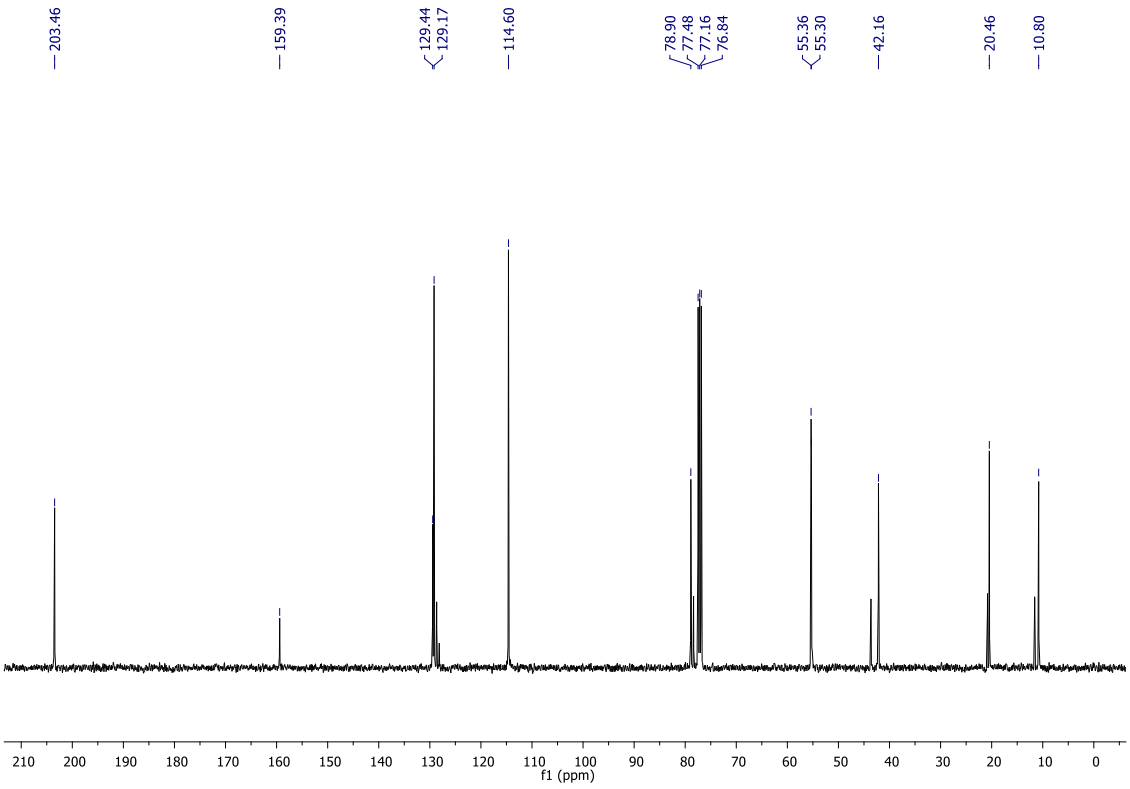
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.735	1181332	46993	37.799	43.045
2	18.582	377420	14605	12.076	13.378
3	21.024	602704	16844	19.285	15.429
4	22.591	963847	30730	30.840	28.148
Total		3125303	109172	100.000	100.000

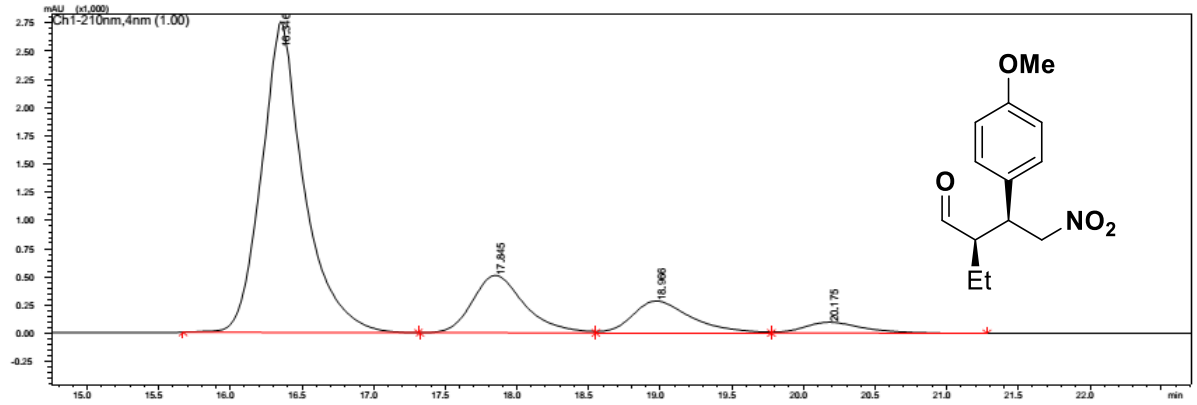


^{1}H NMR spectrum of 2.52e



^{13}C NMR spectrum of 2.52e

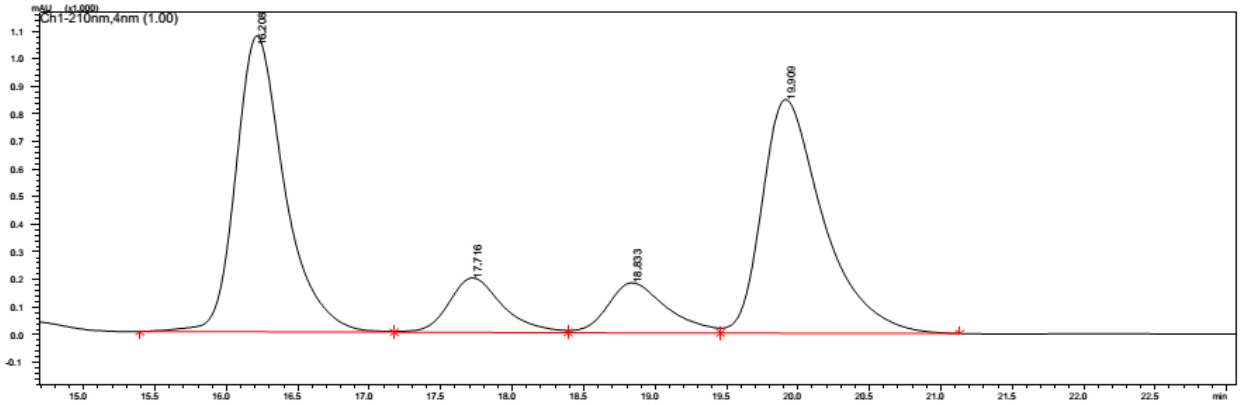
HPLC: Chiracel AD-H column (n-hexane/i-PrOH 95:05, 25ºC) at 0.8 mL/min (91% ee)



PeakTable

PDA Ch1 210nm 4nm

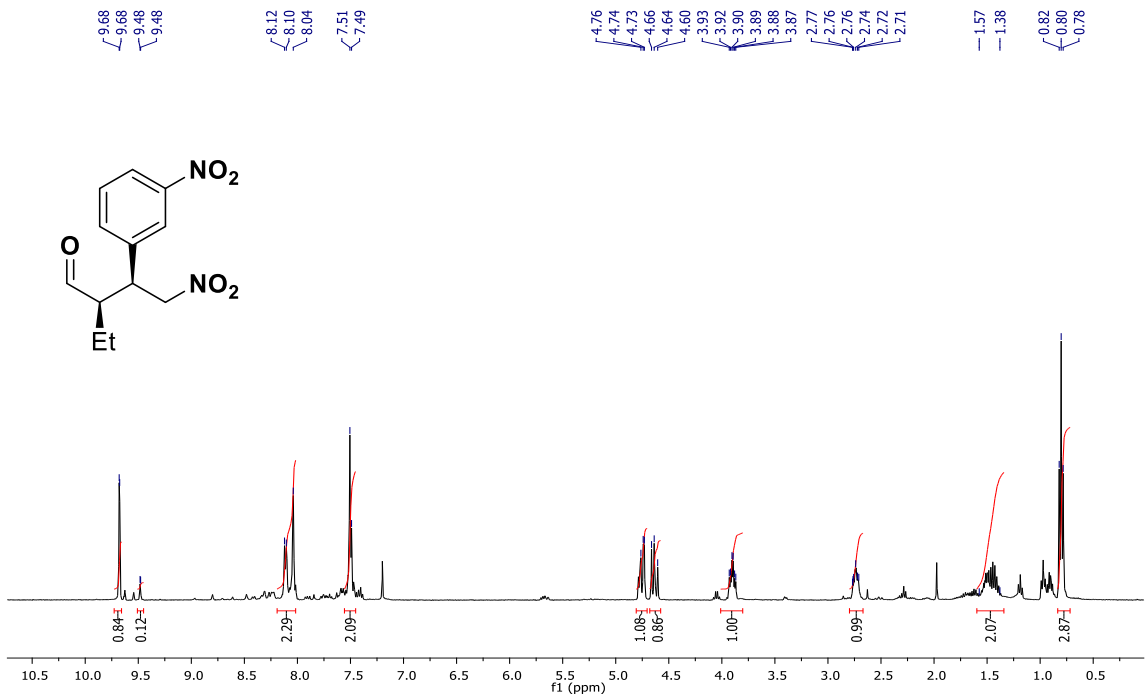
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.346	56792073	2755759	70.590	75.632
2	17.845	12846339	508628	15.968	13.959
3	18.966	8068180	283133	10.028	7.771
4	20.175	2746272	96107	3.414	2.638
Total		80452864	3643626	100.000	100.000



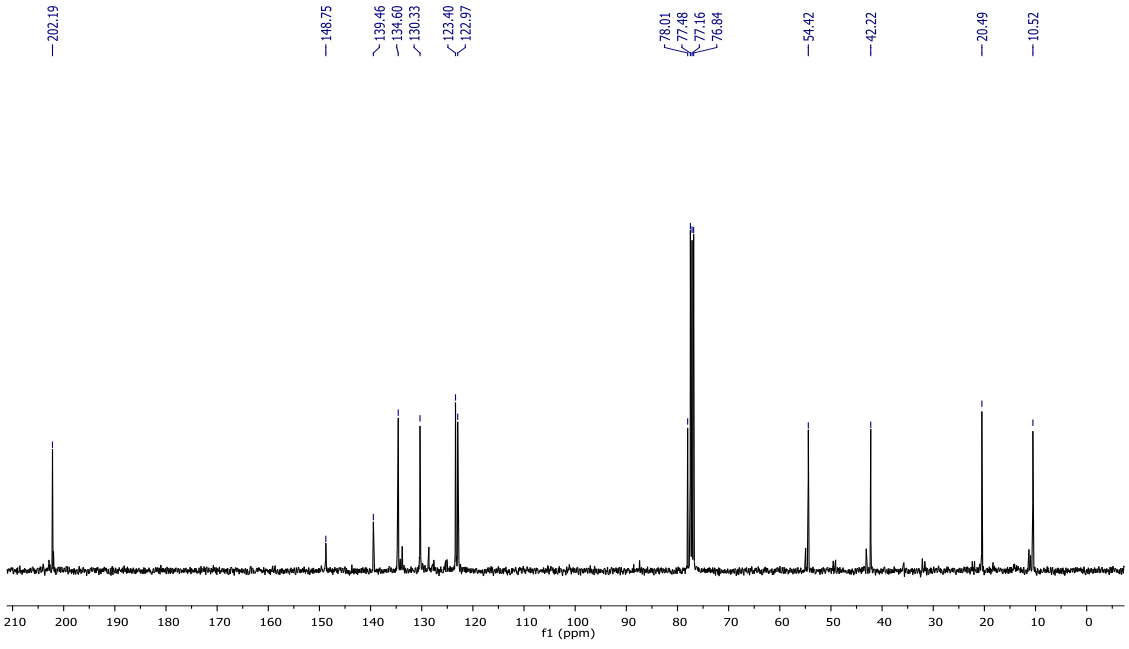
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.208	25562652	1074881	41.739	46.707
2	17.716	5176706	197838	8.453	8.597
3	18.833	5204060	181030	8.497	7.866
4	19.909	25301159	847583	41.312	36.830
Total		61244577	2301332	100.000	100.000

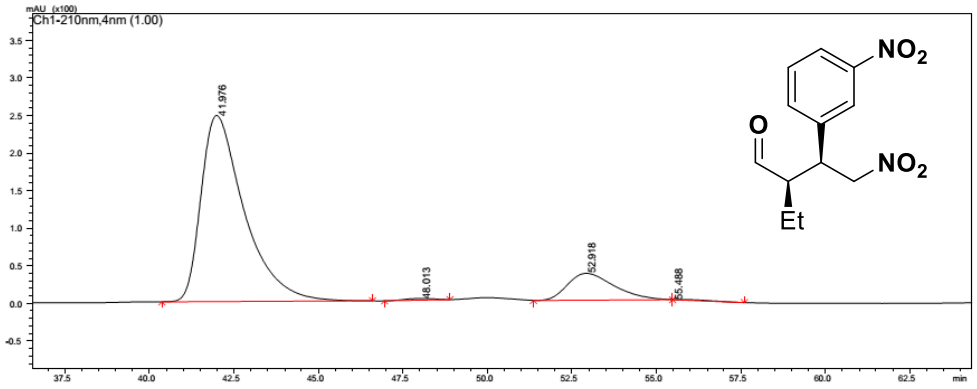


^{1}H NMR spectrum of 2.52f



^{13}C NMR spectrum of 2.52f

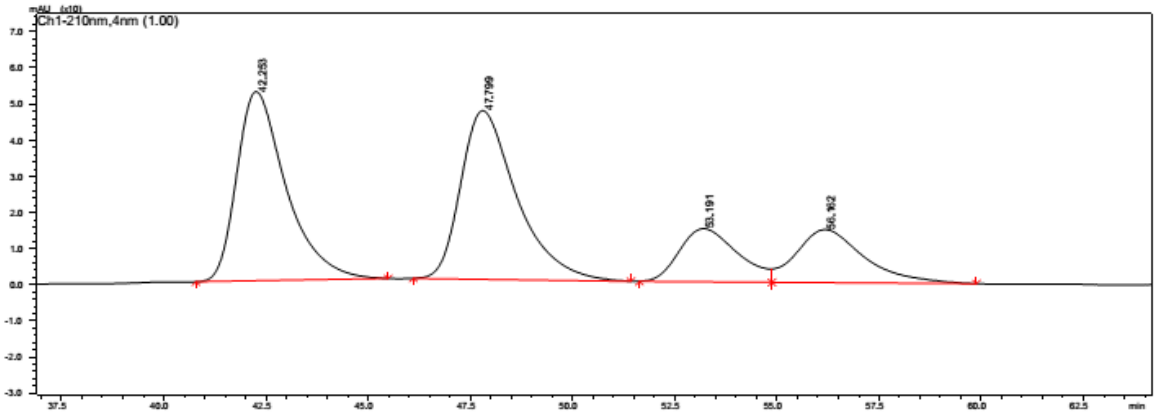
HPLC: Chiracel OD-H column (n-hexane/i-PrOH 90:10, 25ºC) at 1 mL/min (99% ee)



PeakTable

PDA Ch1 210nm 4nm

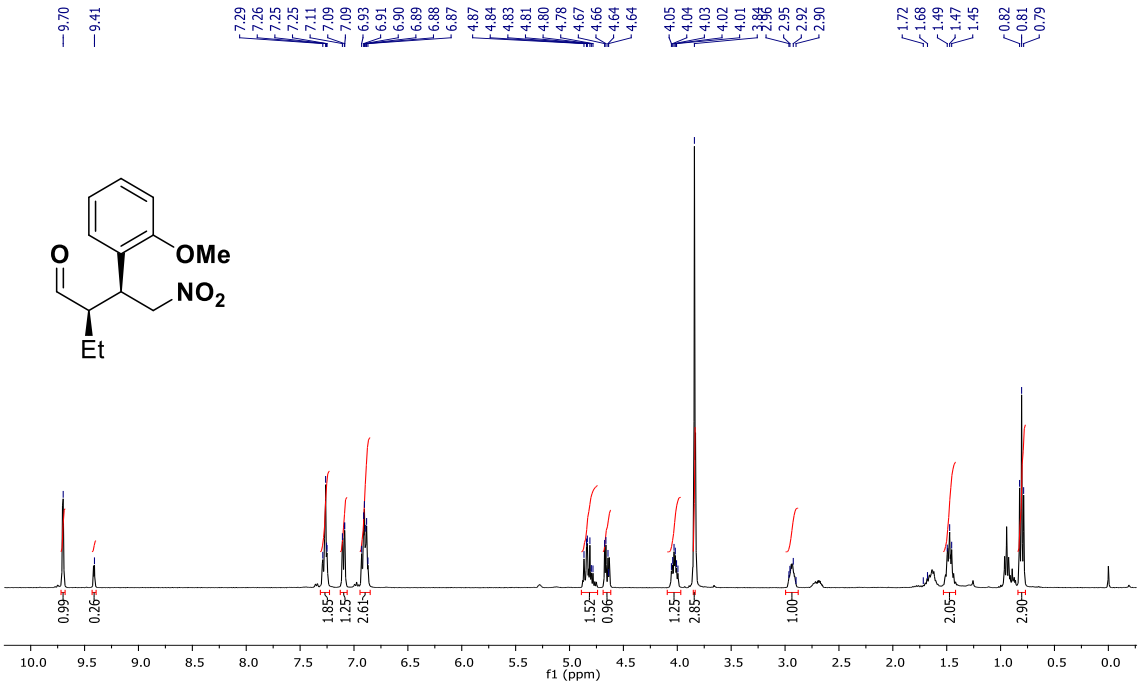
Peak#	Ret. Time	Area	Height	Area %	Height %
1	41.976	22013627	247499	85.838	86.634
2	48.013	130876	2282	0.510	0.799
3	52.918	3431372	35738	13.380	12.510
4	55.488	69770	164	0.272	0.057
Total		25645644	285683	100.000	100.000



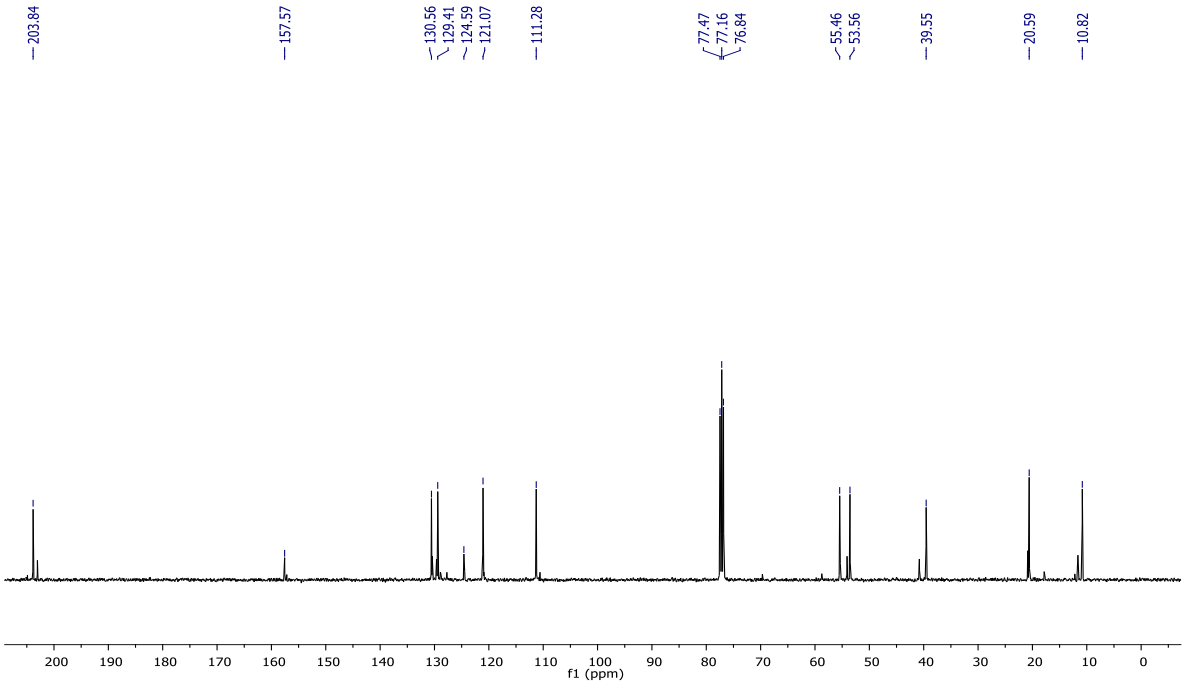
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	42.253	4399573	52337	36.607	40.761
2	47.799	4460646	46658	37.116	36.338
3	53.191	1460219	14706	12.150	11.453
4	56.162	1697791	14700	14.127	11.449
Total		12018229	128401	100.000	100.000

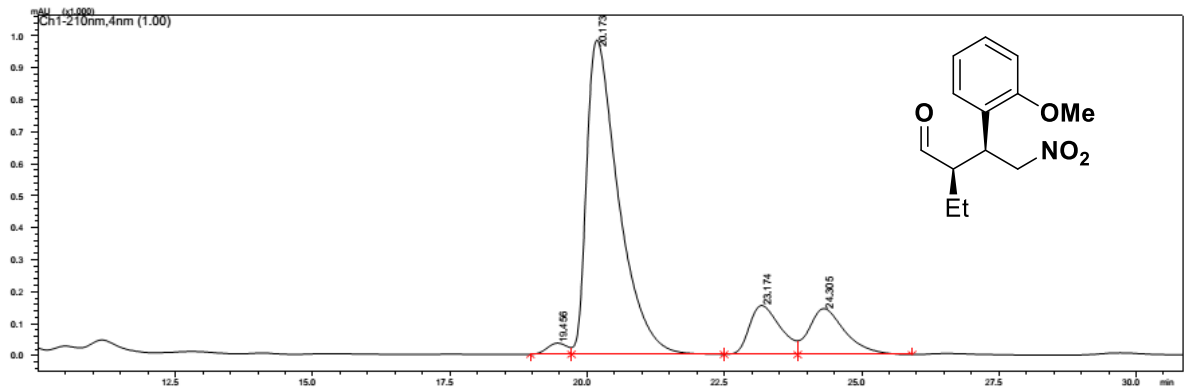


^{1}H NMR spectrum of 2.52g



^{13}C NMR spectrum of 2.52g

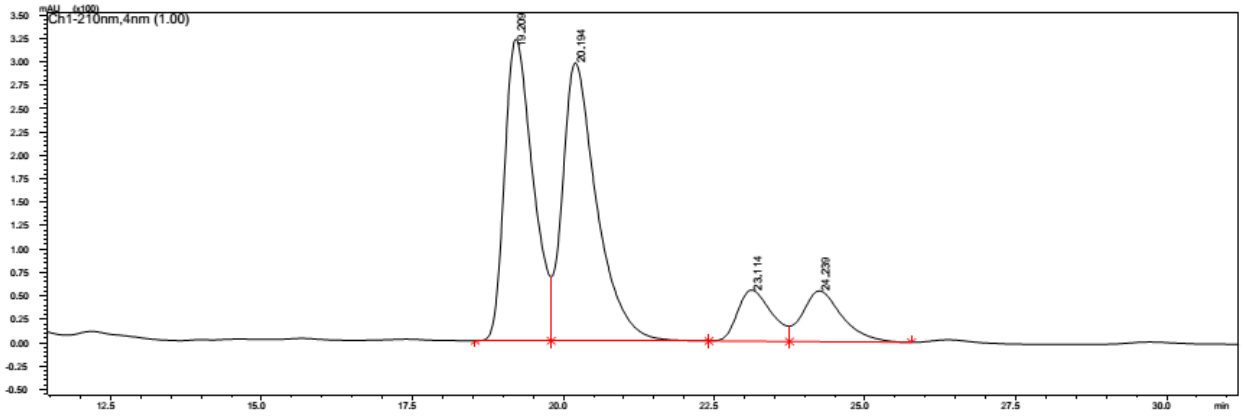
HPLC: Chiracel OD-H column (n-hexane/i-PrOH 95:05, 25ºC) at 1 mL/min (96% ee)



PeakTable

PDA Ch1 210nm 4nm

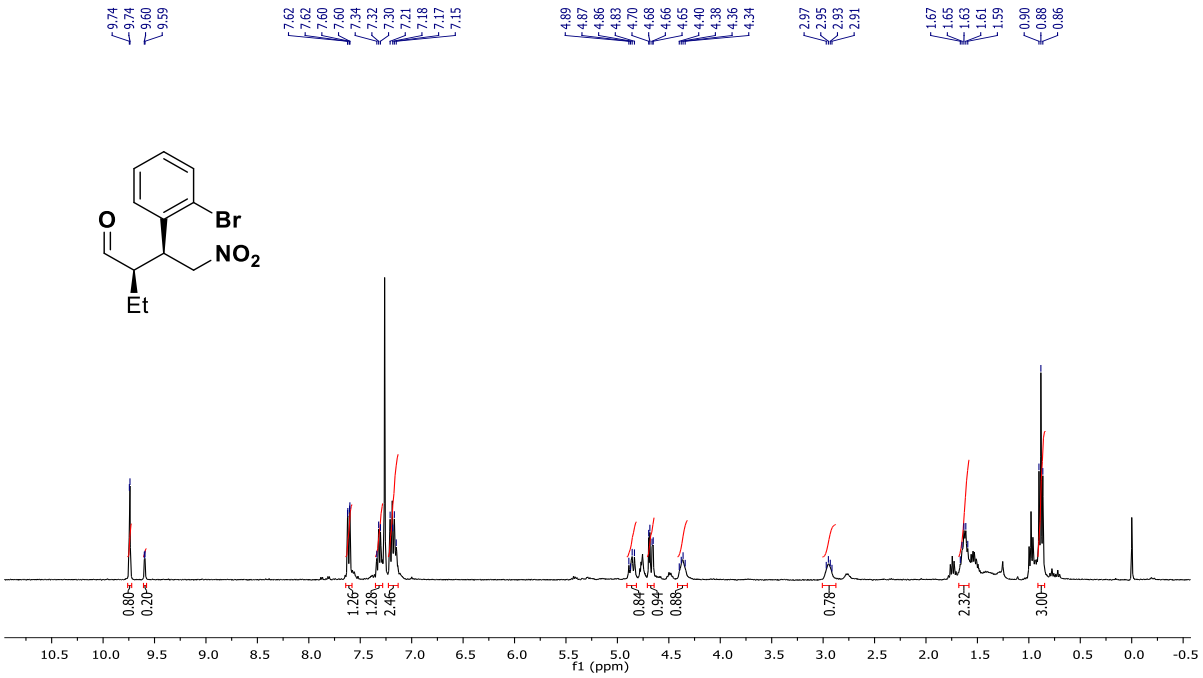
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.456	885406	34777	1.660	2.645
2	20.173	39884513	983325	74.761	74.776
3	23.174	6006592	153201	11.259	11.650
4	24.305	6572705	143724	12.320	10.929
Total		53349216	1315026	100.000	100.000



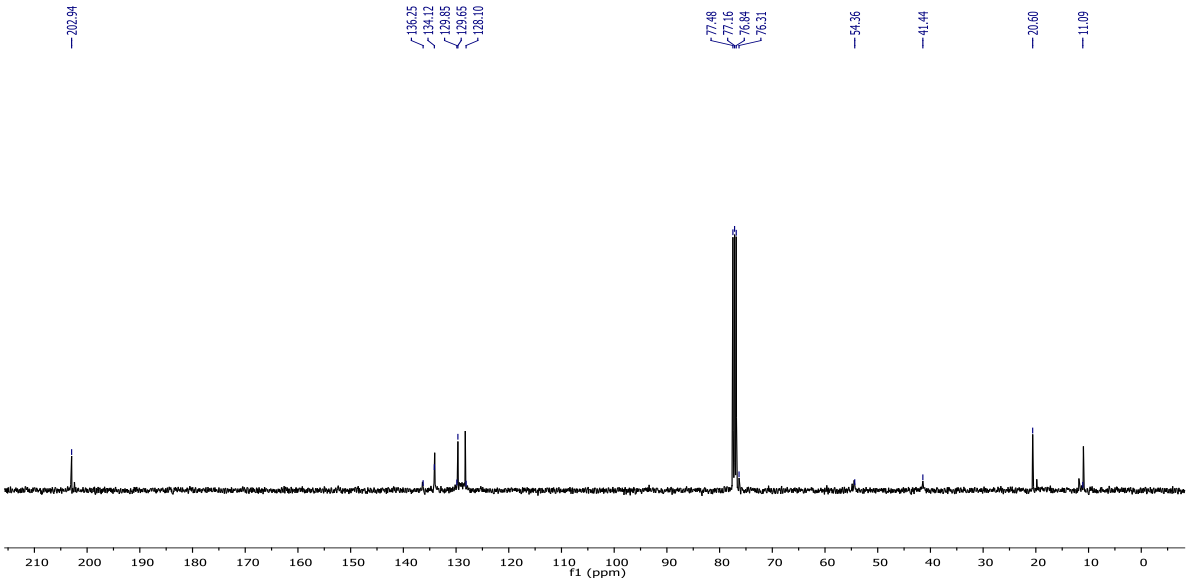
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.209	10533469	322156	39.152	44.236
2	20.194	11748218	296954	43.667	40.776
3	23.114	2146171	54823	7.977	7.528
4	24.239	2476109	54332	9.204	7.460
Total		26903965	728264	100.000	100.000

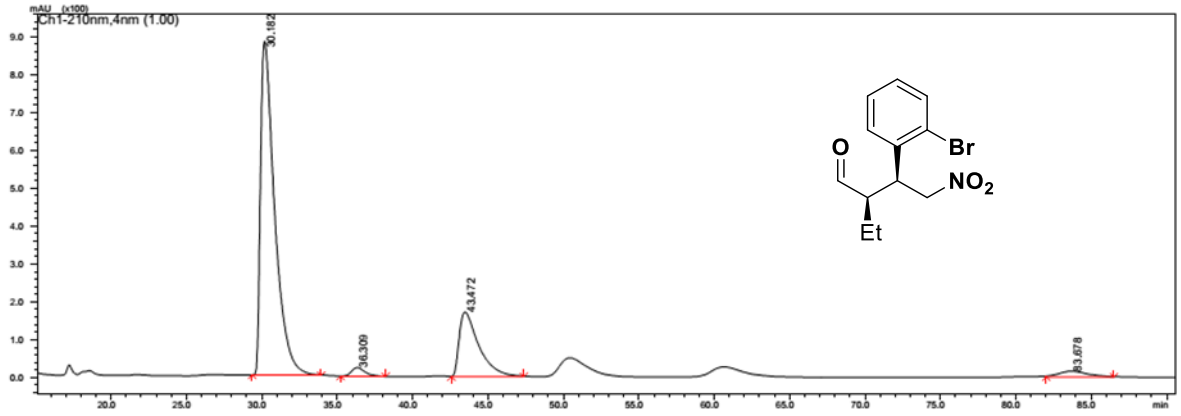


^{1}H NMR spectrum of 2.52h



^{13}C NMR spectrum of 2.52h

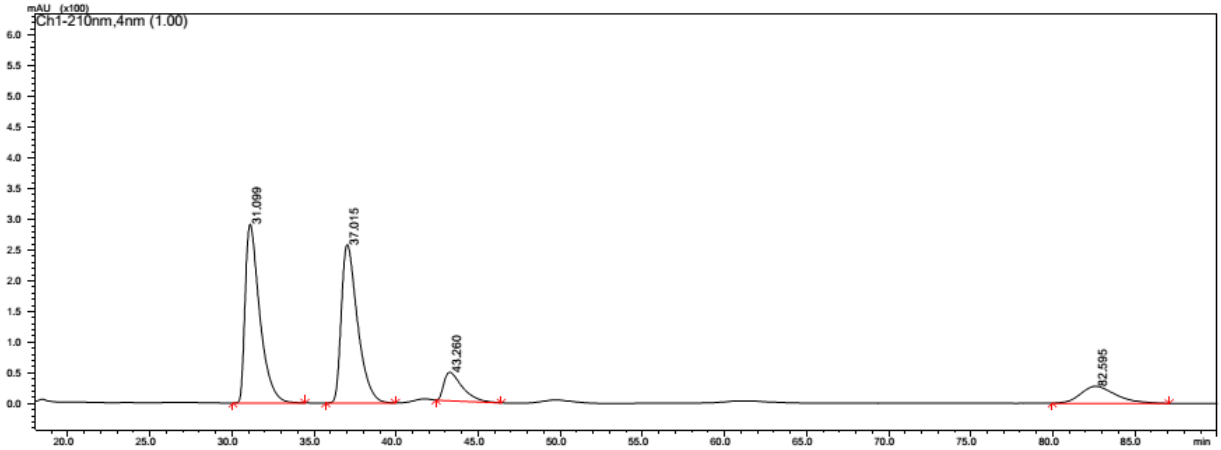
HPLC: Chiracel OD-H column (n-hexane/i-PrOH 95:05, 25ºC) at 1 mL/min (95% ee)



PeakTable

PDA Ch1 210nm 4nm

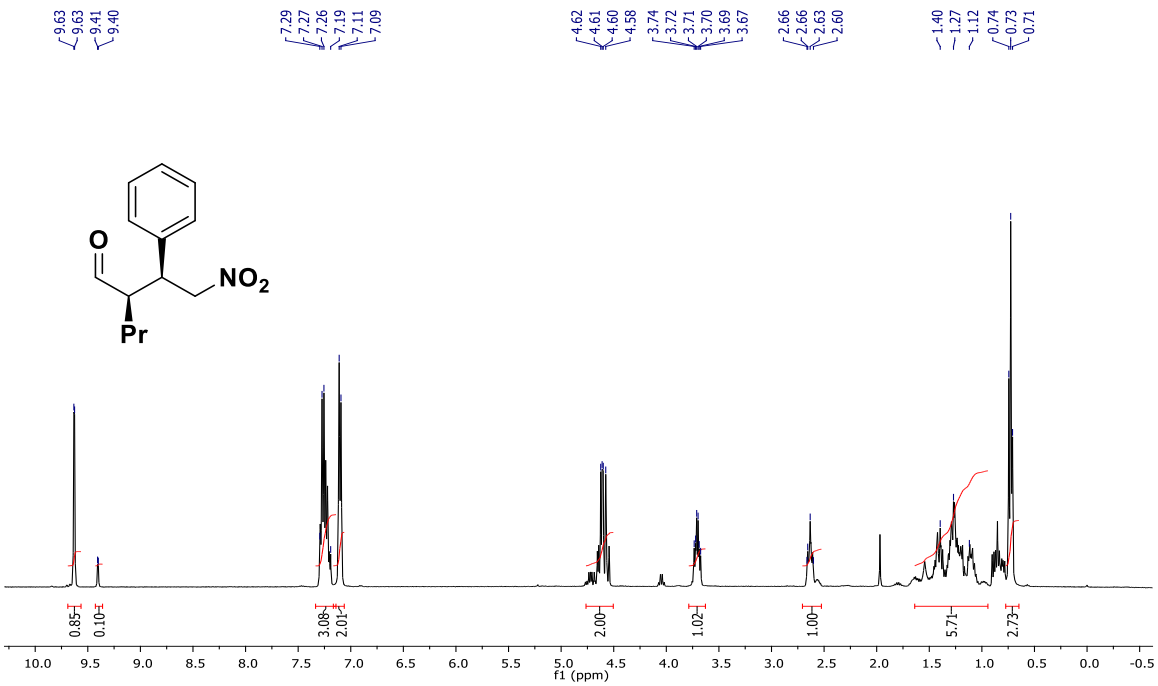
Peak#	Ret. Time	Area	Height	Area %	Height %
1	30.182	57553572	880816	75.266	80.868
2	36.309	1432781	22787	1.874	2.092
3	43.472	15485752	170553	20.252	15.659
4	83.678	1994695	15045	2.609	1.381
Total		76466801	1089201	100.000	100.000



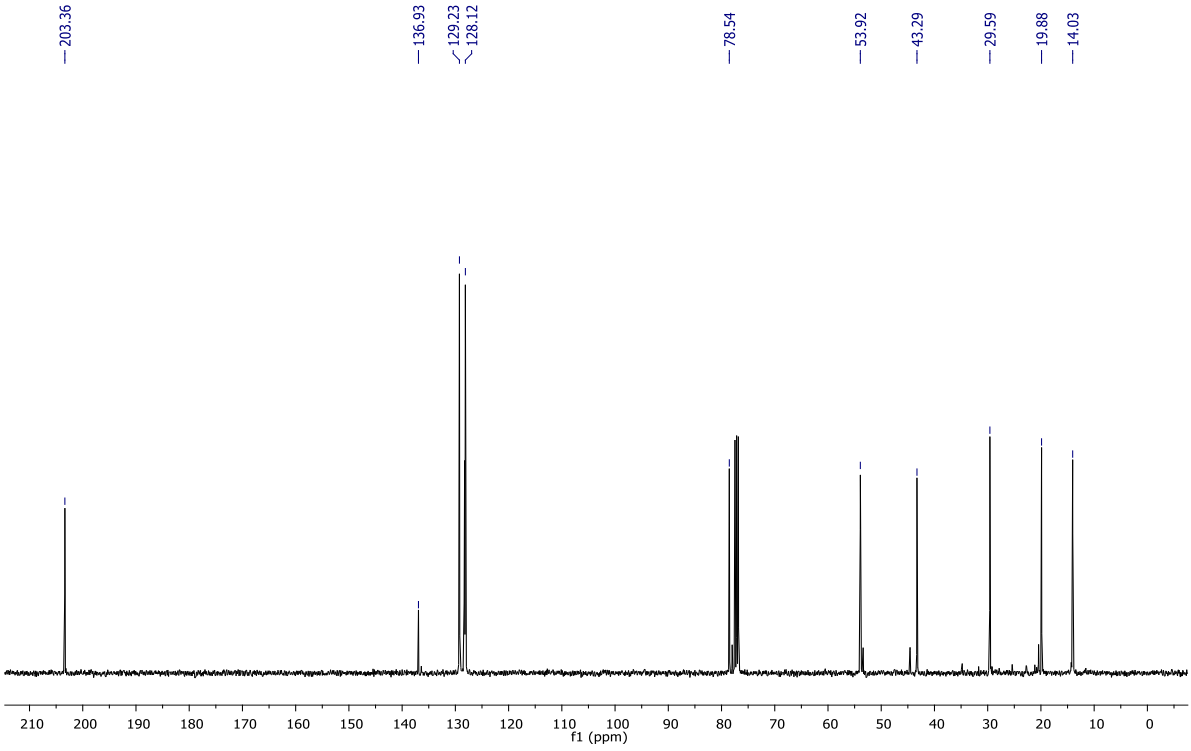
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	31.099	18029233	291323	41.452	46.736
2	37.015	17746888	258153	40.803	41.415
3	43.260	3634125	46419	8.356	7.447
4	82.595	4083517	27444	9.389	4.403
Total		43493762	623340	100.000	100.000

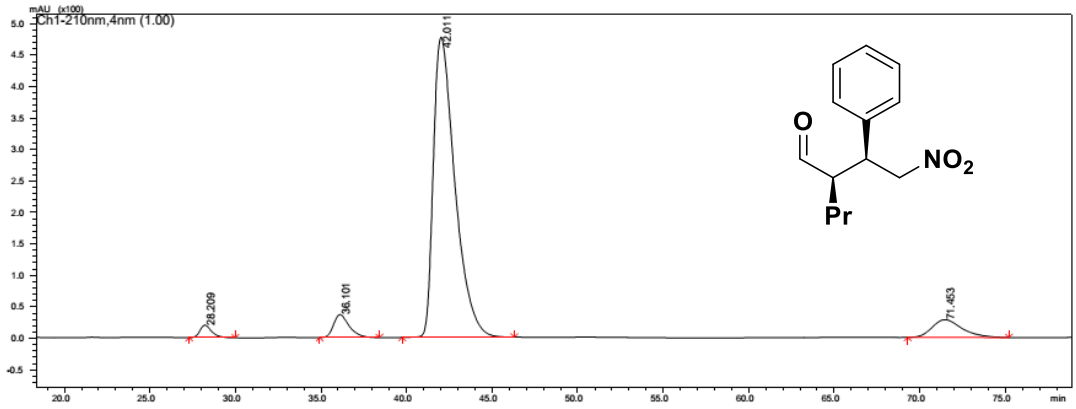


^{1}H NMR spectrum of 2.52i



^{13}C NMR spectrum of 2.52i

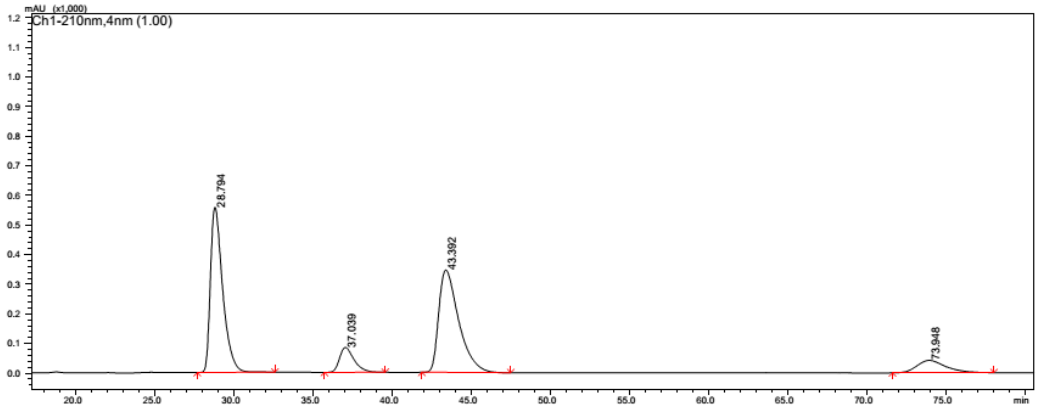
HPLC: Chiracel OD-H column (n-hexane/i-PrOH 95:05, 25ºC) at 1 mL/min (96% ee)



PeakTable

PDA Ch1 210nm 4nm

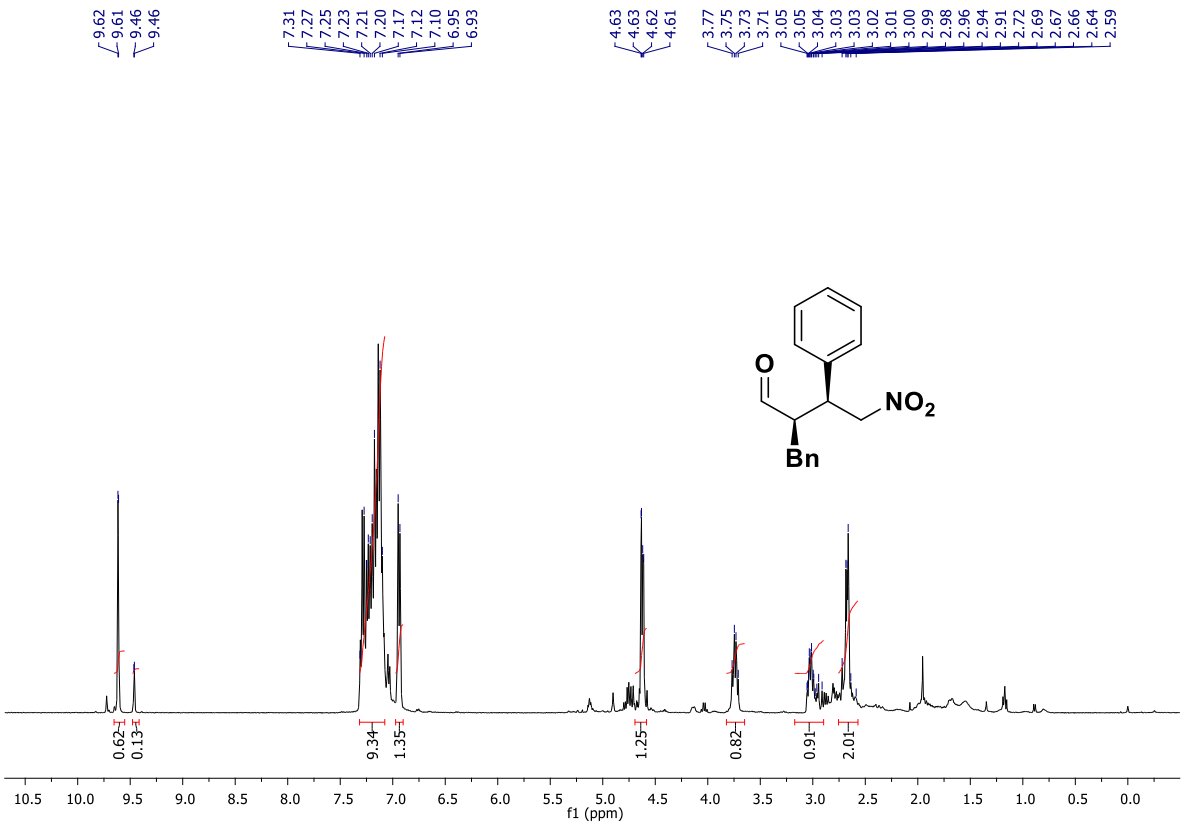
Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.209	959547	19811	1.979	3.530
2	36.101	2313933	36406	4.773	6.488
3	42.011	41771751	476791	86.164	84.968
4	71.453	3434066	28134	7.084	5.014
Total		48479297	561142	100.000	100.000



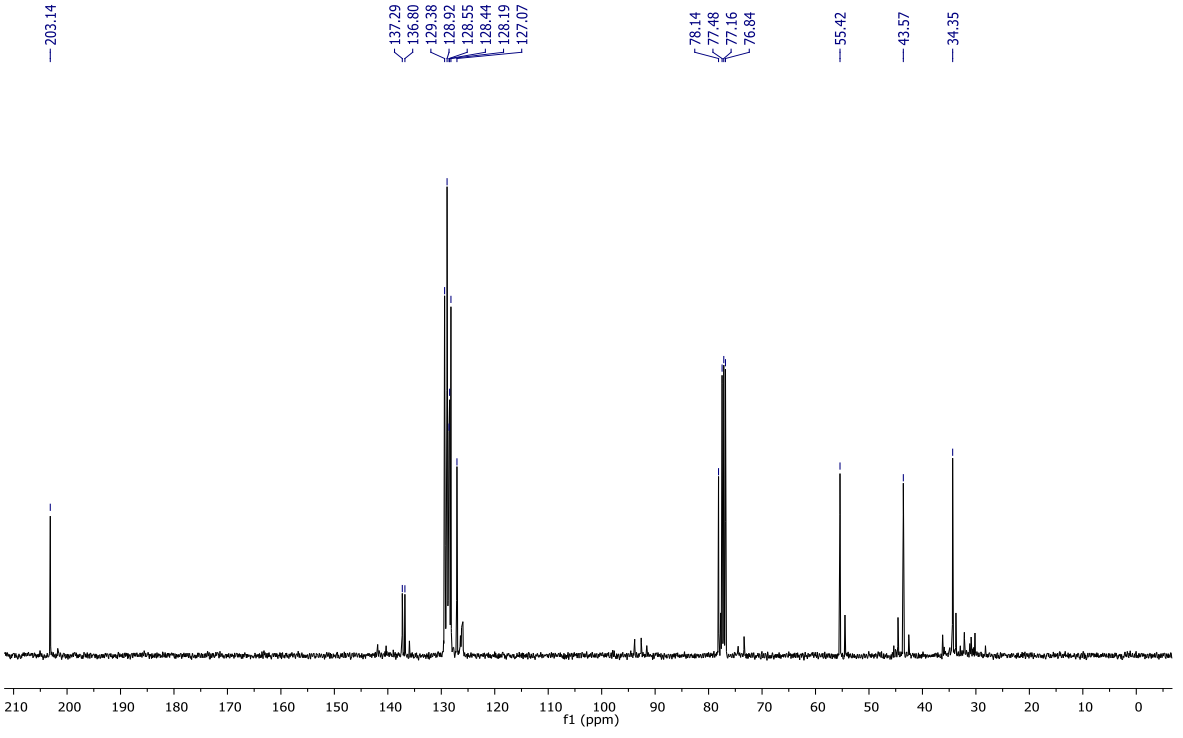
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.794	30160554	558032	42.287	54.233
2	37.039	5418411	83953	7.597	8.159
3	43.392	30467988	345598	42.718	33.587
4	73.948	5276000	41371	7.397	4.021
Total		71322953	1028955	100.000	100.000

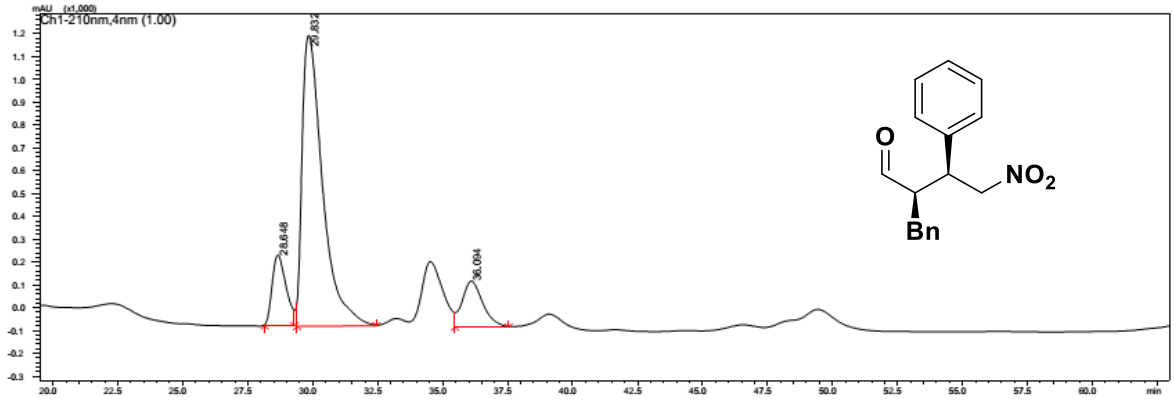


^{1}H NMR spectrum of 2.52j



^{13}C NMR spectrum of 2.52j

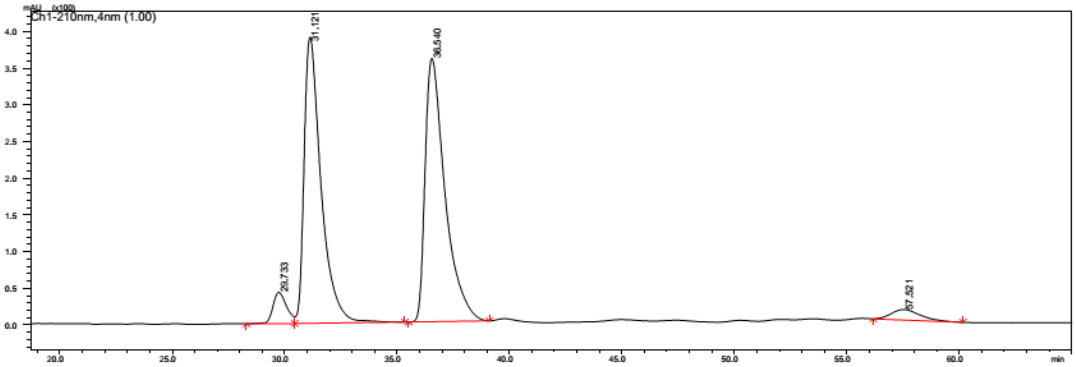
HPLC: Chiracel AD-H column (n-hexane/i-PrOH 99:01, 25ºC) at 1 mL/min (72% ee)



PeakTable

PDA Ch1 210nm 4nm

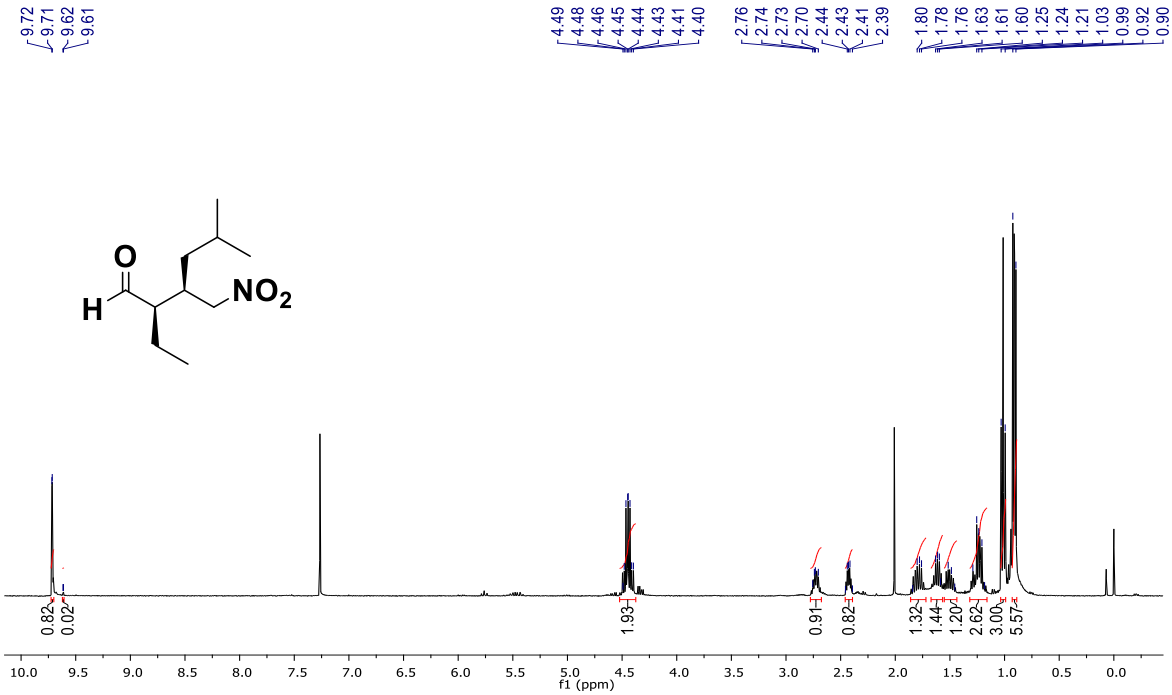
Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.648	11558683	309610	12.532	17.355
2	29.832	69522947	1273340	75.380	71.378
3	36.094	11148613	200988	12.088	11.267
Total		92230243	1783939	100.000	100.000



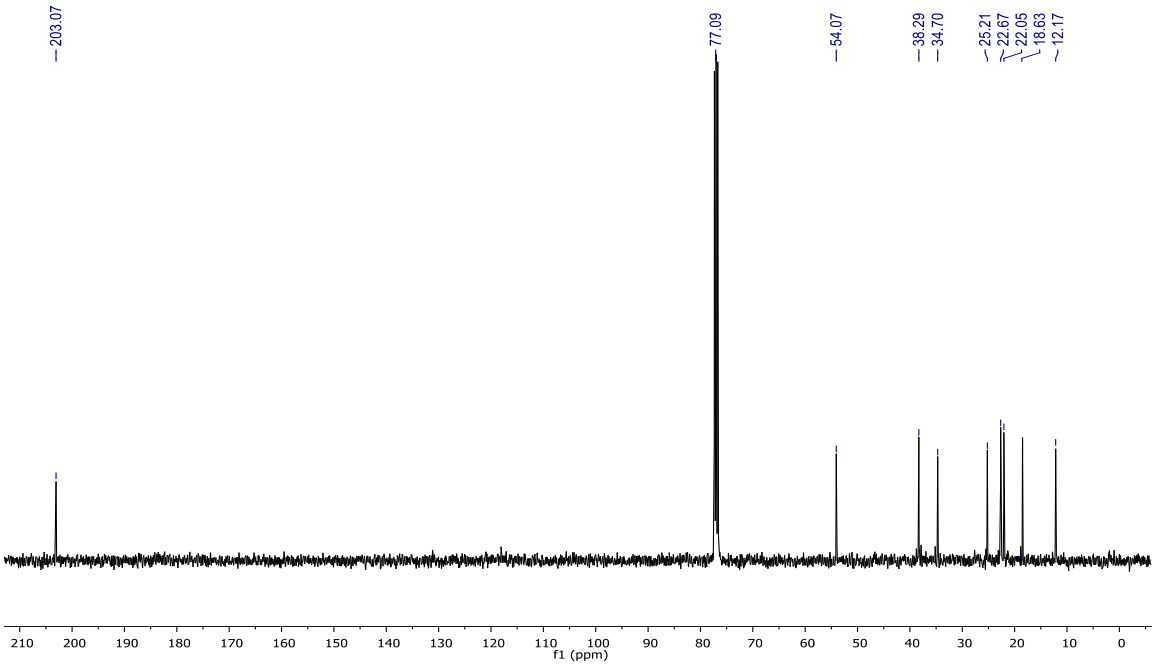
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	29.733	1786881	42339	3.920	5.259
2	31.121	20463196	389848	44.893	48.427
3	36.540	22079447	358784	48.438	44.569
4	57.521	1253110	14044	2.749	1.745
Total		45582633	805016	100.000	100.000

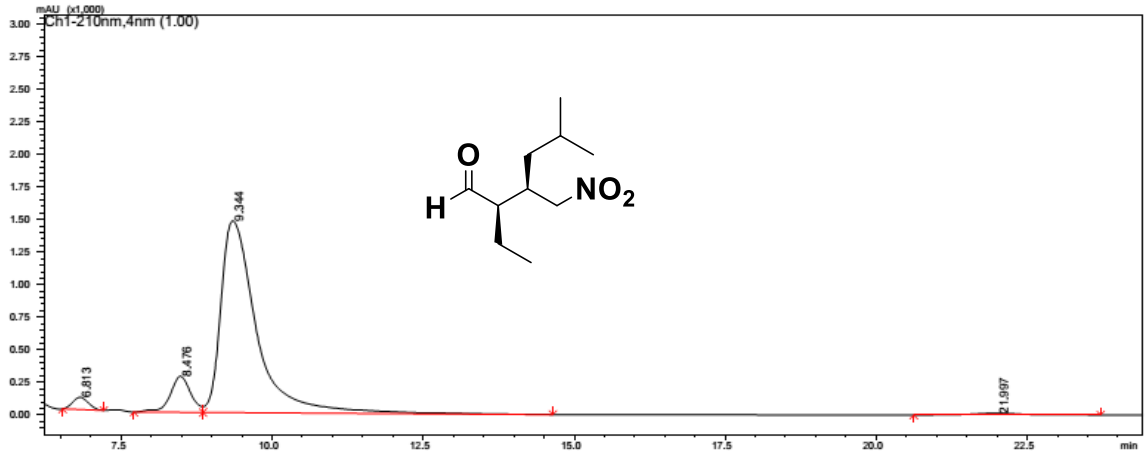


^{1}H NMR spectrum of 2.52k



^{13}C NMR spectrum of 2.52k

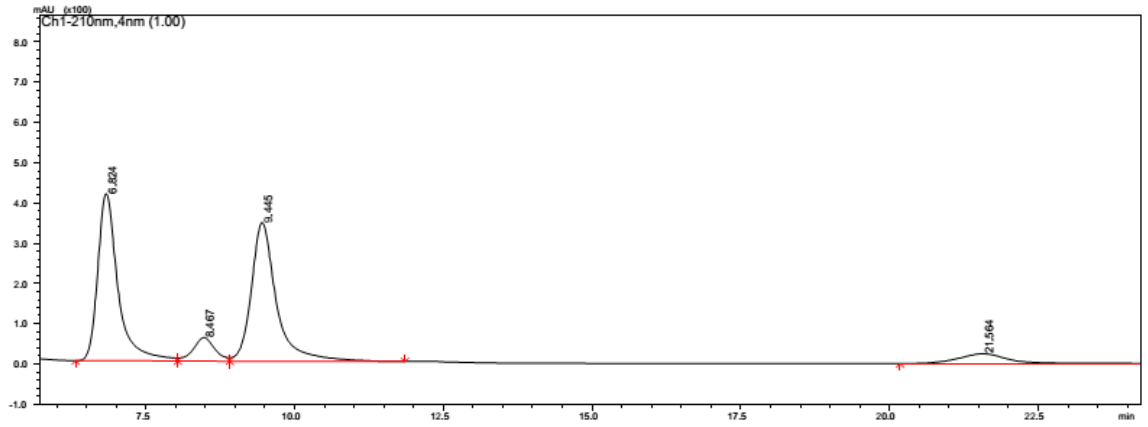
HPLC: Chiracel IC column (n-hexane/i-PrOH 90:10, 25ºC) at 0.2 mL/min (95% ee)



PeakTable

PDA Ch1 210nm 4nm

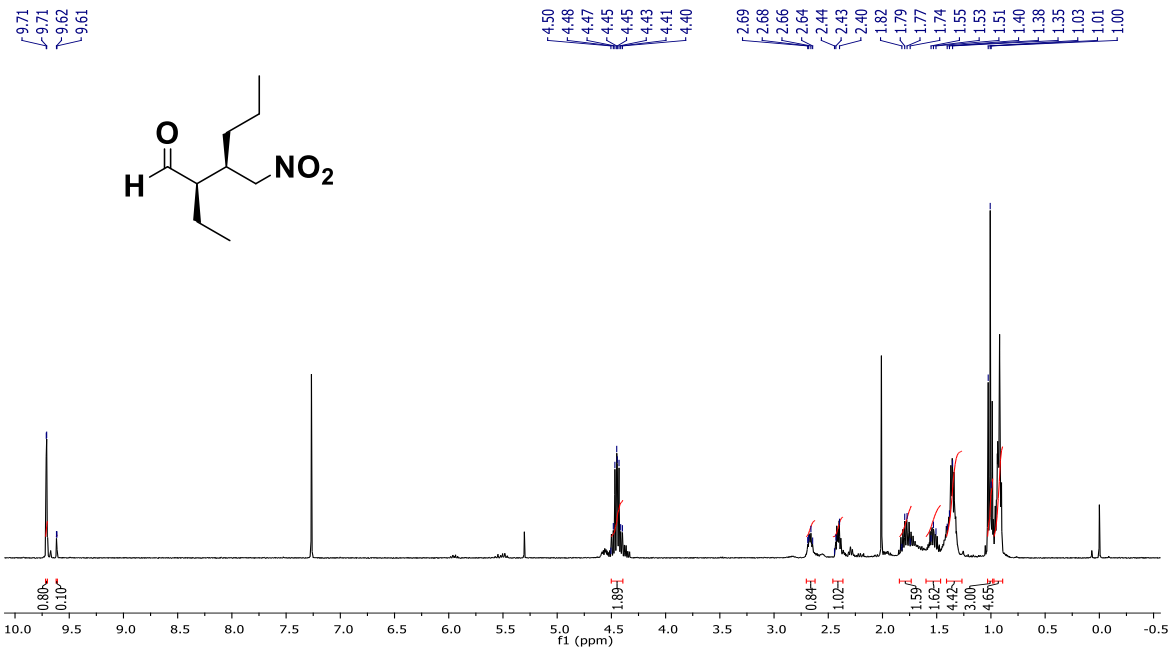
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.813	1699149	93660	2.438	5.050
2	8.476	6562659	276559	9.417	14.913
3	9.344	60731553	1471959	87.142	79.372
4	21.997	698936	12337	1.003	0.665
Total		69692296	1854515	100.000	100.000



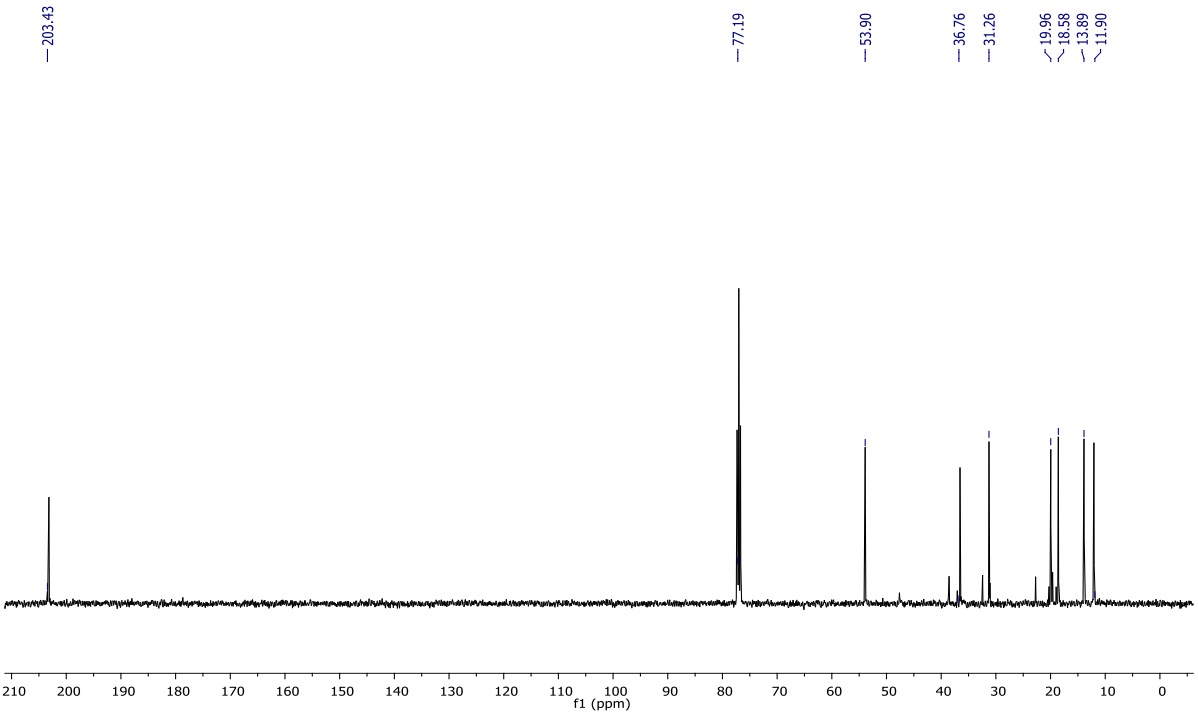
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.824	9875113	415746	43.075	49.280
2	8.467	1472253	58532	6.422	6.938
3	9.445	10167574	344987	44.351	40.893
4	21.564	1410484	24372	6.152	2.889
Total		22925424	843638	100.000	100.000

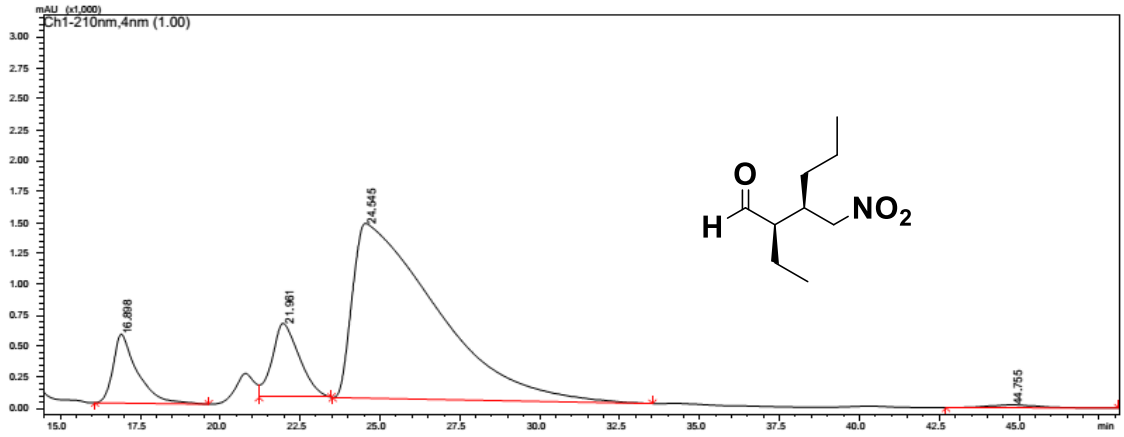


^{1}H NMR spectrum of 2.52l



^{13}C NMR spectrum of 2.52l

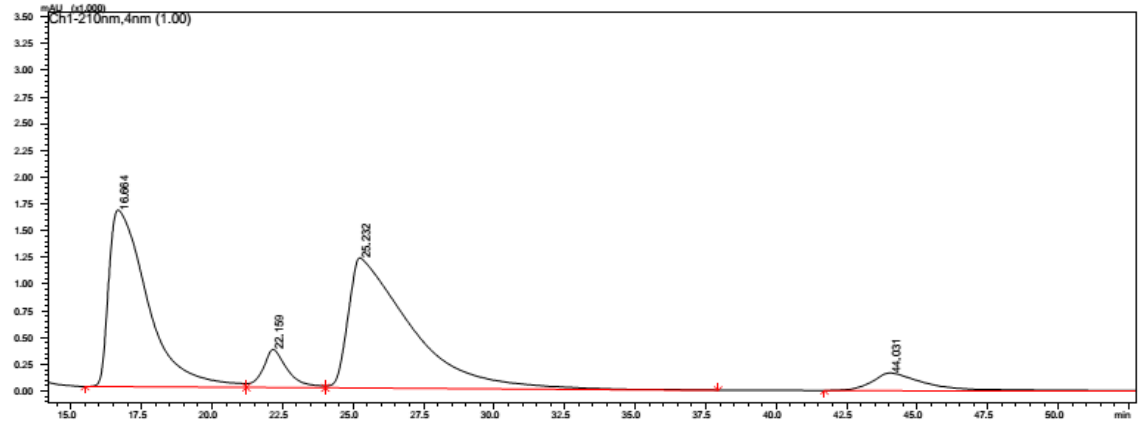
HPLC: Chiracel IC column (n-hexane/i-PrOH 99:01, 25ºC) at 0.2 mL/min (80% ee)



PeakTable

PDA Ch1 210nm 4nm

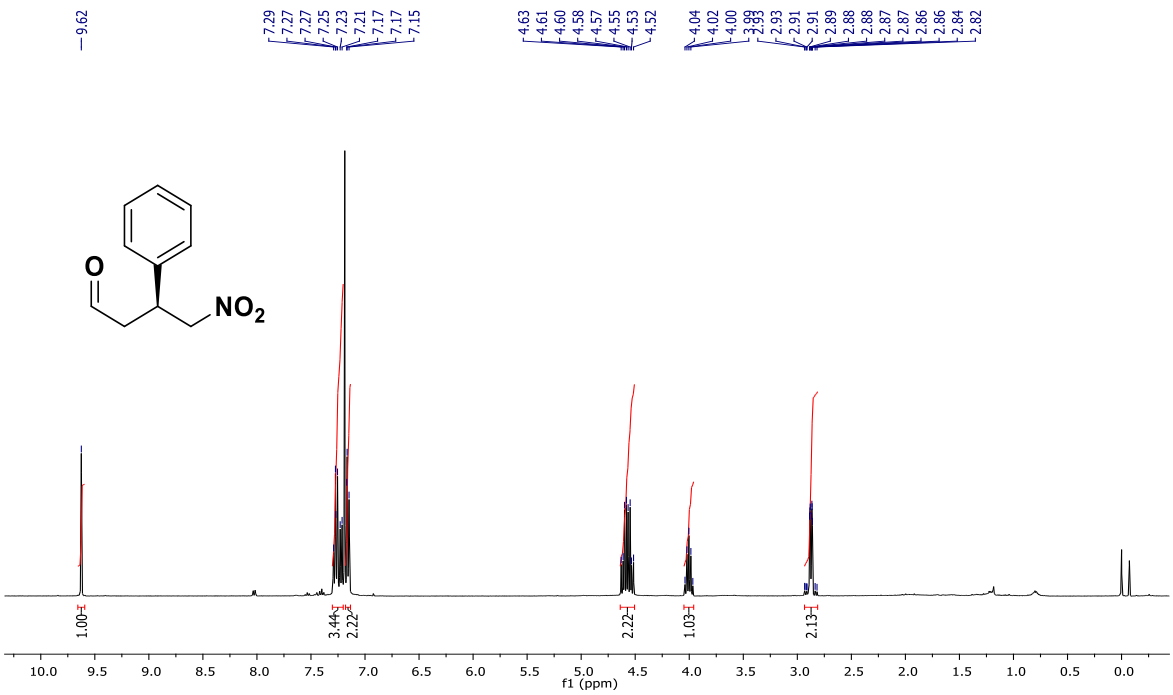
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.898	29136538	555221	8.961	21.466
2	21.961	35454136	596745	10.904	23.072
3	24.545	258037892	1410406	79.360	54.530
4	44.755	2518747	24103	0.775	0.932
Total		325147314	2586476	100.000	100.000



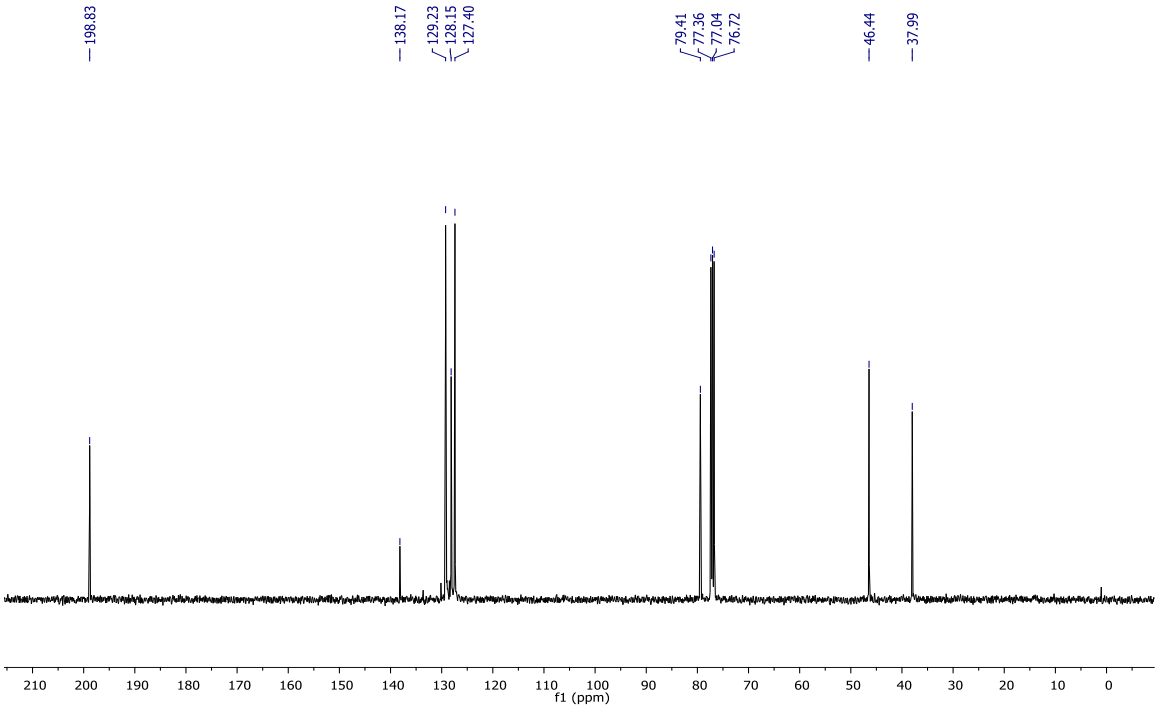
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.664	158471883	1650229	40.737	48.692
2	22.159	21596703	356055	5.552	10.506
3	25.232	187427692	1217595	48.180	35.927
4	44.031	21520373	165227	5.532	4.875
Total		389016650	3389106	100.000	100.000

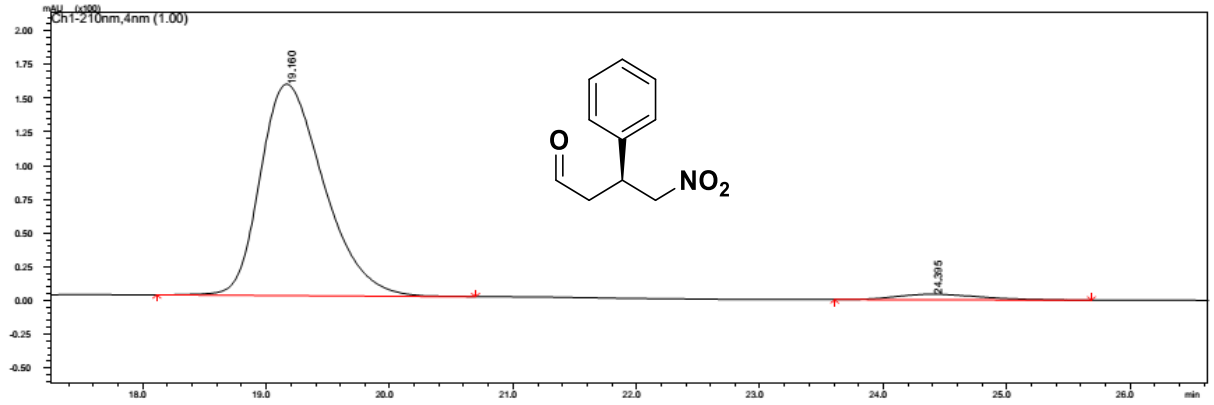


^{1}H NMR spectrum of 2.56a



^{13}C NMR spectrum of 2.56a

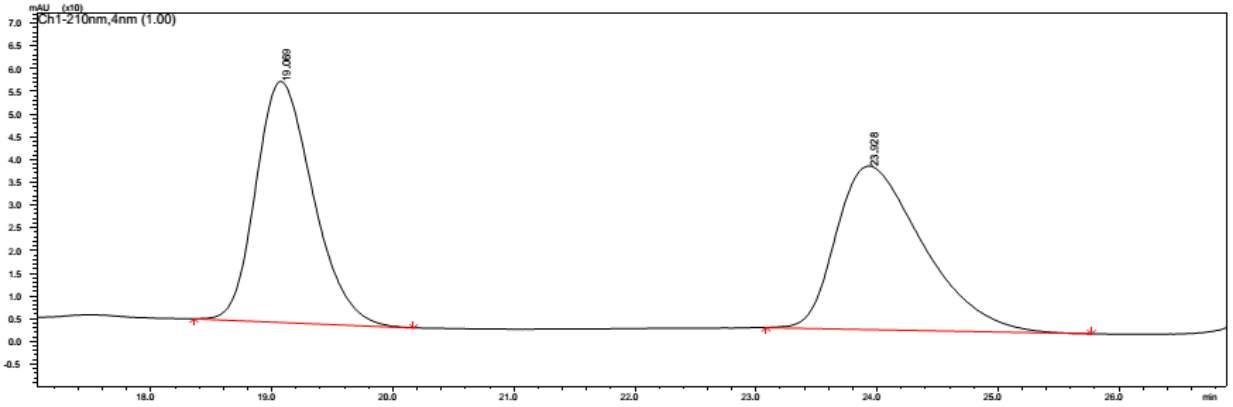
HPLC: Chiracel AS-H column (n-hexane/i-PrOH 70:30, 25ºC) at 1 mL/min (93% ee)



PeakTable

PDA Ch1 210nm 4nm

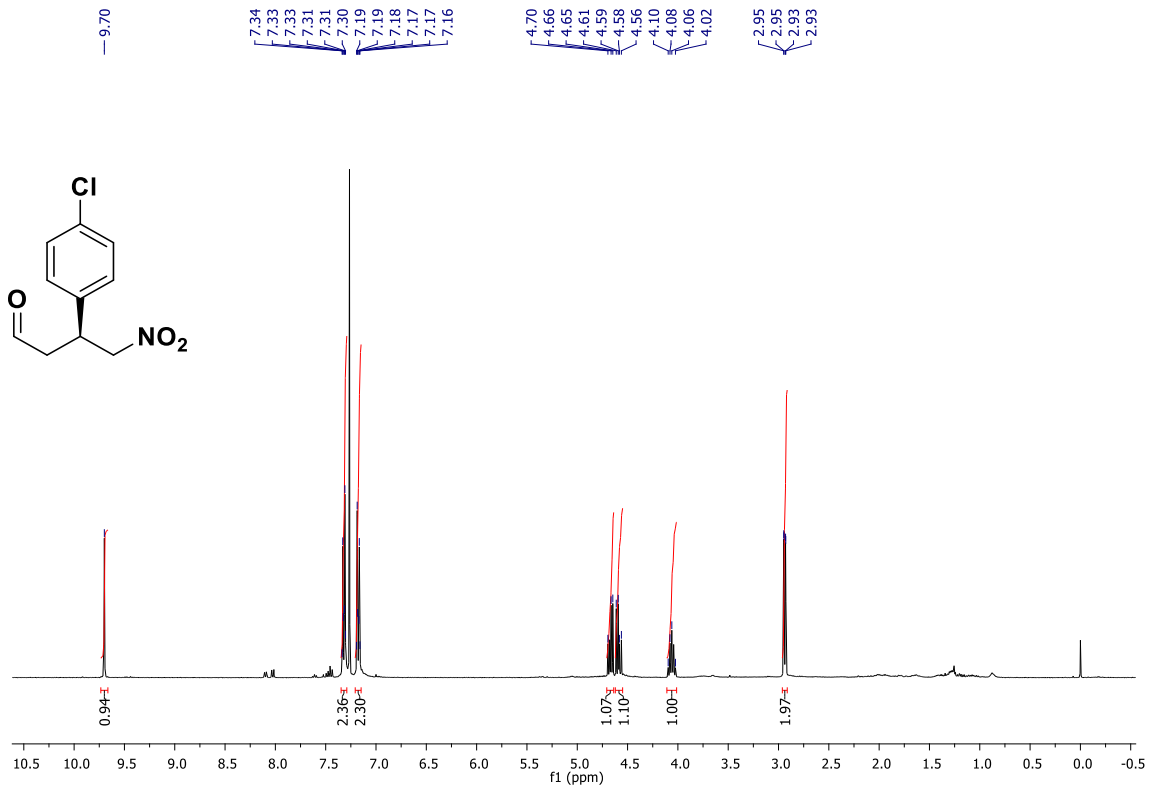
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.160	5618996	156741	96.598	97.349
2	24.395	197904	4268	3.402	2.651
Total		5816900	161009	100.000	100.000



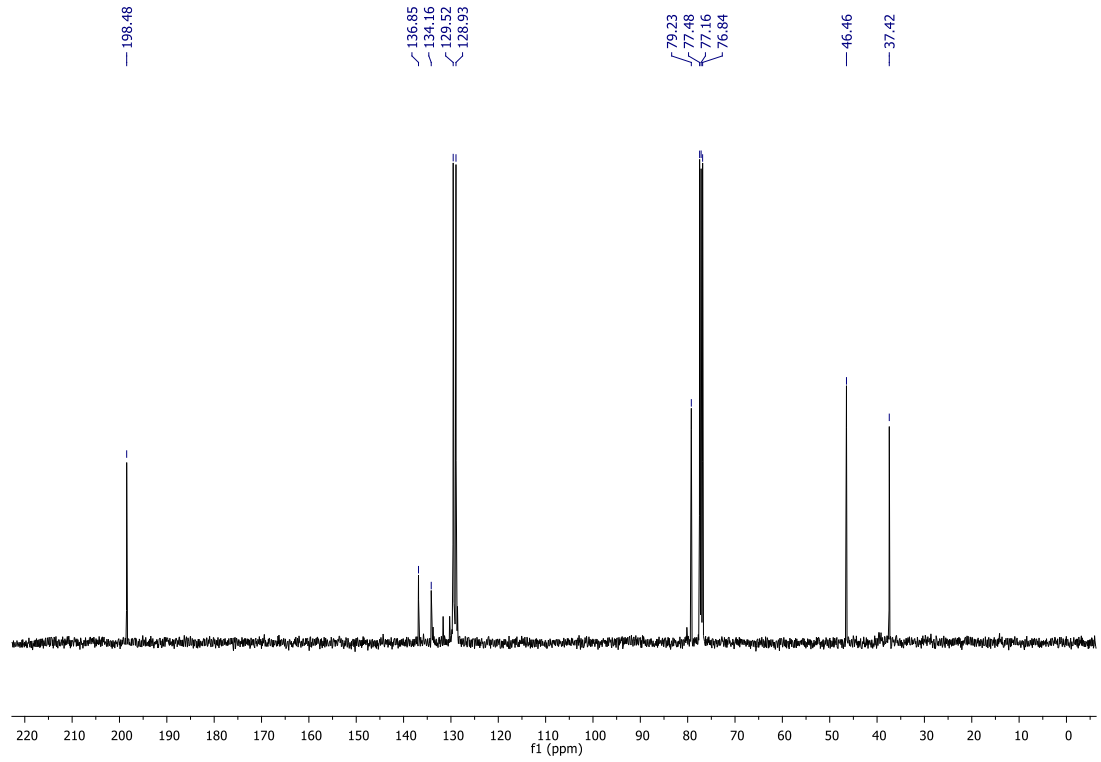
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.069	1740855	53014	49.243	59.568
2	23.928	1794404	35983	50.757	40.432
Total		3535259	88996	100.000	100.000

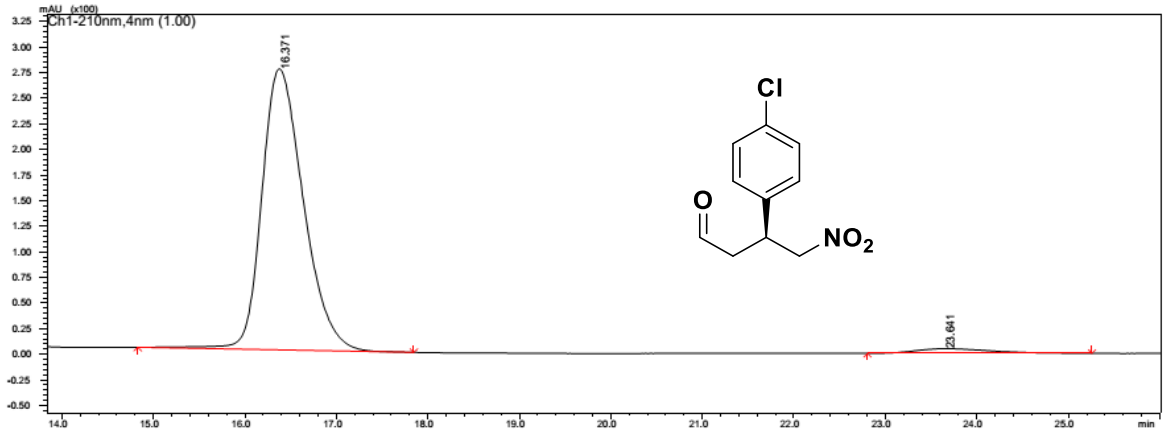


^{1}H NMR spectrum of 2.56b



^{13}C NMR spectrum of 2.56b

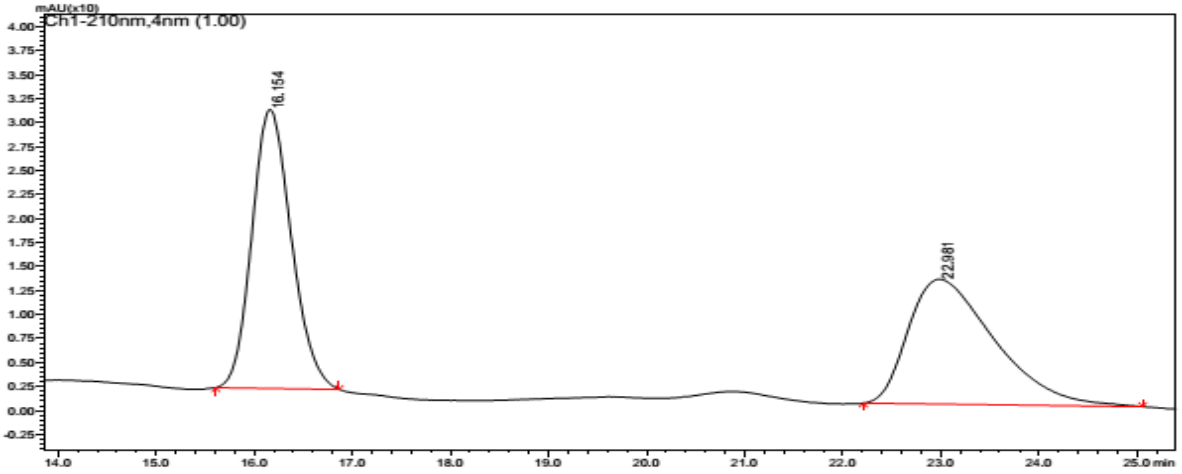
HPLC: Chiracel AS-H column (n-hexane/i-PrOH 70:30, 25ºC) at 1 mL/min (94% ee)



PeakTable

PDA Ch1 210nm 4nm

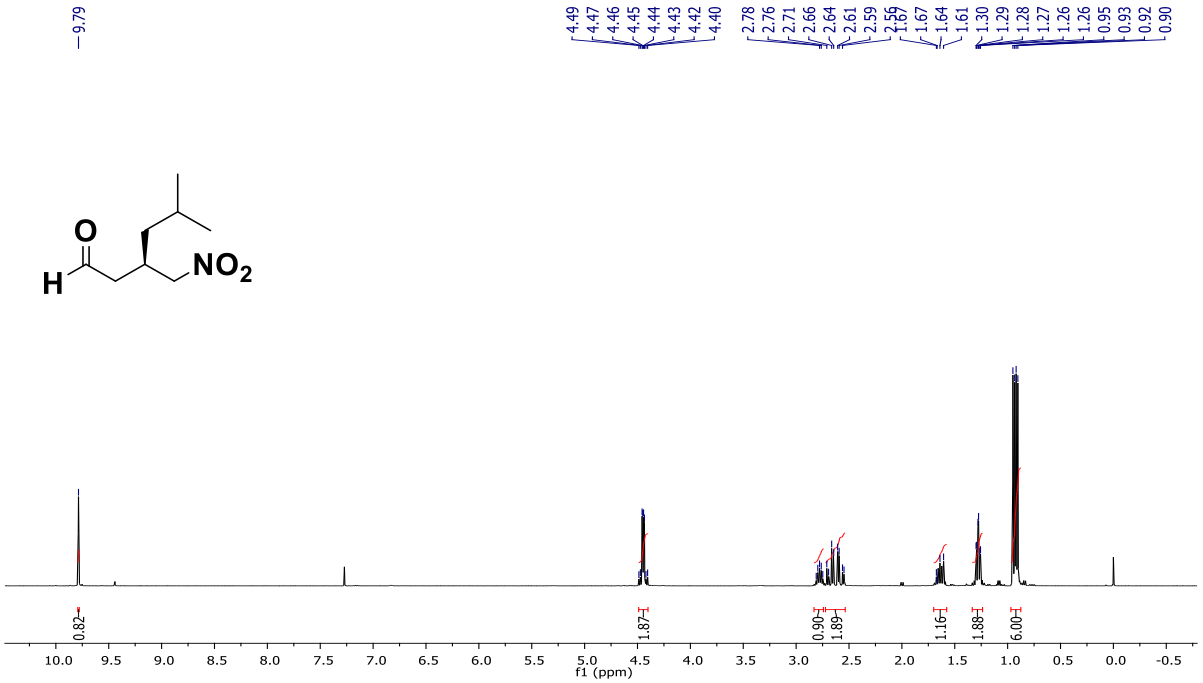
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.371	8686859	274364	97.106	98.409
2	23.641	258934	4435	2.894	1.591
Total		8945793	278799	100.000	100.000



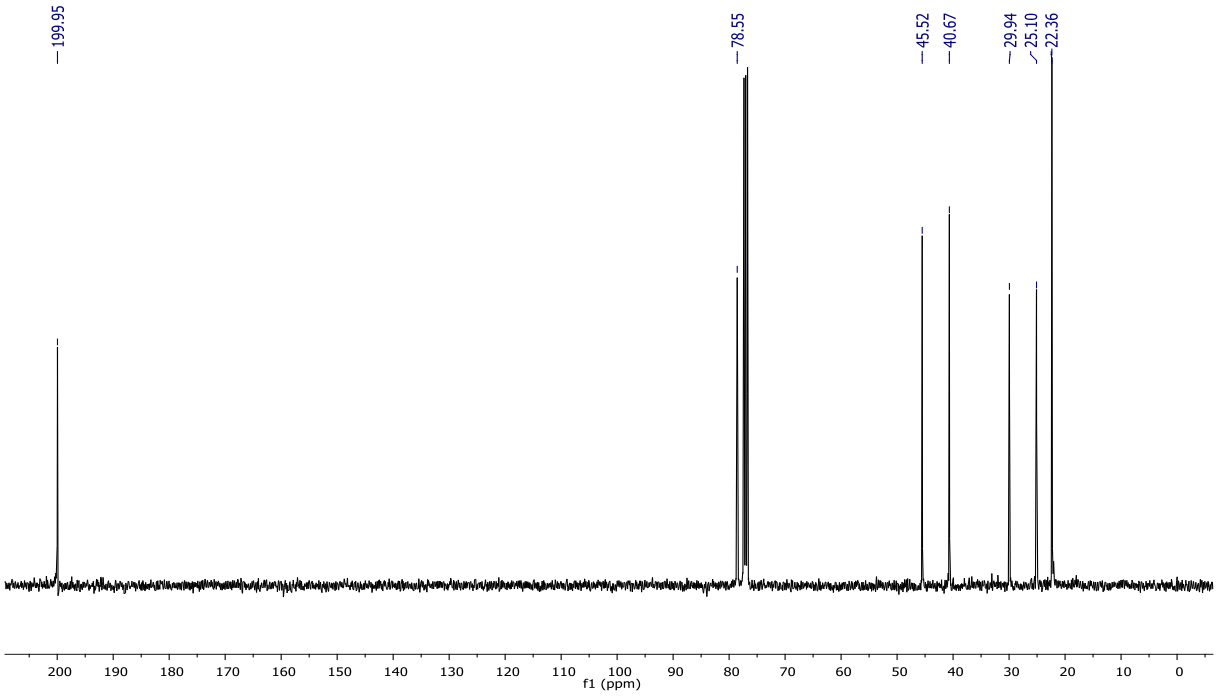
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.154	813477	29075	50.673	69.081
2	22.981	791878	13013	49.327	30.919
Total		1605354	42089	100.000	100.000

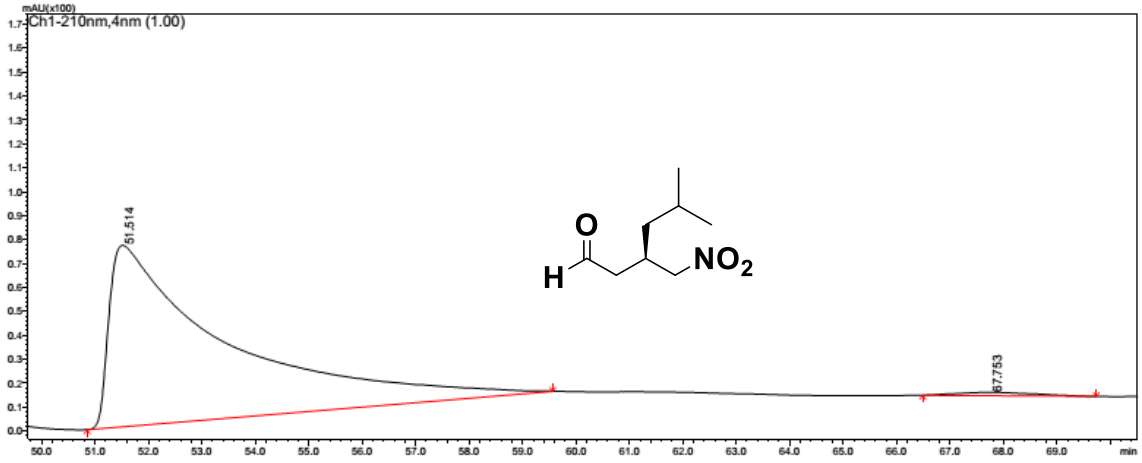


^{1}H NMR spectrum of 2.56c



^{13}C NMR spectrum of 2.56c

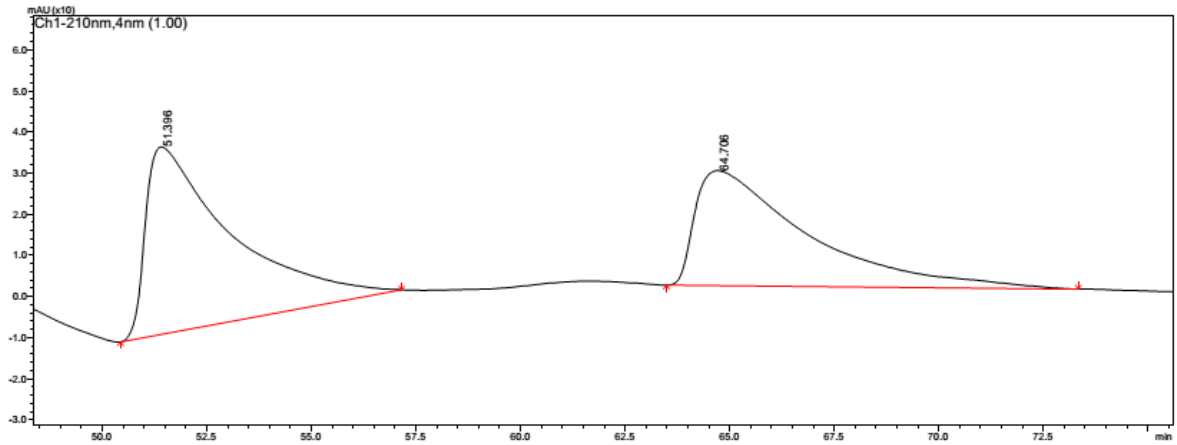
HPLC: Chiracel AS-H column (n-hexane/i-PrOH 99:01, 25ºC) at 0.2 mL/min (80% ee)



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	51.514	11400161	75811	98.791	98.209
2	67.753	139557	1383	1.209	1.791
Total		11539718	77194	100.000	100.000

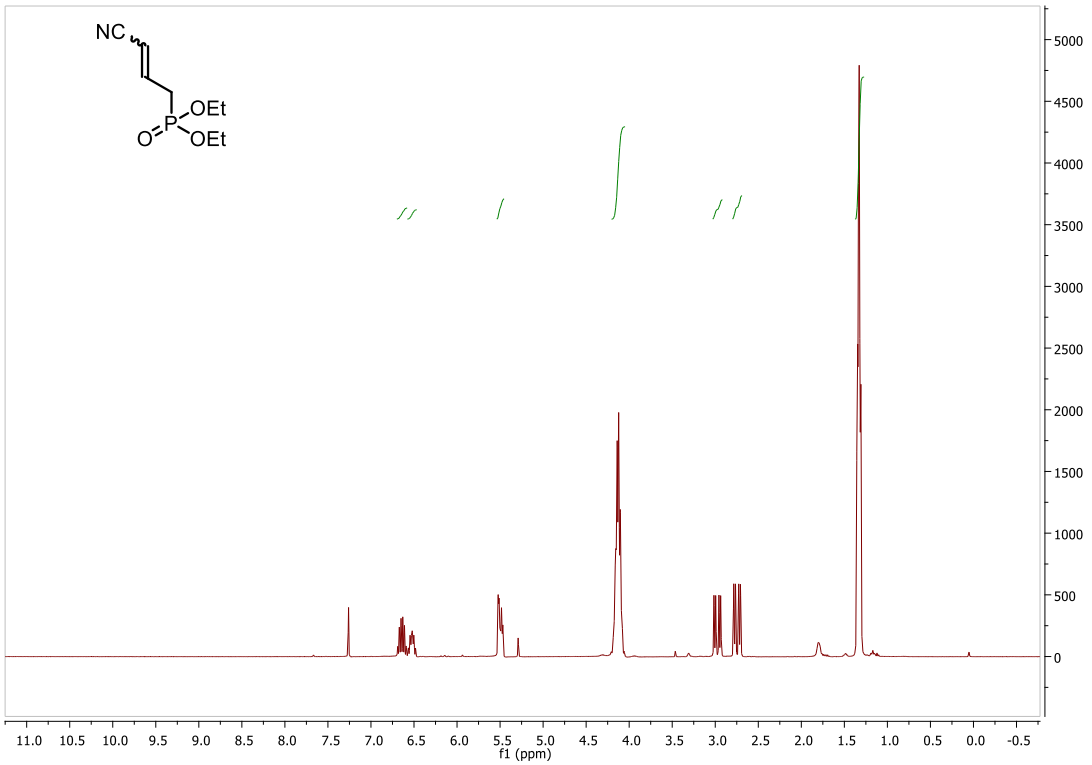


PeakTable

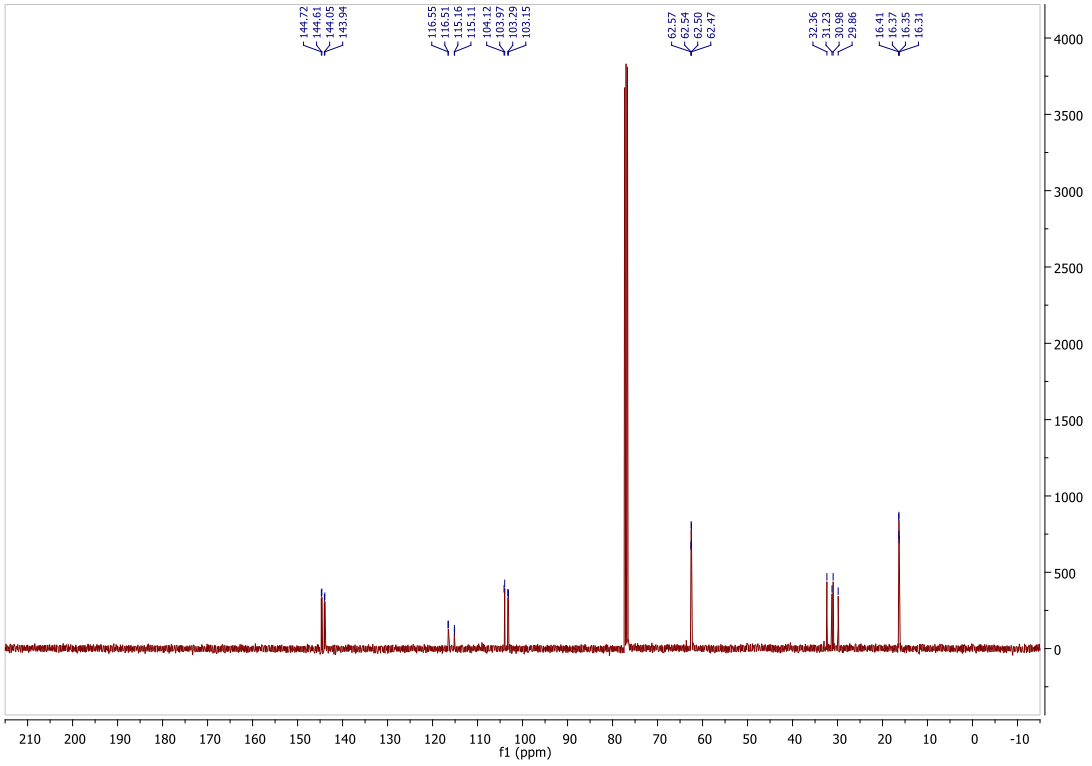
PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	51.396	6484054	45592	55.699	62.007
2	64.706	5157098	27936	44.301	37.993
Total		11641152	73528	100.000	100.000

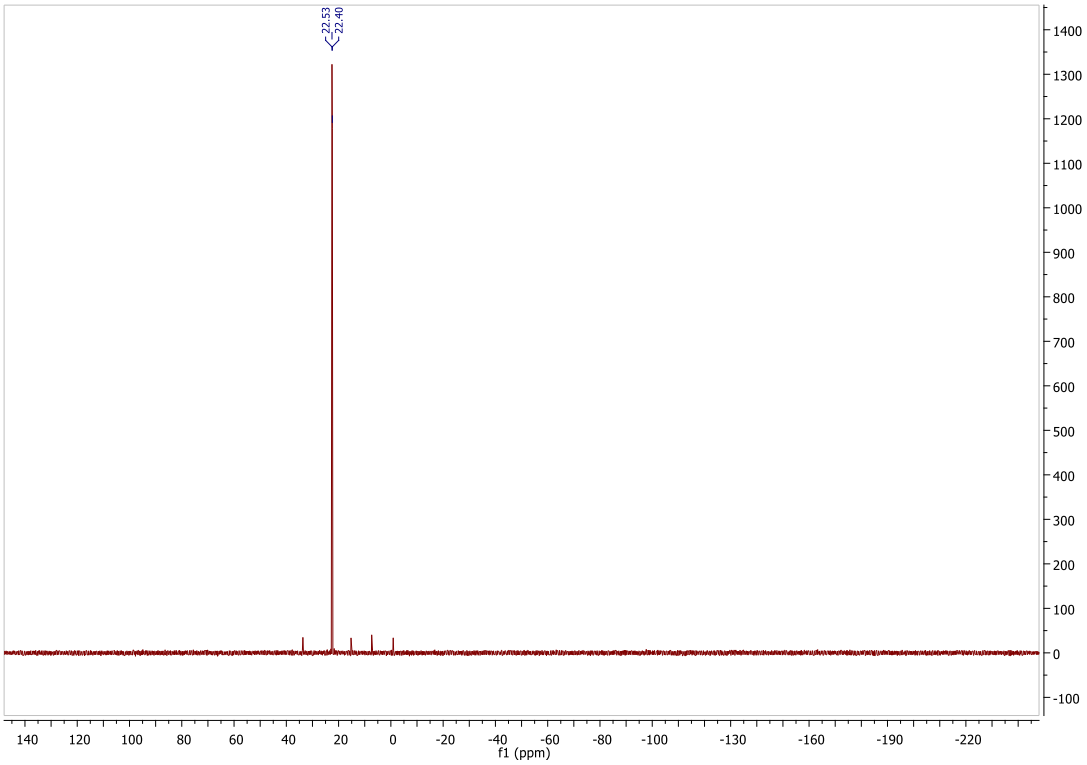
Chapter 3:



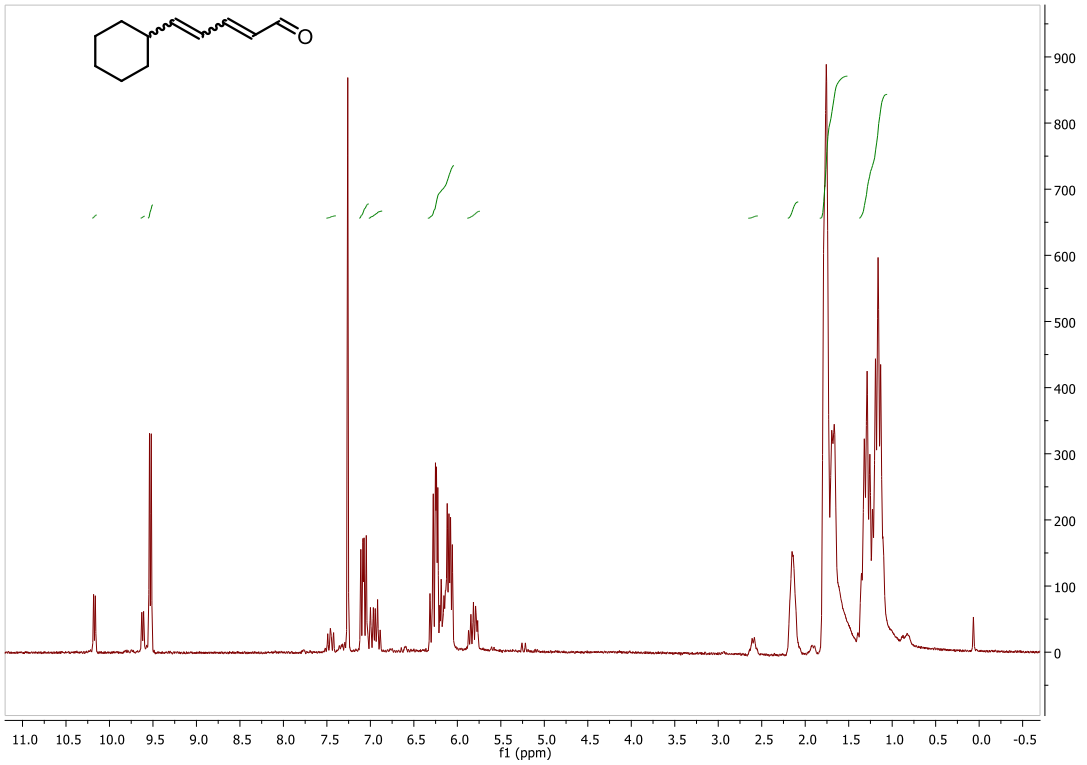
^{1}H NMR spectrum of **3.67**



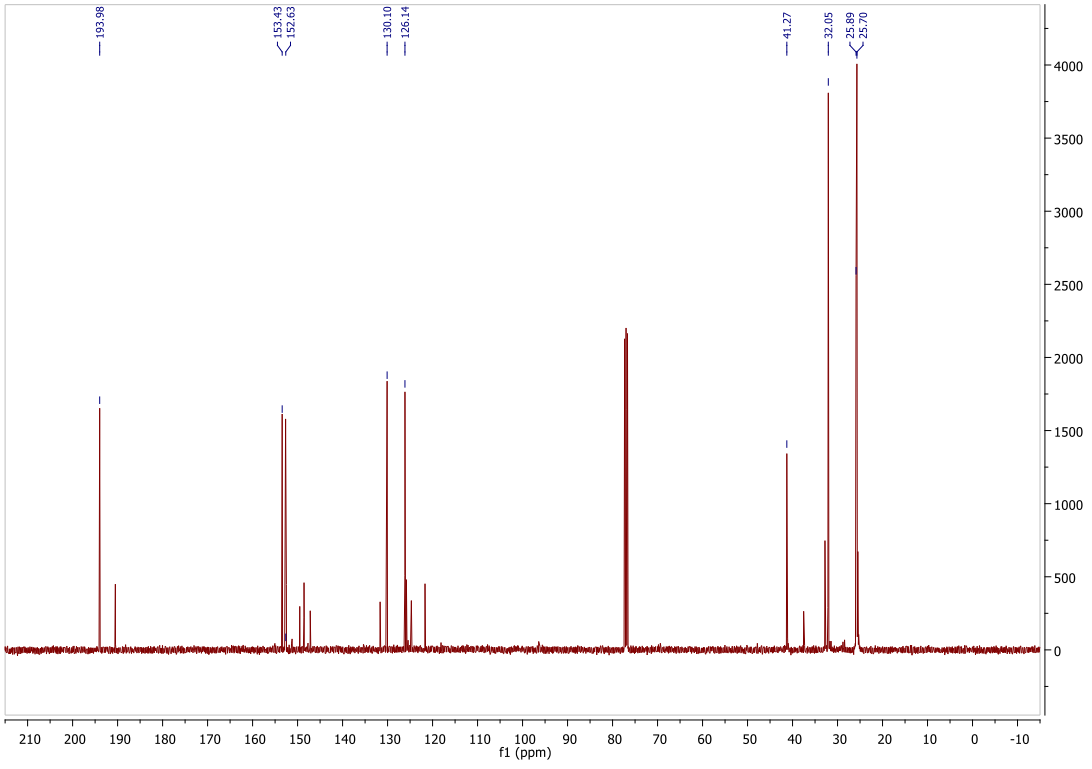
^{13}C NMR spectrum of **3.67**



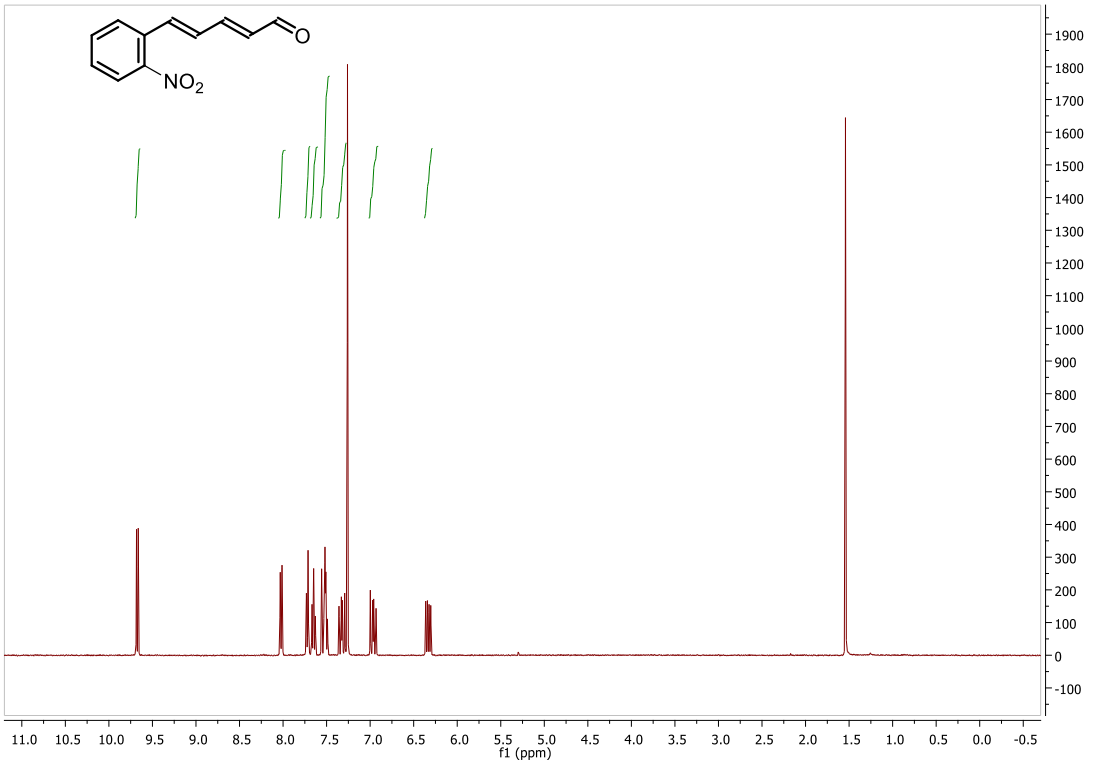
^{31}P NMR spectrum of **3.67**



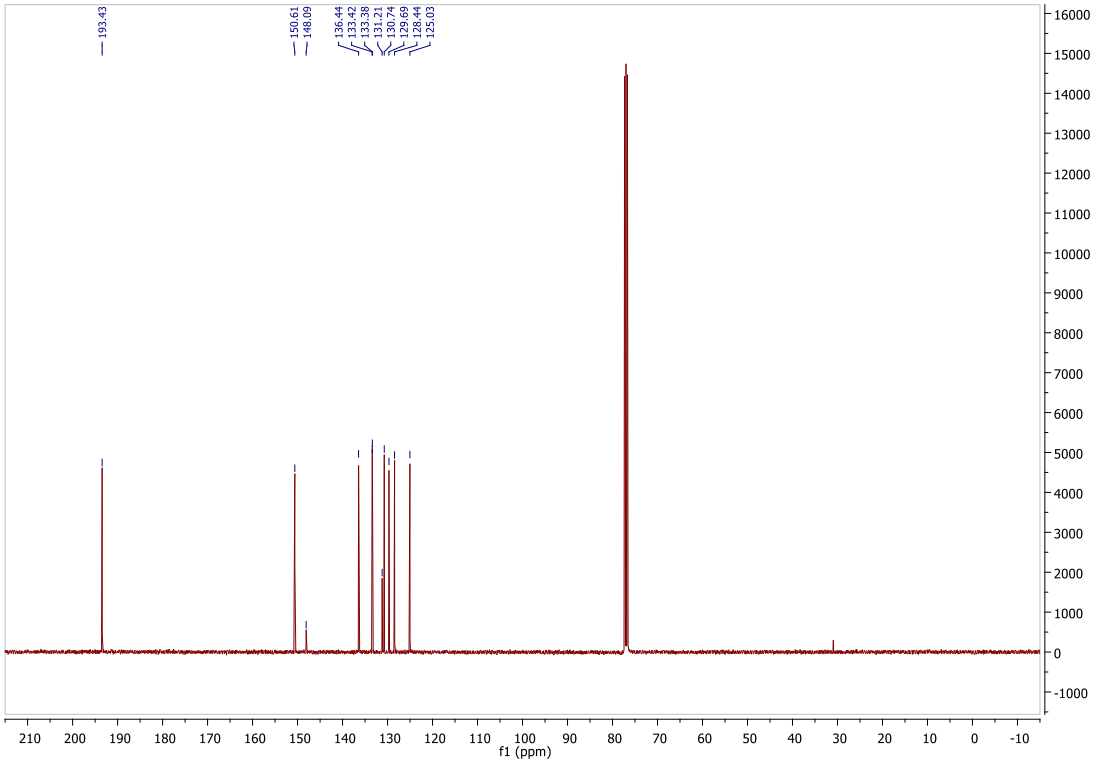
^{1}H NMR spectrum of 3.68c



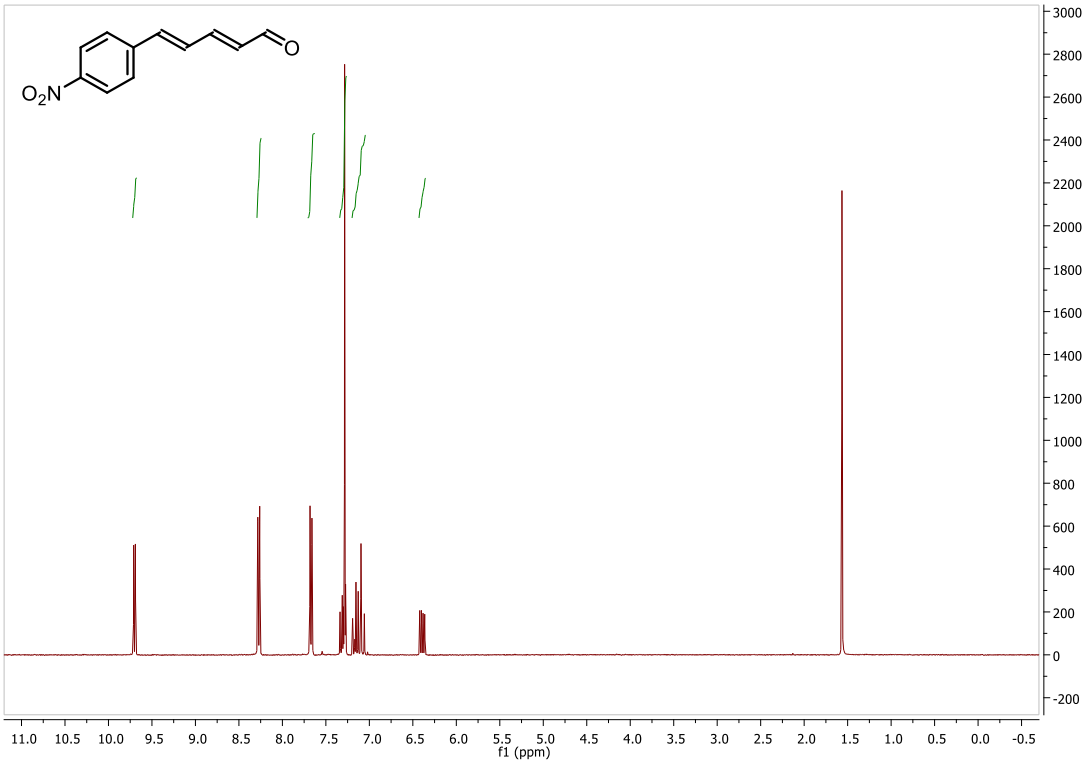
^{13}C NMR spectrum of 3.68c



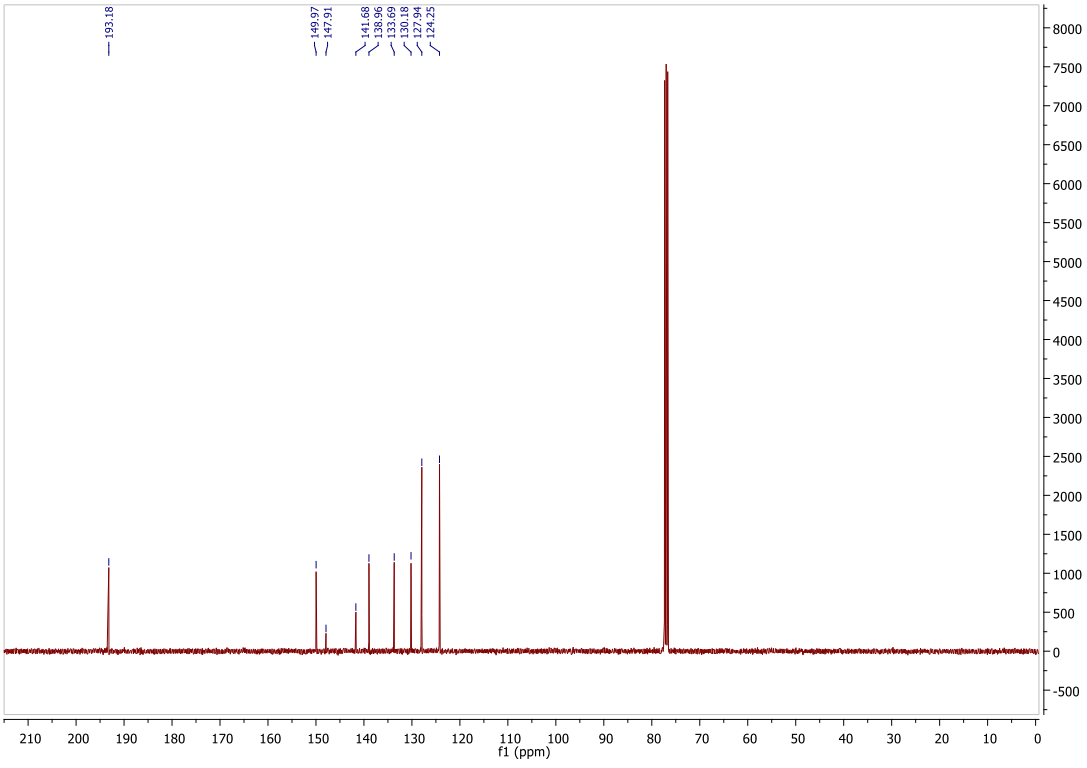
^{1}H NMR spectrum of 3.68d



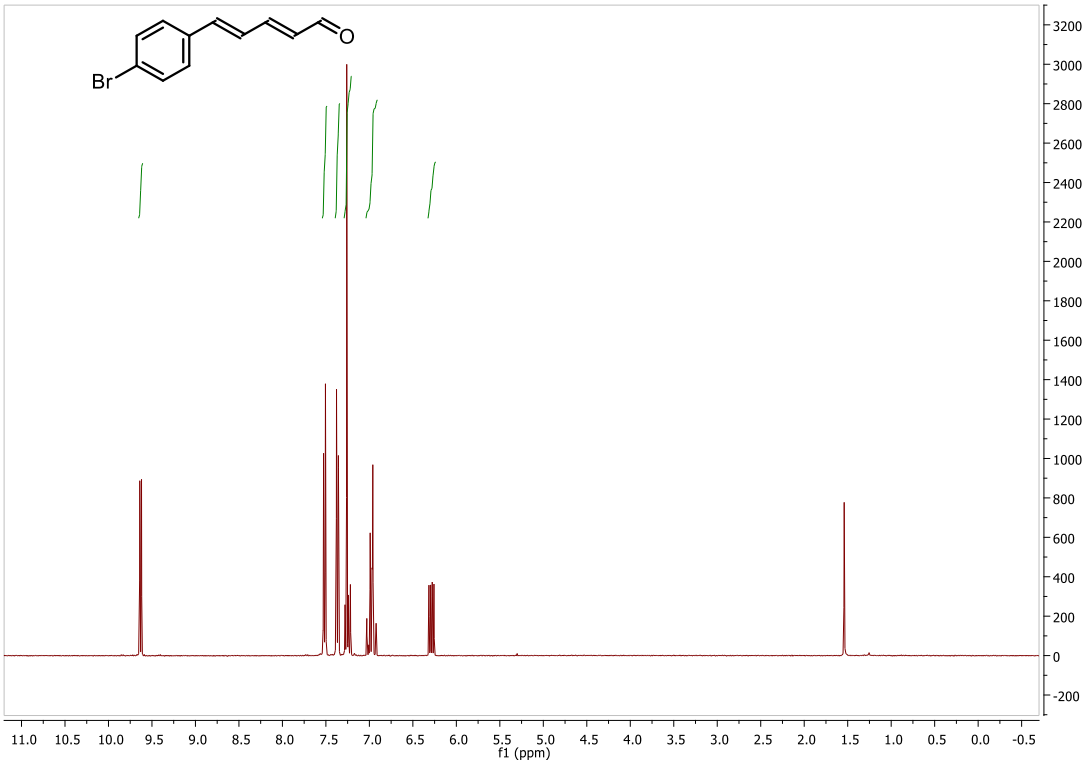
^{13}C NMR spectrum of 3.68d



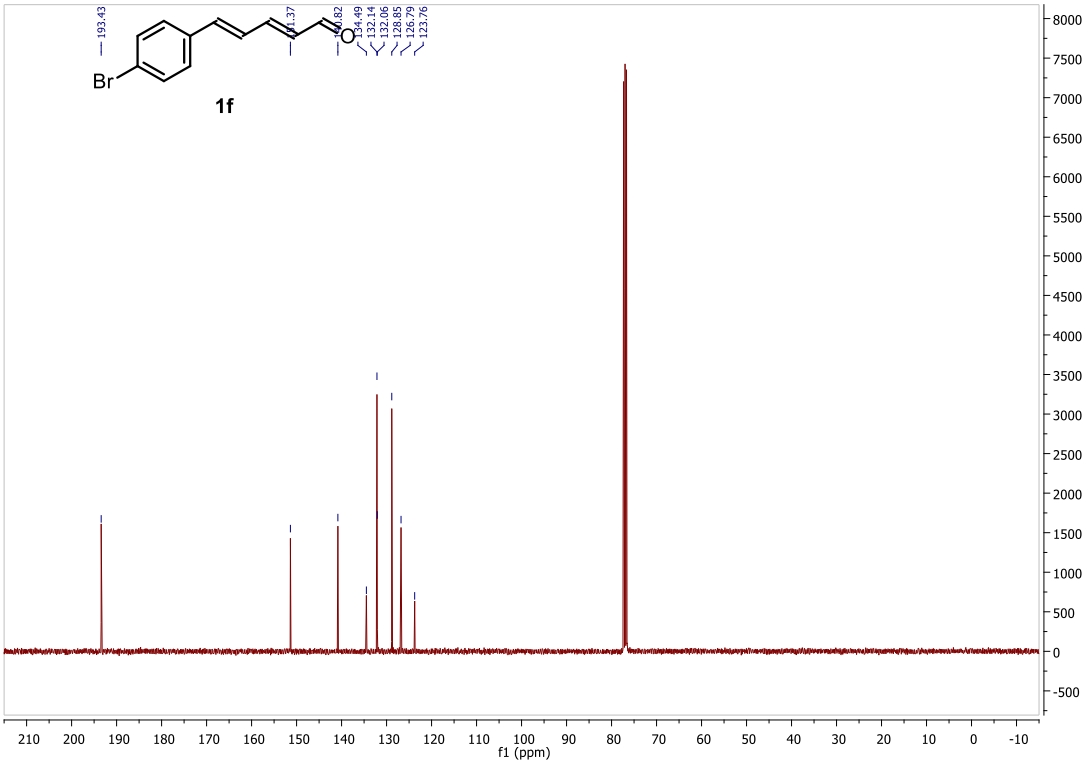
^{1}H NMR spectrum of 3.68e



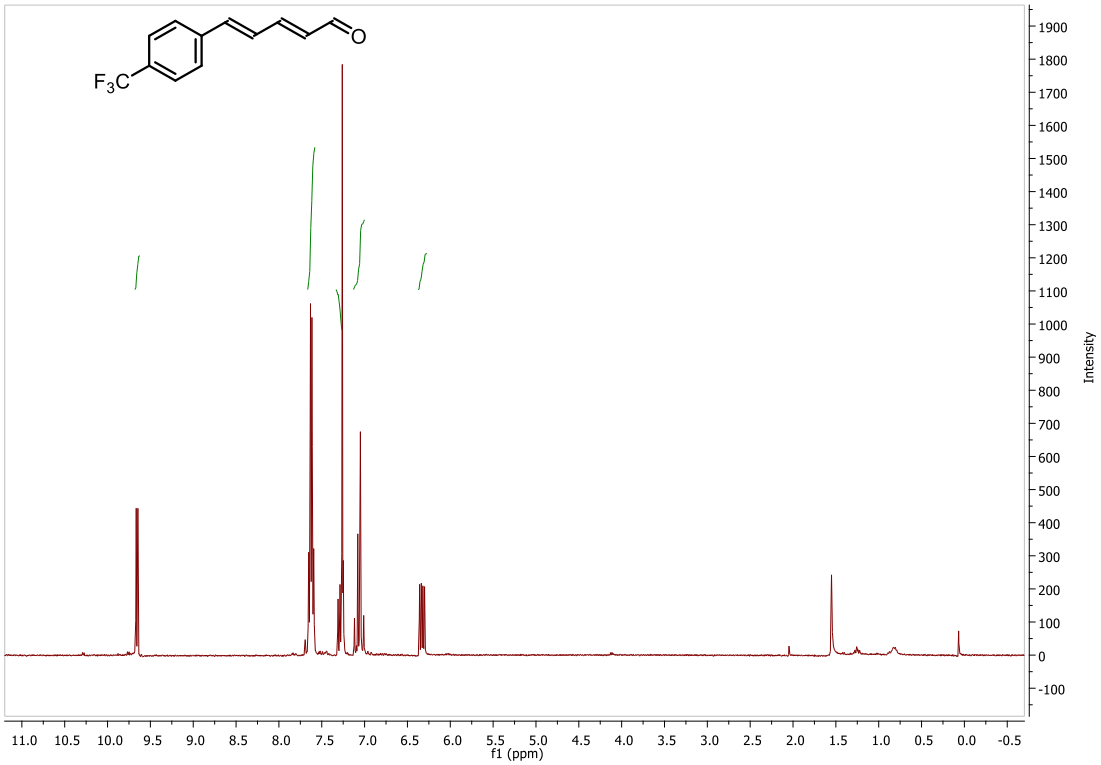
^{13}C NMR spectrum of 3.68e



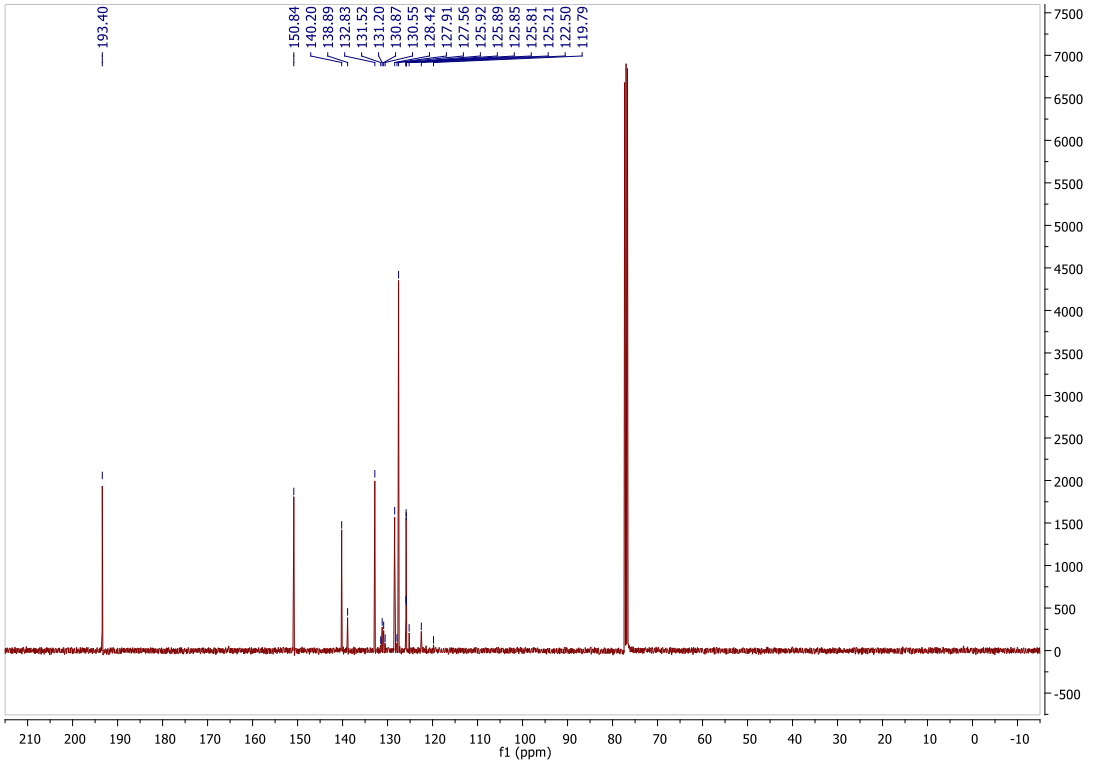
^{1}H NMR spectrum of 3.68f



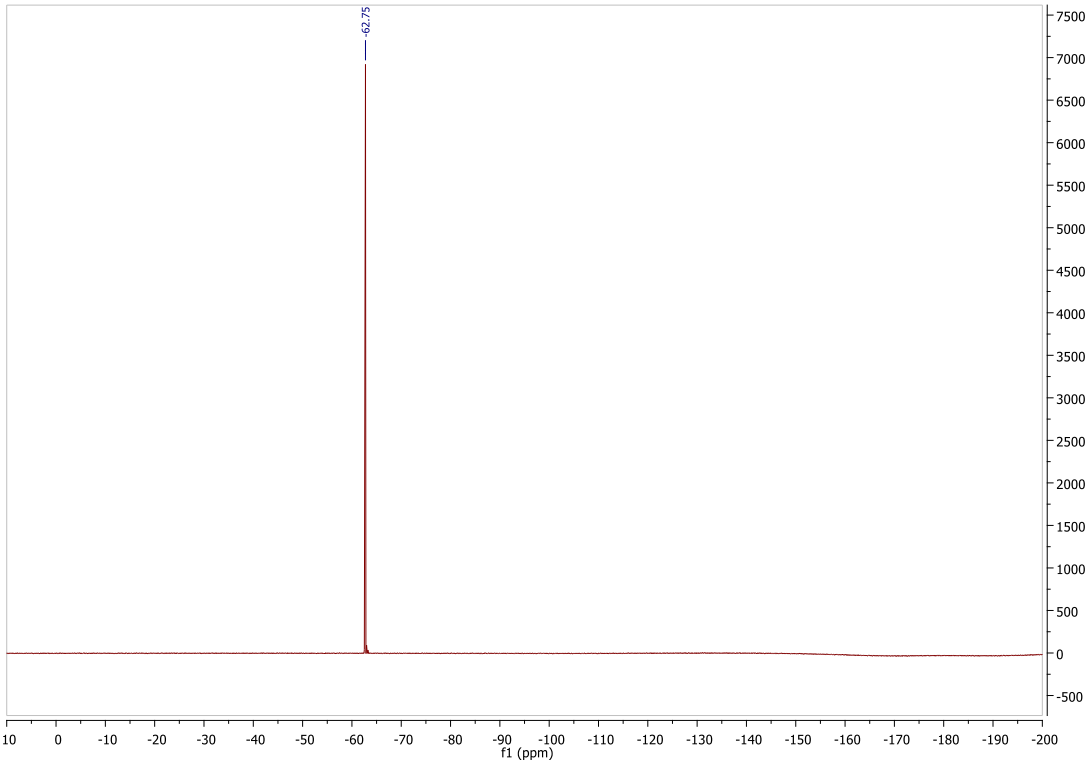
^{13}C NMR spectrum of 3.68f



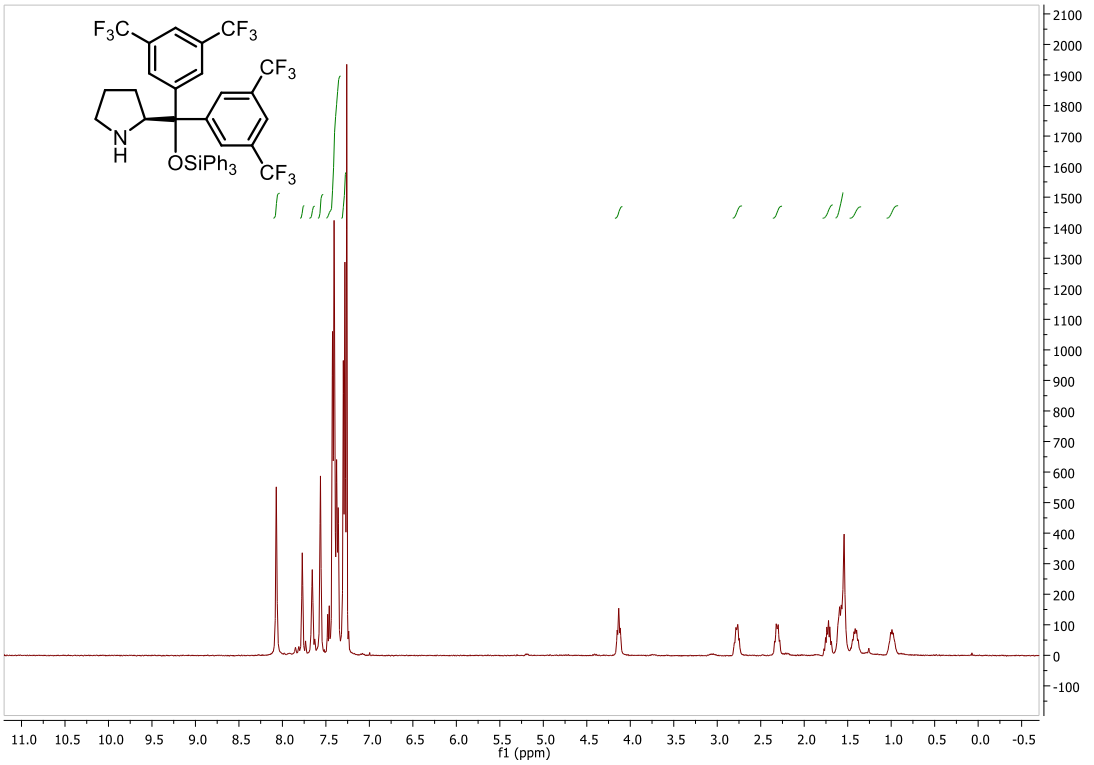
^{1}H NMR spectrum of 3.68g



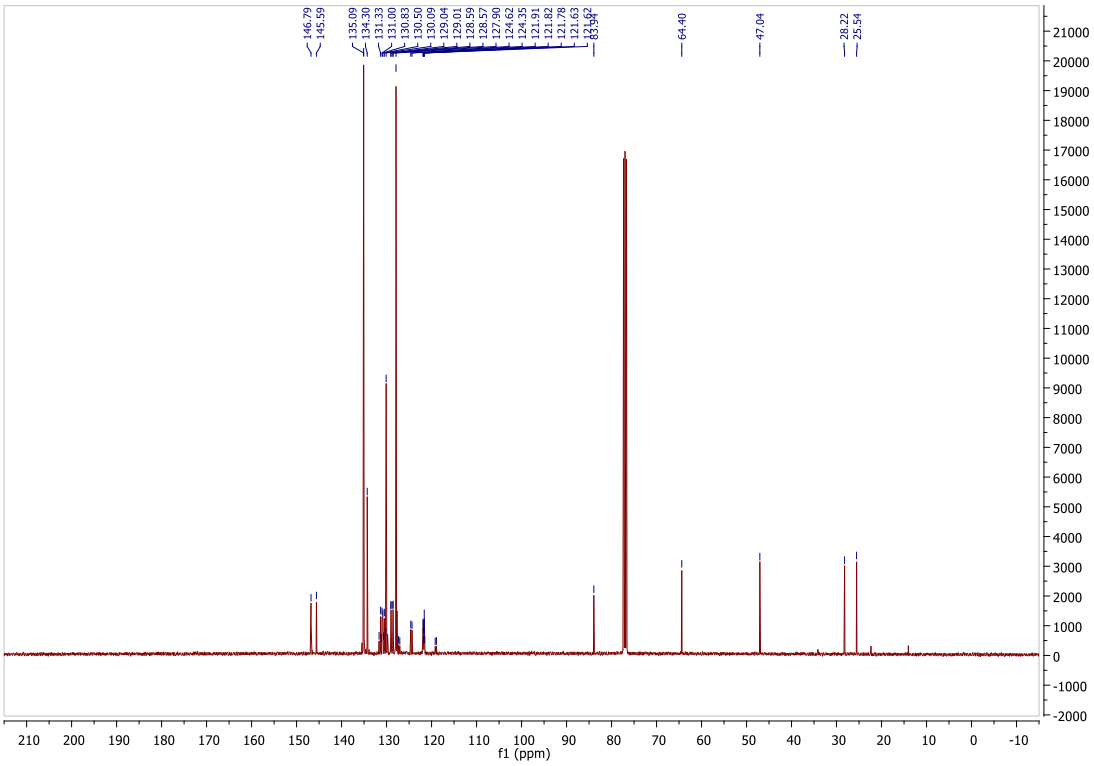
^{13}C NMR spectrum of 3.68g



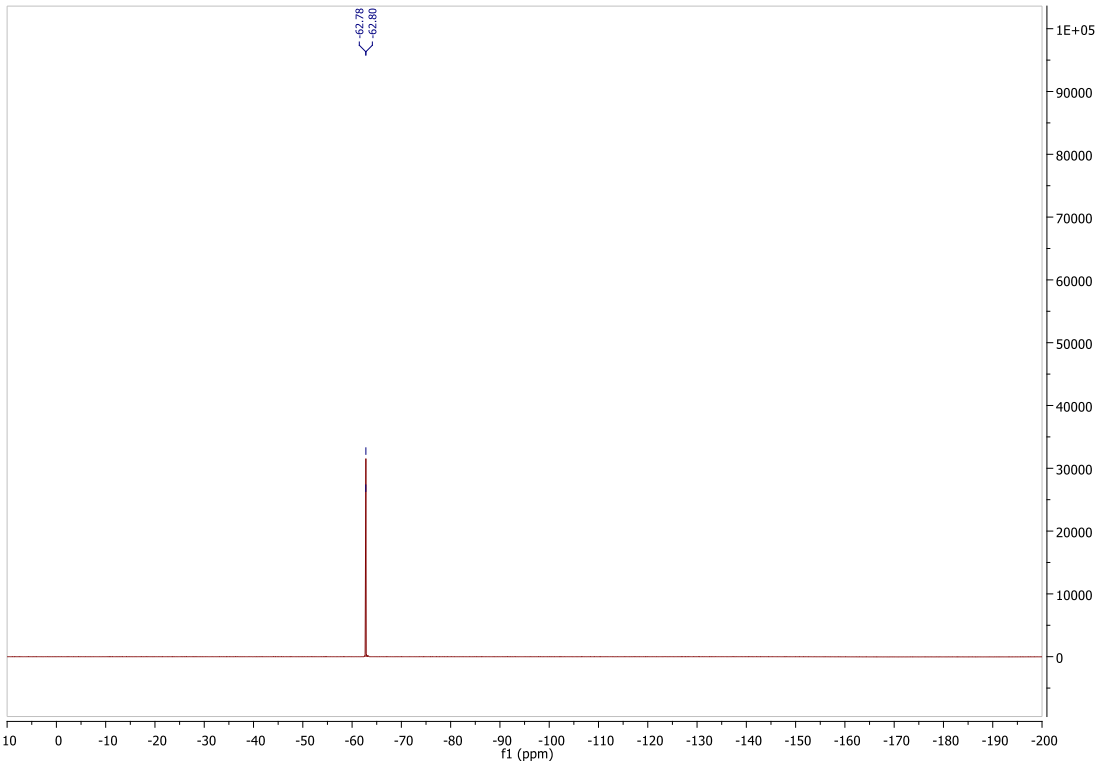
^{19}F NMR spectrum of 3.68g



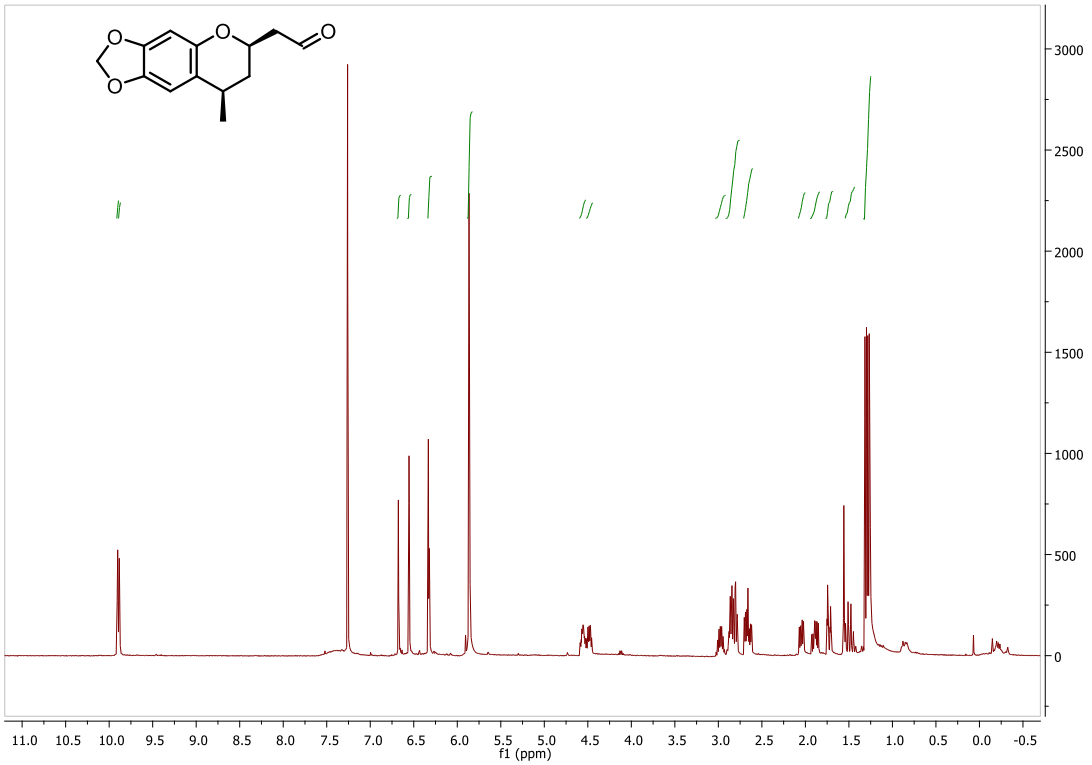
^{1}H NMR spectrum of 3.55



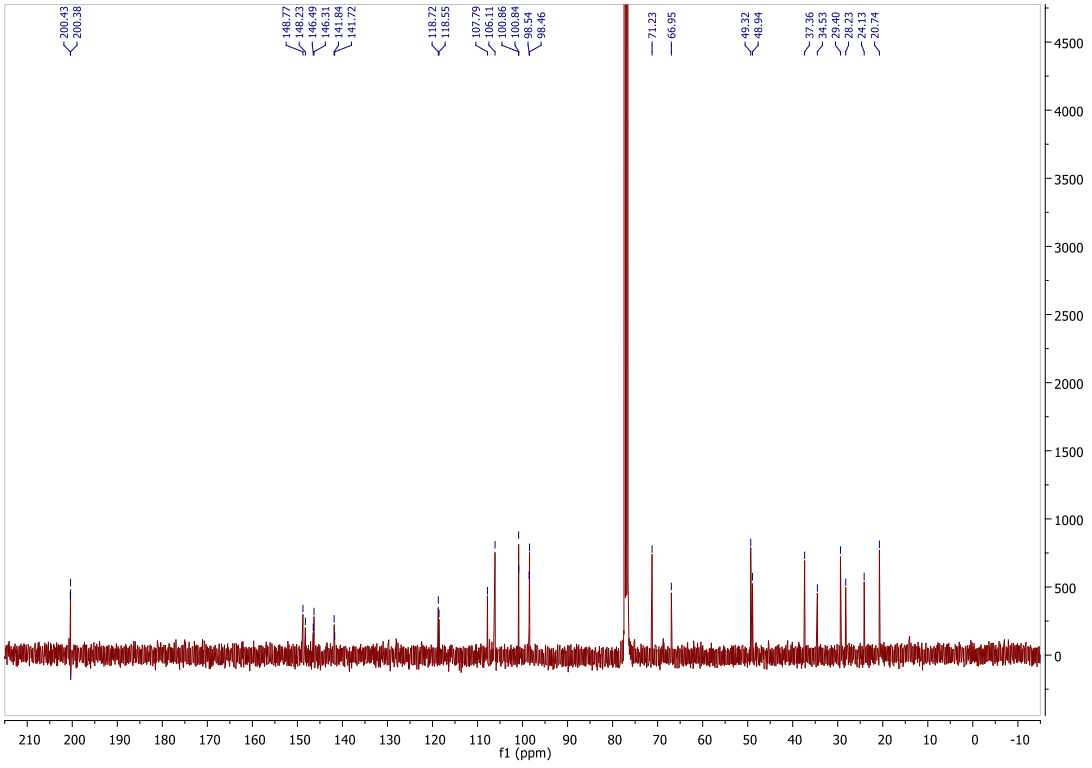
^{13}C NMR spectrum of 3.55



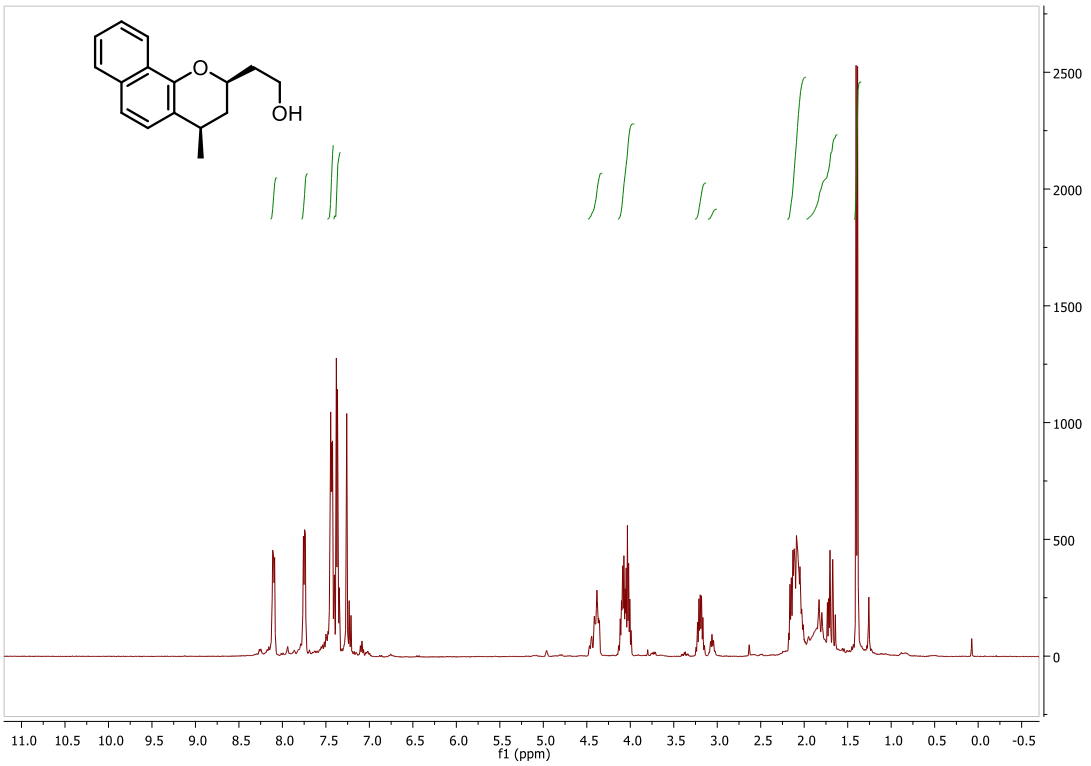
^{19}F NMR spectrum of 3.55



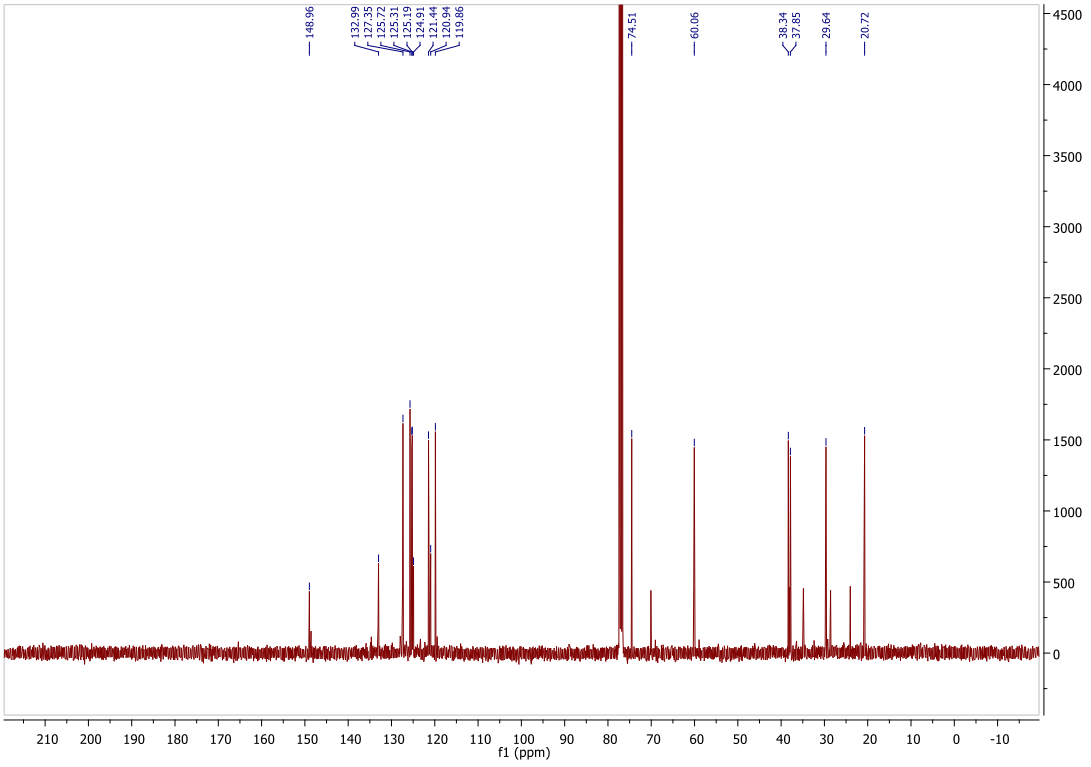
^{1}H NMR spectrum of 3.51



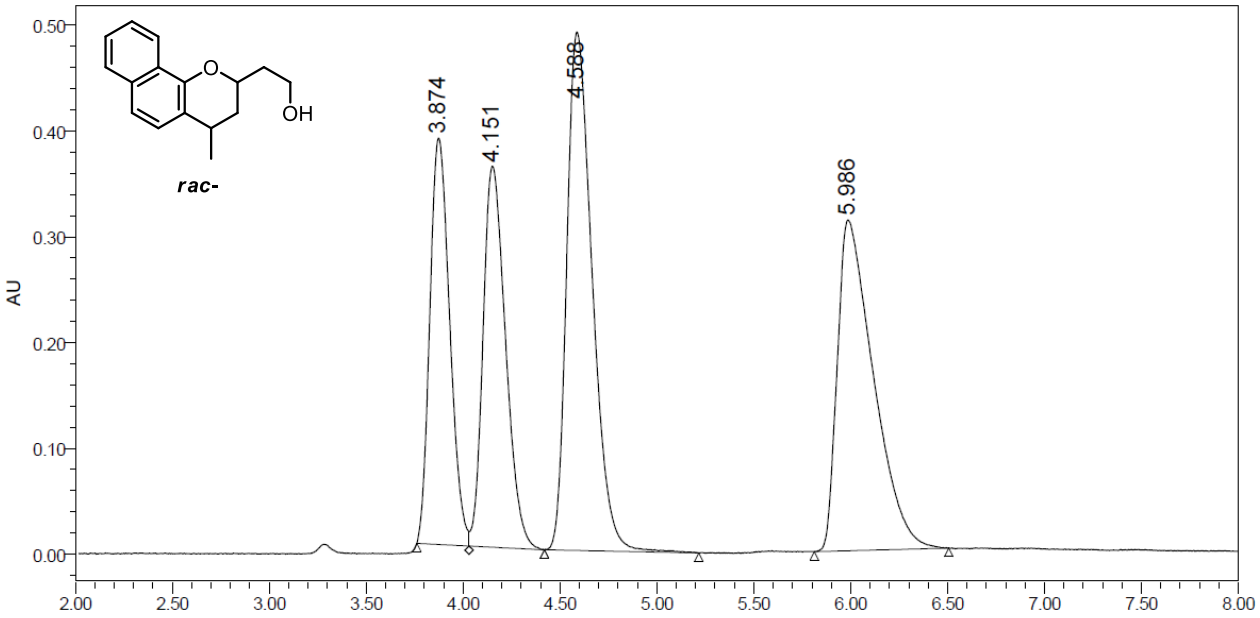
^{13}C NMR spectrum of 3.51



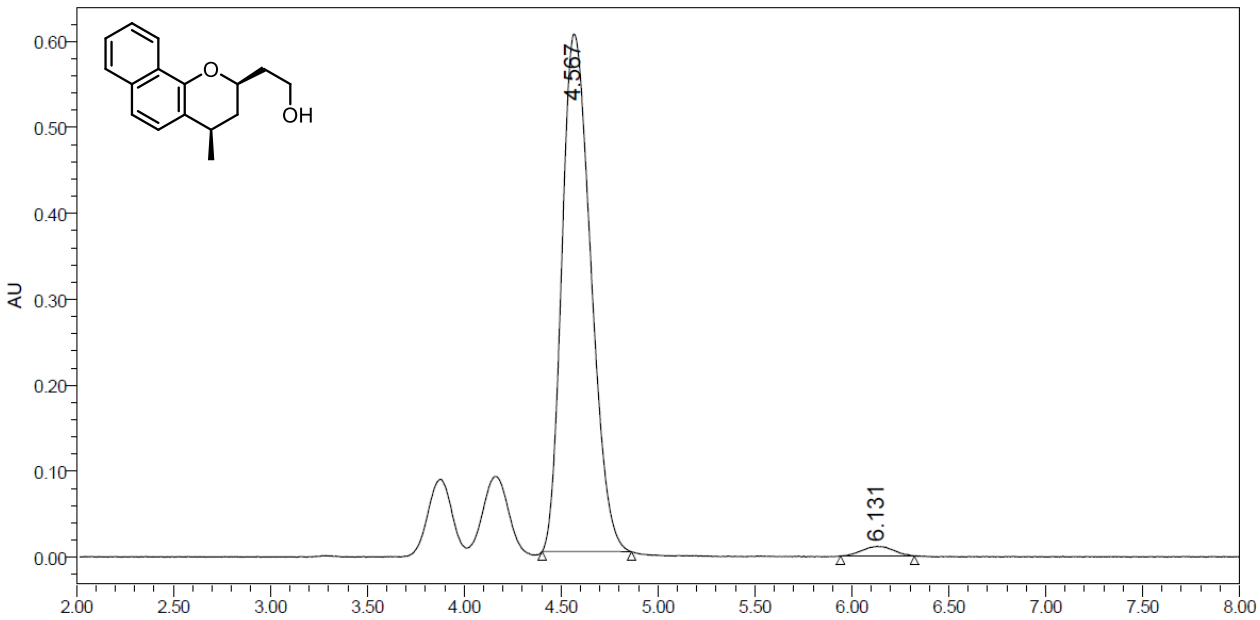
^{1}H NMR spectrum of 3.58b



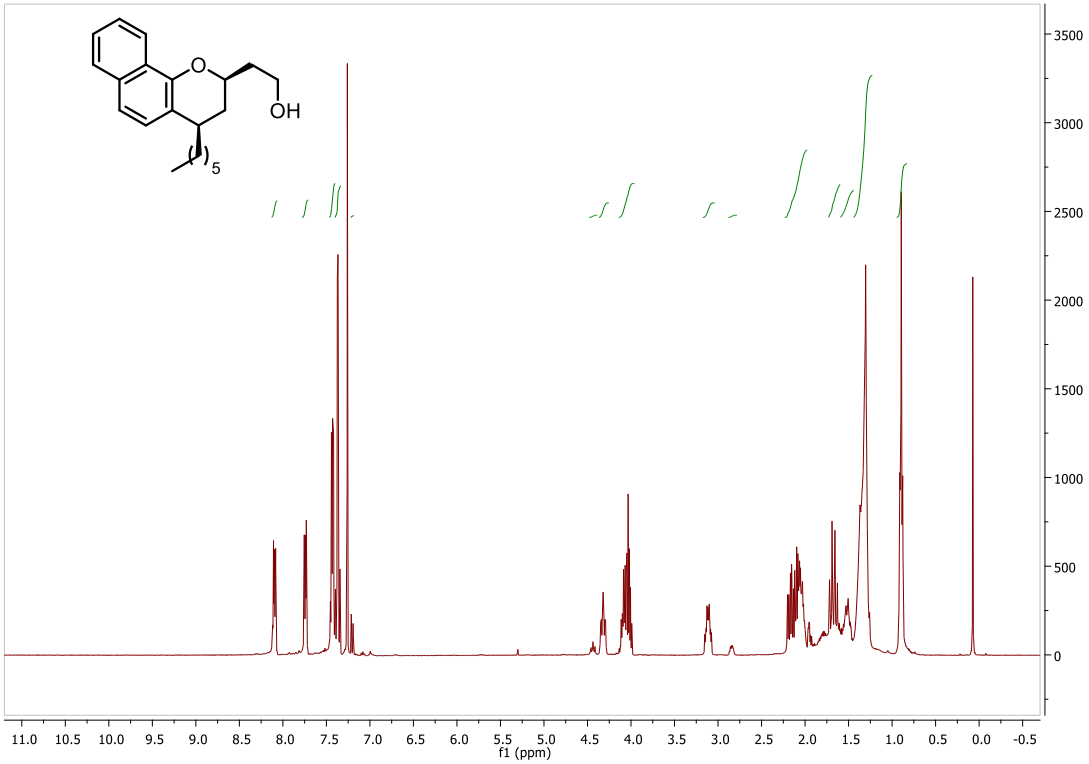
^{13}C NMR spectrum of 3.58b



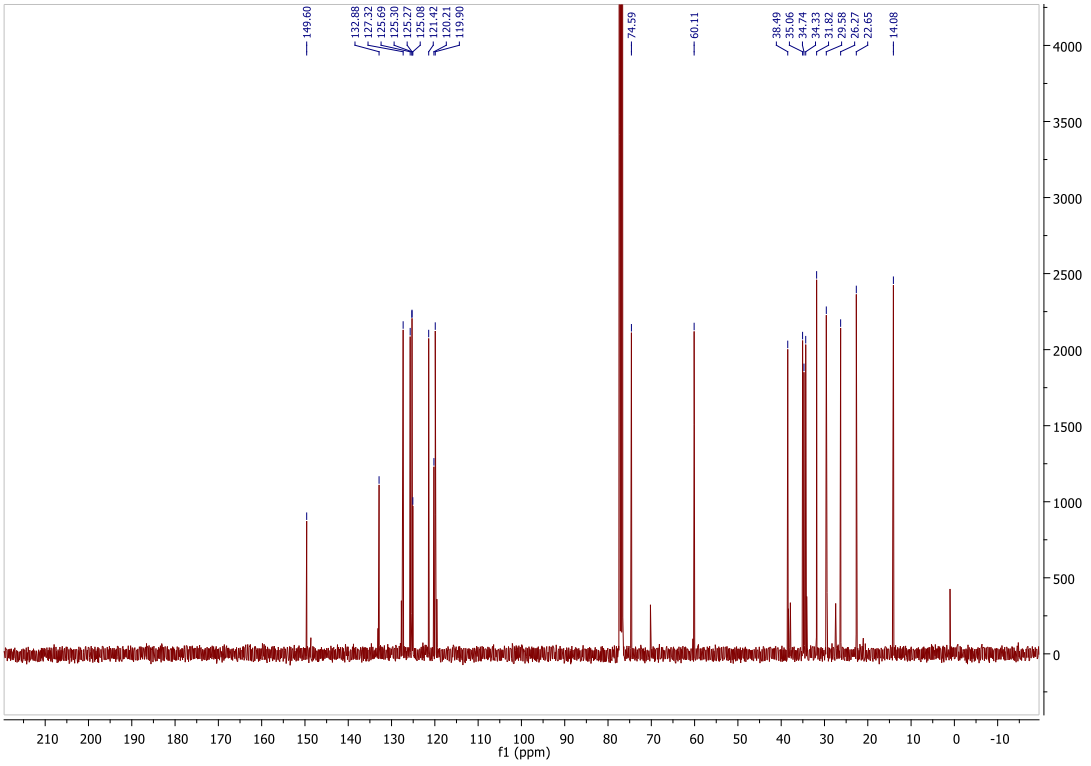
	Retention Time (min)	% Area
1	3.874	19.33
2	4.151	20.57
3	4.588	31.58
4	5.986	28.53



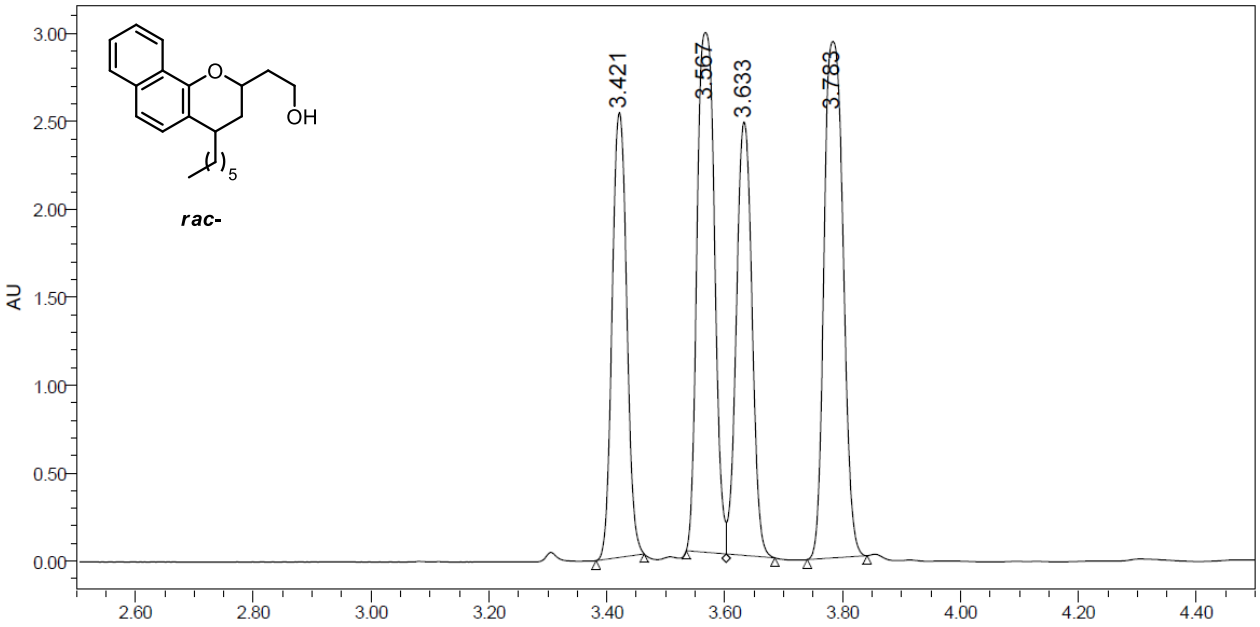
	Retention Time (min)	% Area
1	4.567	98.03
2	6.131	1.97



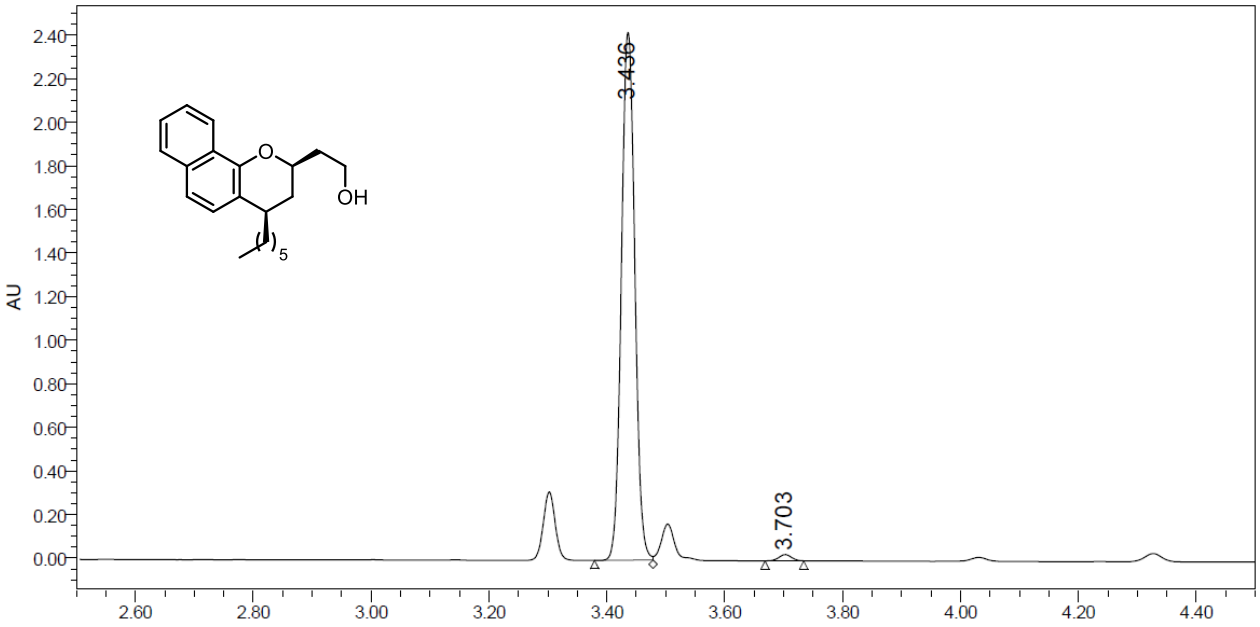
^{1}H NMR spectrum of 3.58c



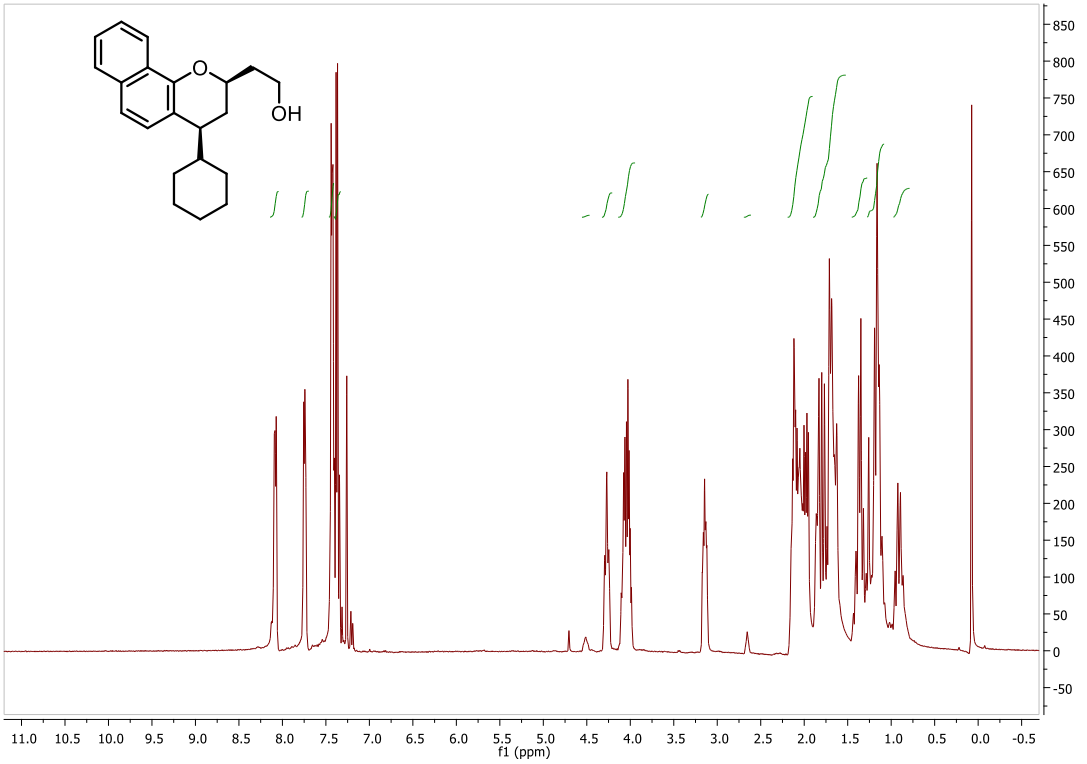
^{13}C NMR spectrum of 3.58c



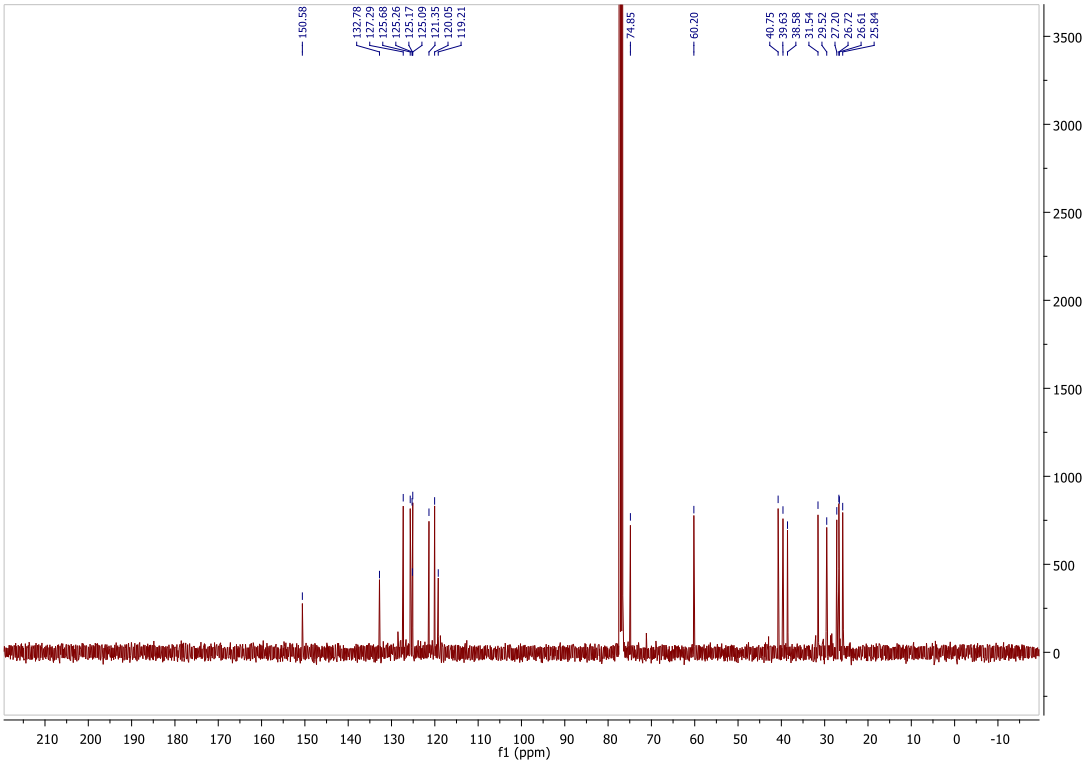
	Retention Time (min)	% Area
1	3.421	20.17
2	3.567	28.18
3	3.633	21.09
4	3.783	30.56



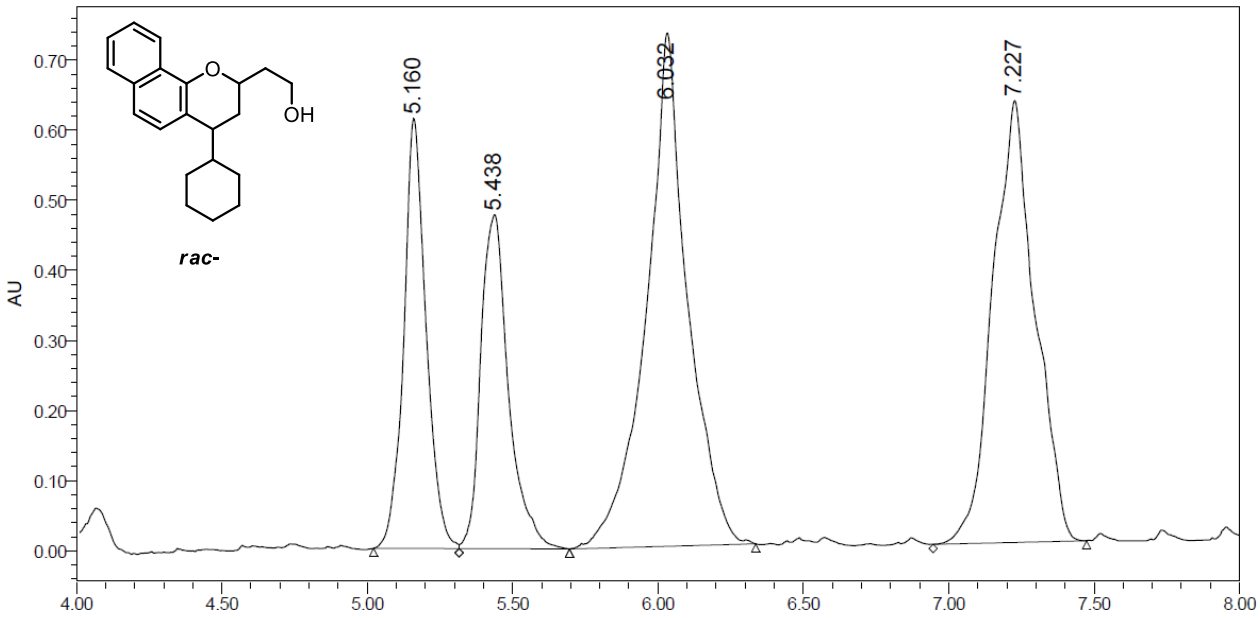
	Retention Time (min)	% Area
1	3.436	98.89
2	3.703	1.11



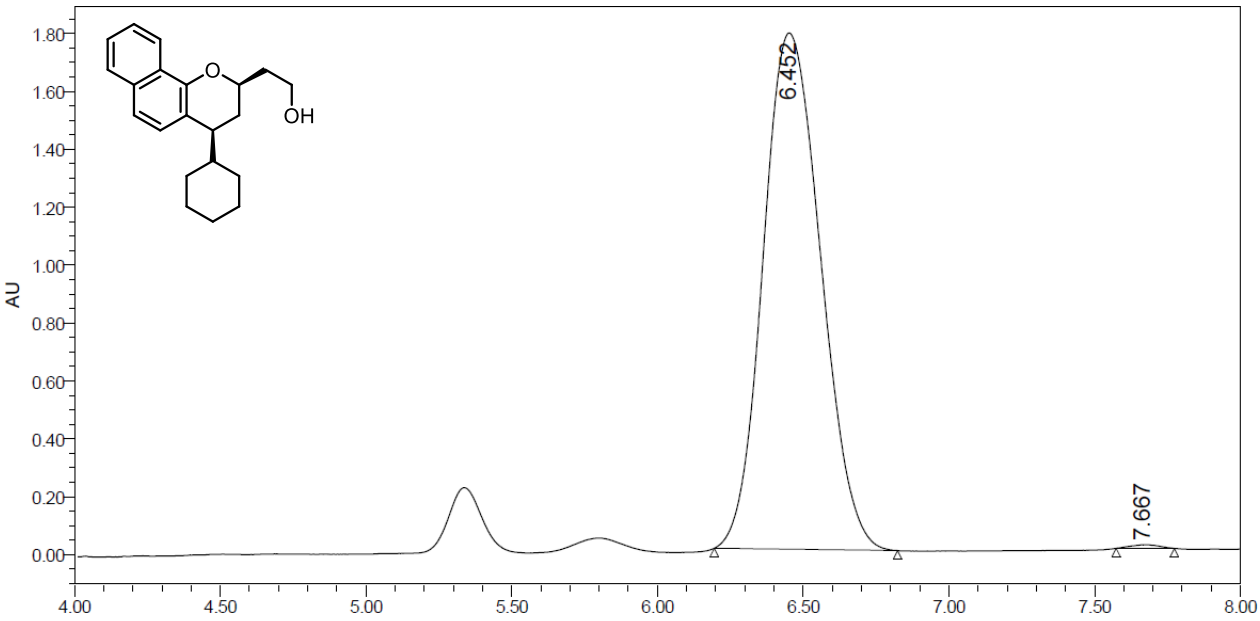
^{1}H NMR spectrum of 3.58d



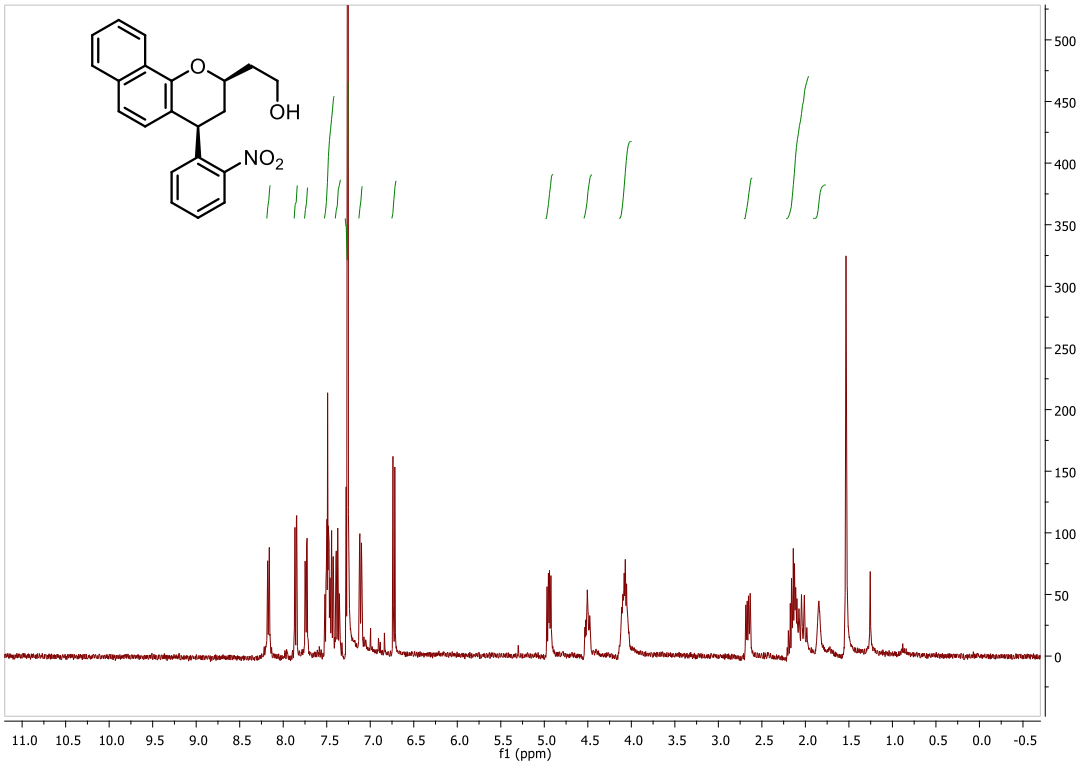
^{13}C NMR spectrum of 3.58d



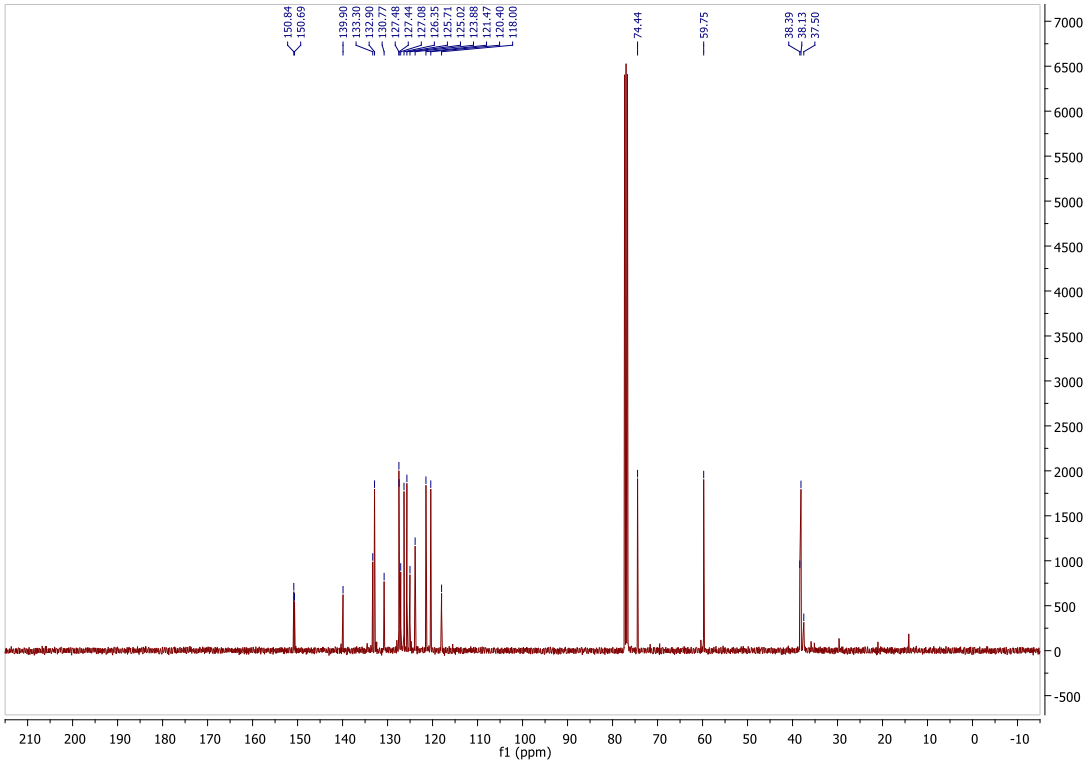
	Retention Time (min)	% Area
1	5.160	16.37
2	5.438	15.76
3	6.032	36.11
4	7.227	31.77



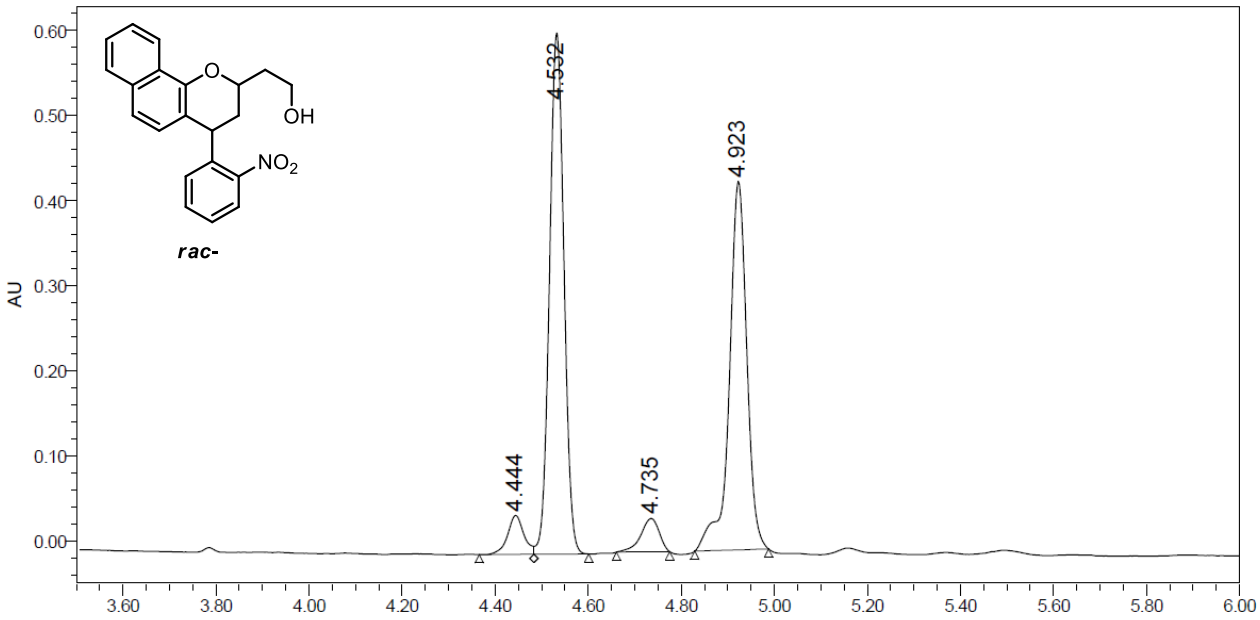
	Retention Time (min)	% Area
1	6.452	99.66
2	7.667	0.34



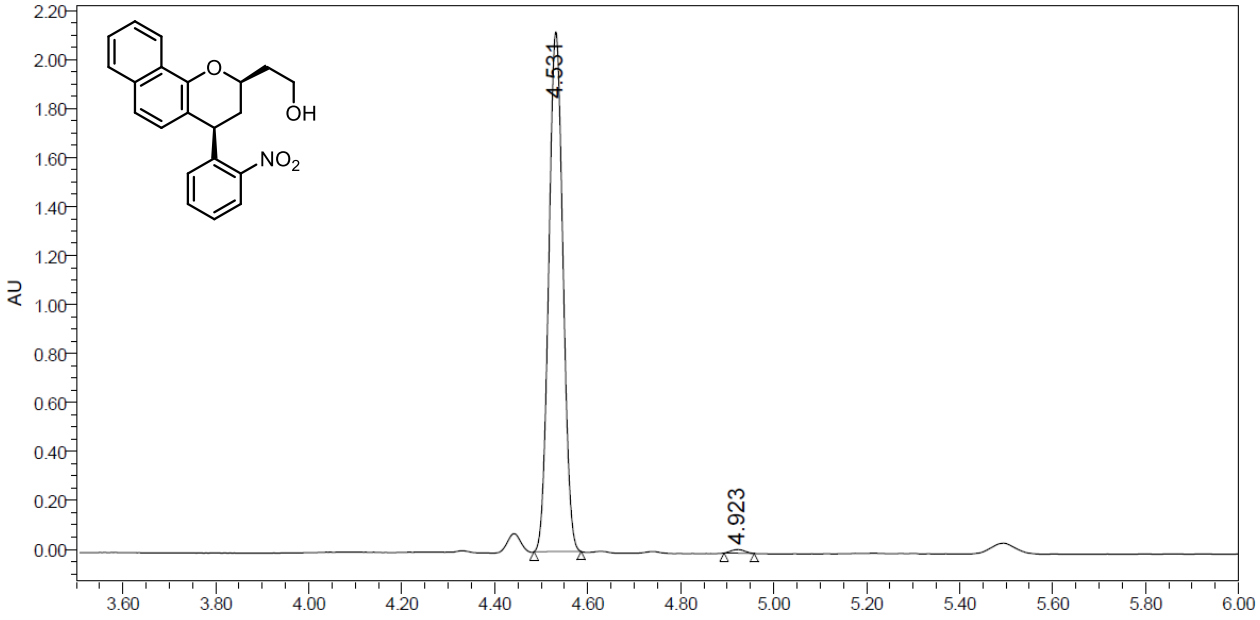
^{1}H NMR spectrum of 3.58e



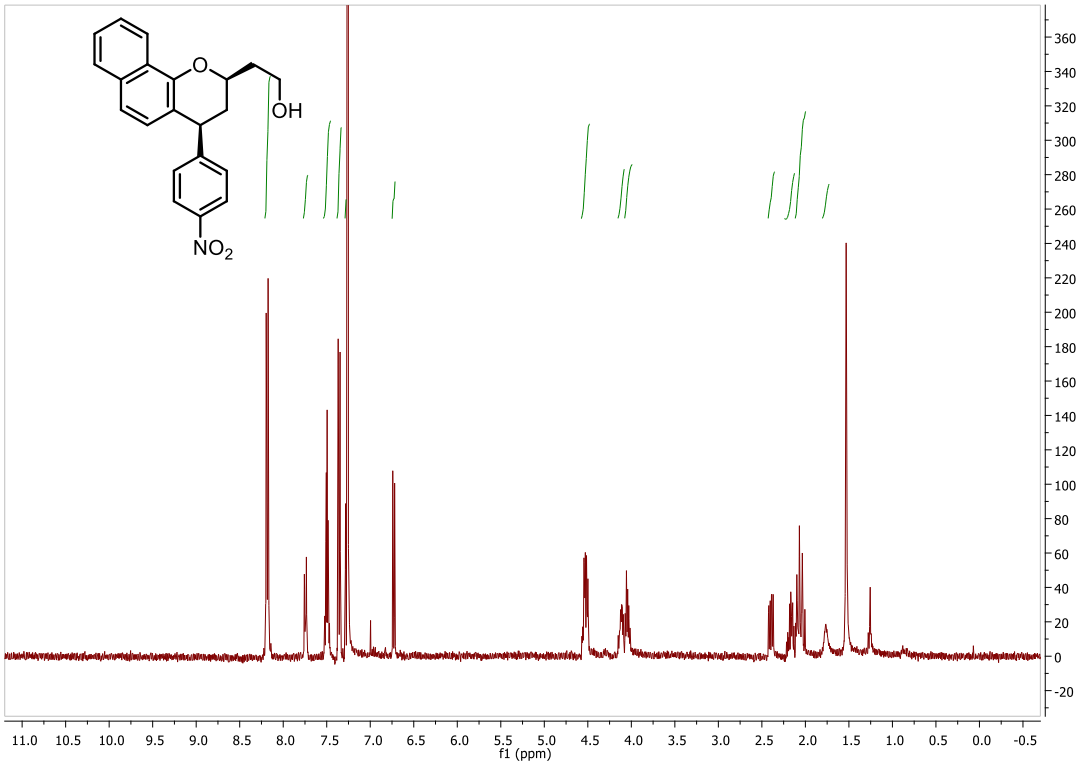
^{13}C NMR spectrum of 3.58e



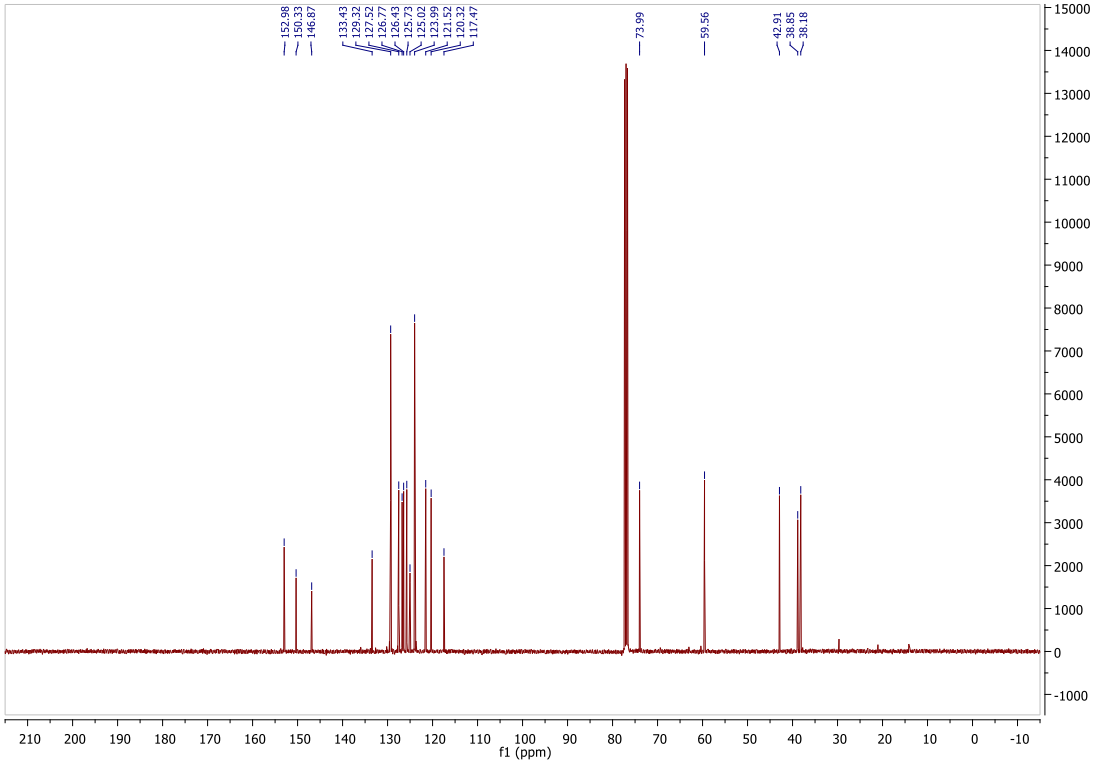
	Retention Time (min)	% Area
1	4.444	4.16
2	4.532	49.37
3	4.735	4.02
4	4.923	42.45



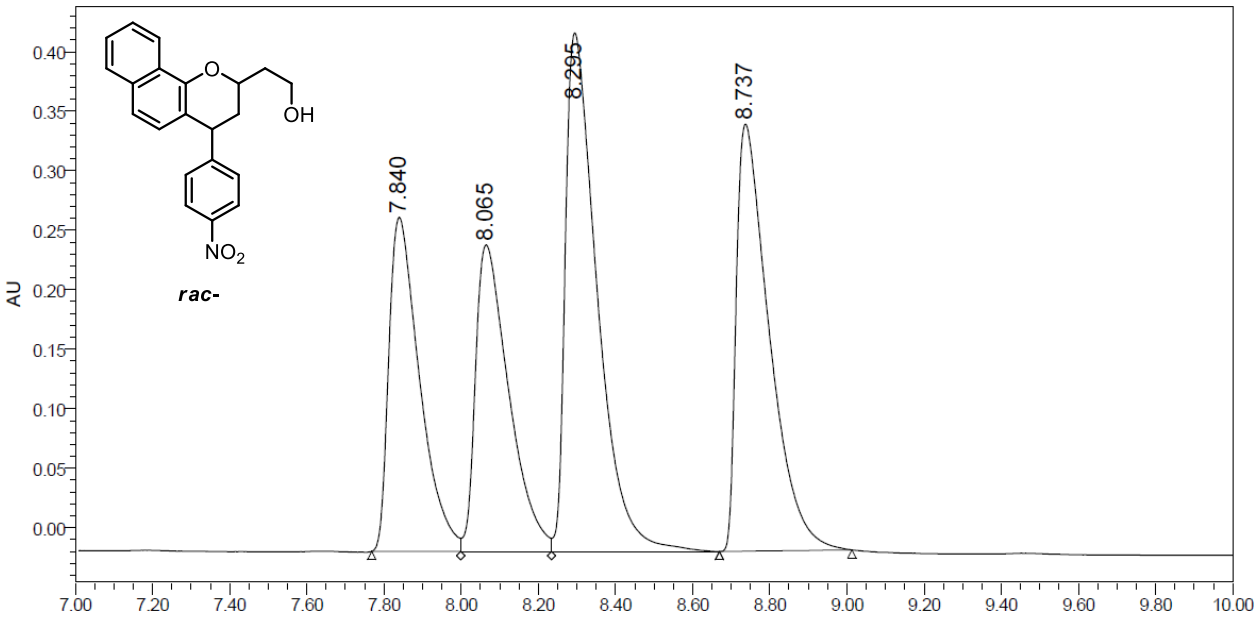
	Retention Time (min)	% Area
1	4.531	99.31
2	4.923	0.69



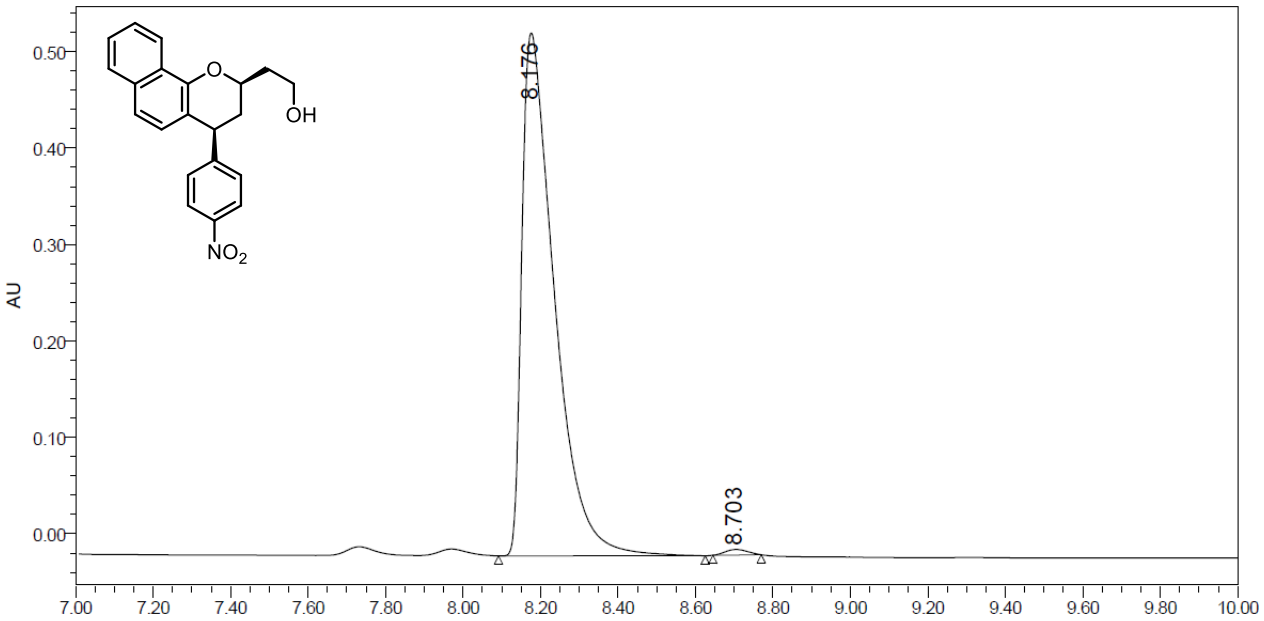
^{1}H NMR spectrum of 3.58f



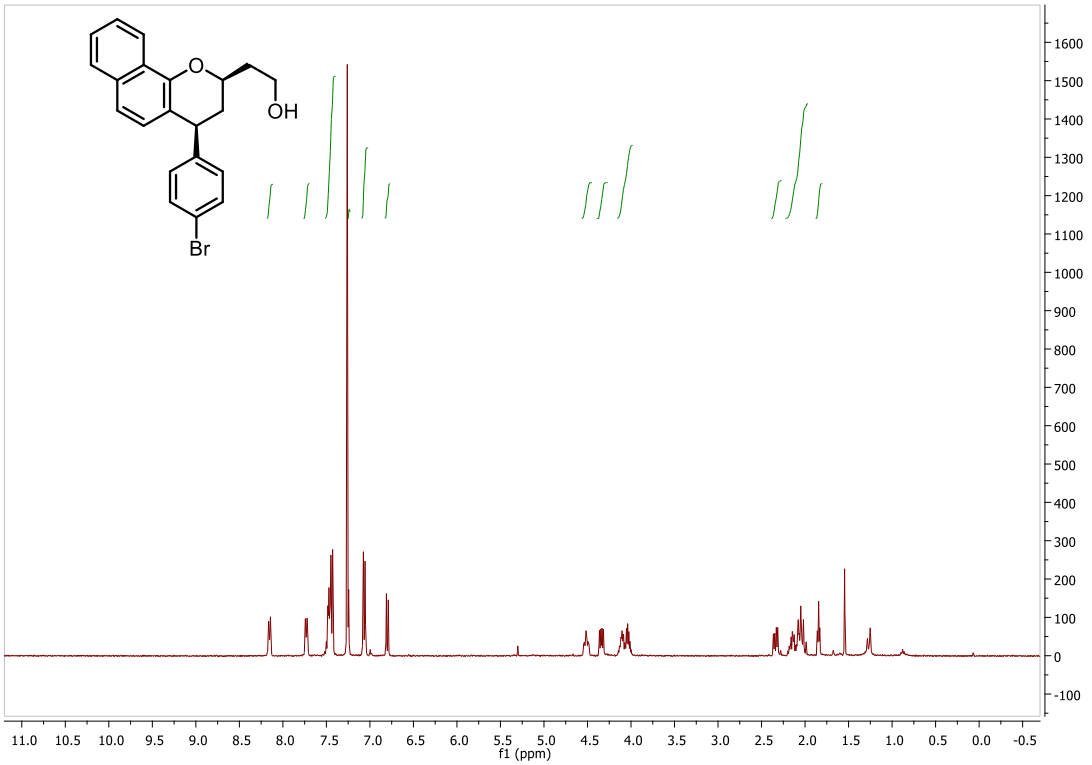
^{13}C NMR spectrum of 3.58f



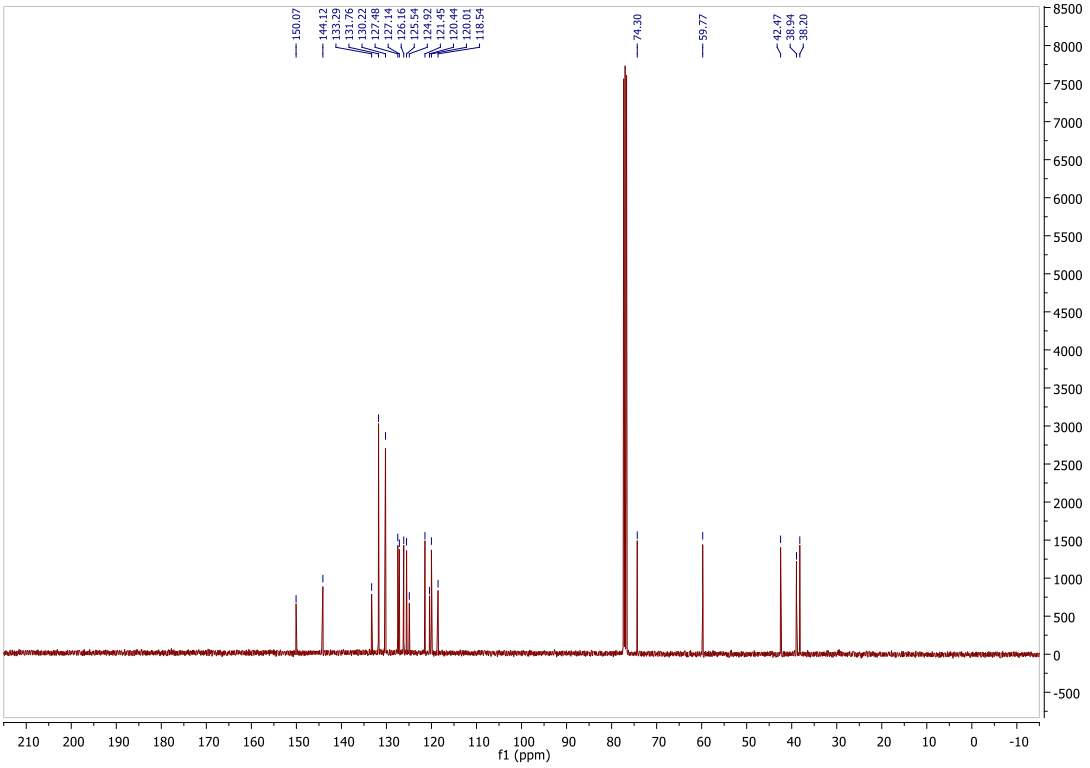
	Retention Time (min)	% Area
1	7.840	20.13
2	8.065	20.03
3	8.295	32.26
4	8.737	27.57



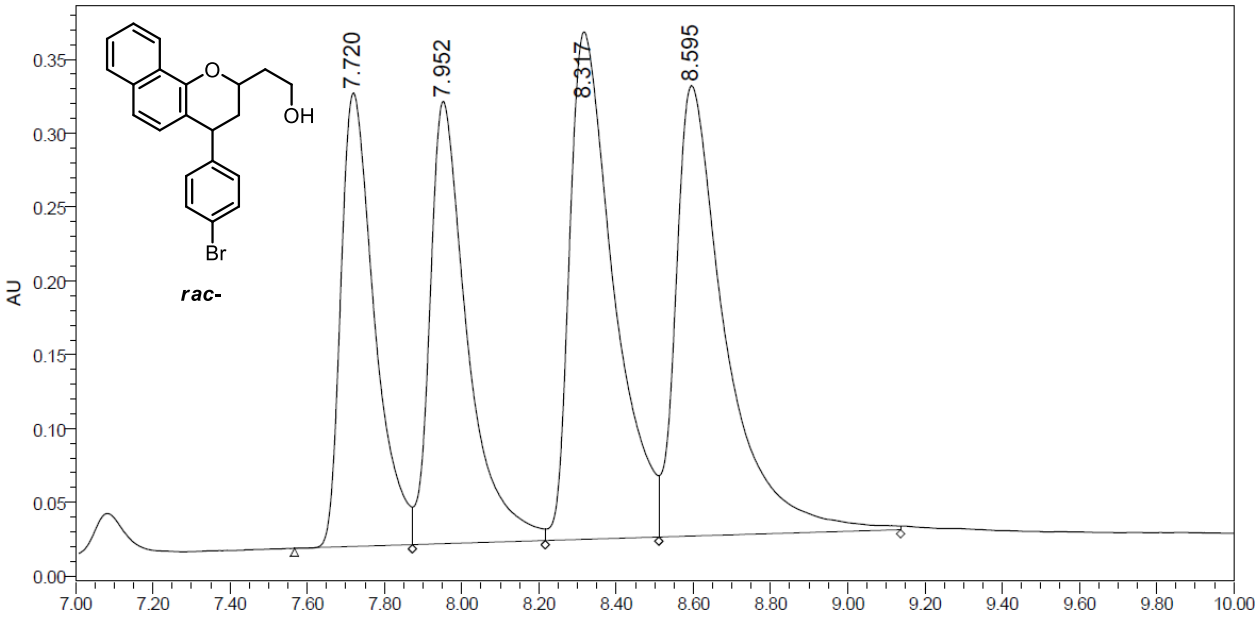
	Retention Time (min)	% Area
1	8.176	99.28
2	8.703	0.72



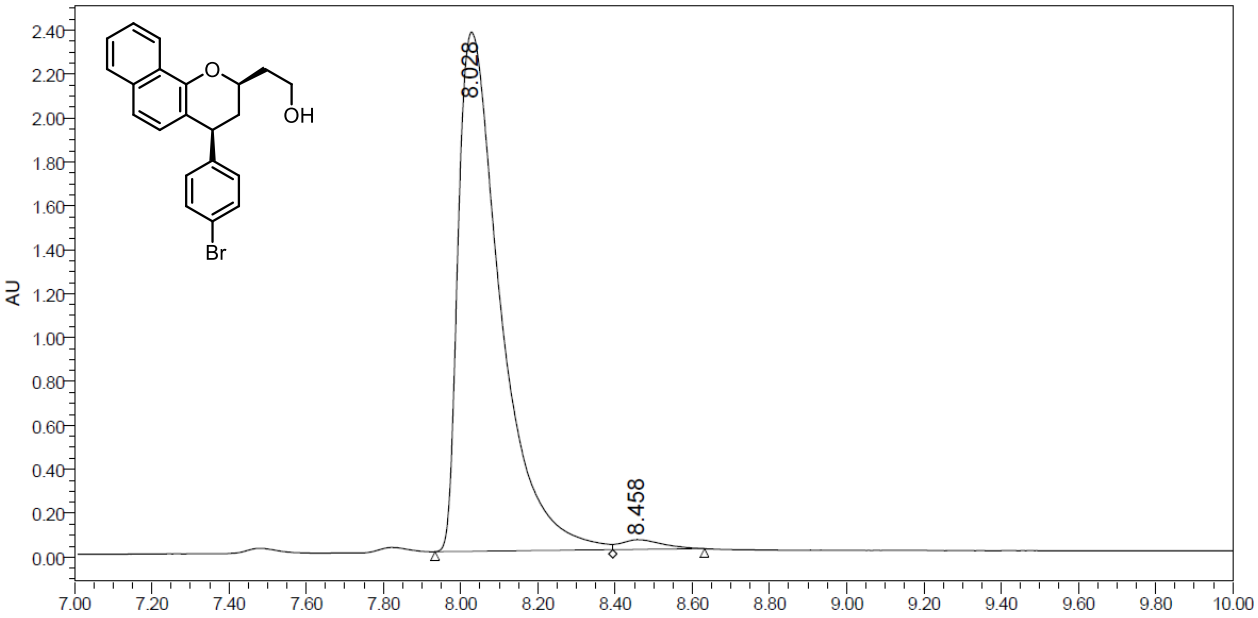
^{1}H NMR spectrum of 3.58g



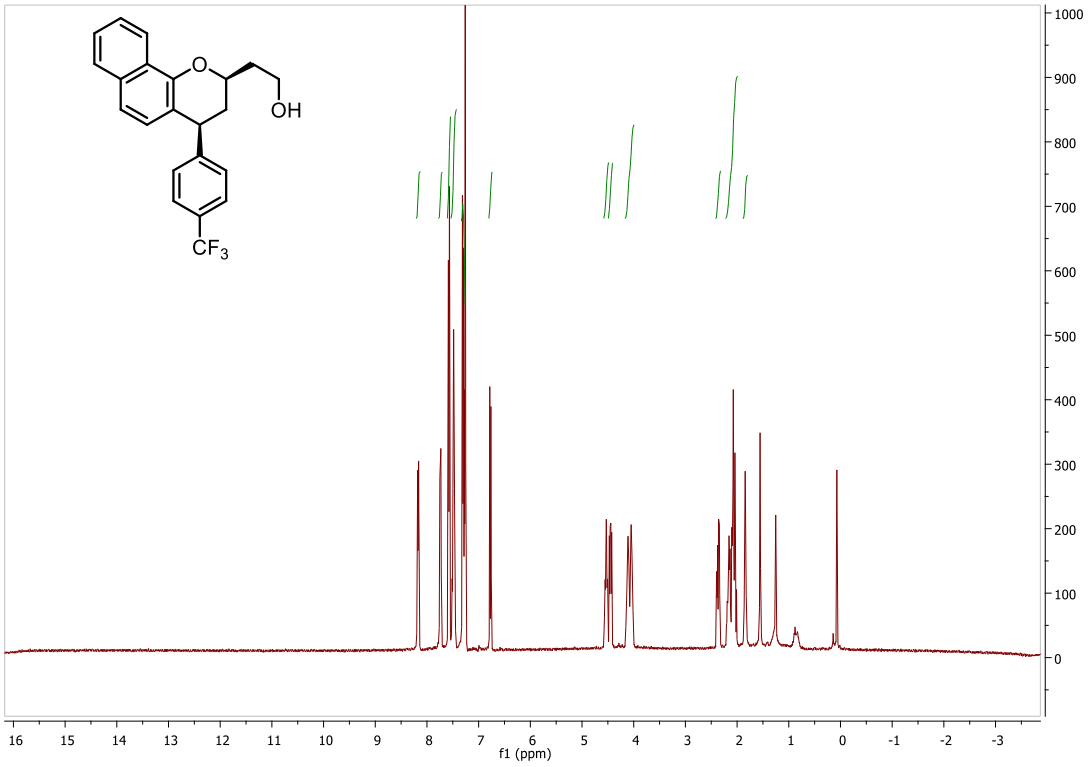
^{13}C NMR spectrum of 3.58g



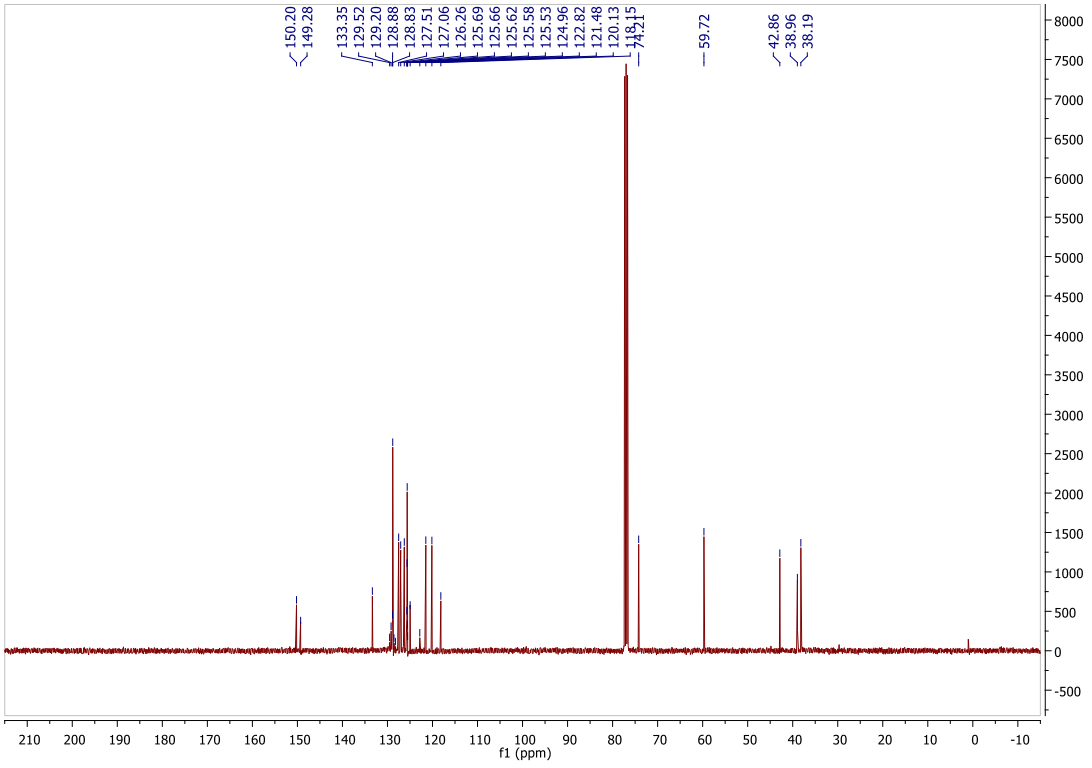
	Retention Time (min)	% Area
1	7.720	19.95
2	7.952	21.60
3	8.317	29.15
4	8.595	29.30



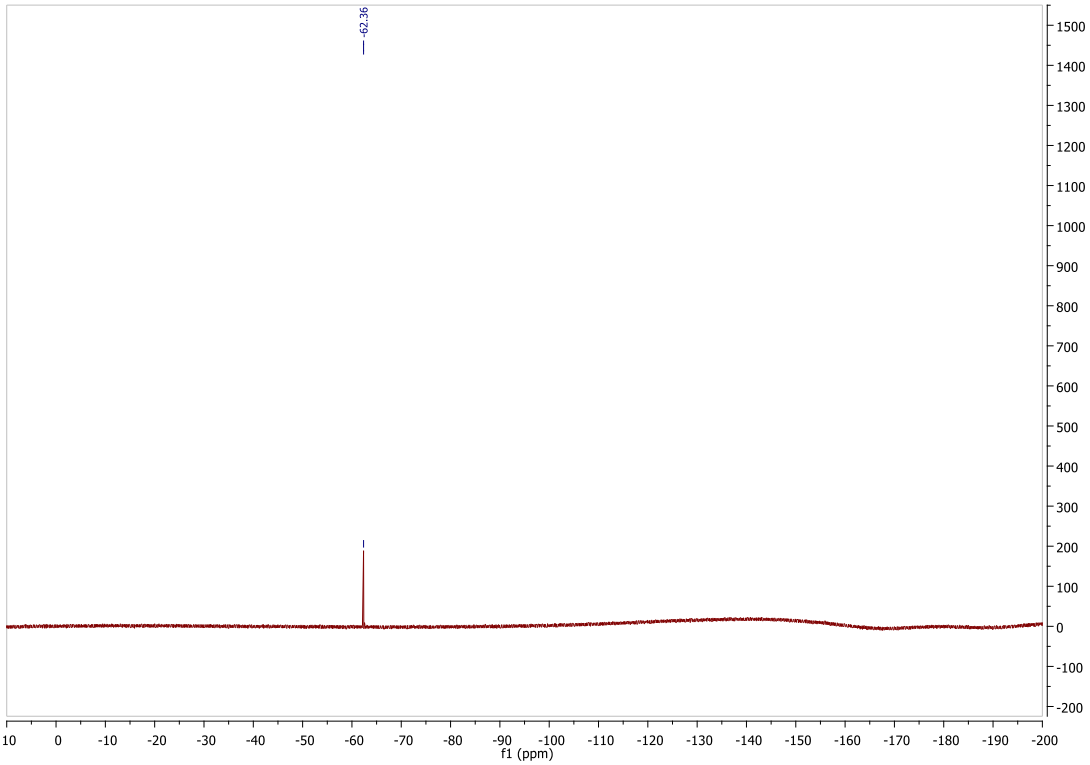
	Retention Time (min)	% Area
1	8.028	98.21
2	8.458	1.79



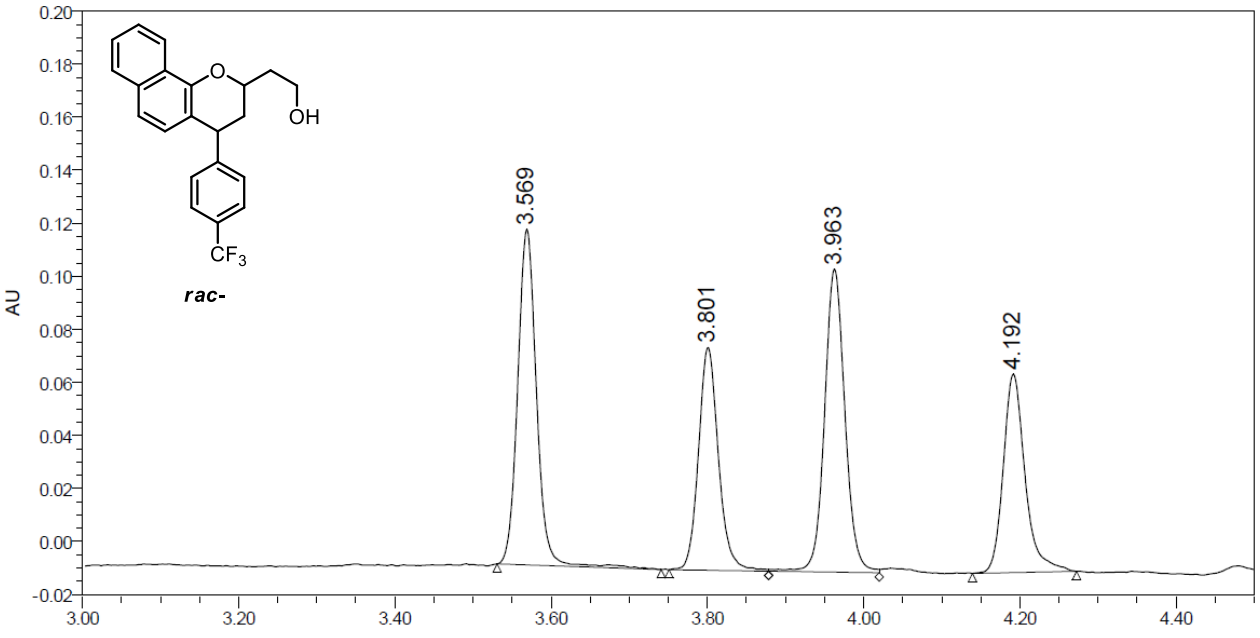
^{1}H NMR spectrum of 3.58h



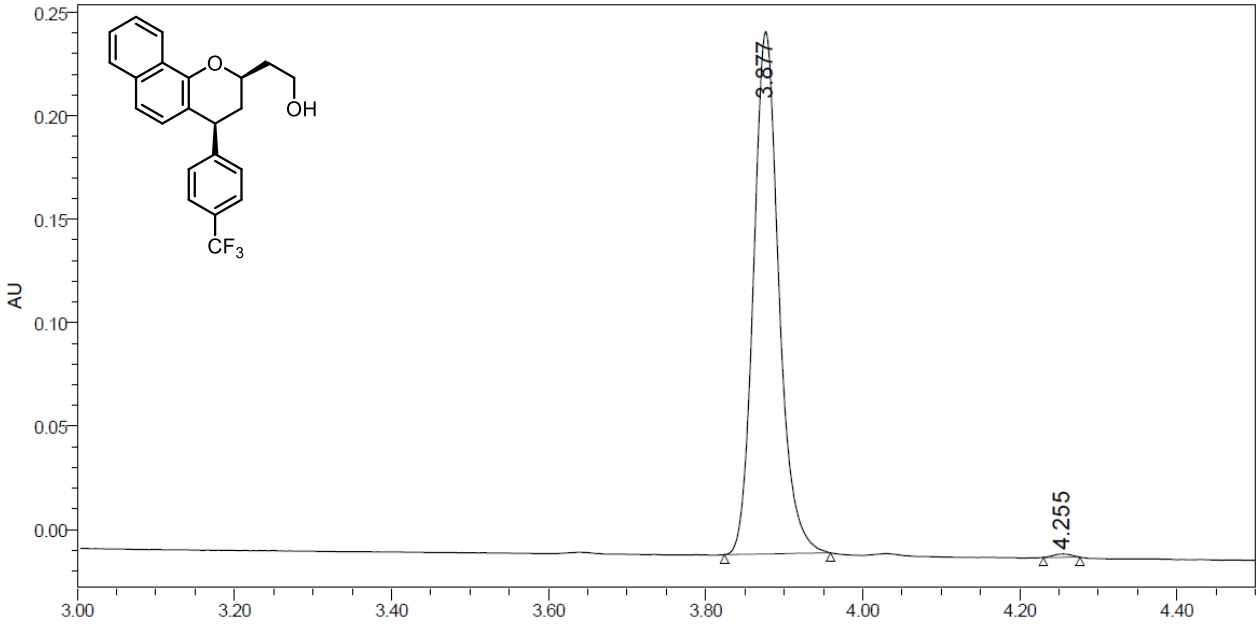
^{13}C NMR spectrum of 3.58h



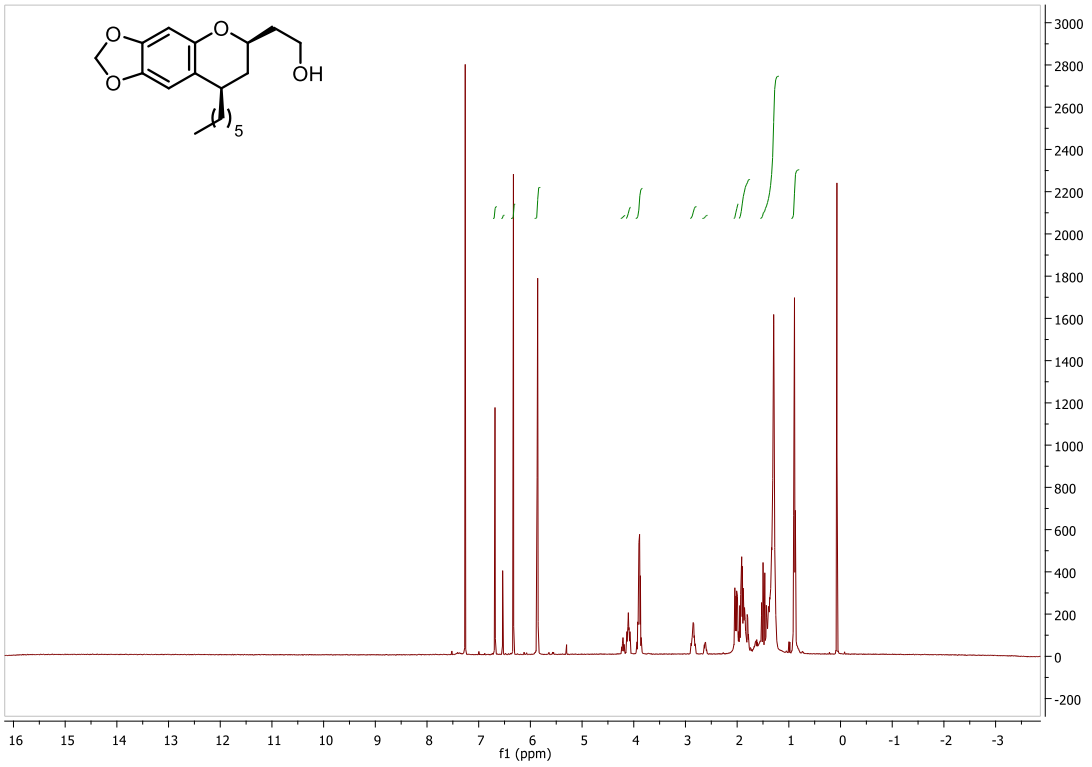
^{19}F NMR spectrum of 3.58h



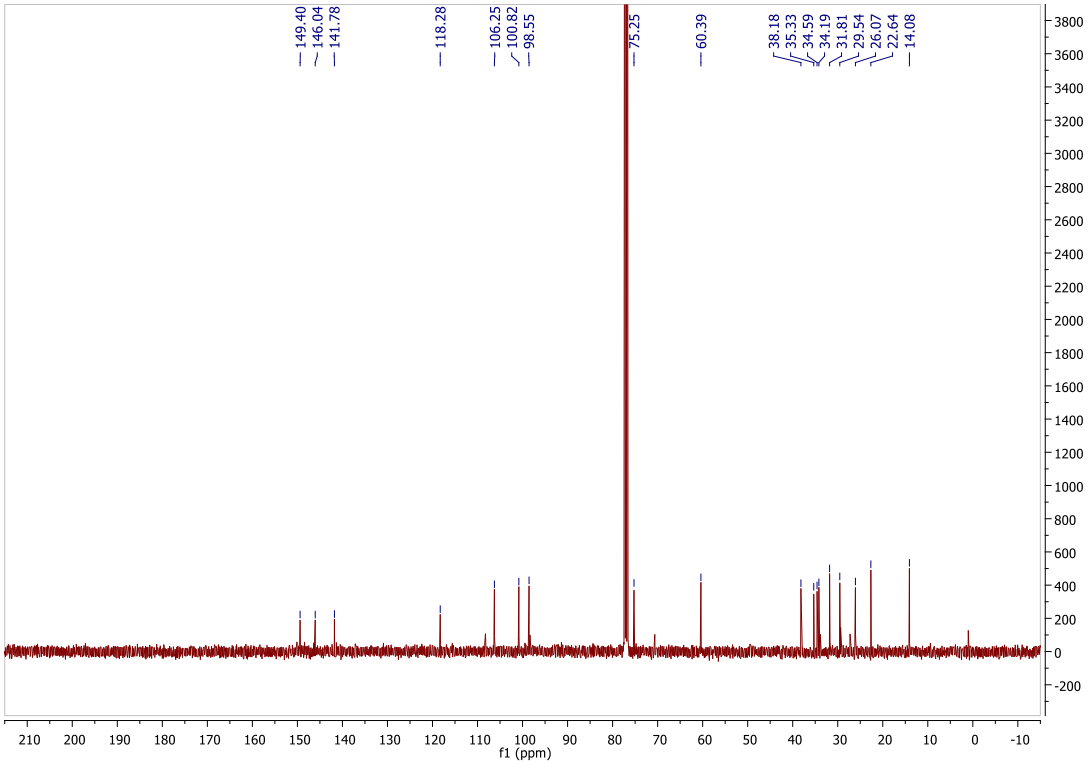
	Retention Time (min)	% Area
1	3.569	29.73
2	3.801	20.89
3	3.963	29.04
4	4.192	20.34



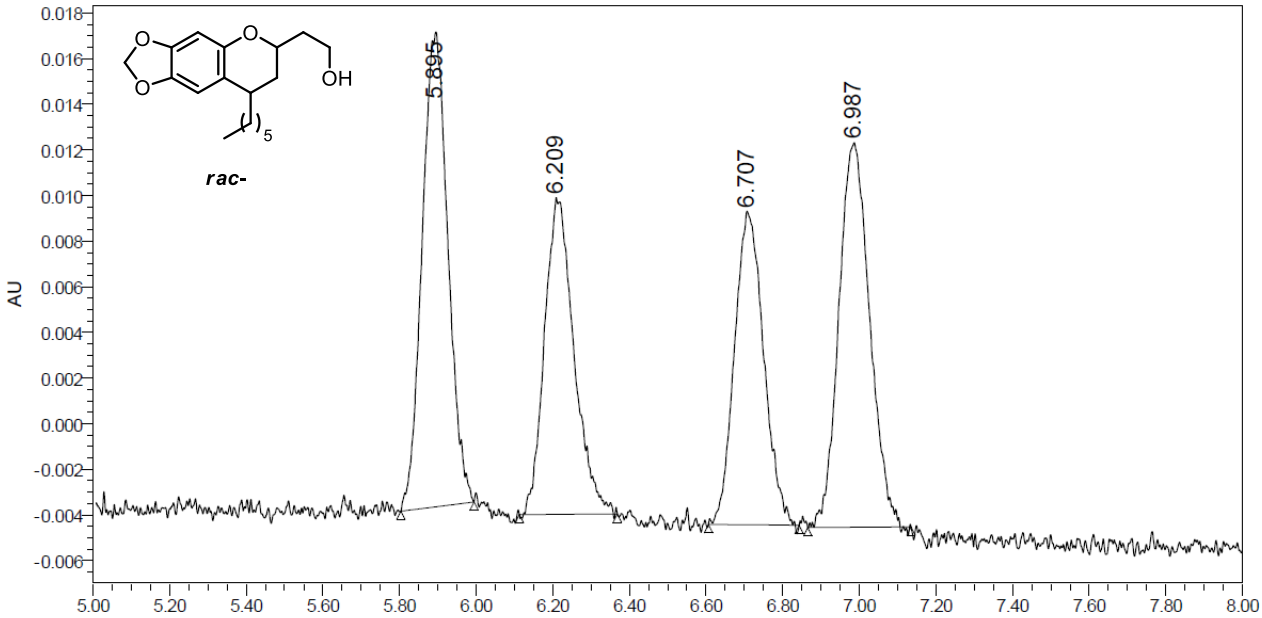
	Retention Time (min)	% Area
1	3.877	99.56
2	4.255	0.44



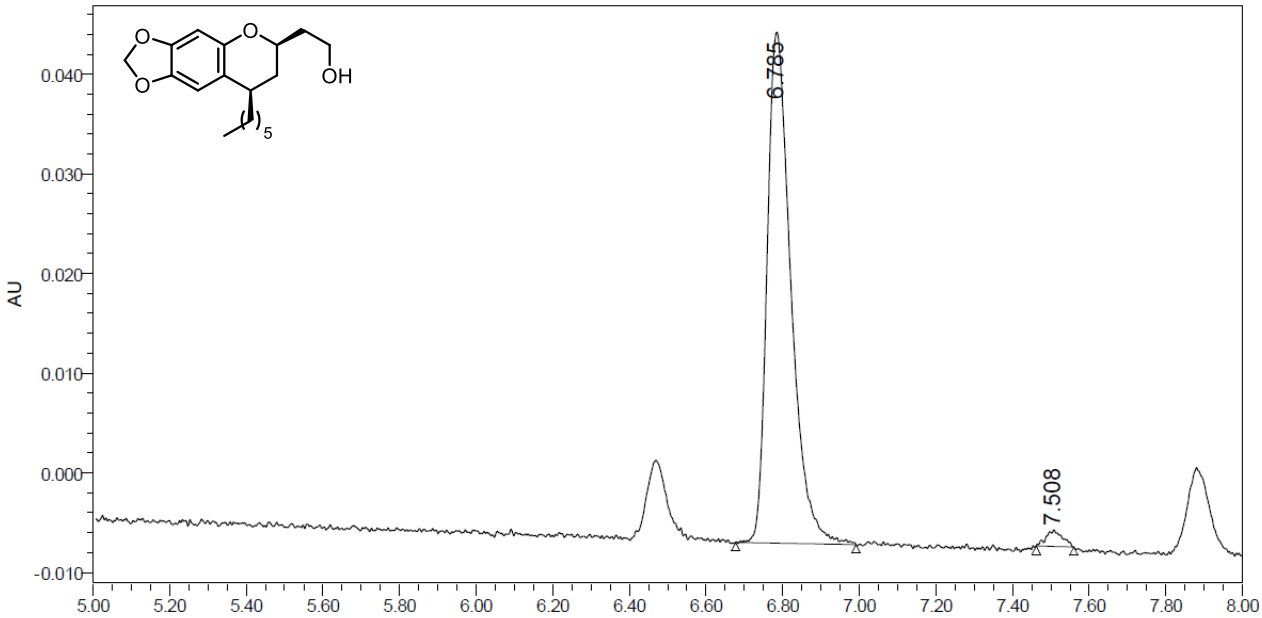
^{1}H NMR spectrum of 3.58a



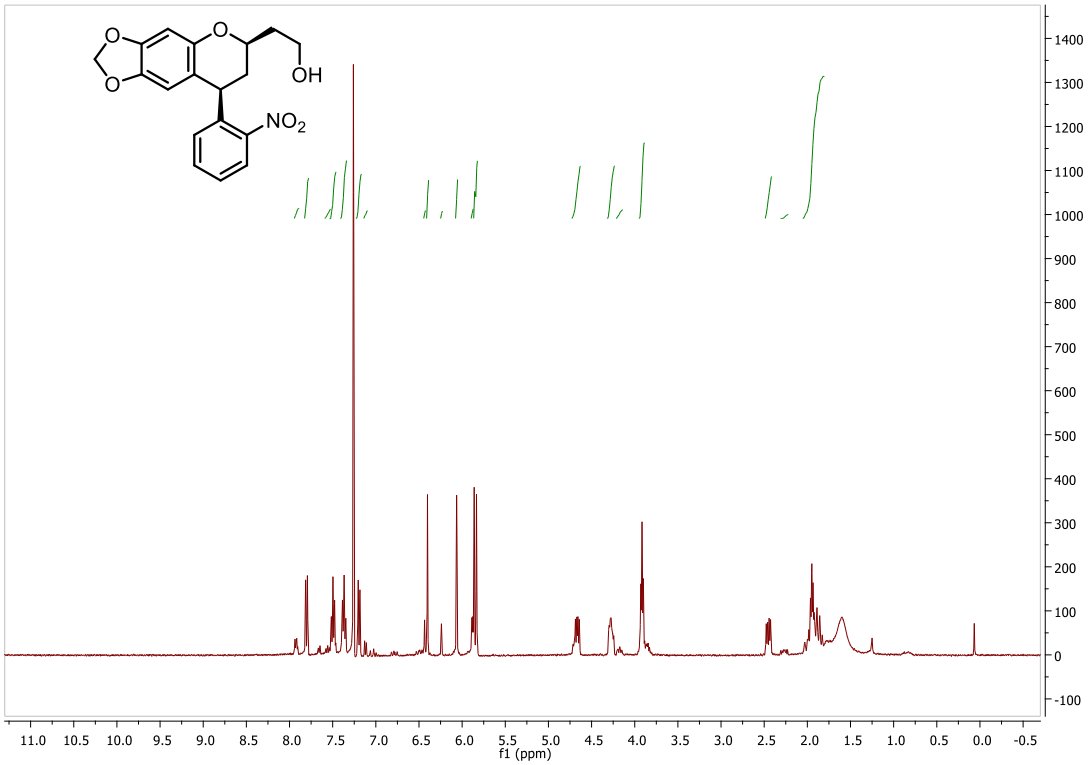
^{13}C NMR spectrum of 3.58a



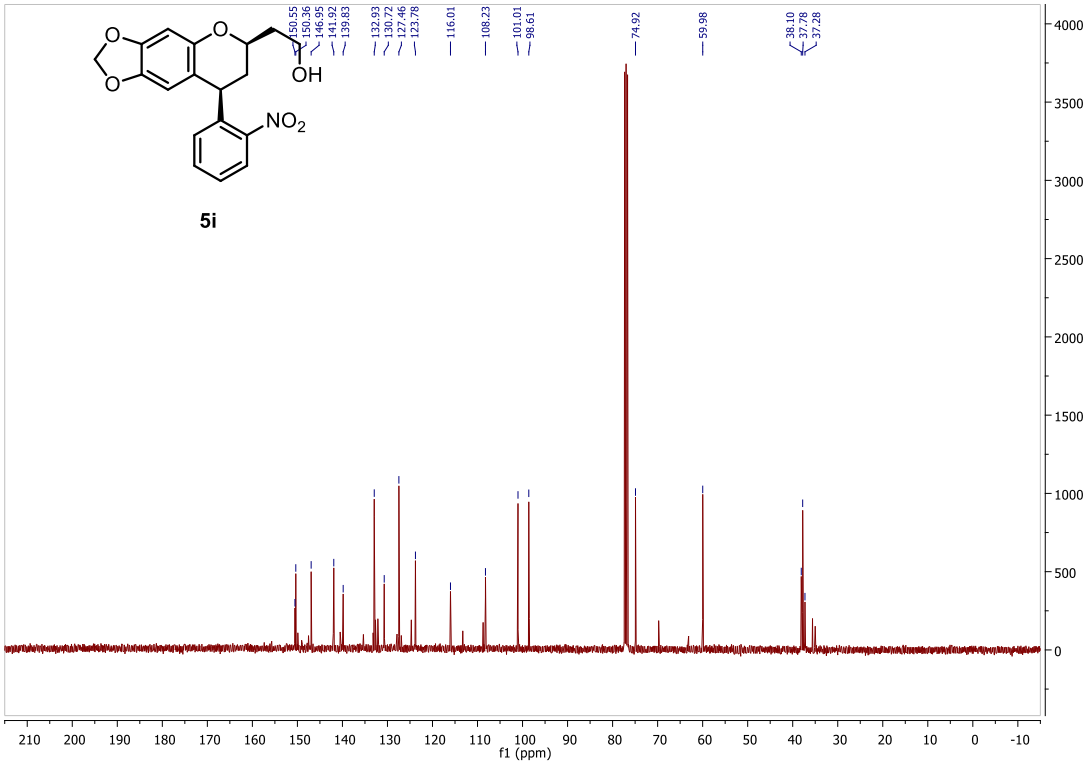
	Retention Time (min)	% Area
1	5.895	28.73
2	6.209	21.90
3	6.707	21.47
4	6.987	27.89



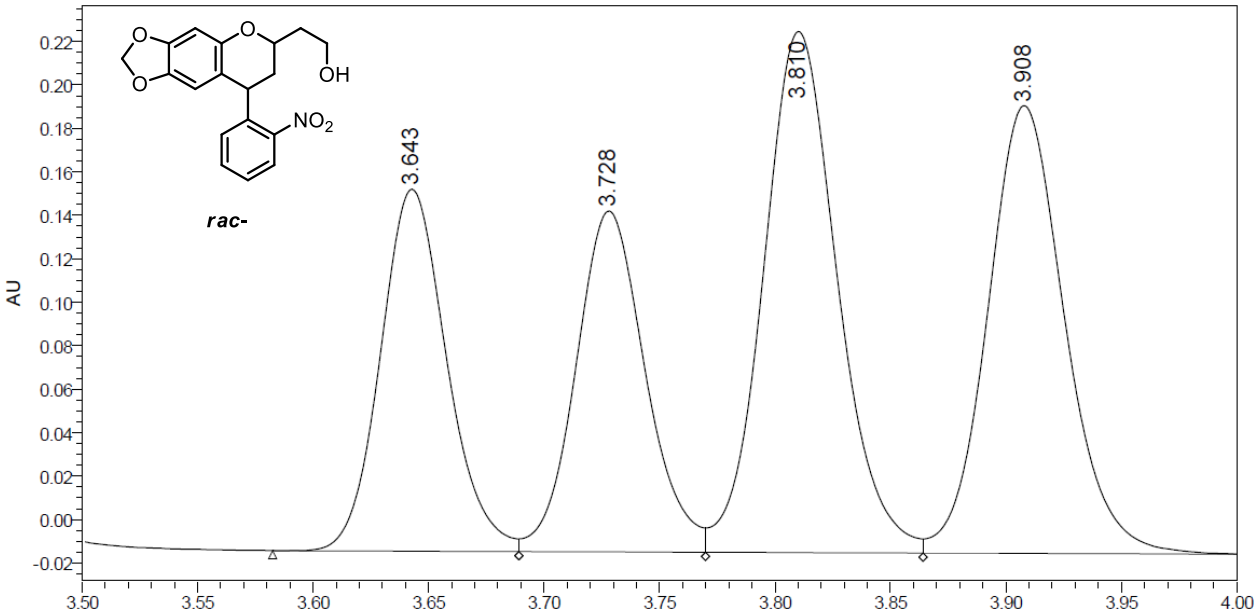
	Retention Time (min)	% Area
1	6.785	97.88
2	7.508	2.12



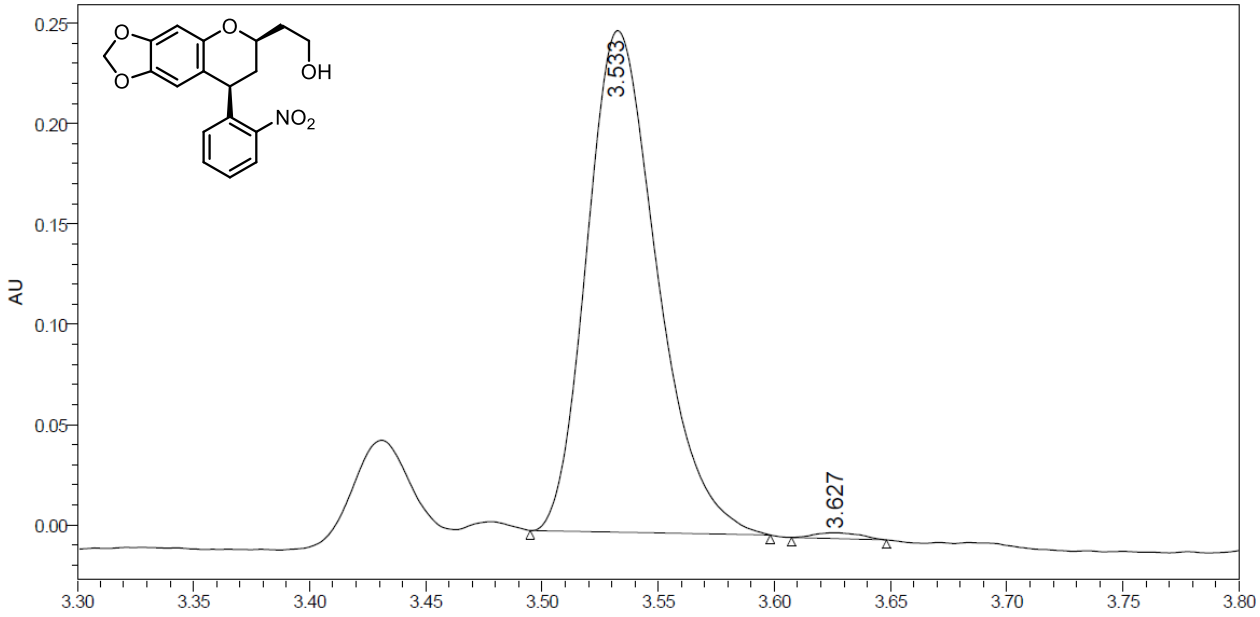
^{1}H NMR spectrum of 3.58i



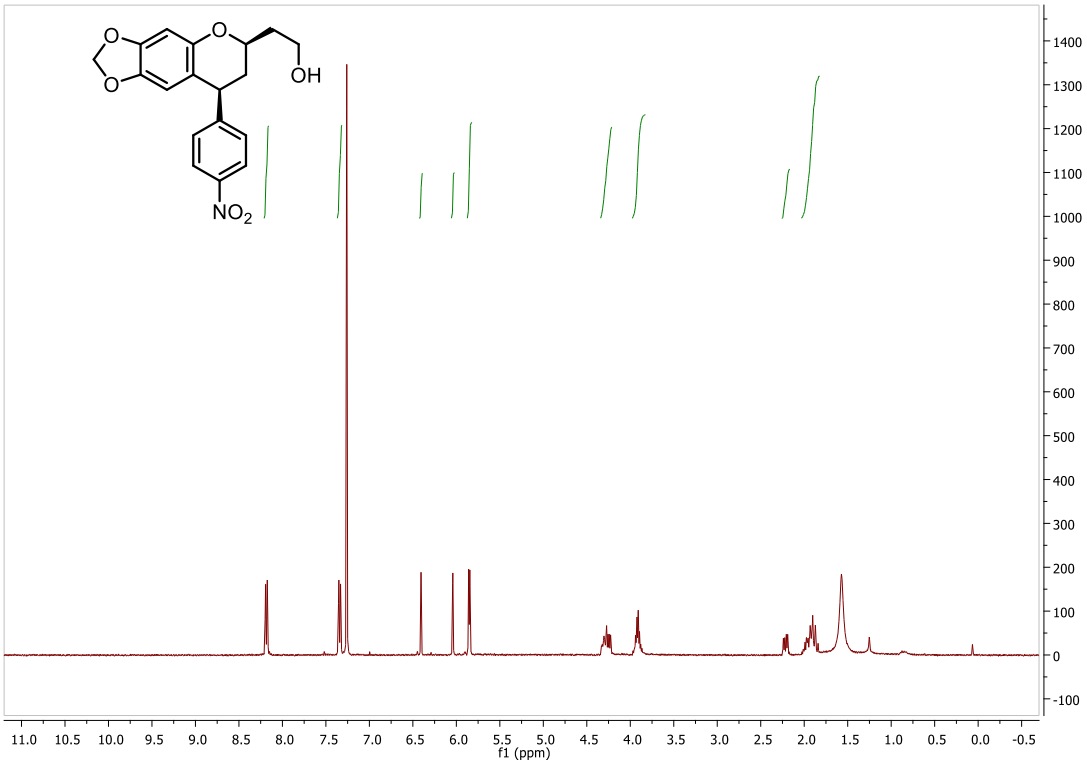
^{13}C NMR spectrum of 3.58i



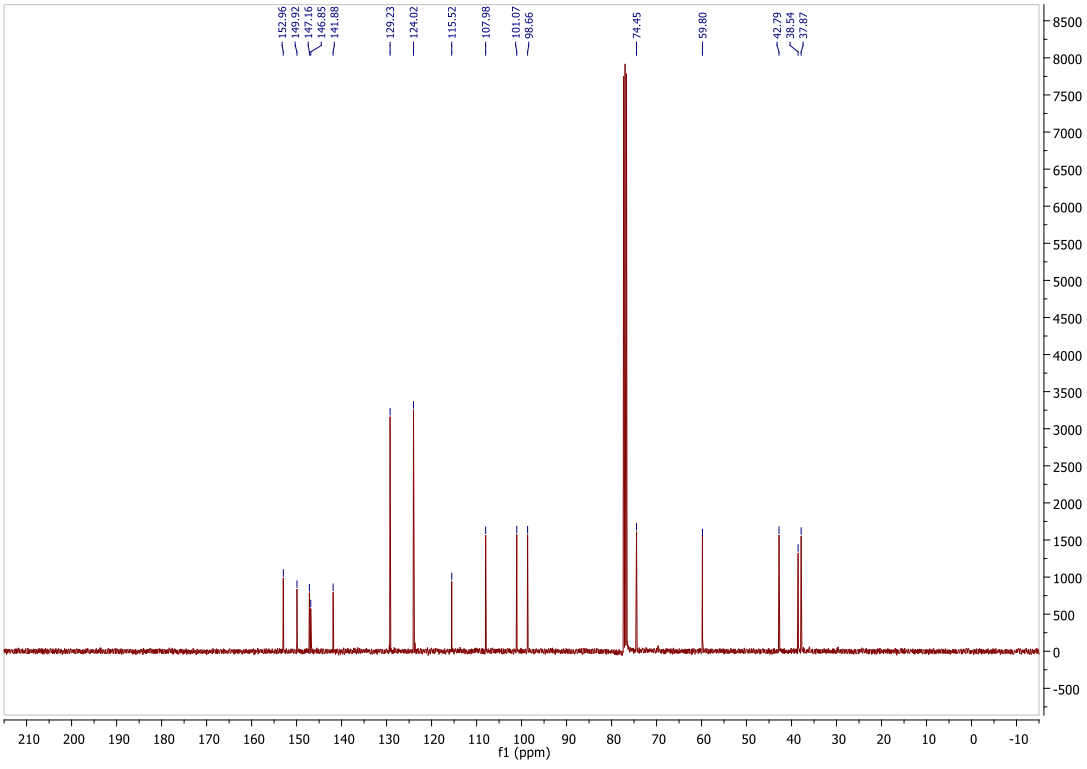
	Retention Time (min)	% Area
1	3.643	19.91
2	3.728	19.63
3	3.810	31.91
4	3.908	28.55



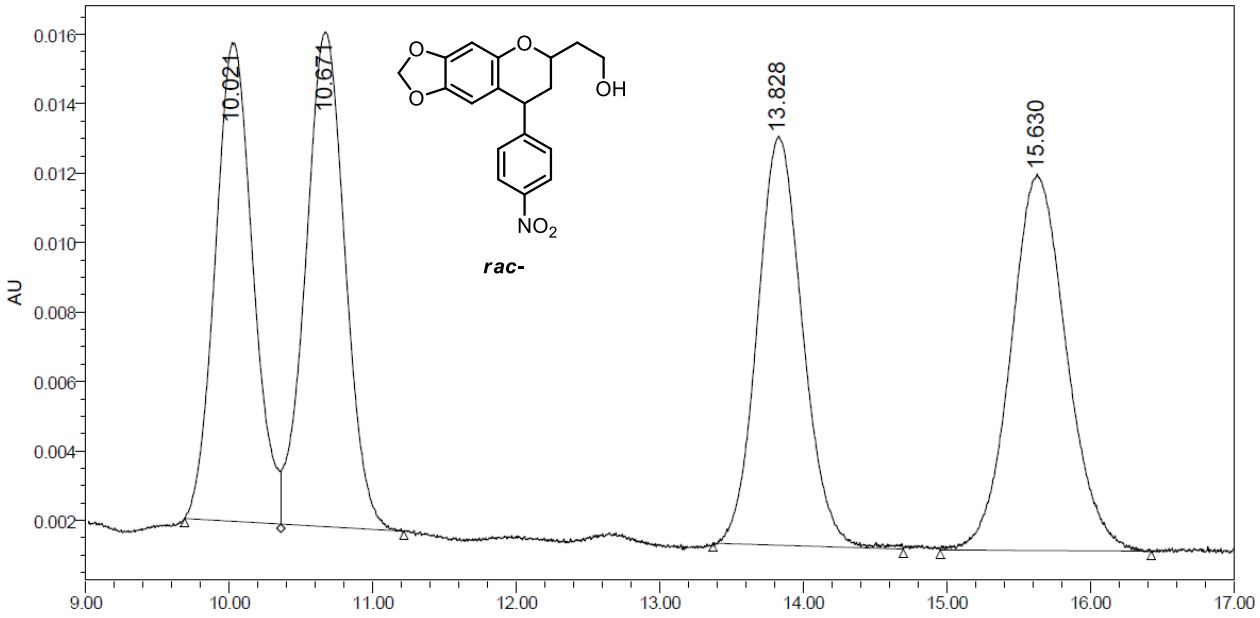
	Retention Time (min)	% Area
1	3.533	99.23
2	3.627	0.77



^{1}H NMR spectrum of 3.58j



^{13}C NMR spectrum of 3.58j



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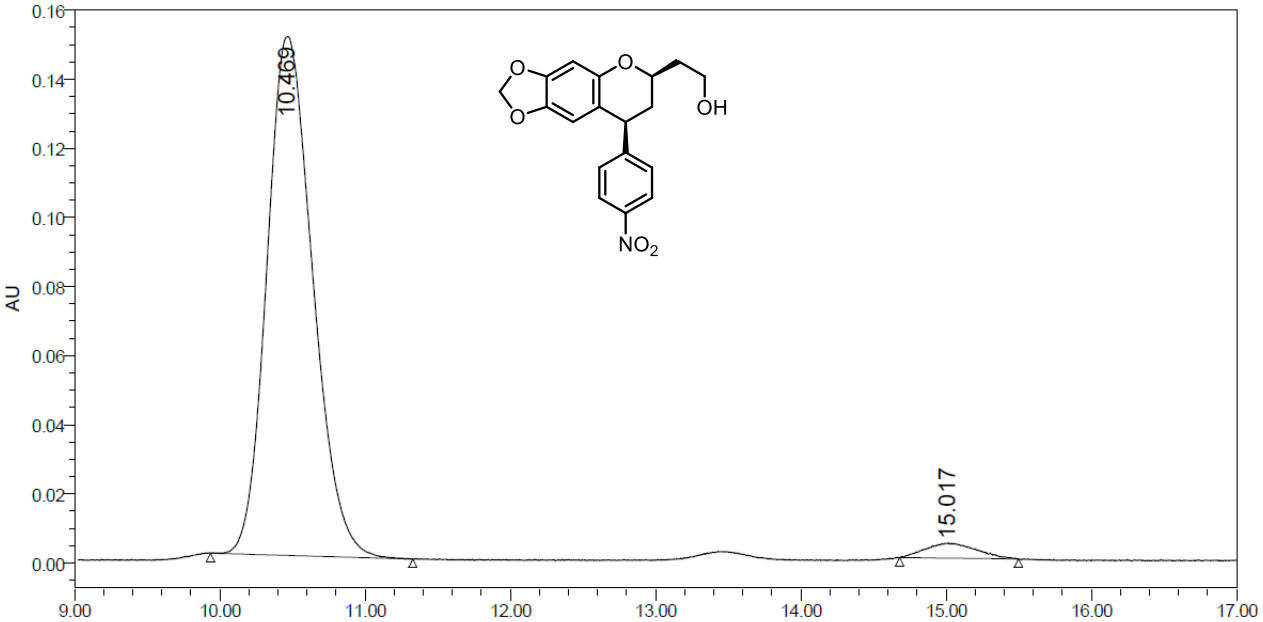
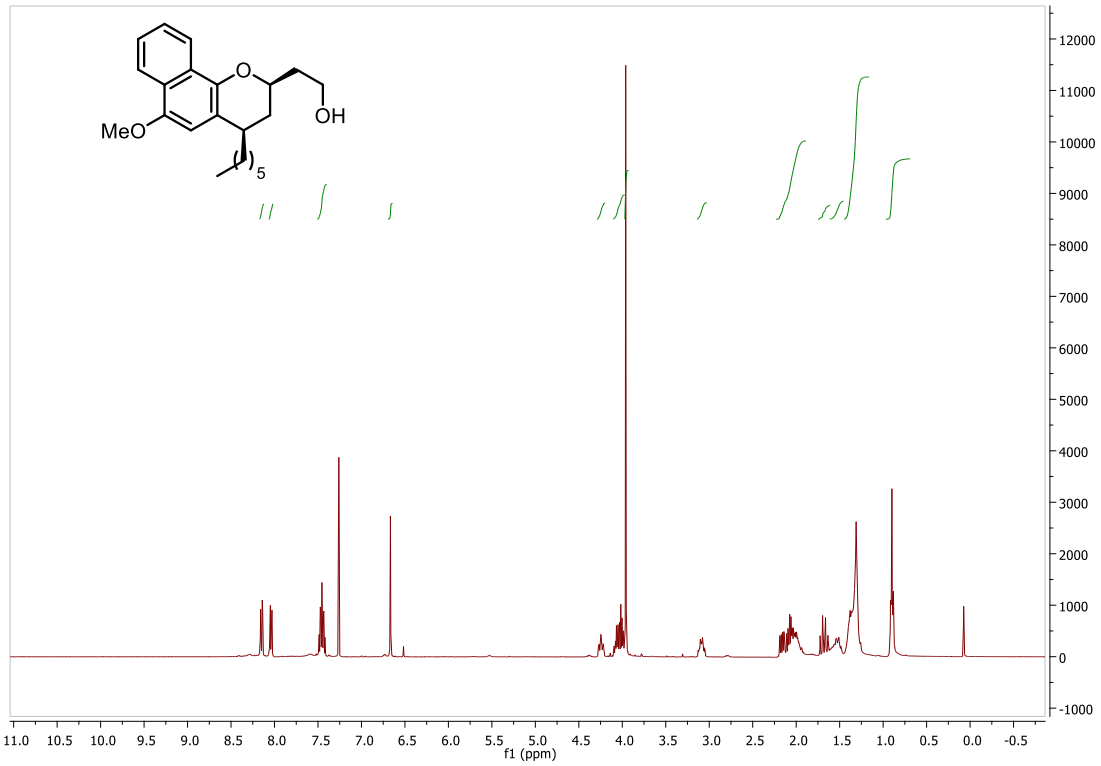
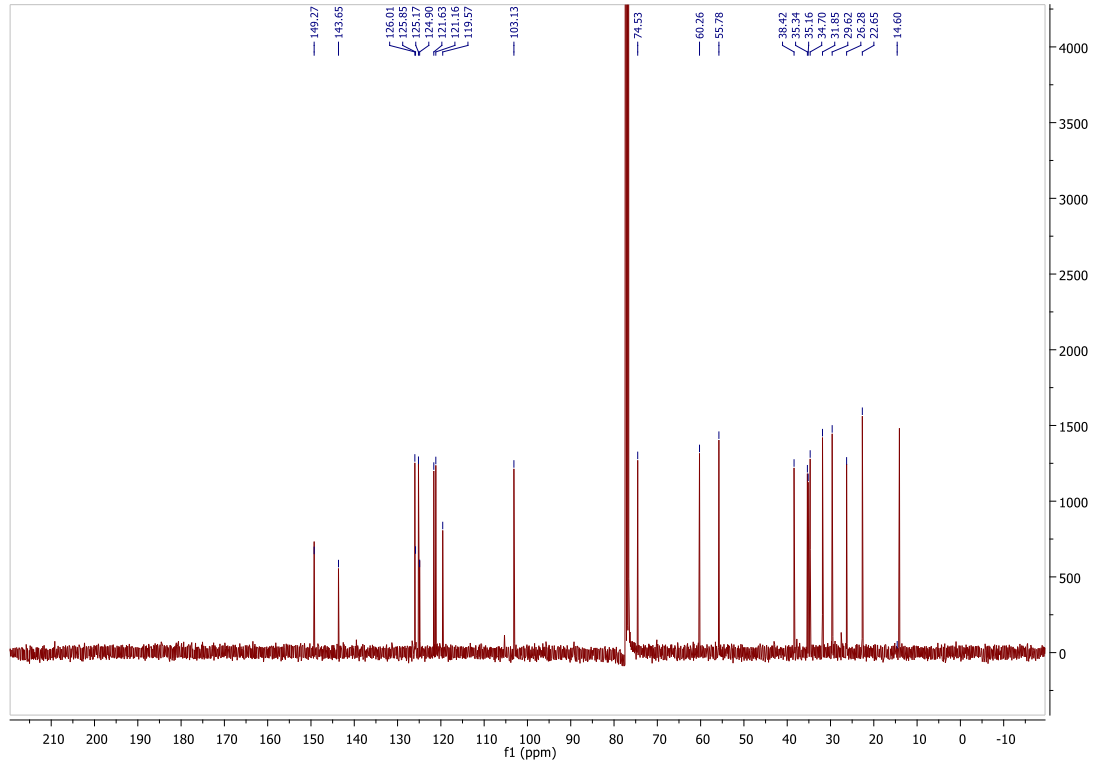
	Retention Time (min)	% Area
1	10.021	23.44
2	10.671	25.39
3	13.828	23.99
4	15.630	27.18



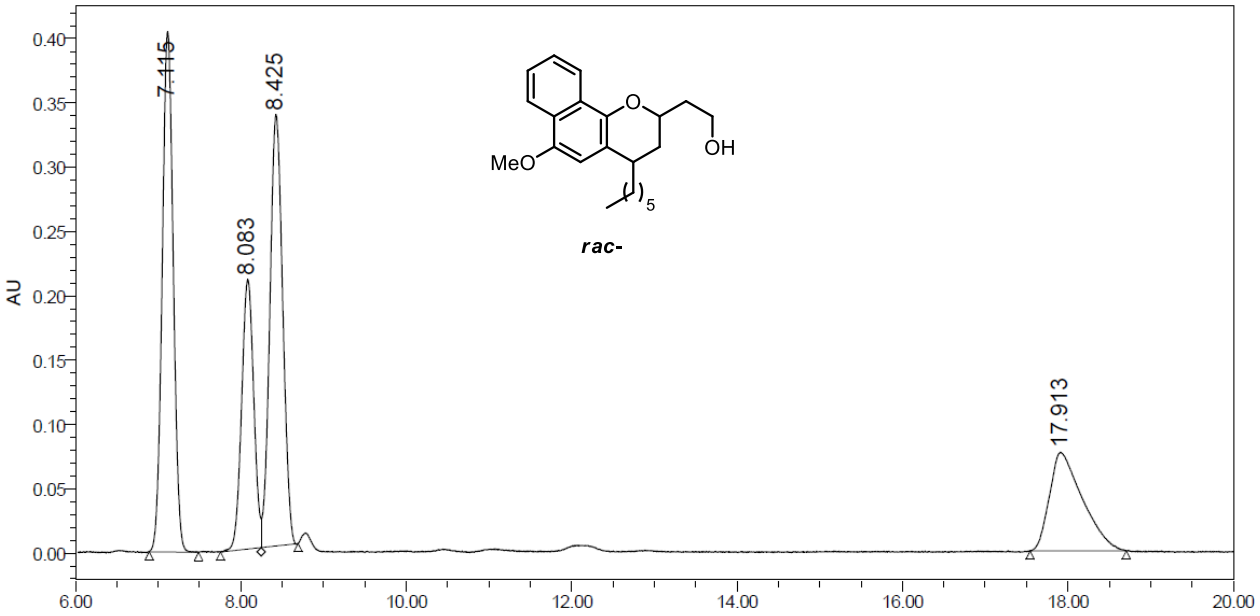
	Retention Time (min)	% Area
1	10.469	96.89
2	15.017	3.11



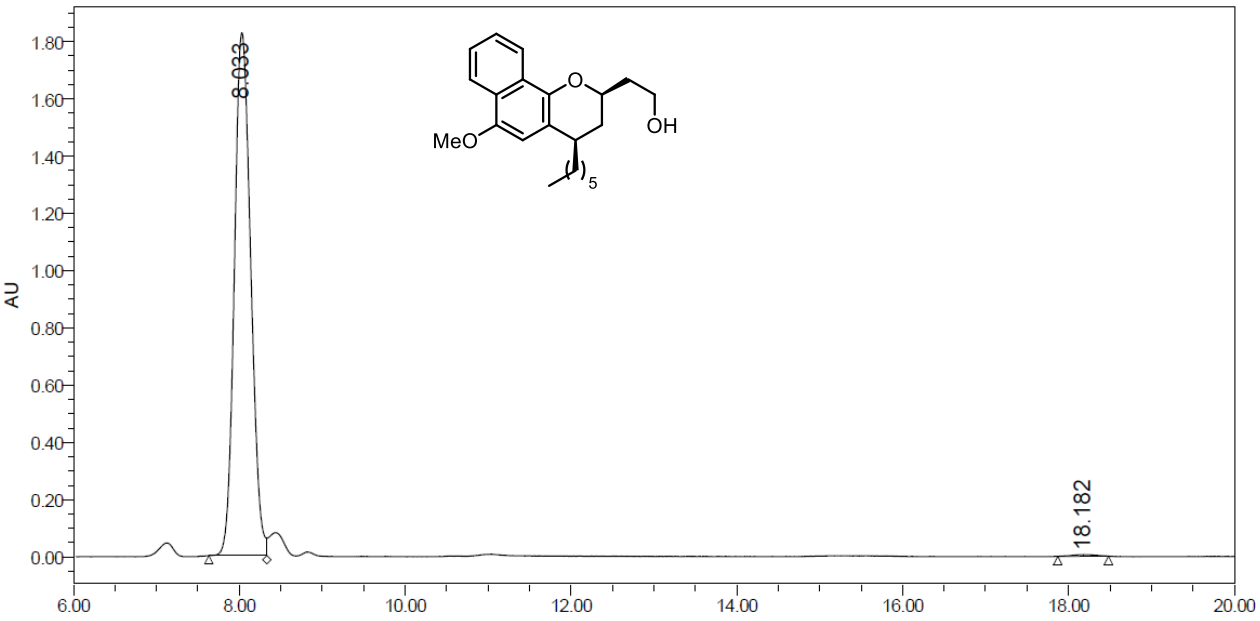
^{1}H NMR spectrum of 3.58k



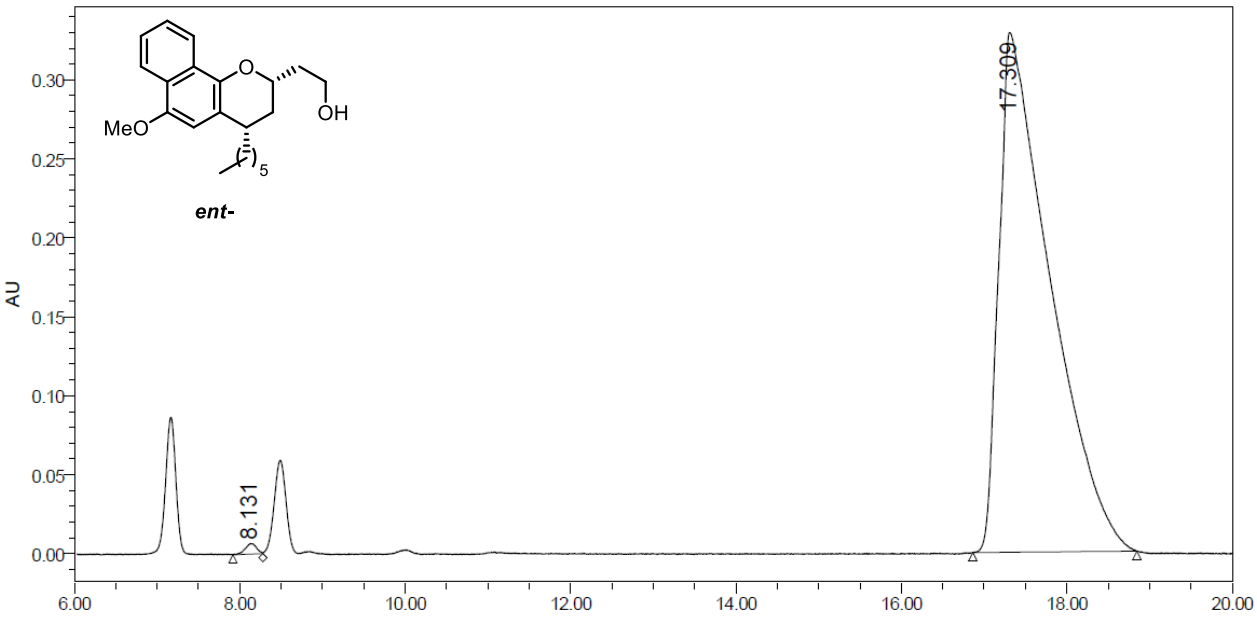
^{13}C NMR spectrum of 3.58k



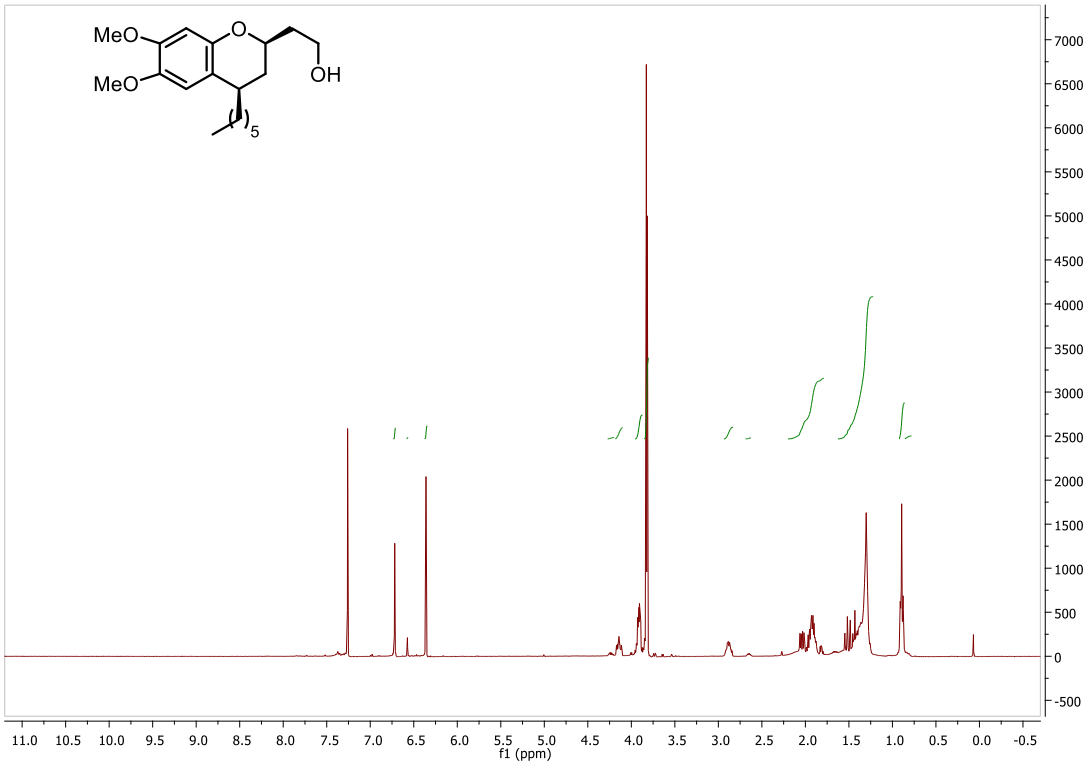
	Retention Time (min)	% Area
1	7.115	32.30
2	8.083	18.32
3	8.425	31.21
4	17.913	18.17



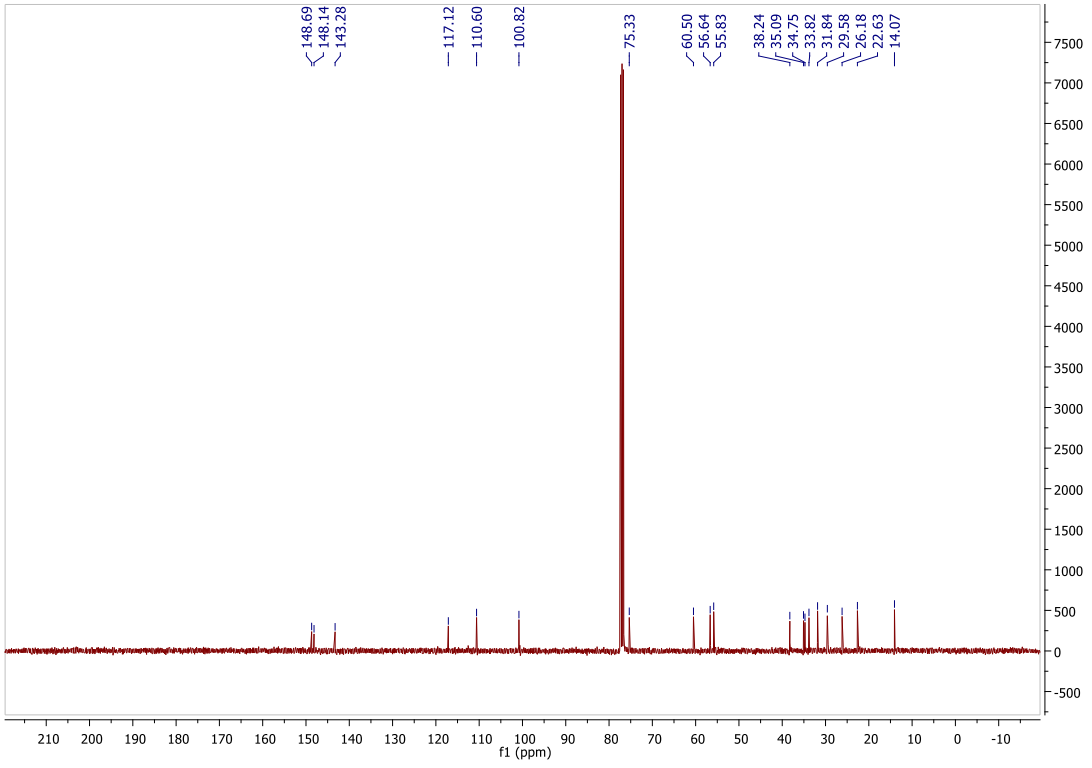
	Retention Time (min)	% Area
1	8.033	99.56
2	18.182	0.44



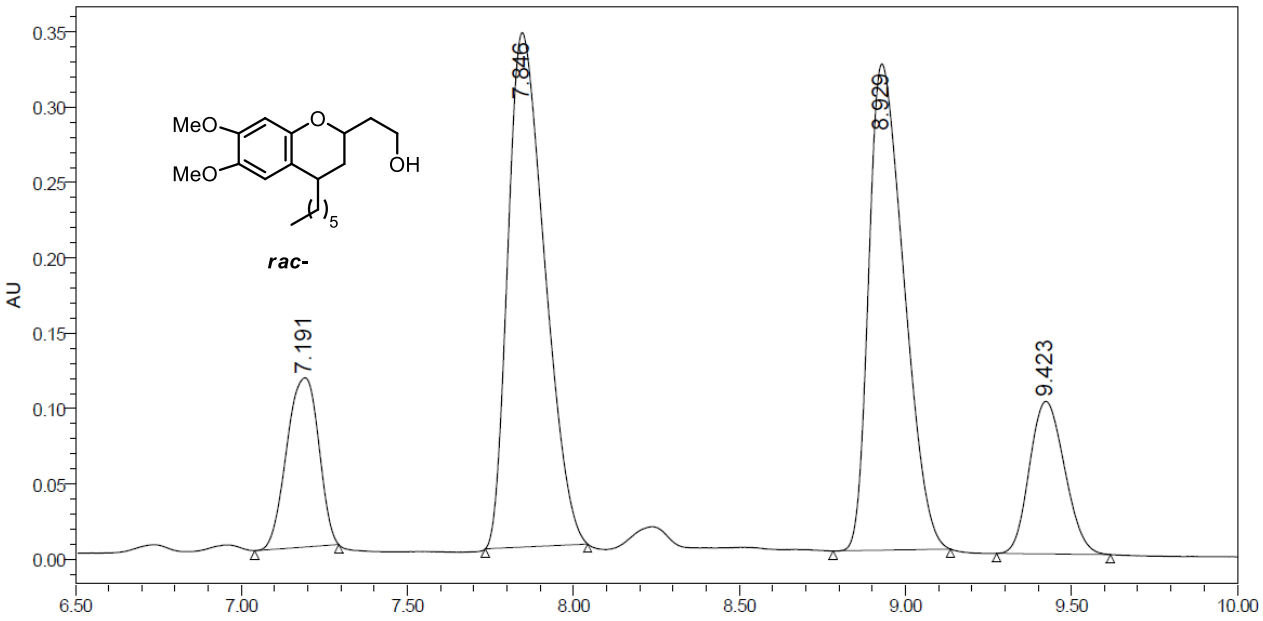
	Retention Time (min)	% Area
1	8.131	0.44
2	17.309	99.56



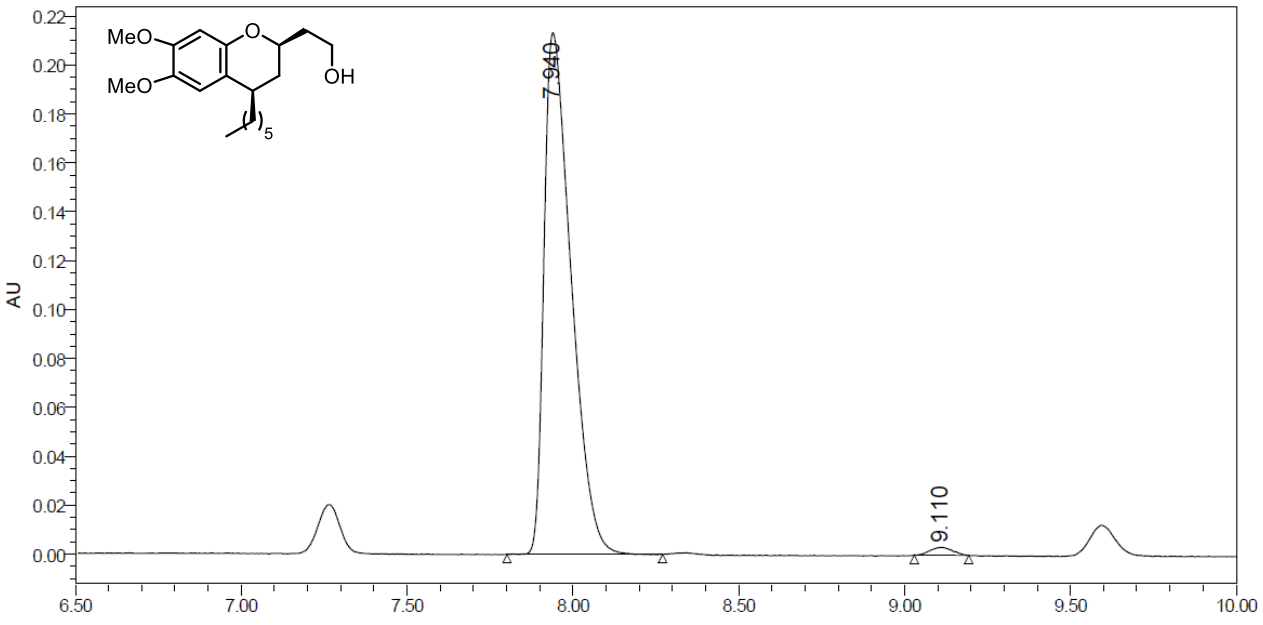
^{1}H NMR spectrum of 3.58l



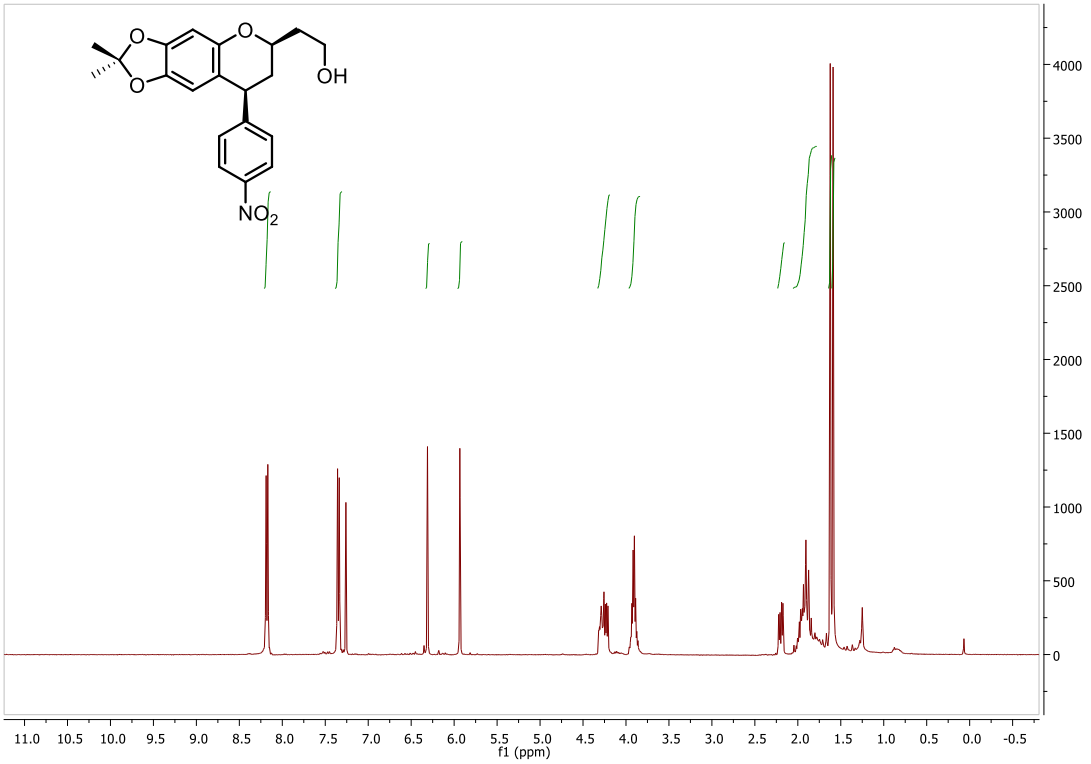
^{13}C NMR spectrum of 3.58l



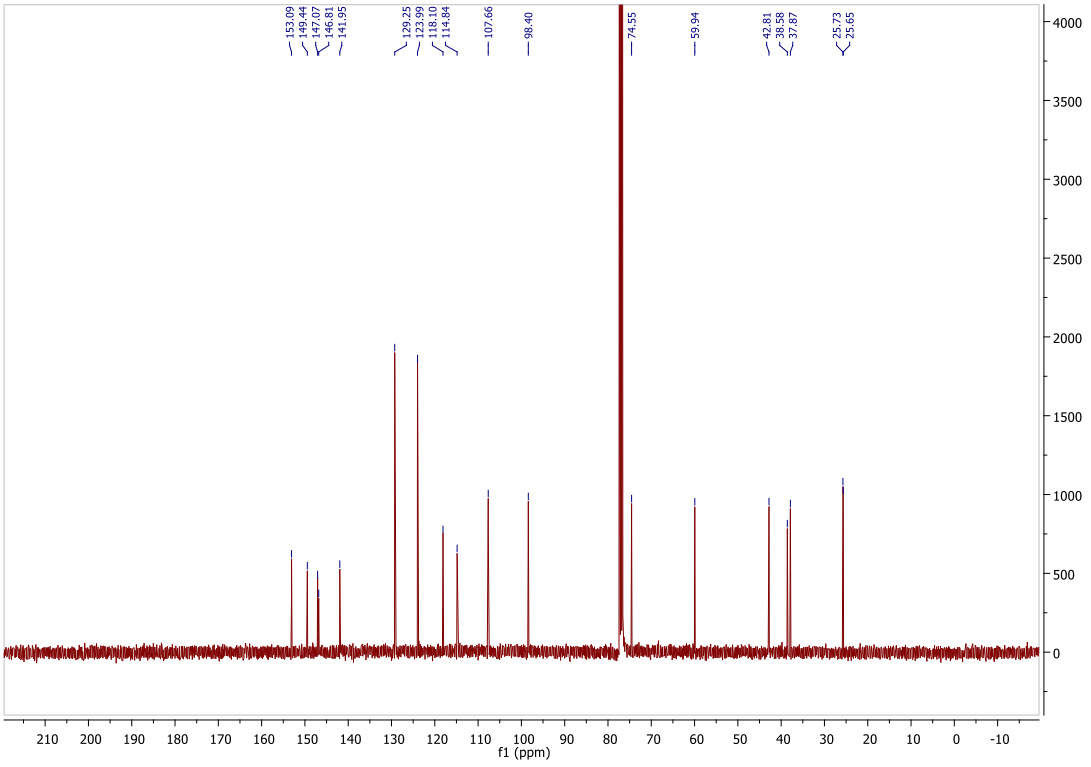
	Retention Time (min)	% Area
1	7.191	11.58
2	7.846	40.43
3	8.929	36.54
4	9.423	11.45



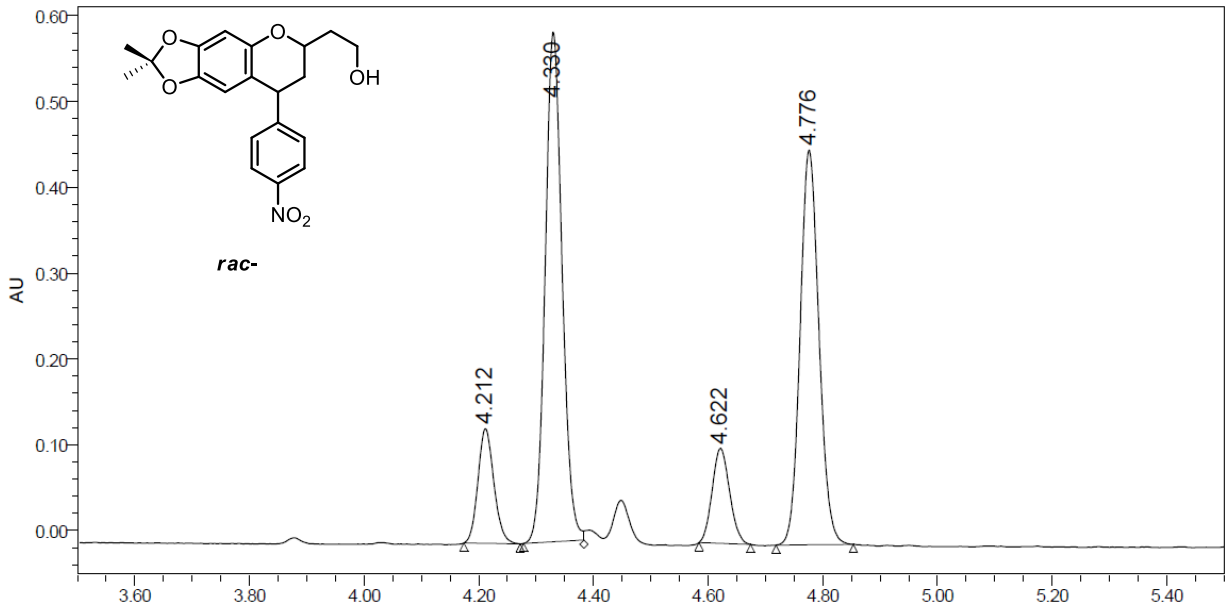
	Retention Time (min)	% Area
1	7.940	98.79
2	9.110	1.21



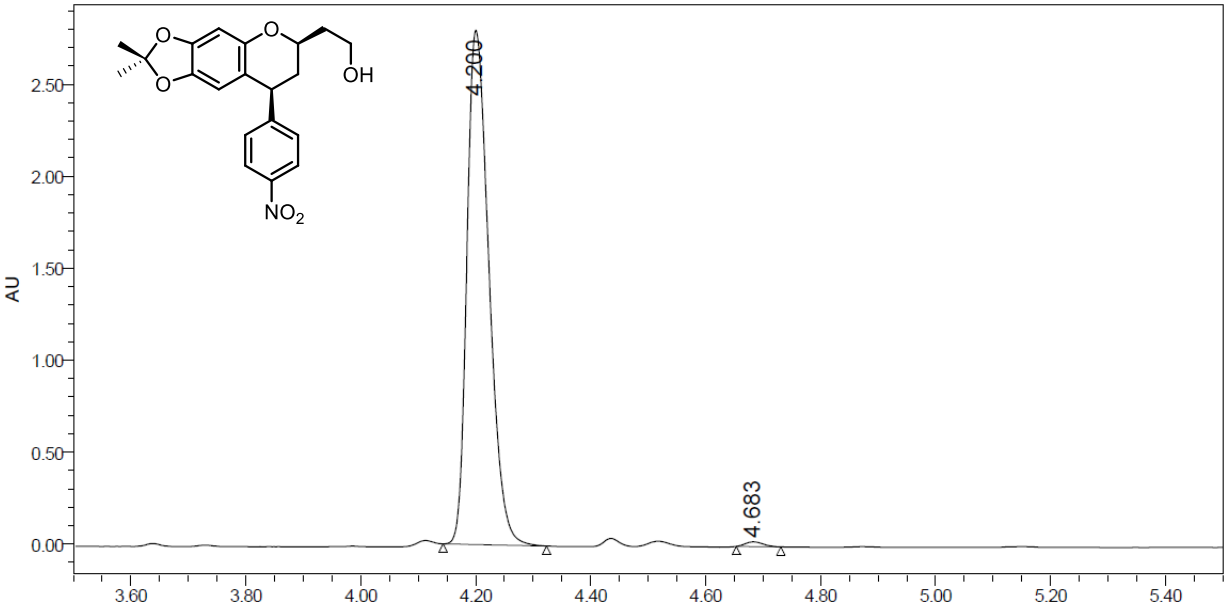
^{1}H NMR spectrum of 3.58m



^{13}C NMR spectrum of 3.58m



	Retention Time (min)	% Area
1	4.212	9.35
2	4.330	44.16
3	4.622	8.48
4	4.776	38.01



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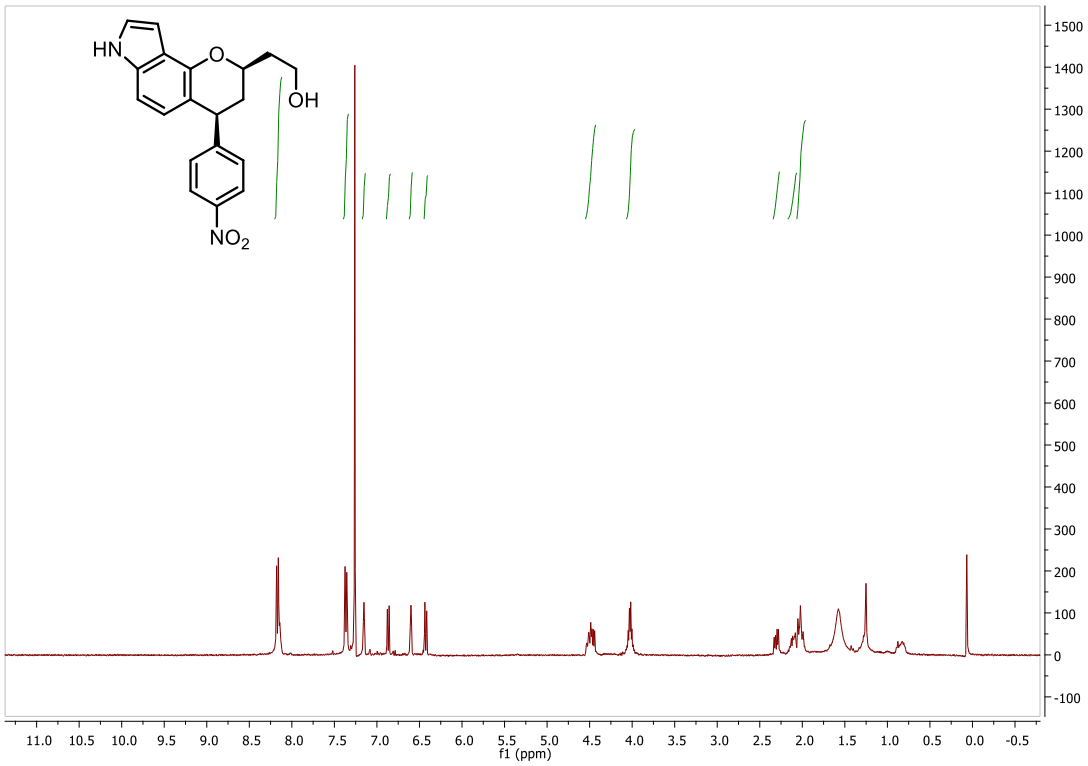
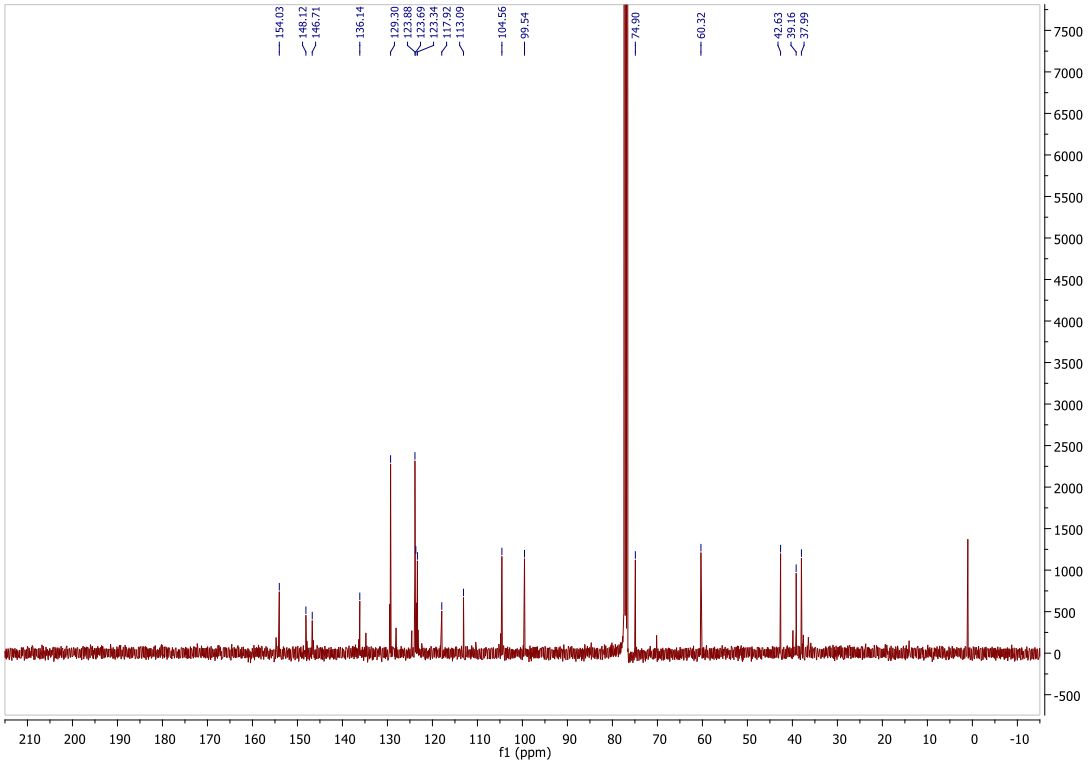
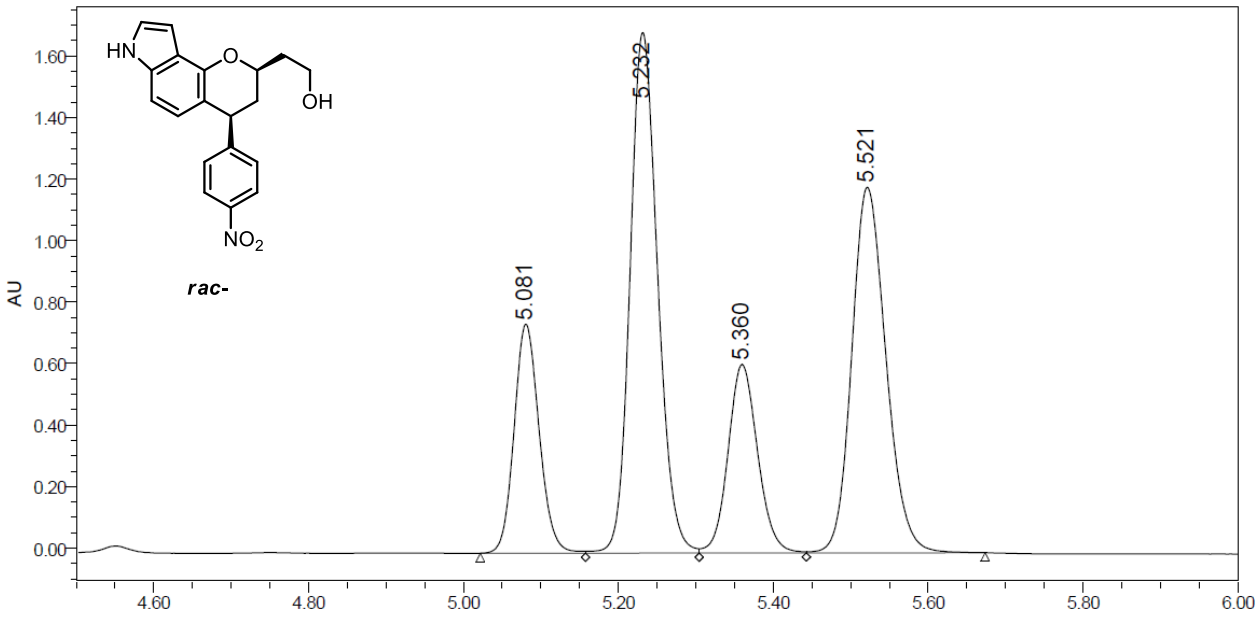


^{1}H NMR spectrum of 3.58n



^{13}C NMR spectrum of 3.58n



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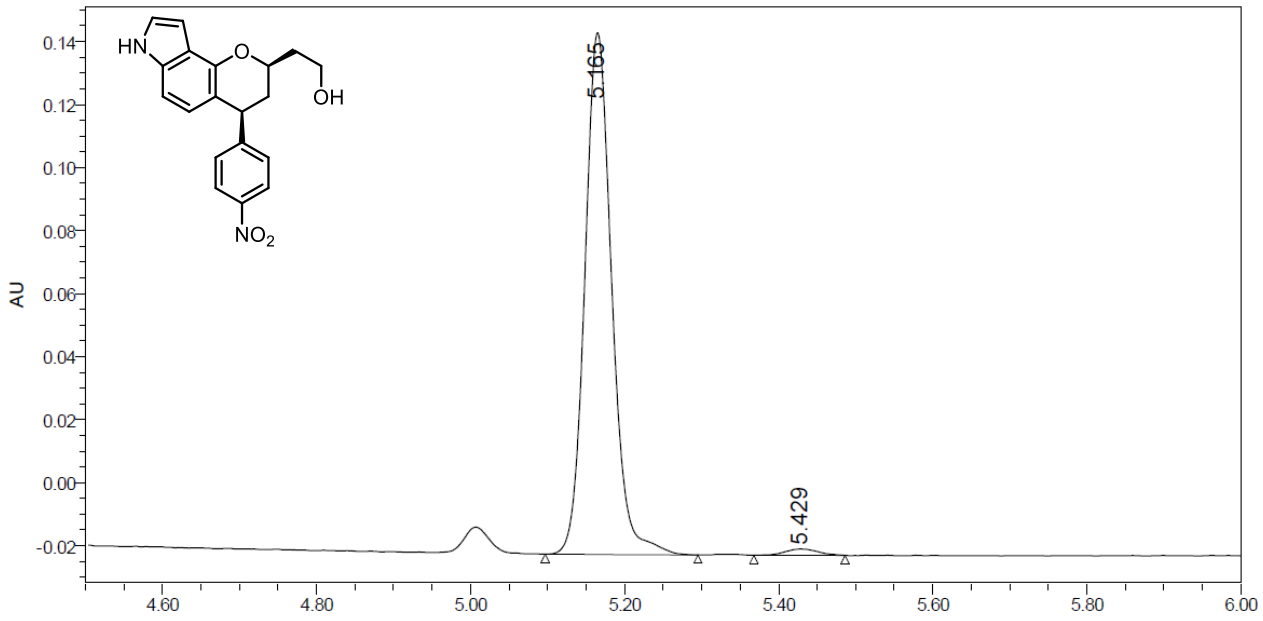
1	5.081	15.06
2	5.232	37.56
3	5.360	14.62
4	5.521	32.76



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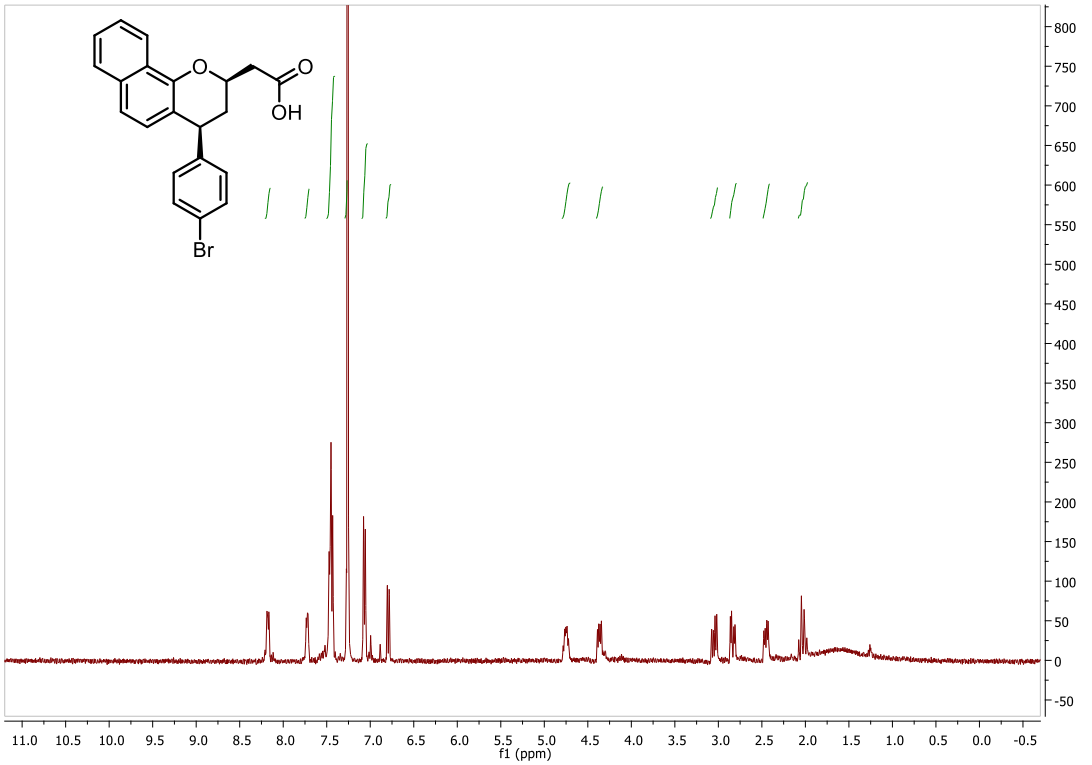
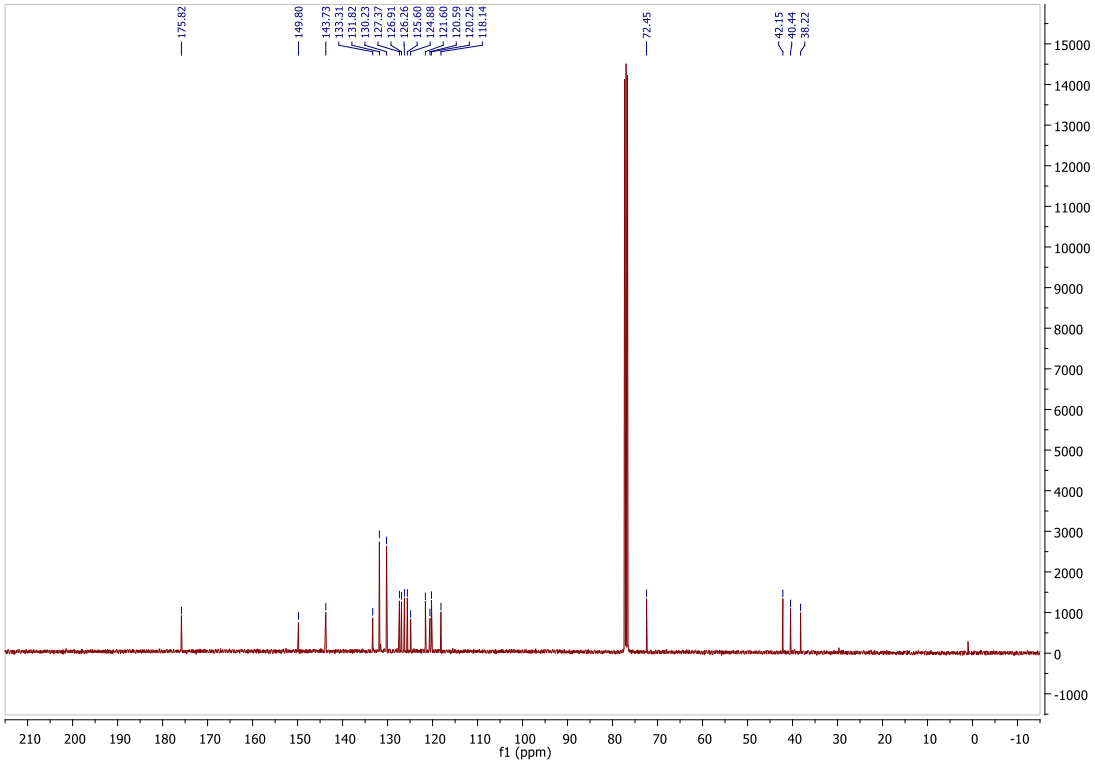
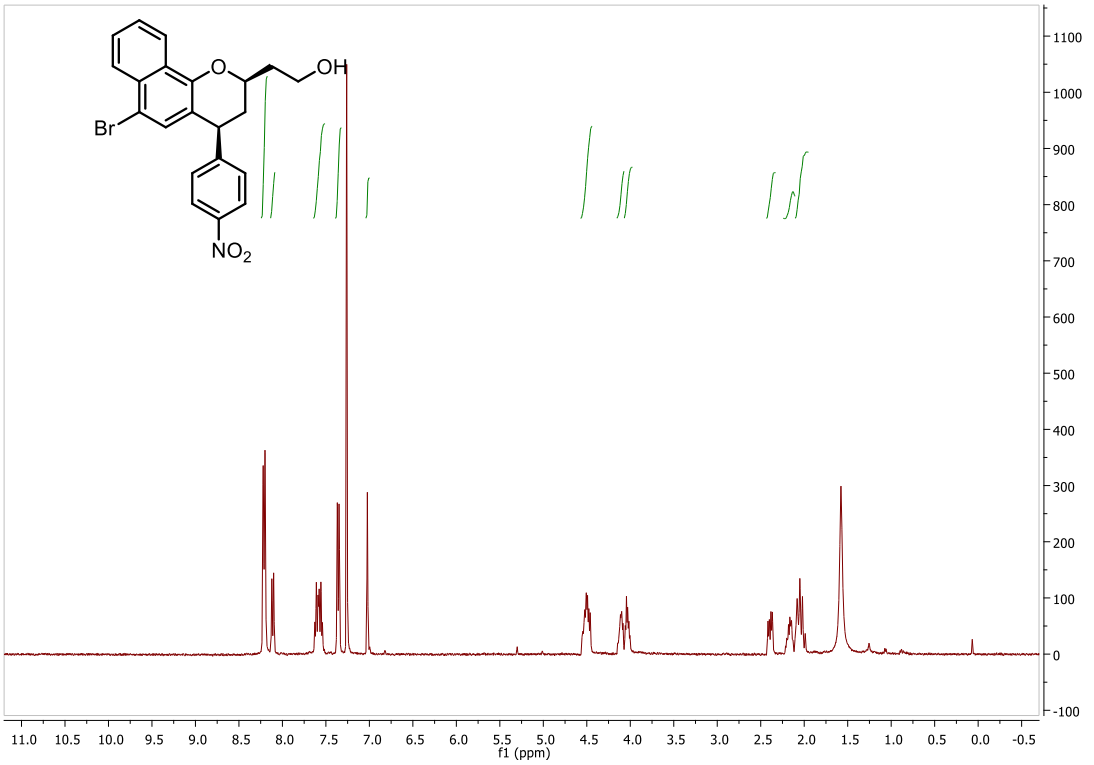
2	5.429	1.47



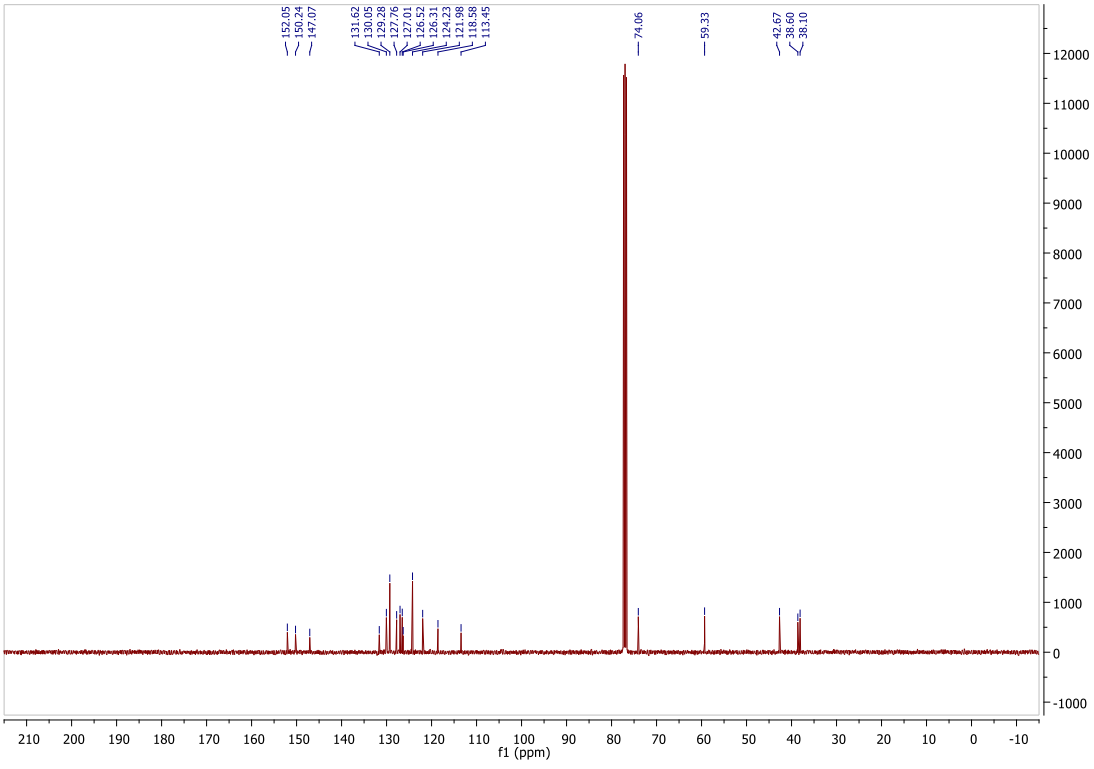
^{1}H NMR spectrum of 3.58g-II



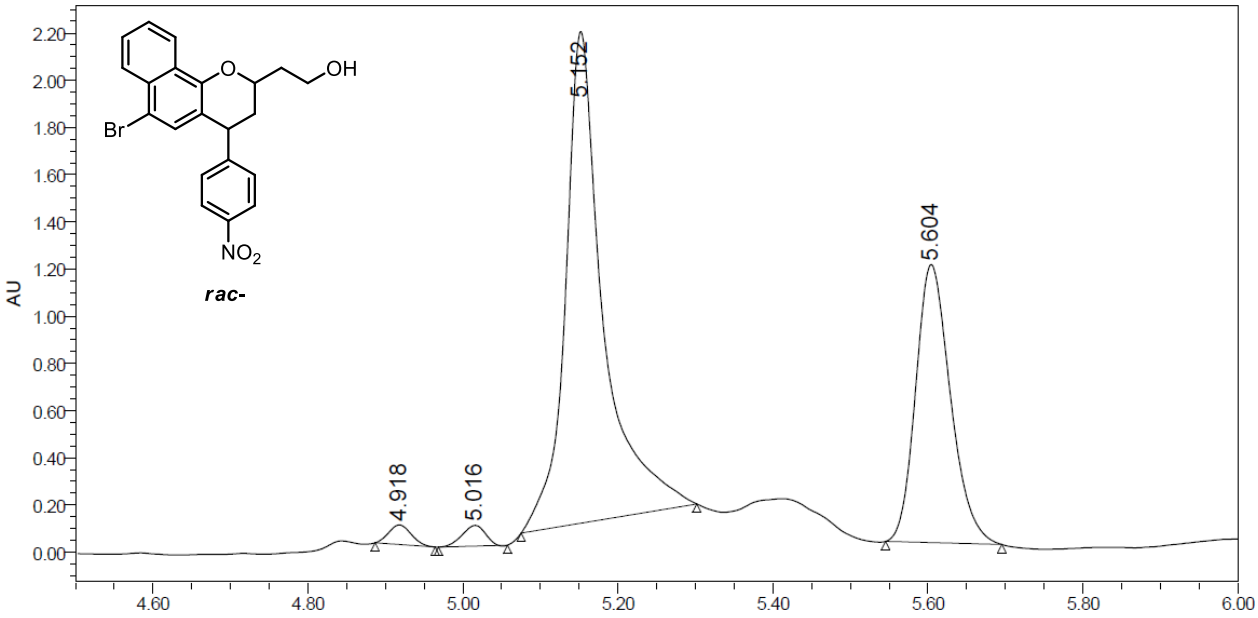
^{13}C NMR spectrum of 3.58g-II



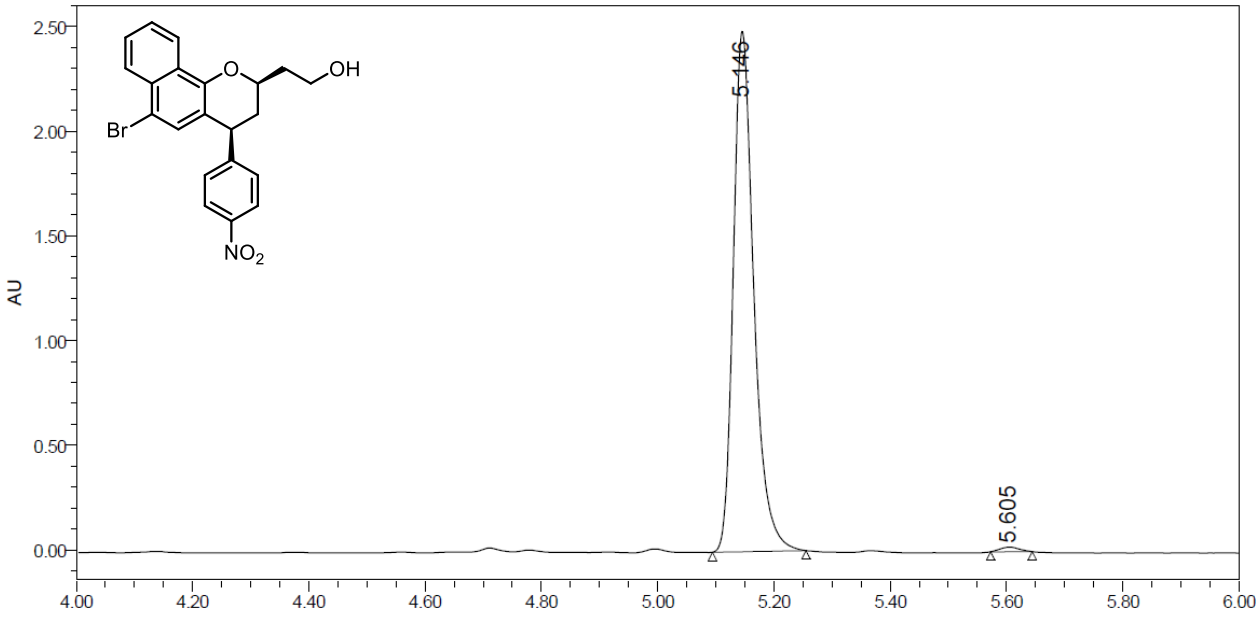
^{1}H NMR spectrum of 3.59



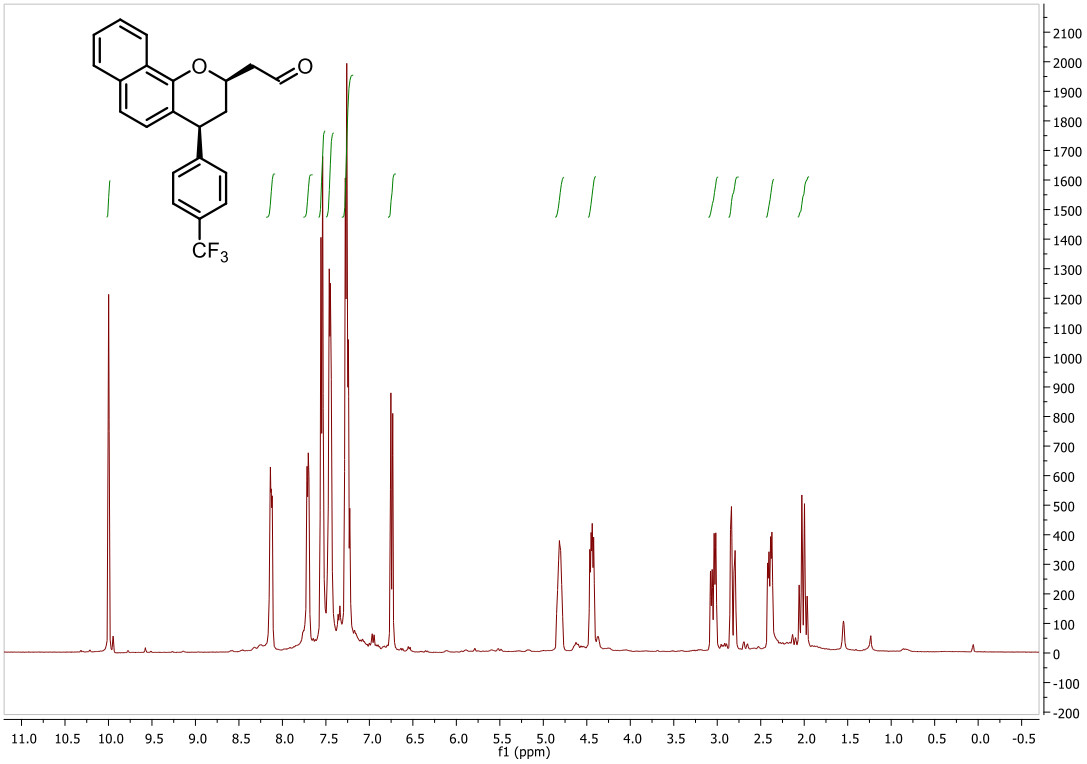
^{13}C NMR spectrum of 3.59



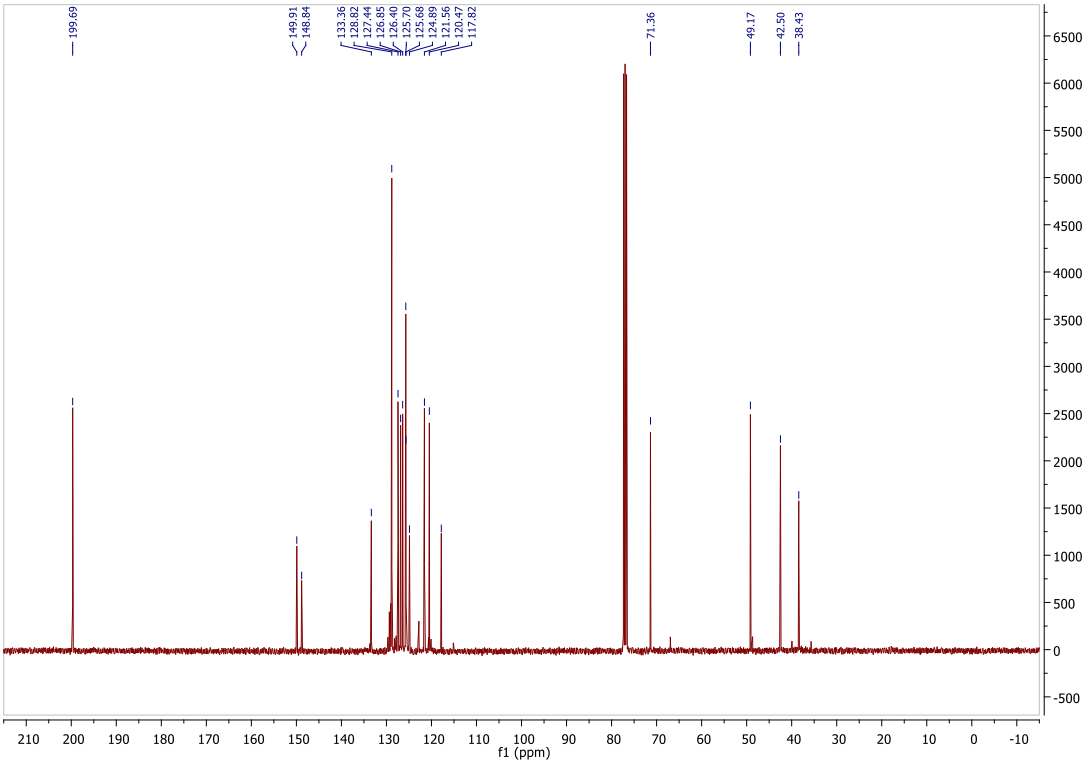
	Retention Time (min)	% Area
1	4.918	1.50
2	5.016	1.65
3	5.152	63.71
4	5.604	33.14



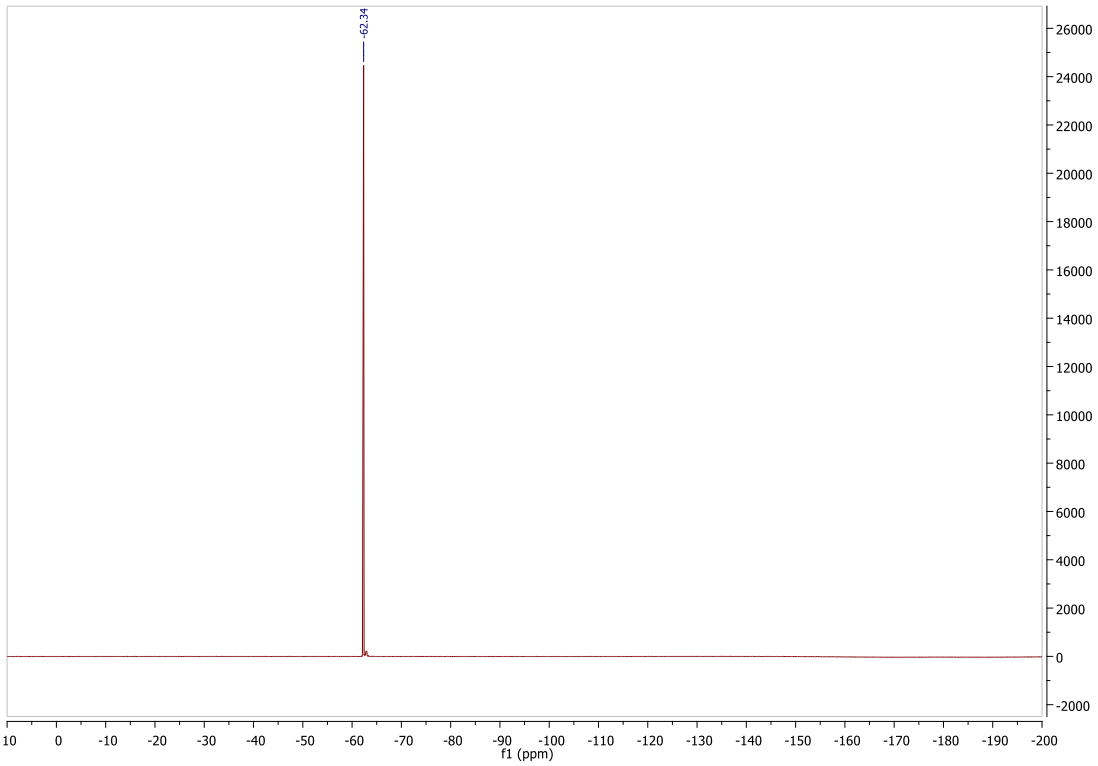
	Retention Time (min)	% Area
1	5.146	99.19
2	5.605	0.81



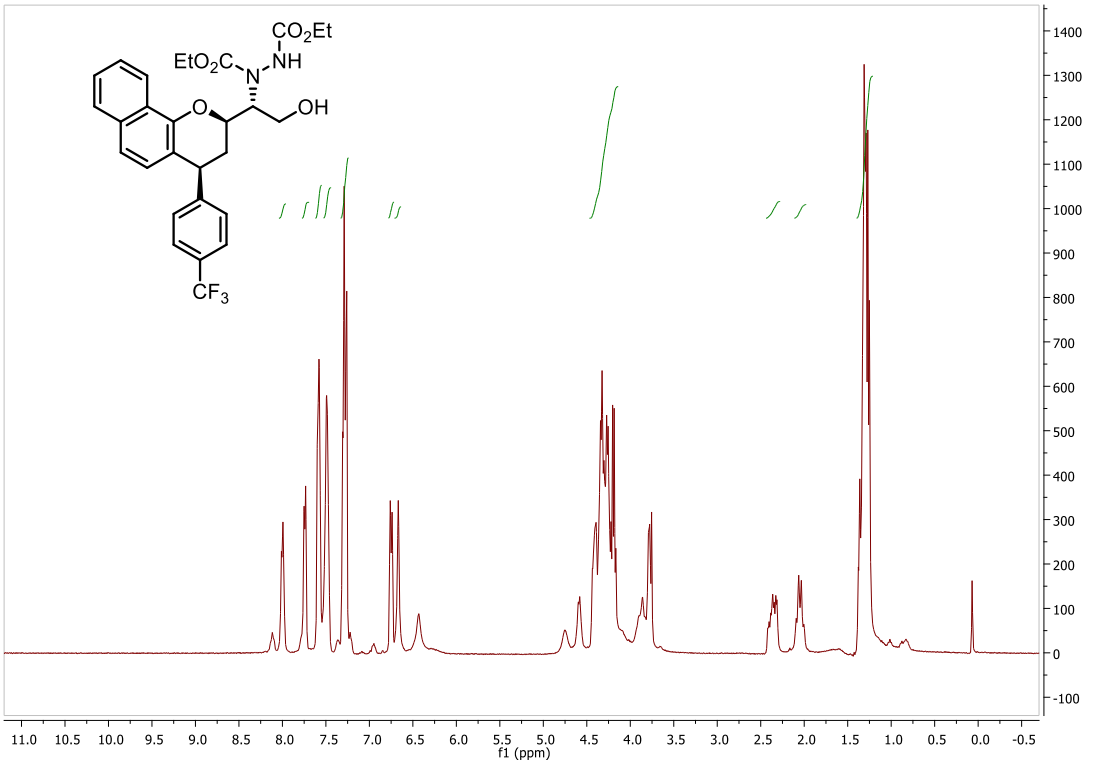
^{1}H NMR spectrum of 3.58h-I



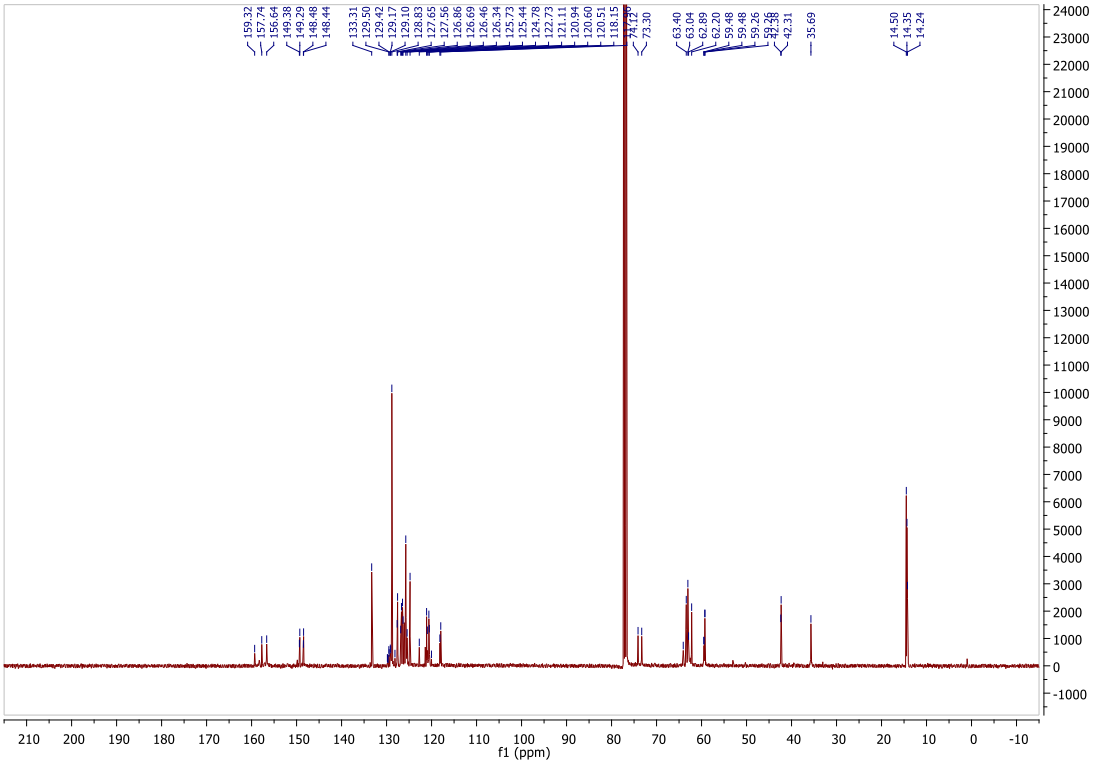
^{13}C NMR spectrum of 3.58h-I



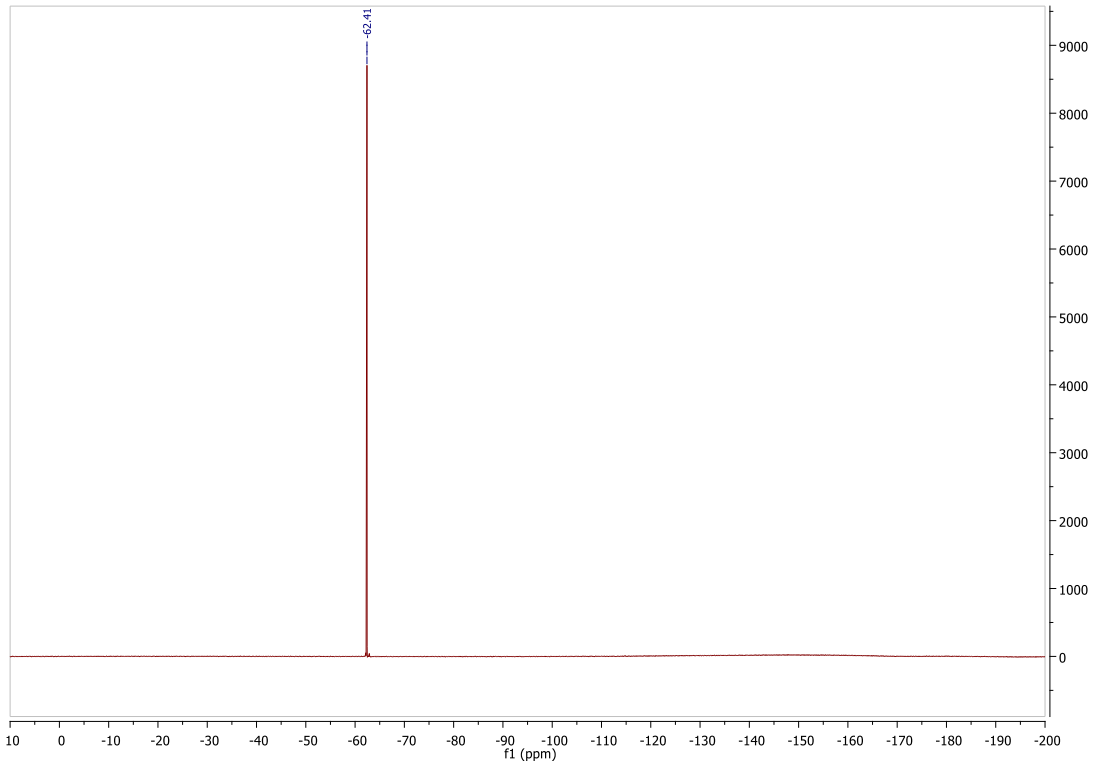
^{19}F NMR spectrum of 3.58h-I



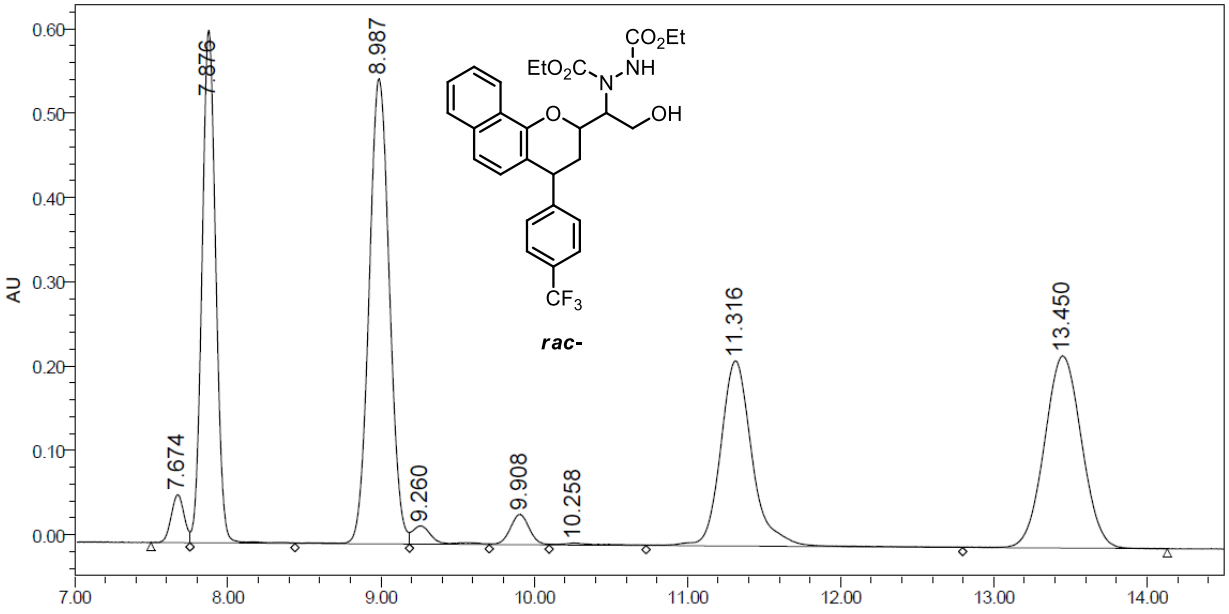
^{1}H NMR spectrum of 3.60a



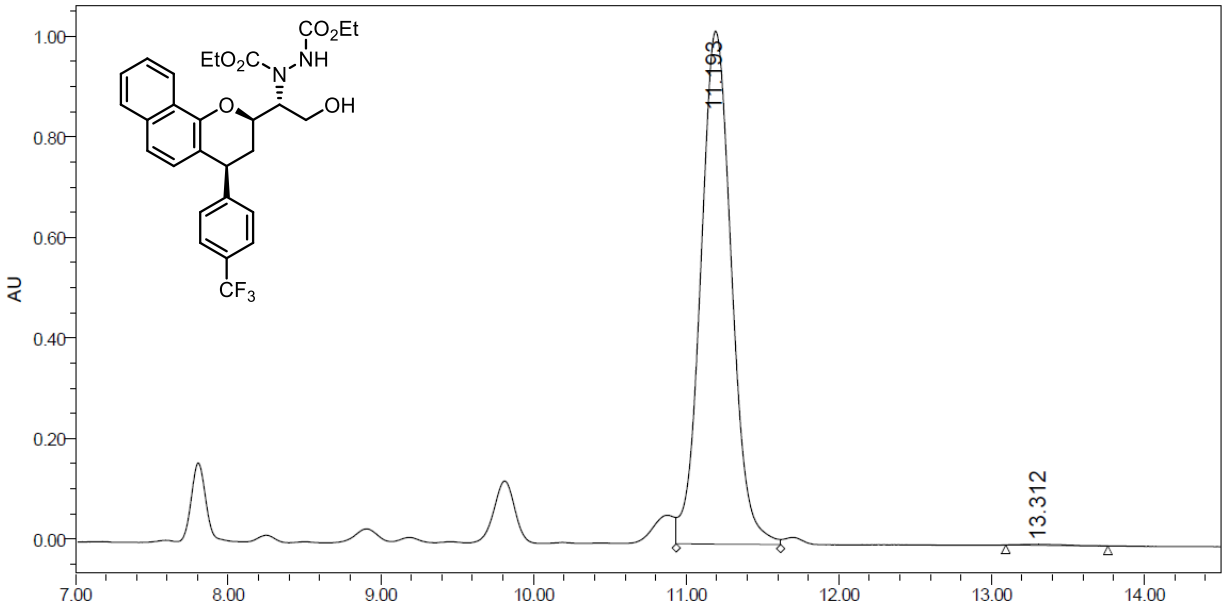
^{13}C NMR spectrum of 3.60a



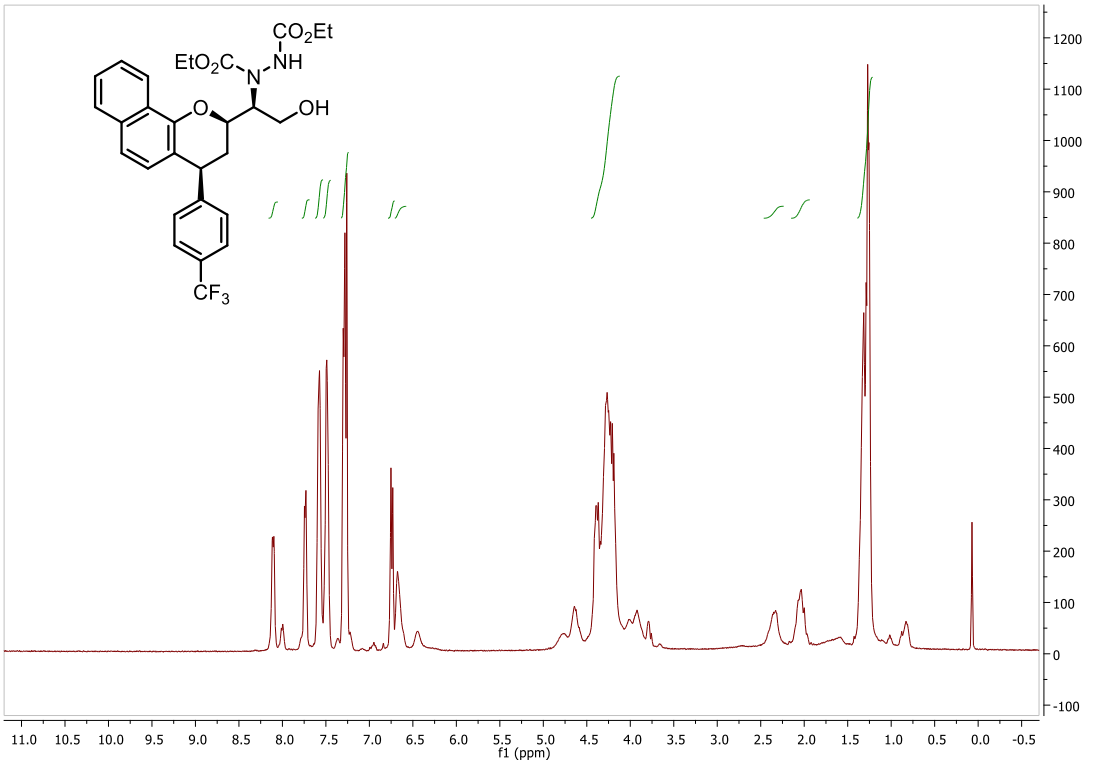
^{19}F NMR spectrum of 3.60a



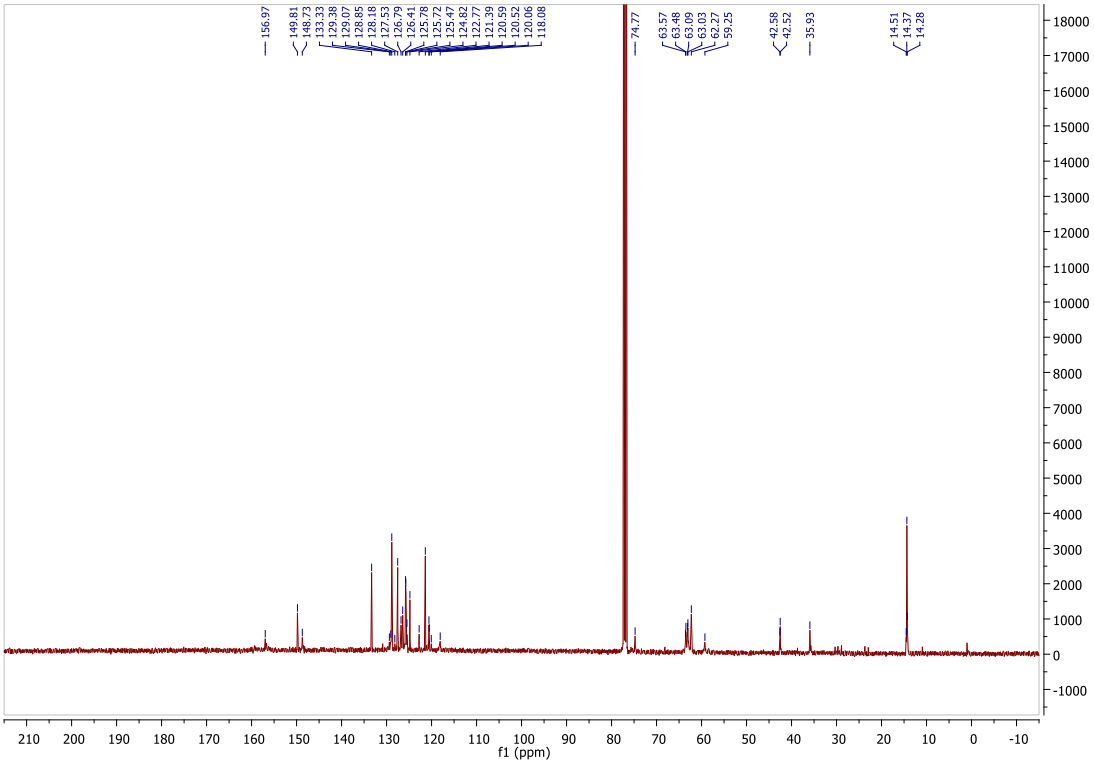
	Retention Time (min)	% Area			
1	7.674	1.99	5	9.908	1.85
2	7.876	22.68	6	10.258	0.24
3	8.987	30.42	7	11.316	18.74
4	9.260	1.19	8	13.450	22.89



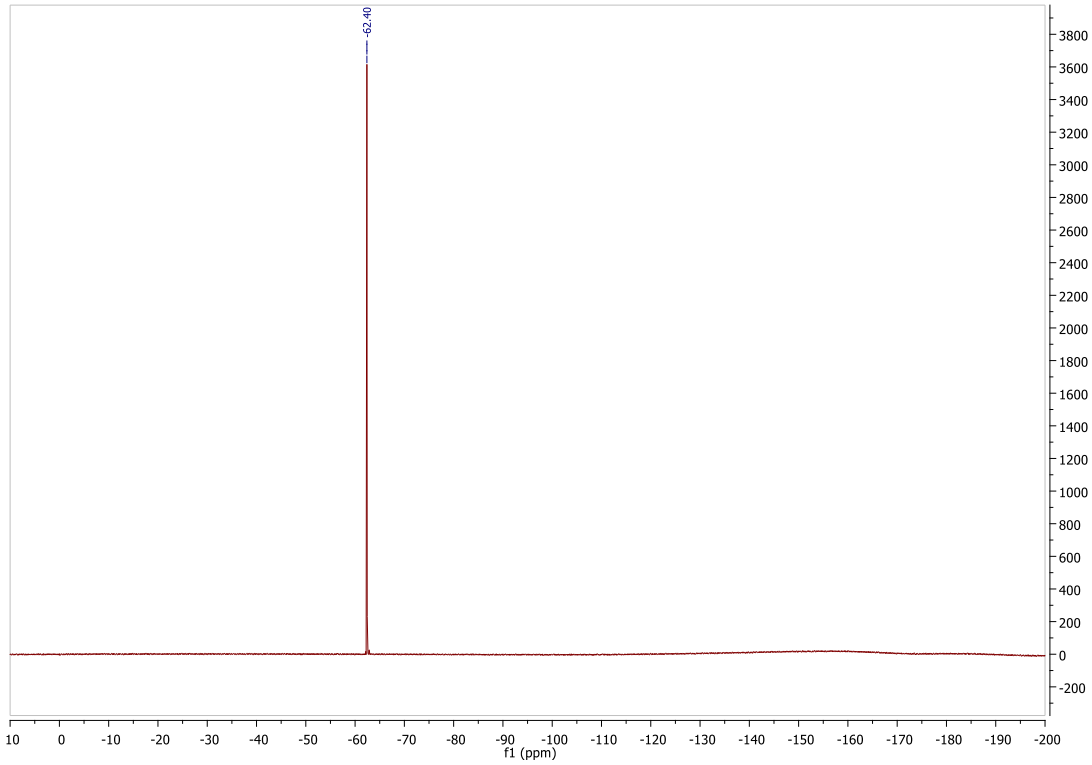
	Retention Time (min)	% Area
1	11.193	99.74
2	13.312	0.26



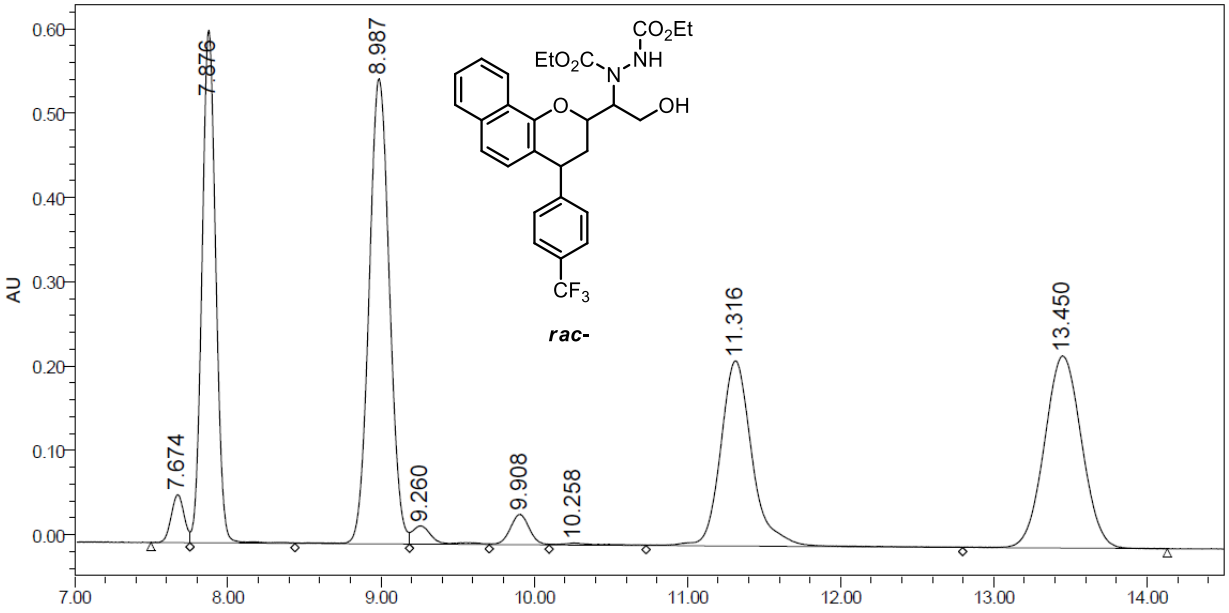
^{1}H NMR spectrum of 3.60b



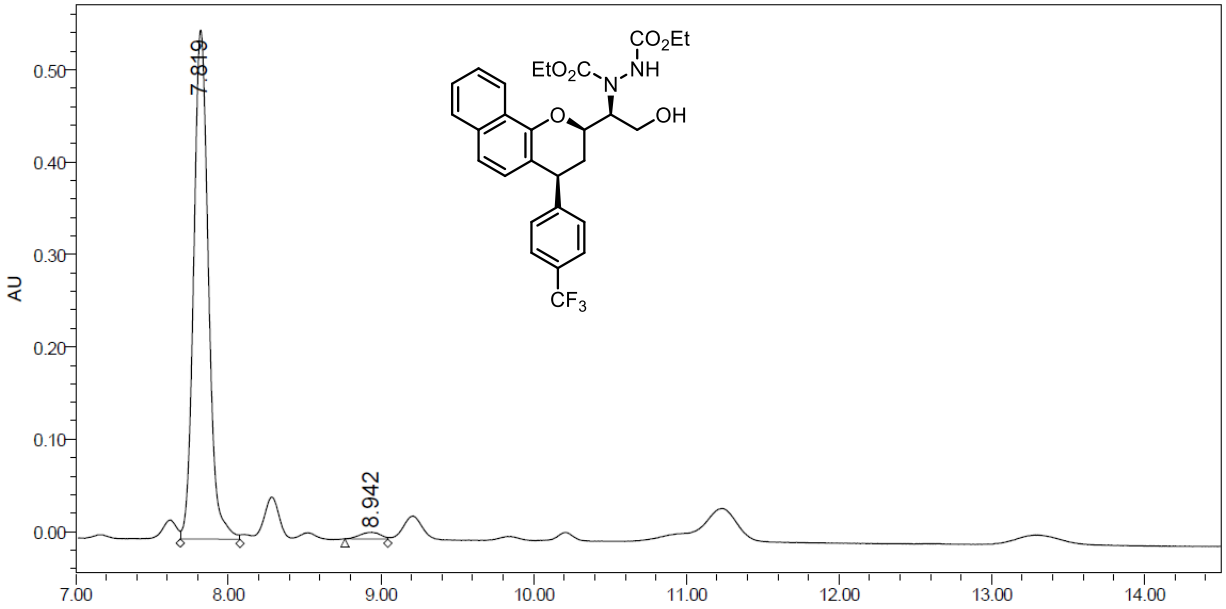
^{13}C NMR spectrum of 3.60b



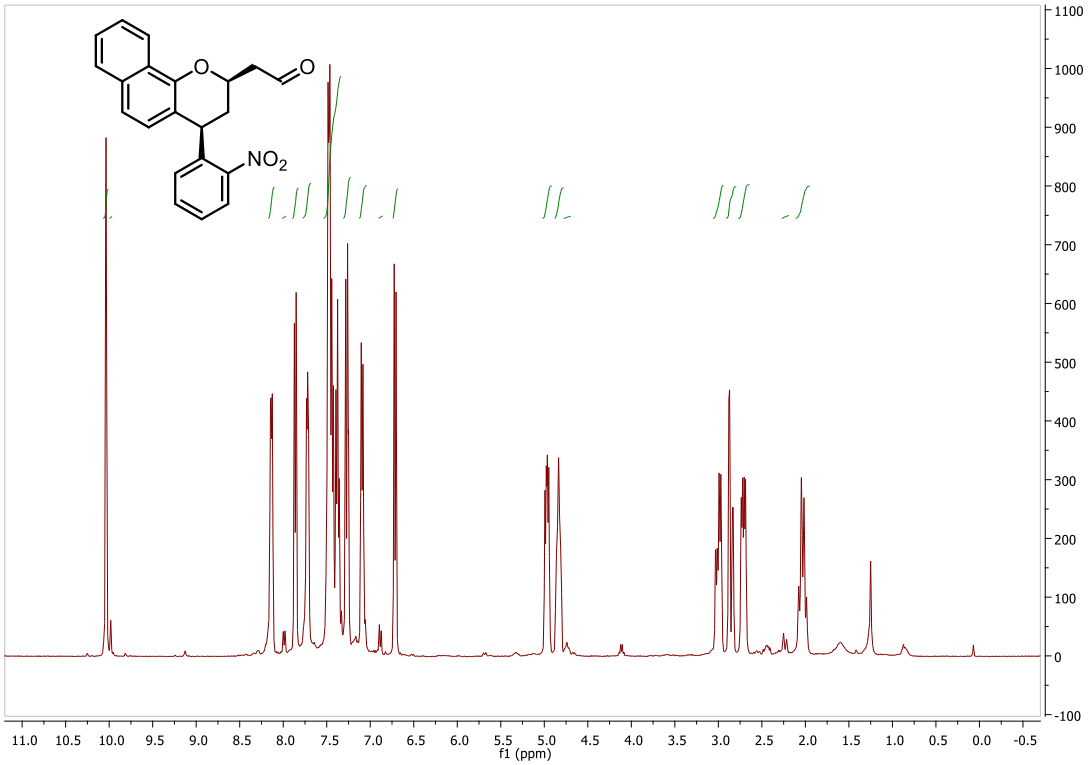
^{19}F NMR spectrum of 3.60b



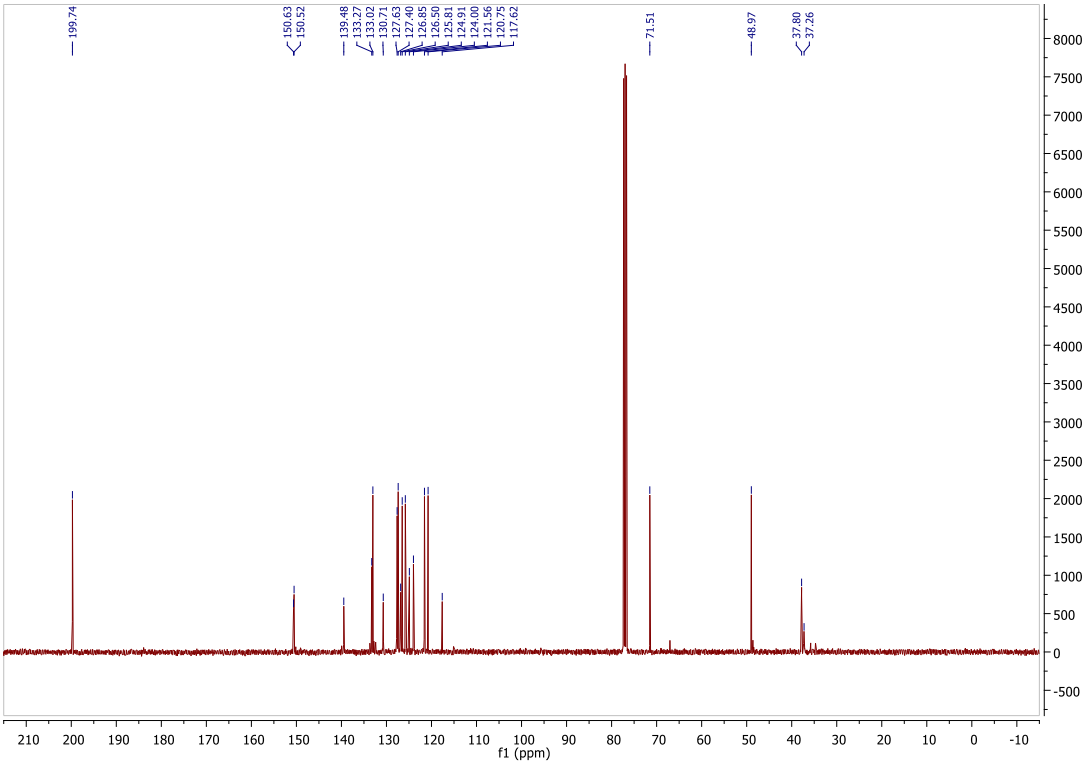
	Retention Time (min)	% Area			
1	7.674	1.99	5	9.908	1.85
2	7.876	22.68	6	10.258	0.24
3	8.987	30.42	7	11.316	18.74
4	9.260	1.19	8	13.450	22.89



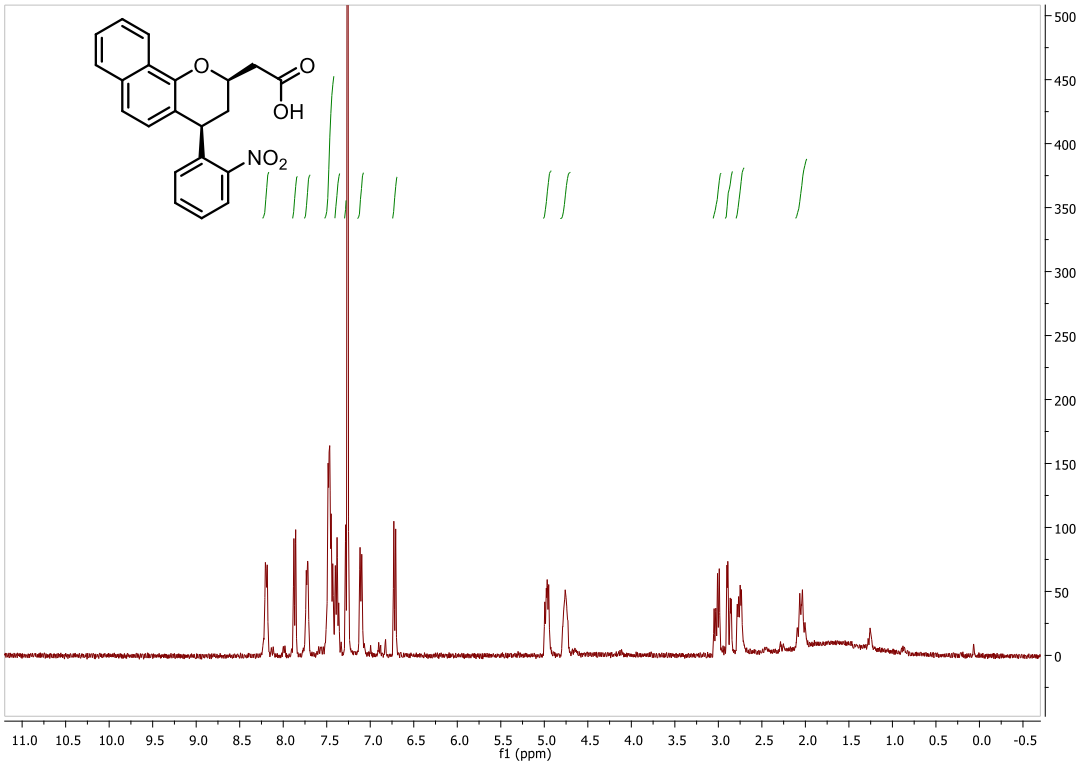
	Retention Time (min)	% Area
1	7.819	98.20
2	8.942	1.80



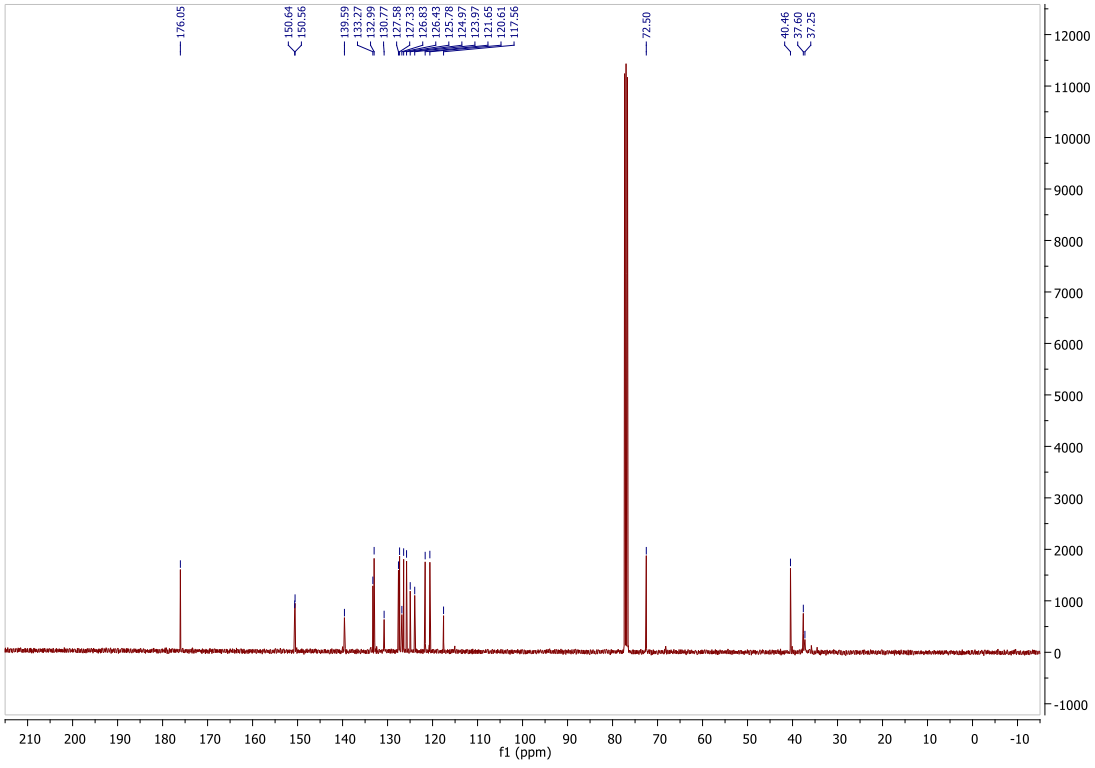
^{1}H NMR spectrum of 3.58e-I



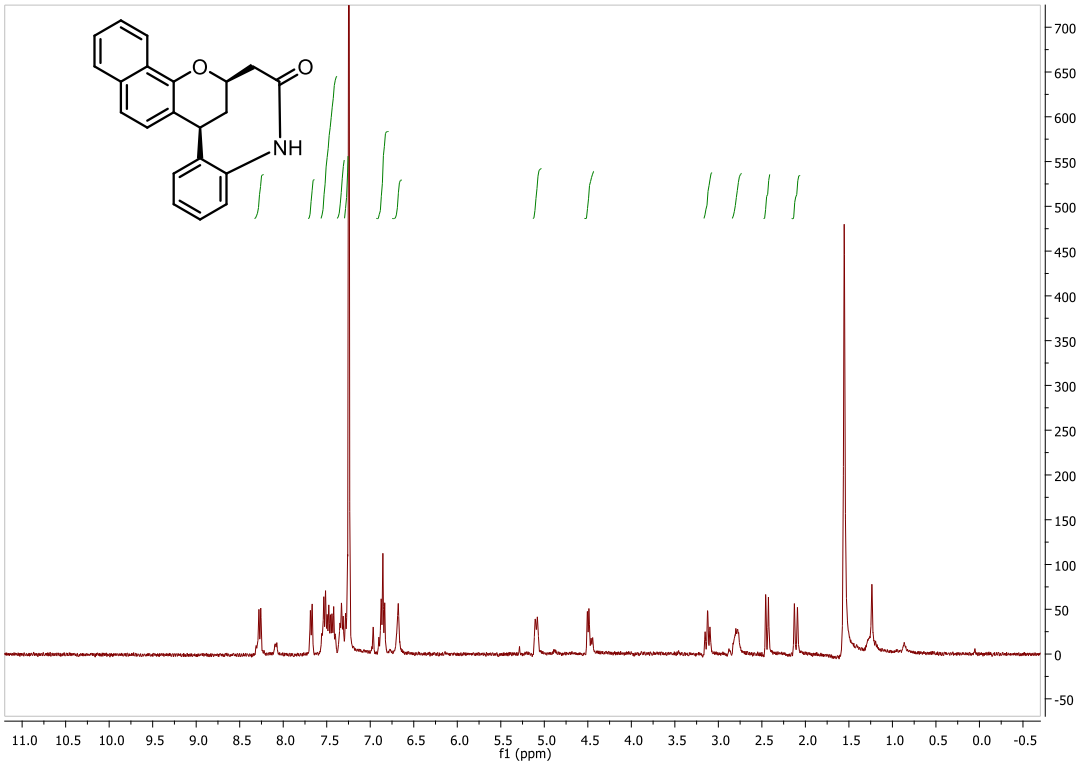
^{13}C NMR spectrum of 3.58e-I



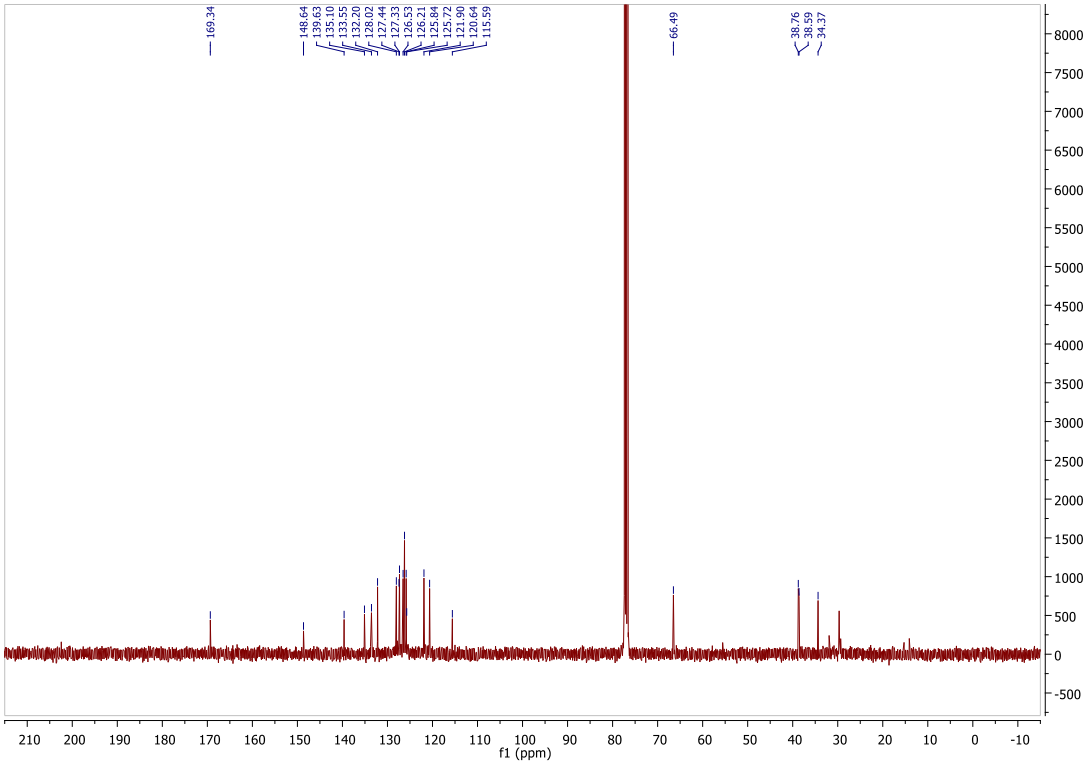
^{1}H NMR spectrum of 3.61



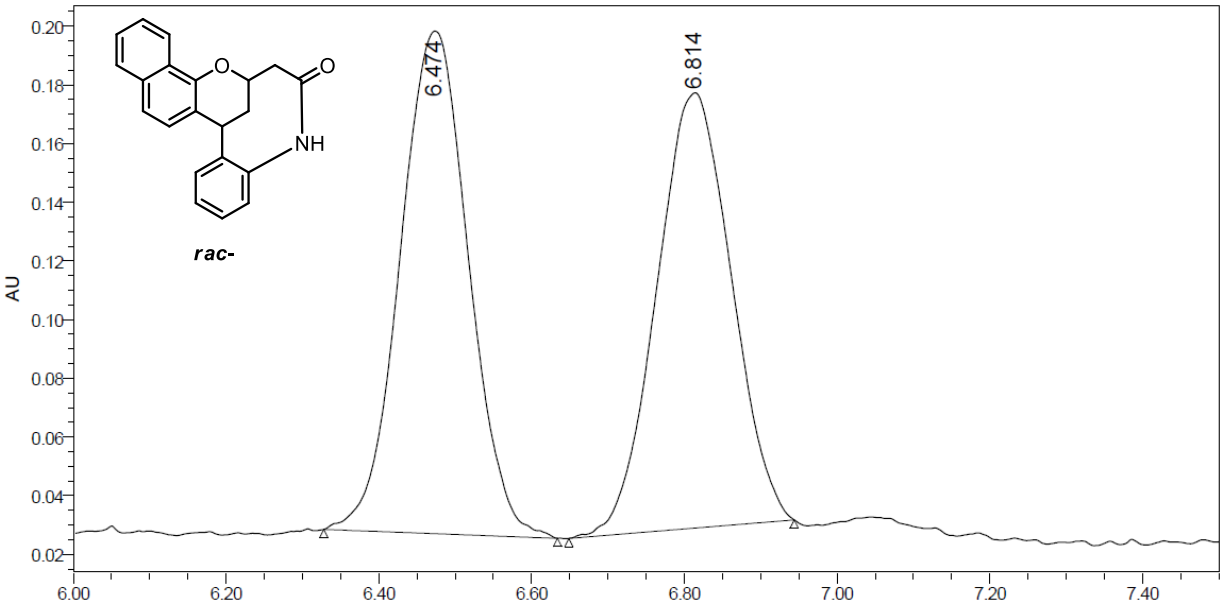
^{13}C NMR spectrum of 3.61



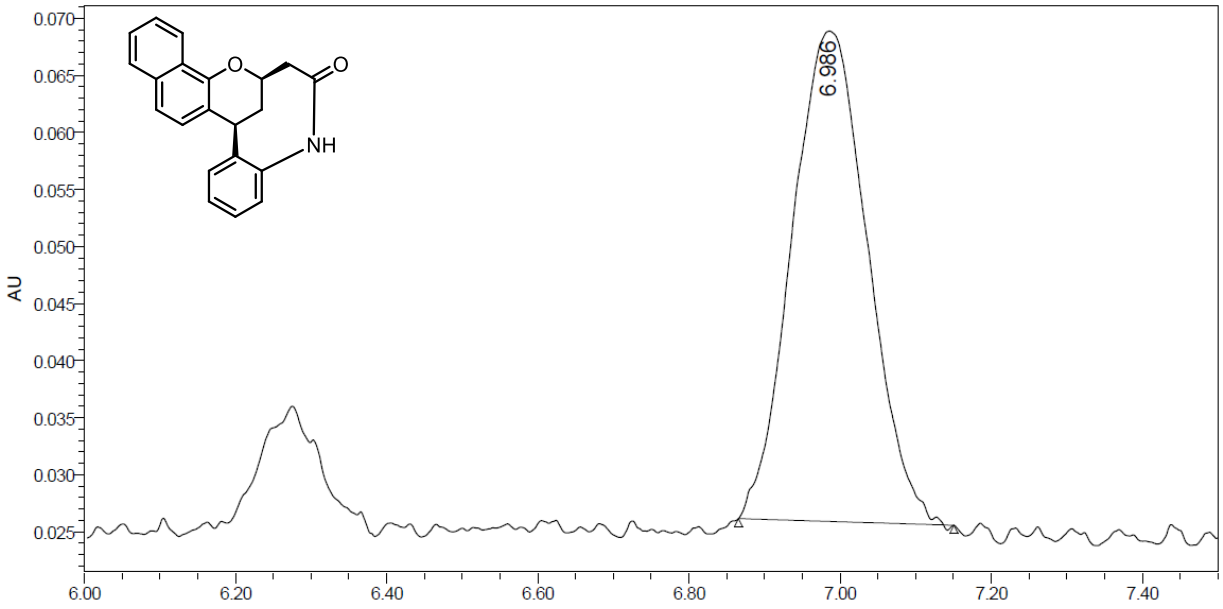
^{1}H NMR spectrum of 3.63



^{13}C NMR spectrum of 3.63



	Retention Time (min)	% Area
1	6.474	51.34
2	6.814	48.66



	Retention Time (min)	% Area
1	6.986	100.00

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APPENDICES

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Basic-functionalized recyclable ionic liquid catalyst: A solvent-free approach for Michael addition of 1,3-dicarbonyl compounds to nitroalkenes under ultrasound irradiation

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ABSTRACT

A task-specific ionic liquid (TSIL) has been introduced as a recyclable catalyst in Michael addition. A series of nitroalkenes and various C-based nucleophiles were reacted in the presence of 30 mol% of recyclable basic-functionalized ionic liquid. Good to excellent yields were obtained in 30 min under ultrasound irradiation.

1. Introduction

Ionic liquids (IL's) are emerging solvents of interest as greener alternatives to conventional organic solvents aimed at facilitating sustainable chemistry. As a consequence of their unusual physical properties, reusability, and eco-friendly nature, ionic liquids have attracted the attention of chemists [1].

It is becoming evident from the increasing number of reports on the use of ionic liquids as solvents, catalysts, and reagents in organic synthesis that they are not totally inert under many reaction conditions [2]. While in some cases, their unexpected reactivity has proven fortuitous and in others, it is imperative that when selecting an ionic liquid for a particular synthetic application, attention must be paid to its compatibility with the reaction conditions.

The Michael addition is a powerful reaction for the formation of carbon–carbon bonds [3]. Moreover, the addition products are important synthetic intermediate, which can be further manipulated into a range of different classes of biologically active compounds [4]. This type of reaction is traditionally promoted by quantitative amount of strong bases that often lead to undesirable side reactions [5]. On the other hand, a range of Lewis acids are found to catalyze this reaction, and these procedures are also not free from disadvantages [6]. Thus, a number of milder reagents such as Al_2O_3, K_2CO_3, rhodium and ruthenium complex, clay-supported nickel bromide, quaternary ammonium salt, and *N*-phenyl-tris(dimethylamino)imino-phosphorane immobilized on polystyrene resin have been developed over the past few years [7]. Moreover, room temperature ionic liquids, particularly BMIM-BF_4, have been used as alternative green solvents to carry out the Michael addition using Ni(acac)$_2$ and Cu(II) triflate as catalysts [8].

Recent development of IL's turned on designing suitable ionic liquids with specific application repetition of ILs many times that can be used both as catalysts/promoters and solvents [9]. Several innovative synthetic procedures on this task lead to successful results and emerge as a new field in task specific ionic liquids (TSIL's). In this way, TSIL's were utilized in many chemical transformations and especially the Michael addition reaction have much paid attention due to the formation of C–C bond [10]. For example, Ranu et al. explored the influence of a new tailor-made, task-specific ionic liquid BMIM-OH on Michael addition reactions. The BMIM-OH was used in quantitative amount which would function as solvent and catalyst [11].

A pressing challenge for organic chemists is to develop new catalytic processes that are not only efficient, byproduct free, and high yielding but also eco-compatible [12]. On account of these factors, here in we report the solvent free Michael addition of 1,3-dicarbonyl compounds to nitroalkenes under ultrasound irradiation using catalytic amount of basic-functionalized ionic liquid as a recyclable catalyst (Fig. 1).

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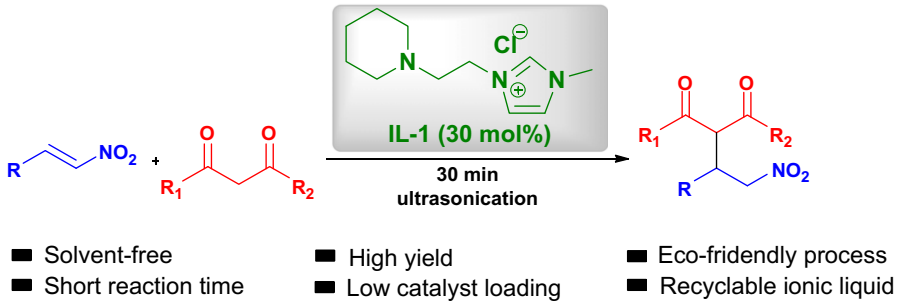


Fig. 1. Michael addition reactions of 1,3-dicarbonyl compounds to nitroalkenes.

2. Results and discussion

The efficacy of this protocol was initially evaluated by the reaction of 2,4-pentanedione (2 equivalents) to trans-β-nitrostyrene (1 equivalent) in the presence of 30 mol% of five different ionic liquids under sonication for 30 min. In the initial experiment, a range of ionic liquids were screened for the Michael addition (Table 1, entries 1–5). The result for IL-1 significantly better as compared with other ionic liquids (entry 1, Table 1) [13]. After selecting the appropriate ionic liquid, the amount of ionic liquid required to promote the completion of the reaction was also evaluated. Reactions with 20 and 10 mol% of IL-1 showed significant decrease in yields (Table 1, entries 1 *vs* 6 and 7). A decrease in yield was observed when the reaction time was reduced from 30 to 15 min (Table 1, entry 1 *vs* entry 8). In the absence of ultrasonication, the conjugate adduct was obtained in only 73% of yield in 120 min reaction time at room temperature under magnetic stirring (entry 9). No product was formed in the absence of IL-1 (entry 10).

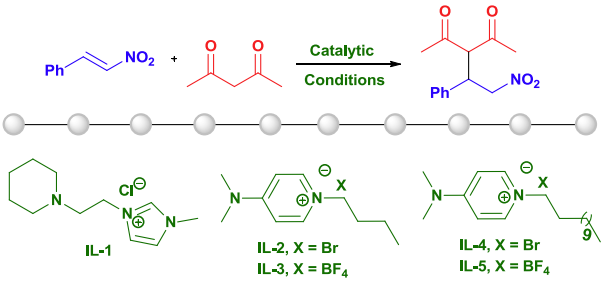
Therefore, an optimum combination for the conjugate addition of nitroalkenes with 1,3-dicarbonyl compounds is using 30 mol% of IL-1 catalyst under 30 min ultrasonication under solvent free conditions.

The results of the optimization process to decode the scope and applicability of reactions are summarized in Tables 2 and 3. The Michael addition of 2,4-pentanedione to a variety of nitroalkenes was examined considering the usefulness and versatility of adducts in organic synthesis [14]. It is apparent from results that all reactions of nitroalkenes proceeded smoothly affording the desired products with good to excellent yields. Electronic effects had small influence on the reaction course, with electron-withdrawing groups attached to the aromatic ring of β-nitrostyrenes afforded the products with good to excellent yield (Table 2, entries 2–5 and 8–9). By using 30 mol% IL-1, the reactions of nitrostyrenes, bearing *ortho* or *para* electron donating substituent, with 2,4-pentanedione proceeded smoothly, and afforded the corresponding Michael adducts in 99% yield (Table 2, entries 6 and 7). We also employed other nitrostyrene in this reaction, e.g. heterocyclic. For instance, 2-(2-nitrovinyl) thiophene reacted with 2,4-pentanedione, allowing the conjugate adduct in 76% yield (Table 2, entry 10).

Next, the scope of the reaction was investigated with different nucleophilic species. As shown in Table 3, various ketoesters effectively reacted with trans-β-nitrostyrene in the presence of 30 mol% IL-1 (Table 3, entries 1–3). An important feature of our methodology is the use of different nucleophiles, such as cyclic-β-ketoester, giving the corresponding products in good yields (Table 3, entries 4–6). This result demonstrates the potential wide ranging utility of this methodology by the preparation of various conjugate adducts.

Although steps toward sustainability can be made by reusing solvents, recycling is rarely accomplished with complete efficiency.

Table 1
Screening of reaction: ionic liquid, catalyst loading, and reaction time.



Entry	TSIL's	IL (% mol)	Time (min)	Yield (%)[a,b]
1	IL-1	30	30	98
2	IL-2	30	30	42
3	IL-3	30	30	10
4	IL-4	30	30	23
5	IL-5	30	30	16
6	IL-1	20	30	81
7	IL-1	10	30	66
8	IL-1	30	15	88
9[c]	IL-1	30	120	73
10[d]	–	–	30	–

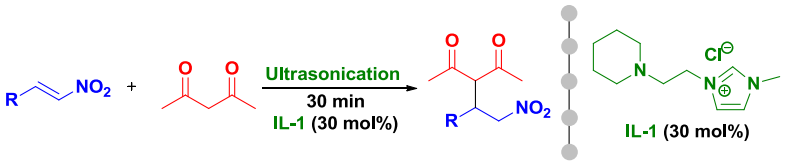
[a] Unless otherwise specified, the reactions were performed using trans-β-nitrostyrene (0.25 mmol), 2,4-pentanedione (0.5 mmol), and ionic liquid (30 mol%) under ultrasonication for 30 min.
[b] Isolated yield.
[c] Reaction was performed without ultrasonication under room temperature for 2 h.
[d] Reaction was performed without ionic liquid.

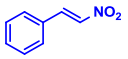
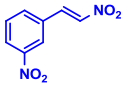
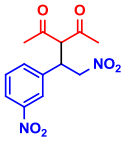
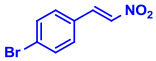
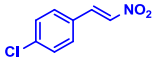
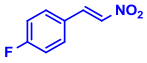
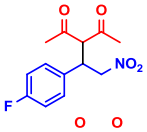
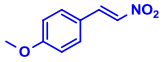
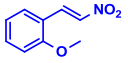
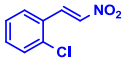
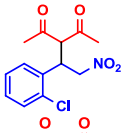
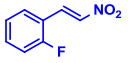
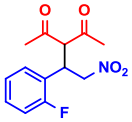
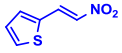
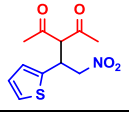
Hence, we attempted to reuse the ionic liquid/catalyst, which was one of the prime objectives in our quest. In this regard, we performed a set of experiments to explore whether the ionic liquid can be reused for further reactions (Fig. 2). After completion of the reaction, task-specific ionic liquid catalyst was recovered and subjected to another run, affording the product in 98% yield. This process was repeated four more times, affording the desired product in excellent yields. The simple experimental and product isolation procedures combined with the ease of recovery and reuse of the reaction medium is expected to contribute to the development of a green strategy for the Michael addition reactions.

3. Experimental section

For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. All solvents were used as purchased unless otherwise noted. Purification of products was carried out by flash chromatography on silica gel.

Table 2
Michael addition reactions of 2,4-pentanedione to nitroalkenes.



Entry	Substrate	Product	Yield [a,b]
1			98
2			52
3			71
4			74
5			99
6			99
7			99
8			>99
9			81
10			61(76)[c]

[a] Unless otherwise specified, the reactions were performed using nitrostyrene (0.25 mmol), 2,4-pentanedione (0.5 mmol) and ionic liquid (30 mol%) under ultrasonication for 30 min at room temperature.
[b] Isolated yield.
[c] Yield in parenthesis refer to 1 h reaction time under ultrasonication.

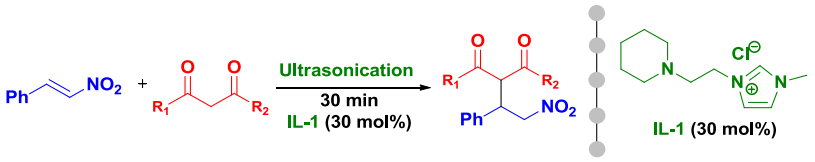
Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were obtained using deuterated solvents ($CDCl_3$ and DMSO-d_6) in a Bruker Avance III spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard. All ionic liquids were prepared according literature procedure [13]. ^{1}H and ^{13}C NMR spectral data of the compounds are identical to those reported.

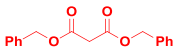
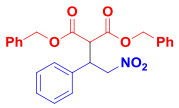
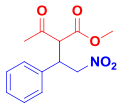
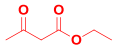
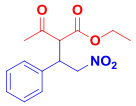
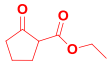
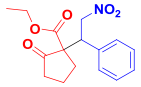
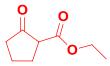
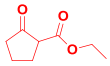
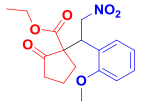
3.1. 1General synthetic procedure of ionic liquid

3.1.1. Synthesis of-1-methyl-3-(2-(piperidin-1-yl)ethyl)-1H-imidazol-3-ium-chloride (IL-1)

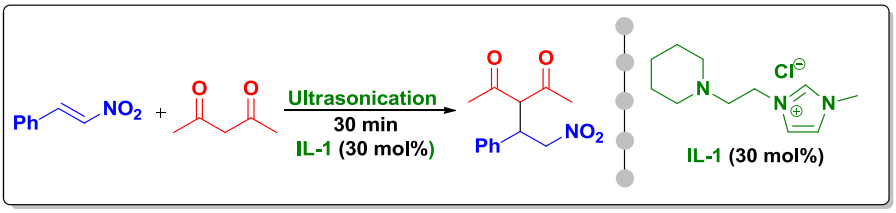
In a two neck 100 mL round-bottomed flask equipped with reflux condenser and magnetic stirrer, N-methyl imidazole (1.025 g, 12.5 mmol), 1-(2-chloroethyl)piperidine hydrochloride (1.84 g,

Table 3
Variation of nucleophiles in reaction with trans-β-nitrostyrene catalyzed byIL-1.



Entry[a]	Nucleophile	Product	Yield[b,c]
1			92
2			83(1:1)
3			80(1:1)
4			62(8:2)
5			>99(7:3)
6			89(7:3)

[a] Unless otherwise specified, the reactions were performed using trans-β-nitrostyrene (0.25 mmol), nucleophile (0.5 mmol), and ionic liquid (30 mol%) under ultrasonication.
[b] Isolated yield.
[c] d.r. (in parenthesis) was determined by NMR analysis.



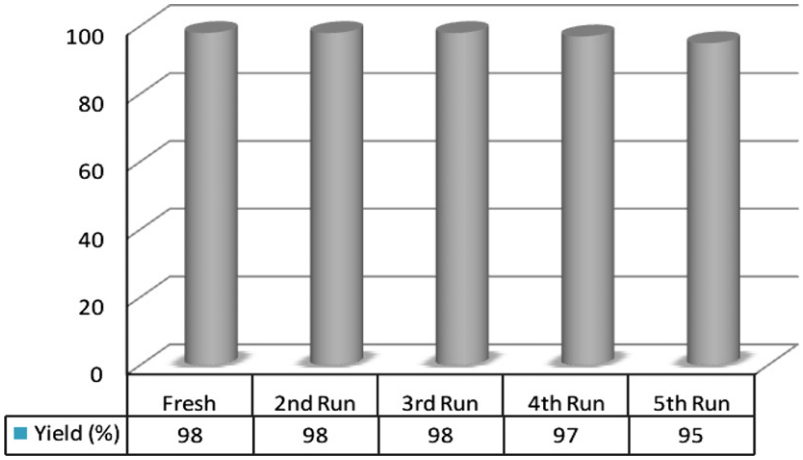


Fig. 2. Recyclability of ionic liquid for the conjugate addition.

10 mmol) and absolute ethanol (10 mL) were added. The mixture was refluxed for 24 h. After the reaction, the solvent was removed under vacuum, the residue was washed with dichloromethane and dried at 70 °C under vacuum. The white solid was dissolved in the mixture of ethanol (5 mL) and water (5 mL), and neutralized by NaOH (0.4 g, 10 mmol). After removal of solvents, the product was extracted with dichloromethane, dried at 70 °C under vacuum for 10 h. Pale yellow oily liquid was obtained in 90% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.52–1.37 (m, 6 H), 2.53–2.59 (m, 4 H), 2.90–2.94 (m, 2 H), 3.86 (s, 3 H), 4.42–4.47 (m, 2 H), 7.76 (s, 1 H), 7.86 (s, 1H), 9.41 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.1, 24.4, 35.7, 45.0, 53.2, 56.5, 122.5, 123.2, 137.0 ppm.

3.1.2. Synthesis of 1-butyl-4-(dimethylamino)pyridinium bromide (IL-2)

A mixture of 4-dimethylaminopyridine (5 mmol) and butyl bromide (6 mmol) and MeCN (10 mL) was allowed to stir 24 h at 70 °C. The resulting mixture was then evaporated affording the yellow crystals. The resulting crystalline mass was washed twice with ether (20 mL) and, after vacuum drying, a pale yellow crystals was obtained in 95% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (t, J = 7.3 Hz, 3 H), 1.27–1.16 (m, 2 H), 1.76–1.68 (m, 2 H), 3.17 (s, 6 H), 4.17 (t, J = 7.3 Hz, 2 H), 7.03 (d, J = 7.8 Hz, 2 H), 8.34 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.3, 18.7, 32.3, 39.7, 56.3 (2C), 107.7, 142.0, 155.8 ppm.

3.1.3. Synthesis of 1-butyl-4-(dimethylamino)pyridinium tetrafluoroborate (IL-3)

A mixture of 1-butyl-4-(dimethylamino)pyridinium bromide (5 mmol), sodium tetrafluoroborate (6 mmol) and distilled water (1 mL) was vigorously stirred for 60 min. The lower aqueous phase was separated and discarded and, to the remaining liquid, dichloromethane (20 mL) was added. The organic phase was separated and solvent evaporation afforded the desired 1-butyl-3-methylimidazolium tetrafluoroborate in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (t, J = 7.3 Hz, 3 H), 1.27–1.16 (m, 2 H), 1.76–1.68 (m, 2 H), 3.17 (s, 6 H), 4.17 (t, J = 7.3 Hz, 2 H), 7.03 (d, J = 7.8 Hz, 2 H), 8.34 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.3, 18.7, 32.3, 39.7, 56.3 (2C), 107.7, 142.0, 155.8 ppm.

3.1.4. Synthesis of 4-(dimethylamino)-1-dodecylpyridinium bromide (IL-4)

A mixture of 4-dimethylaminopyridine (5 mmol) and dodecyl bromide (6 mmol) and MeCN (10 mL) was allowed to stir 24 h at 70 °C. The resulting mixture was then evaporated affording the yellow crystals. The resulting crystalline mass was washed twice with ether (20 mL) and, after vacuum drying, pale yellow crystals was obtained in 99% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.83 (t, J = 7.25 Hz, 3 H), 1.30–1.13 (m, 18 H), 1.78–1.69 (m, 2 H), 3.17 (s, 6 H), 4.16 (t, J = 7,2 Hz, 2H), 7.03 (d, J = 7,6 Hz, 2H), 8.33 (d, J = 7.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 25.4, 28.4, 28.7, 28.8, 28.9, 29.0 (2C), 31.3, 39.7, 56.6, 107.6, 142.0, 155.8 ppm.

3.1.5. Synthesis of 4-(dimethylamino)-1-dodecylpyridinium tetrafluoroborate (IL-5)

A mixture of 4-(dimethylamino)-1-dodecylpyridinium bromide (5 mmol), sodium tetrafluoroborate (6 mmol) and distilled water (1 mL) was vigorously stirred for 60 min. The lower aqueous phase was separated and discarded and, to the remaining liquid, dichloromethane (20 mL) was added. The organic phase was separated and solvent evaporation afforded the desired 4-(dimethylamino)-1-dodecylpyridinium tetrafluoroborate in 100% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.83 (t, J = 7.25 Hz, 3 H), 1.30–1.13 (m, 18 H), 1.78–1.69 (m, 2 H), 3.17 (s, 6 H), 4.16 (t, J = 7,2 Hz, 2H), 7.03 (d, J = 7,6 Hz, 2H), 8.33 (d, J = 7.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 25.4, 28.4, 28.7, 28.8, 28.9, 29.0 (2C), 31.3, 39.7, 56.6, 107.6, 142.0, 155.8 ppm.

3.2. General procedure for the synthesis of Michael adduct

In a vial, ionic liquid (30 mol%), trans-β-nitrostyrene (0.25 mmol) and 1,3-dicarbonyl compound (0.5 mmol) was added and the reaction mixture was allowed under ultrasonication for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was washed with Et_2O (3 × 5 mL) and dried over Na_2SO_4. The crude was purified by silica column chromatography affording the corresponding pure Michael adducts. The NMR data's of products were in accordance with literature data [15].

3.3. General procedure for ionic liquid recycle experiments

Following extraction with diethyl ether, the ionic liquid solution was subjected to vacuum to remove traces of diethyl ether, flushed with inert gas and charged with further portions of *trans*-β-nitrostyrene (1 eq) and 2,4-pentanedione (2 eq) at room temperature.

4. Conclusions

In conclusion, we have developed an efficient solvent free conjugate Michael addition of 1,3-dicarbonyl compounds to various nitroalkenes in the presence of catalytic amount of base-behavior ionic liquid under ultrasonication providing the desired conjugate adducts in good to excellent yields. The versatility, economic and high yield of this method, in addition to the shorter reaction time and low loading of catalyst/ionic liquid, highlights the potential for the use of this developed method in large scale library synthesis involving carbon–carbon bond formation. Most importantly, the recovery and recycling of the ionic liquid in further reactions was successfully achieved and can be reused for at least four successive runs without observing significant decrease in yield.

We believe that the ionic liquids which enable the easy recycling in organic reactions will have great synthetic value and potentially find wide applications in organic synthesis. Further investigations to clarify the mechanism and explore applications in asymmetric transformations are currently underway in our laboratory.

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Polyethylene glycol (PEG) as a reusable solvent medium for an asymmetric organocatalytic Michael addition. Application to the synthesis of bioactive compounds†

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A highly stereoselective organocatalytic Michael addition of aldehydes to *trans*-β-nitrostyrenes using PEG as a recyclable solvent medium is presented. The scope of this organocatalytic system is demonstrated by the formation of several Michael adducts in good yields and stereoselectivities. Furthermore, applying this new protocol to acetaldehyde, we have disclosed an easy formal synthesis of (*R*)-pregabalin, (*R*)-phenibut and (*R*)-bacoflen with good yields and outstanding enantioselectivities.

Introduction

Environmental concerns associated with synthetic organic chemistry have posed stringent and compelling demands for greener processes. The development of cost-efficient and environmentally benign catalytic systems has become one of the main subjects in modern chemistry.[1] In many chemical processes, organic solvents are widely used and had been a cause of major environmental concern due to the hazards they pose.[2] A recent benchmarking study performed by the pharmaceutical industry[3] unveiled that solvents are the foremost contributors to the amount of waste produced in pharmaceutical manufacturing processes – the so-called E-factor.[4] Therefore, the social and economical imperative for sustainability has prompted the scientific community to search for alternative reaction media in place of volatile, pyrophoric, often toxic and difficult to recover solvents.[5] To overcome these limitations, attempts have been made in the development of new protocols using water and/or other aqueous solutions as greener solvents.[6] Furthermore, similar alternatives also include: (a) supercritical fluids,[7] (b) ionic liquids,[8] (c) fluorous based systems,[7b,9] (d) and more recently the use of liquid polymers.[10] To address the concerns raised by volatile organic solvents, liquid PEGs have been subjected to an increasing number of scientific investigations.[11] Chemical reactions carried out in PEGs have a different thermodynamic and kinetic behaviour with respect to those in conventional solvents, and, in addition, PEGs have a number of intrinsic properties that may be of importance for industrial application. Therefore, PEGs could be attractive greener options due to their non-toxic and non-hazardous characteristics and the lack of measurable vapour pressure associated with their air and moisture stability.[12] However, relatively few articles have been focused on the use of PEG solutions in catalytic asymmetric synthesis.

Over the past few years, especially with the conception of the organocatalysis field, many organic reactions that were conventionally believed to occur only in traditional organic solvents have been successfully performed in an environmentally benign reaction medium. Among all the methods developed, the asymmetric organocatalytic Michael reaction[13] is an excellent example and has strongly contributed to the green chemistry perspective. This elegant and atom-economic methodology proves to be one of the most versatile tools for carbon–carbon and carbon–heteroatom bond formation,[14] as exemplified by the large number of publications in this field over the last few years.[15] Moreover, the addition products are important synthetic intermediates, which can be further manipulated into a range of different classes of biologically active compounds.

A pressing challenge facing organic chemists, therefore, is to advance new asymmetric catalytic processes that are not only efficient, by-product free, and high yielding but also eco-compatible. On account of these factors, herein we report the application of PEG 400 as a recyclable reaction medium in the asymmetric organocatalytic Michael addition of aldehydes to *trans*-β-nitrostyrenes.

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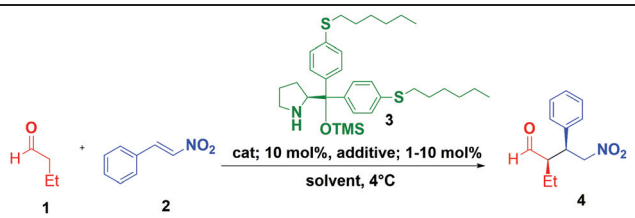
Results and discussion

The directed Michael addition of butyraldehyde **1** to *trans*-β-nitrostyrene **2** was selected as the model reaction to evaluate the feasibility of our organocatalytic system in environmentally benign solvents (Table 1). In order to optimize the reaction conditions, different solvents, catalysts and catalytic additives were carefully evaluated. We started the screening studies, by using 10 mol% derivative catalyst of proline with a sulphur alkyl chain, **3**, recently described by our group[16,17] and benzoic acid (10 mol%) as a catalytic additive.

When the reactions were carried out in EtOH, water or glycerol, the desired products were obtained with moderate chemical yields as well as diastereoselectivities, and high enantioselectivities (Table 1, entries 1, 2 and 3). Having toluene as the solvent, an increment in the chemical yield was observed, with no variation in the diastereo- and enantioselectivity (entry 4). Moreover, diethylene glycol provided the product after only 2 h, with higher yield and stereoselectivities than those evaluated before. These results have prompted us to evaluate a greener, non-volatile and recoverable solvent such as PEG-400 (entry 6). To our delight, the desired product **4** was smoothly obtained within 2 h in a quantitative yield and excellent enantioselectivity (entry 6 *vs.* 5). In order to further optimize the protocol, different parameters were also varied. When the reaction temperature was raised to 30 °C, a decrease in yield, ee and dr was noted compared to the reaction at 4 °C (entry 7). Encouraged by these results, a set of cocatalytic additives was screened for further optimization. In doing so, when the reactions were performed in the presence of 10 mol% of 4-nitrophenol, L-tartaric acid or L-maleic acid (entries 8–10), a slight decrease in the reaction yield and in the stereoselectivities was observed. Changing the additive to 10 mol% of CSA led to a complete degradation of the product (entry 11). On the other hand, decreasing the loading of CSA to 1 mol% achieved the formation of the Michael adduct in lower yield (89%), maintaining good stereoselectivities (entry 12). Compared to benzoic acid, the accomplishment of the reaction with 4-nitrobenzoic acid did not affect significantly the yield and stereoselectivity (entry 13) indicating that, among all tested additives, benzoic acid provides the optimal yield, ee and dr. As expected, in the absence of the cocatalytic additive, the reaction yield dropped to 84%, maintaining good selectivity (entry 14). Having optimized both the solvent and additive, we turned our attention to study the amount of organocatalyst and additive in the reaction. Lowering the loading of both the organocatalyst and additive to 5 mol%, the desired product was obtained in a quantitative yield with excellent enantioselectivity in a longer reaction time; nevertheless, a better diastereoisomeric ratio was obtained. Unfortunately, decreasing the catalytic loading from 5 to 1 mol% produced erosion in terms of yield (47%), albeit without substantial changes in the dr and ee (Chart 1).

We next investigated the architecture of diarylprolinol silyl ether based organocatalysts to further increase the reactivity and selectivity of the catalytic system. All evaluated organocata-

Table 1 Optimization of reaction conditions: solvent and additive studies[a]



Entry	Solvent	Additive	Time (h)	Yield[b] (%)	Diastereomeric ratio[c] (dr)	Enantiomeric excess[d] (ee %)
1	EtOH	Benzoic acid	48	68	64 : 36	94
2	H_2O	Benzoic acid	48	46	60 : 40	94
3	Glycerol	Benzoic acid	48	57	60 : 40	95
4	Toluene	Benzoic acid	48	92	67 : 33	97
5	Diethylene Glycol	Benzoic acid	2	96	88 : 12	97
6	**PEG-400**	**Benzoic acid**	**2**	**99**	**80 : 20**	**97**
7[e]	PEG-400	Benzoic acid	1	92	65 : 35	95
8	PEG-400	4-Nitrophenol	5	93	84 : 16	95
9	PEG-400	L-Tartaric acid	3	85	78 : 22	96
10	PEG-400	L-Malic acid	2	92	84 : 16	96
11	PEG-400	CSA	24	—	—	—
12[f]	PEG-400	CSA	3	89	77 : 23	94
13	PEG-400	4-Nitrobenzoic acid	2	98	77 : 23	96
14	PEG-400	—	11	84	90 : 10	96

[a] Unless otherwise specified, all reactions were performed using *trans*-β-nitrostyrene (0.3 mmol), butyraldehyde (0.6 mmol), an additive (10 mol%) and an organocatalyst (10 mol%) in an environmentally benign solvent (0.15 mL) at 4 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral-phase HPLC analysis of the *syn*-product. [e] The reaction was carried out at room temperature. [f] 1 mol% of the additive was used.

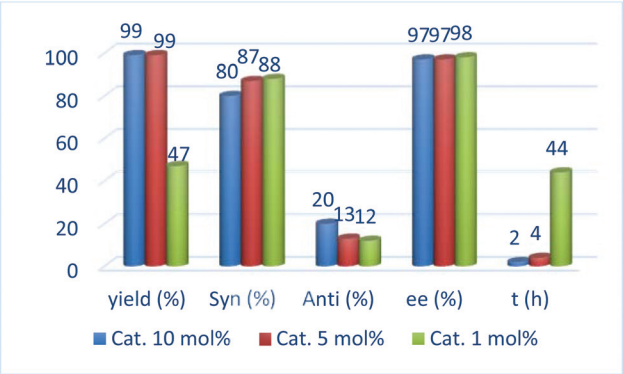
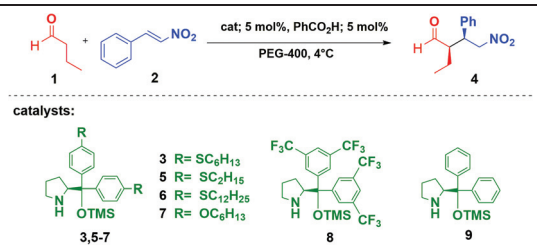


Chart 1 Optimization of catalyst loading.

Table 2 Optimization of the reaction conditions: catalyst screening[a]



Entry	Cat.	[mol L^{-1}]	Time (h)	Yield[b] (%)	ee[c] (%)	dr[d]
1	**4**	2	4	99	97	87 : 13
2	**5**	2	19	99	97	90 : 10
3	**6**	2	19	52	98	91 : 09
4	7	2	4	98	95	86 : 14
5	**8**	2	19	16	97	93 : 07
6	**9**	2	19	62	97	72 : 28
7	**4**	—	2	67	97	91 : 09
8	**4**	0.6	19	99	97	92 : 08
9	**4**	0.3	19	73	96	89 : 11

[a] Unless otherwise specified, all reactions were performed using *trans*-β-nitrostyrene (0.3 mmol), butyraldehyde (0.6 mmol), benzoic acid (0.015 mmol – 5 mol%) and an organocatalyst (0.015 mmol – 5 mol%) in PEG 400 (0.15 mL – 2 mol L^{-1}). [b] Isolated yield. [c] The ee values were determined by chiral HPLC. [d] The dr values were determined by chiral HPLC and NMR of the crude mixture.

lysts were able to promote the Michael addition in an environmentally benign reaction medium, although the reaction outcome varies as a function of the alky side-chain length. Thus, when the length of the hydrophobic alkyl chain was decreased to ethyl (**5**), the desired Michael adduct was obtained with slight erosion in the chemical yield along with a longer reaction time (Table 2, entry 1). Increasing the alkyl chain to dodecyl (**6**) led to a dramatic drop in the chemical efficiency of the Michael addition; however, the degree of stereocontrol remained high (entry 3). Similar yield, ee and dr were obtained using an oxygen-based analogue of the organocatalyst **3**, within 4 h (entries 1 *vs.* 4). Despite the extended reaction time, catalysts **8** and **9** proved to be less effective, producing the desired Michael adducts in only 16% and 62% yields, respectively (Table 2, entries 5 and 6).

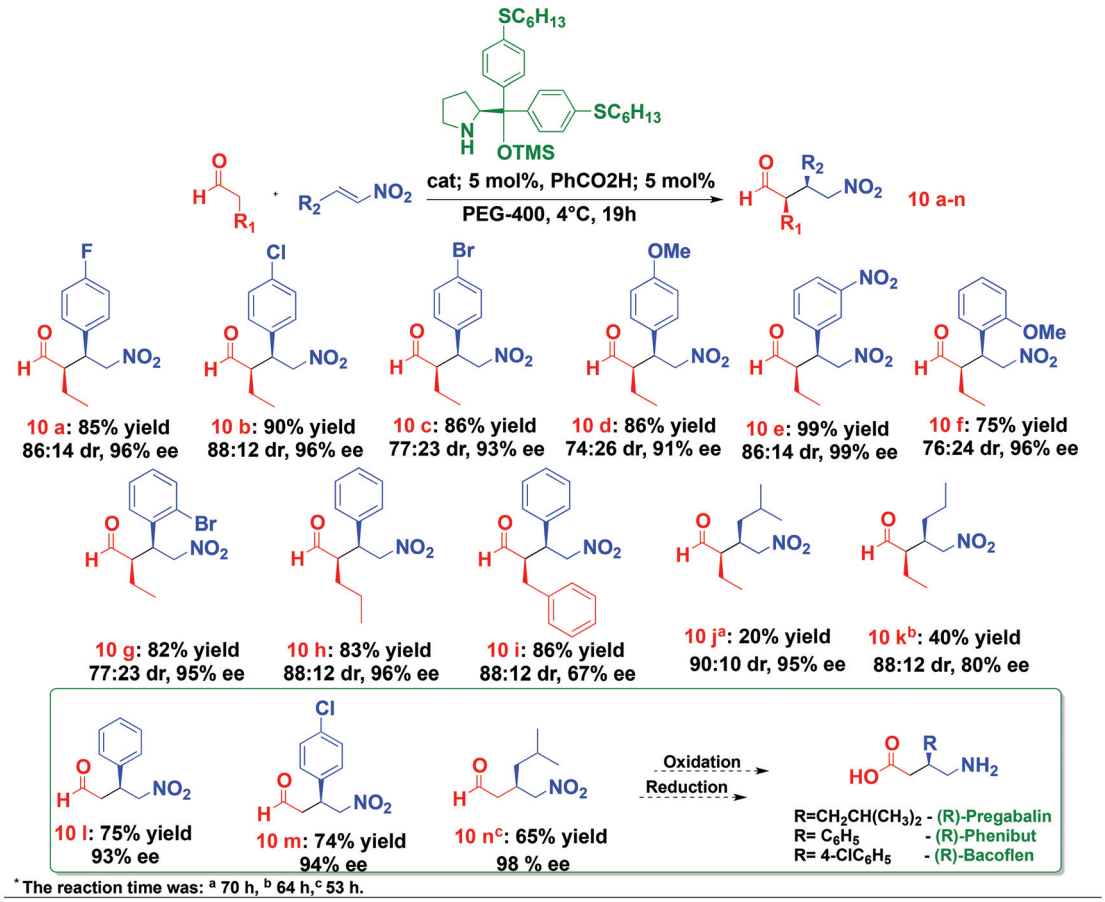
In order to conclude the optimization studies of this catalytic system, the reaction was carried out in different concentrations. In the absence of the solvent, the product was obtained in a lower yield with a higher diastereomeric ratio (Table 2, entry 7). Furthermore, diluting the reaction media to 0.6 M (Table 2, entry 8), notwithstanding the longer time (19 h), the reaction proceeded with excellent selectivities (92 : 8 dr and 97% ee) and these results indicate that no further improvements in yield or selectivity were observed for lower concentrations.

With these notably improved reaction conditions in hand, we explored the scope of the Michael addition of aldehydes to nitroolefins mediated by organocatalyst **3** in PEG 400 as the solvent (Scheme 1). Initially, a representative selection of nitroolefins was evaluated to establish the generality of this asymmetric catalytic system. As depicted in Scheme 1, nitrostyrenes bearing β-aryl substituents with either electron-donating (*e.g.* methoxyl) or electron-withdrawing groups (*e.g.* chloro, bromo, fluoro, and nitro) are almost equally tolerated, thus giving the desired Michael adducts in excellent chemical yields with good diastereomeric ratios and ee values in the range of 91–99%, **10a–g**. Even β-alkyl-substituted nitroolefins participate in this catalytic system to give the desired adduct with good dr as well as ee, albeit in a modest chemical yield, **10j** and **10k**. When valeraldehyde was used as the donor, the reaction proceeded very efficiently, affording the corresponding product **10h** in 83% yield, with high levels of stereoselectivities.

A sterically hindered aldehyde provoked a decrease in the enantioselectivity, but with a good yield and dr, **10i**. Furthermore, aliphatic nitroolefins reacted in a Michel fashion with excellent enantioselectivities; however, the chemical yield of the product was low compared to the other substrates (products **10j** and **10k**).

Recently, the Michael-type addition involving acetaldehyde has emerged as a versatile, yet challenging, transformation in asymmetric catalysis.[18] However, examples including its use as a donor are scarcely described. It could be explained since acetaldehyde is very reactive and volatile. For these reasons, it needs to be carefully manipulated and the reactions normally involve an inert atmosphere and high catalyst loading to deliver the desired product in an acceptable yield. The nitroaldehyde products are versatile synthetic intermediates, easily transformed into γ-aminobutyric acid derivatives (GABAs), which are very important inhibitors of neurotransmission in the brain. Gratifyingly, when we applied our optimized reaction conditions to promote the Michael reaction of acetaldehyde with β-nitrostyrene, *p*-chloro-nitrostyrene and β-alkyl-substituted nitroolefins, these reactions proceeded smoothly, leading to the desired products in 60–75% yields, with an excellent enantiomeric excess, **10l–n** (Scheme 1).

These excellent results can be explained due to the use of PEG-400 (a green and recoverable solvent), which might play an important role in the retention of the acetaldehyde in solution.



Scheme 1

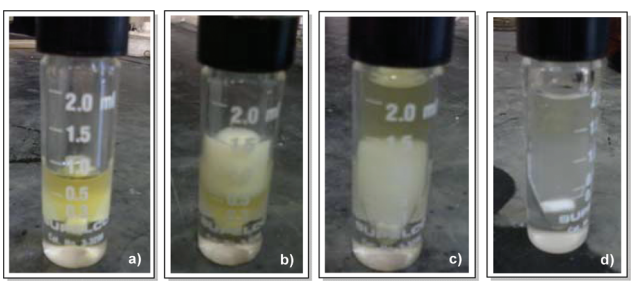


Fig. 1 PEG recovering. (a) The reaction mixture at the end time, (b) 0.25 mL of water was added – emulsion appears, (c) extraction with ether, (d) the emulsion disappears – with total recovery of PEG.

The recyclability of the solvent in the catalytic system was also evaluated for the reaction of *trans*-β-nitrostyrene and *n*-butyraldehyde (Fig. 1).

Hence, we attempted to reuse the PEG, which was one of the prime objectives in our quest. In this regard we performed a set of experiments to explore whether the PEG can be reused for further reactions (Table 3). After completion of the reaction, task specific PEG was recovered and subjected to another run, affording the product in almost the same yield, dr and ee. This process was repeated four more times, affording the product in excellent yields, dr and ee. In order to verify the reproducibility of runs, the standard deviation (σ) and also the correlation coefficient (CV) were calculated (Table 3). Consequently, as the CV was less than 5%, the experimental values are acceptable. The simple experimental and product isolation procedures combined with the easy recovery and reuse of PEG is expected to contribute to the development of a green strategy for the Michael addition reactions.

Table 3 Recyclability of PEG for the conjugate addition[a]

Runs	1	2	3	4	5	σ	C.V.
Yield[b] (%)	99	95	95	94	89	3.2	3.38%
ee[c] (%)	97	97	96	97	97	0.4	0.41%

[a] Reactions were performed using *trans*-β-nitrostyrene (0.3 mmol), butyraldehyde (0.6 mmol), benzoic acid (0.015 mmol – 5 mol%) and an organocatalyst (0.015 mmol – 5 mol%) in PEG 400 (0.5 mL – 0.6 mol L^{-1}). [b] Isolated yield. [c] The ee values were determined by chiral HPLC.

Experimental

General information

^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 (400 and 100 MHz respectively). All NMR spectra were obtained in $CDCl_3$.

HPLC chromatograms of Michael adducts were obtained on Shimadzu apparatus equipped with a LC-20AT Pump, SPD-M20A UV-Vis Detector, CBM-20A System Controller, using a Chiralcel OD-H (4.6 mm × 250 mm, particle size 5 μm), Chiralpak AD-H (4.6 mm × 250 mm, particle size 5 μm) and a Chiralcel AS-H (4.6 mm × 250 mm, particle size 5 μm).

Optical rotations were measured with a Schmidt + Haensch Polartronic H Polarimeter, at 589 nm, 23 °C, using a 1 mL cell with a 1 dm path length and reported as follows: $[\alpha]_D^{23}$ (c in g per mL of the solvent).

All the compounds synthesized in the manuscript are known. The relative and absolute configurations of the products were determined by comparison with the known ^{1}H and ^{13}C NMR, chiral HPLC analysis, and optical rotation values.

Column chromatography was performed using Merck Silica Gel (230–400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with $KMnO_4$ solution.

General procedure for Michael addition

The aldehyde (0.6 mmol), nitroolefin (0.3 mmol) and benzoic acid (0.015 mmol) were added to a solution of the catalyst (0.015 mmol) in PEG-400 (0.5 mL). The reaction mixture was stirred for 19 h and then was directly purified by flash column chromatography on silica gel using *n*-hexane–EtOAc as the eluent. The enantiomeric excess was determined by chiral-stationary-phase HPLC analysis by comparison with the authentic racemic material. Assignment of the stereoisomers was performed by comparison with literature data.

Conclusions

In conclusion, taking advantage of the benign nature of PEG 400, we have developed a highly efficient organocatalysed asymmetric Michael addition of aldehydes to *trans*-β-nitrostyrenes, allowing a faster and high stereoselective reaction when compared with other eco-friendly solvents. This innovative and good result can be due to a host–guest complex, PEG-nitrostyrene, which facilitates the nucleophilic addition of enamine resulting from the reaction between the aldehyde and the organocatalyst. Moreover and noteworthily, after Michael addition product extraction with ether, PEG was efficiently totally recovered and reused. Regarding the architecture of the diaryl prolinol silyl ether organocatalyst, we have concluded that hydrophobic alkyl side chains greatly influence the reaction, being better organocatalysts than the ones which possess ethyl and hexyl chains on their structure. The best catalytic system (with organocatalyst **3**) in PEG proved to be very effective for the enamine based Michael reactions, providing good yields and stereoselectivities for a broad range of aldehydes and *trans*-β-nitroolefins. When this system is applied to acetaldehyde, which is known to be very difficult to handle and highly reactive (translated into undesired side reactions and moderate yields), we have found, to our delight, good yields and excellent ee, proving to be an excellent and easy methodology for the formal synthesis of three pharmaceuticals: (*R*)-enantiomer of pregabalin, (*R*)-phenibut and (*R*)-bacoflen. In fact, the eco-friendly procedure, high yields and stereoselectivities, easy work up, efficient synthesis of pregabalin, phenibut and bacoflen precursors and the total recyclability of PEG are the very notable features of this work.

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Asymmetric Synthesis

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Organocatalytic Asymmetric 1,6-Addition/1,4-Addition Sequence to 2,4-Dienals for the Synthesis of Chiral Chromans**

*Pernille H. Poulsen, Karla Santos Feu, Bruno Matos Paz, Frank Jensen, and Karl Anker Jørgensen**

Abstract: *A novel asymmetric organocatalytic 1,6-addition/1,4-addition sequence to 2,4-dienals is described. Based on a 1,6-Friedel–Crafts/1,4-oxa-Michael cascade, the organocatalyst directs the reaction of hydroxyarenes with a vinylogous iminium-ion intermediate to give only one out of four possible regioisomers, thus providing optically active chromans in high yields and 94–99% ee. Furthermore, several transformations are presented, including the formation of an optically active macrocyclic lactam. Finally, the mechanism for the novel reaction is discussed based on computational studies.*

The enantioselective synthesis of small chiral molecules, containing biologically relevant frameworks, by a general and efficient strategy is an important goal in modern organic chemistry. One such class of molecules is the chiral chromans, which are encountered in nature and have been found as core elements commonly present in synthetic and natural compounds possessing broad and interesting biological activities (Figure 1).[1]

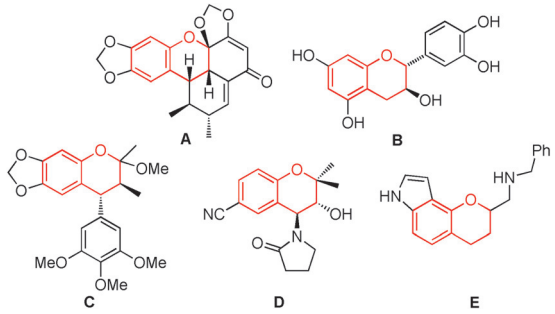

Figure 1. Structures containing a chiral chroman core. Carpanone (**A**; natural product). Catechin (**B**; antitumor agent). NCS 381582 (**C**; podophyllotoxin analogue, antimitotic agent). Cromakalim (**D**; potassium channel opener). Dopamine D_2 partial agonist (**E**).

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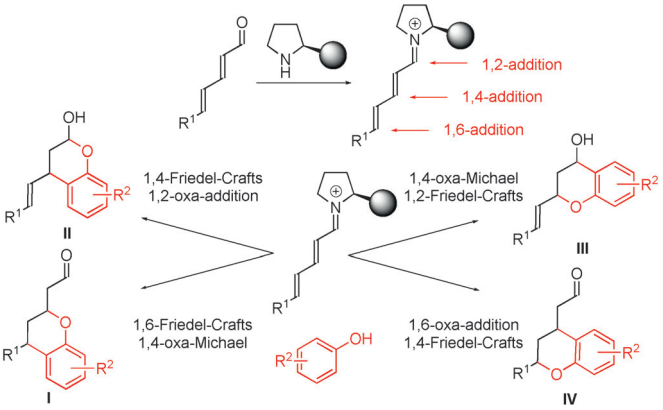
Given the intriguing properties of chiral chroman derivatives, we decided to investigate the feasibility of a novel organocatalytic asymmetric cascade reaction between hydroxyarenes and 2,4-dienals through vinylogous iminium-ion activation,[2] thus giving rise to the chroman core structure. However, several challenging issues have to be addressed for such an approach. The regioselectivity has to be taken into account as both electrophile and nucleophile have multiple reaction sites (Scheme 1). First, the competition



Scheme 1. The four different regioselective approaches of hydroxyarenes to the vinylogous iminium-ion.

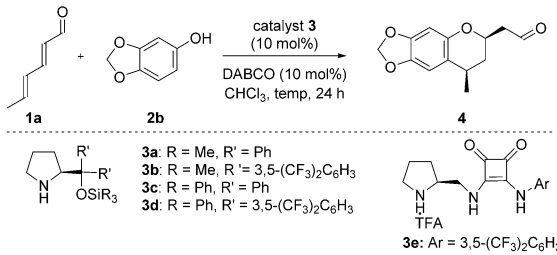
between 1,6- versus 1,4-addition of the first nucleophilic attack is crucial. Experimental and computational studies have shown that the organocatalytic 1,4-addition is frequently favored over the 1,6-addition.[3] Except for one single example[4] in which unbiased aliphatic 2,4-dienals were used, all previous studies of regio- and enantioselective 1,6-additions to 2,4-dienals have relied on sterically blocking the 4-position to suppress the competing 1,4-addition.[5] Second, the hydroxyarene can react either through the hydroxy group or a Friedel–Crafts-type reaction in the first step (Scheme 1). Furthermore, the control of stereoselectivity is another equally important challenge which must be addressed as the initial stereocenter is formed at the 6-position of the aldehyde, six bonds away from the stereocenter of the catalyst. Finally, both the diastereo- and enantioselectivities of the product have to be controlled. The four different regioselective approaches of the hydroxyarene to the vinylogous iminium-ion intermediate are outlined in Scheme 1.

Herein, we present the first asymmetric Friedel–Crafts reaction[6,7] of hydroxyarenes with aliphatic and aromatic 2,4-

dienals, followed by a ring-closing oxa-Michael reaction[8] in a 1,6-addition/1,4-addition cascade. This novel reaction concept is based on the regio- and stereoselective Friedel–Crafts 1,6-addition reaction of hydroxyarenes to a vinylogous iminium-ion intermediate and subsequent oxa-Michael 1,4-addition to the iminium-ion formed in the first step (Scheme 1, lower left). This organocatalytic cascade proceeds with full regioselectivity in the two addition steps and the chiral chroman products are formed with excellent enantioselectivity and good to high diastereoselectivity. Importantly, no substituents on the 2,4-dienal are required to ensure complete remote selectivity in the first step.

We initiated our studies of the 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction by performing the reaction between (*E*,*E*)-2,4-hexadienal (**1a**) and sesamol (**2b**; Table 1). The

Table 1: Organocatalytic asymmetric 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction: Screening results.[a]



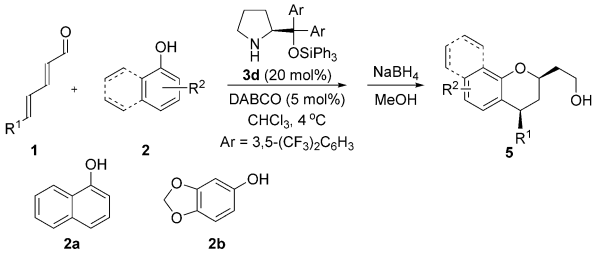
Entry	**1a**/**2b**	**3**	Solvent	*T* [°C]	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	3:1	**3a**	$CHCl_3$	RT	87	1:1.2	34
2	3:1	**3b**	$CHCl_3$	RT	41	2.7:1	87
3	3:1	**3c**	$CHCl_3$	RT	15	1.2:1	63
4	3:1	**3d**	$CHCl_3$	RT	40	6.0:1	98
5	3:1	**3e**	$CHCl_3$	RT	–	–	–
6	3:1	**3d**	$CHCl_3$	40	49	4.5:1	97
7	3:1	**3d**	CH_2Cl_2	40	50	3.1:1	93
8	3:1	**3d**	MTBE	40	–	–	–
9	3:1	**3d**	toluene	40	19	1.6:1	69
10	1:2	**3d**	$CHCl_3$	RT	83	3.3:1	93
11[e]	1:2	**3d**	$CHCl_3$	4	71	4.9:1	98

[a] Reactions were performed on a 0.1 mmol scale. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess was determined by UPC^2 (ultra performance convergence chromatography) (see the Supporting Information). [e] 20 mol% of **3d** and 5 mol% of DABCO applied. DABCO = 1,4-diazobicyclo [2.2.2] octane, MTBE = methyl *tert*-butyl ether, TFA = trifluoroacetic acid.

reaction was conducted in the presence of 10 mol% of the TMS-protected diphenylprolinol catalyst **3a**[9] and 10 mol% of DABCO in $CHCl_3$ at room temperature. Delightfully, only one product, **4**, corresponding to the 1,6-Friedel–Crafts/1,4-oxa-Michael reaction, was observed, albeit with poor stereocontrol (1:1.2 d.r. and 34% *ee*). The screening of a series of catalysts revealed that the catalyst **3d**, possessing both CF_3-disubstituted aryl groups and a triphenylsilyl-protecting group, led to improvements in both enantio- and diastereoselectivity (entry 4). The hydrogen-bond directing catalyst **3e** was unable to catalyze the reaction (entry 5). The reaction was very solvent dependent, while an increase in temperature to 40°C resulted in decreased stereoselectivity and did not improve the conversion (entries 6–9). A higher conversion was obtained by applying an excess of **2b**, but resulted in decreased diastereoselectivity (entry 10). This decrease in diastereoselectivity was solved by lowering the temperature to 4°C and using 20 mol% of **3d** and 5 mol% of DABCO (entry 11; for further screening results see the Supporting Information).

The scope of the organocatalytic asymmetric cascade reaction was then explored for various 2,4-dienals (**1**) reacting with either 1-naphthol (**2a**) or sesamol (**2b**) in the presence of **3d** as the catalyst (Table 2). The results show that both

Table 2: Aldehyde scope for the organocatalytic asymmetric 1,6-Friedel–Crafts/1,4–oxa-Michael cascade reaction.[a]

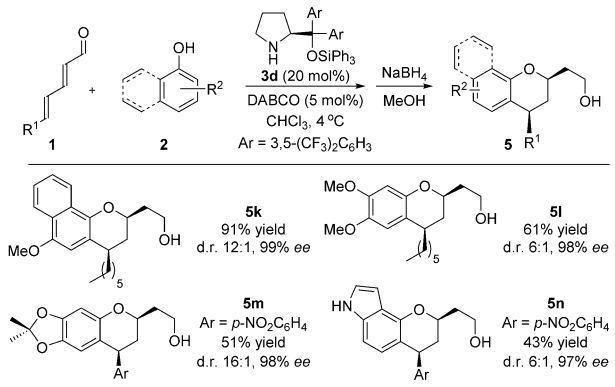


Entry	R^1	**2**	Yield [%]	d.r.[b]	*ee* [%][c]
1	Me (**1a**)	**2a**	**5a**: 72	4:1	96
2	*n*-hexyl (**1b**)	**2a**	**5b**: 82	6:1	98
3	cyclohexyl (**1c**)	**2a**	**5c**: 63	16:1	99
4	*o*-$NO_2C_6H_4$ (**1d**)	**2a**	**5d**: 70	16:1	99
5	*p*-$NO_2C_6H_4$ (**1e**)	**2a**	**5e**: 67	7:1	99
6	*p*-BrC_6H_4 (**1f**)	**2a**	**5f**: 66	6:1	96
7	*p*-$CF_3C_6H_4$ (**1g**)	**2a**	**5g**: 77	13:1	99
8	*n*-hexyl (**1b**)	**2b**	**5h**: 54	5:1	96
9	*o*-$NO_2C_6H_4$ (**1d**)	**2b**	**5i**: 66	6:1	98
10	*p*-$NO_2C_6H_4$ (**1e**)	**2b**	**5j**: 69	5:1	94

[a] Reactions were performed on a 0.1 mmol scale. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Enantiomeric excess was determined by UPC^2 (ultra performance convergence chromatography) (see the Supporting Information).

aliphatic and aromatic 2,4-dienals react smoothly in the 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction with **2a** and the optically active chromans are obtained in 63–82% yield with excellent enantioselectivity (96–99% *ee*) and a diastereomeric ratio ranging from 4:1 to 16:1 (entries 1–7). The highest enantioselectivity is obtained for the cyclohexyl-substituted 2,4-dienal **1c** and the majority of the aromatic 2,4-dienals (**1d**,**e**,**g**), while the highest diastereoselectivity is found for the cyclohexyl- and *ortho*-nitrophenyl-substituted 2,4-dienals, **1c** and **1d**, respectively. The reaction for the various 2,4-dienals also proceeds with the same excellent enantioselectivity for **2b**, but the diastereoselectivity is slightly lower compared to the results obtained for **2a**.

Scheme 2 shows that applying a more nucleophilic hydroxyarene, such as 4-methoxy-1-naphthol, leads to an increase in both yield and diastereo- and enantioselectivity for the chroman **5k** compared to those for 1-naphthol

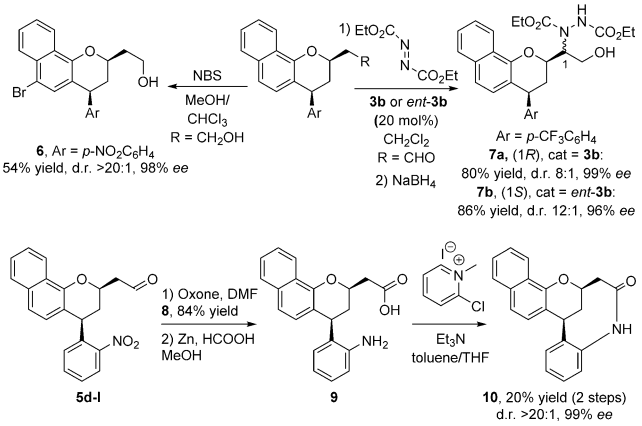


Scheme 2. Reaction of different nucleophiles in the organocatalytic asymmetric 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction.

(Table 2, entry 2). The increase in stereoselectivity might be due to the more sterically demanding nucleophile having a methoxy substituent, rather than a hydrogen atom. A similar increase in stereoselectivity is also observed for the dimethyl-substituted sesamol (**5m**). 3,4-Dimethoxy phenol also reacts smoothly and the product **5l** is obtained in good yield and diastereoselectivity with 98% *ee*. An interesting nucleophile is the one derived from indole, which provides the chroman **5n** with similar results. Notably, the developed methodology could be scaled up while maintaining the high selectivity; the product *ent*-**5k** was obtained in 69% yield (0.7 g), 14:1 d.r. and 99% *ee* when performing the reaction on a 3.0 mmol scale.

The absolute configuration of the chiral chromans obtained was unambiguously assigned by X-ray analysis of the carboxylic acid derivative of **5f** (see the Supporting Information).

It has been observed that hydroxyarenes having electron-withdrawing substituents are not reactive under the present reaction conditions.[10] However, optically active chromans, in which the hydroxyarene is substituted with a bromine, can be obtained by bromination of **5e**, thus providing **6** in 54% yield,



Scheme 3. Selective bromination of the aromatic moiety in the chroman (top left), diastereoselective α-amination of the aldehyde (top right), and formation of a macrocyclic lactam (bottom). DMF = *N*,*N*-dimethylformamide, NBS = *N*-bromosuccinimide.

> 20:1 d.r., and 98% *ee* (Scheme 3). The optically active chroman aldehydes can also be selectively functionalized at the α-position of the aldehyde, thereby adding an additional step to the cascade sequence. However, this step requires the less sterically hindered catalyst **3b**, and by using both enantiomers of **3b** access to both diastereomeric forms of the α-aminated aldehydes **7a**,**b** is achieved in good yields and excellent stereoselectivities (Scheme 3); thus a new stereocenter is introduced. Furthermore, the synthesis of the macrocyclic lactam chroman core structure **10**[11] is shown (Scheme 3).

The four different regioselective approaches of a hydroxyarene to the vinylogous iminium-ion intermediate are outlined in Scheme 1. The complete regioselectivity of the 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction observed is in sharp contrast to what has been found in the other investigations involving linear 2,4-dienals, as the 1,4-addition is normally favored compared to the 1,6-addition.[3,5b,c] The 1,4-selectivity has, for example, been accounted for by computational studies which show that C4 in the vinylogous iminium-ion intermediate has both a higher positive charge and orbital coefficient in the LUMO, compared to C6.[3] We have performed calculations, which support these results. To change the reaction course from a 1,4-addition to a selective 1,6-addition, previous work on regio- and enantioselective 1,6-additions to 2,4-dienals relied on sterically blocking the 4-position to suppress the competing 1,4-addition.[5] The remarkable selectivity of the 1,6-addition/1,4-addition cascade in the present development encouraged us to try to elucidate the origin of this selectivity.

Scheme 1 shows the four possible products (**I**-**IV**) of the cascade reaction, but only **I** is observed. Based on DFT-calculations (wB97XD/pcseg-1 using the $CHCl_3$ IEFPCM solvent model[12]) for the model reaction of 2,4-hexadienal with 1-naphthol, the relative energies of **I**/**II**/**III**/**IV** are 5:36:57:0 kJ mol^{-1}. To probe the reaction mechanism we have located transition structures for the four possible addition reactions corresponding to either the Friedel–Crafts (C-addition) or oxa-Michael (O-addition) addition at the 4-position and 6-position of a vinylogous iminium-ion, formed from pyrrolidine and 2,4-hexadienal. The 1-naphthol reagent was modelled either as the free 1-naphtolate, as a 1-naptholate-1-naphthol complex,[13] or as 1-naphthol interacting with DABCO, acting as a base. The conformational degrees of freedom were sampled using the MMFF force field followed by full optimizations at the DFT level mentioned above. All transition structures were confirmed by frequency calculations and the conformational lowest energy transition structure was characterized by following the IRC to both sides.

The four possible transition-state and product energies ($\mathbf{6}_C$, $\mathbf{6}_O$, $\mathbf{4}_C$, $\mathbf{4}_O$) for the three models are shown in Figure 2. Addition of 1-naphthol to the vinylogous iminium-ion gives significantly higher transition-state energies for carbon acting as nucleophile, and no stable adducts when oxygen is the nucleophile. The series shows an inverse Hammond-type relationship, with the lowest transition-state energy leading to the least stable intermediate, and vice versa. The lowest activation energy is for the 1,4-oxa-Michael addition forming

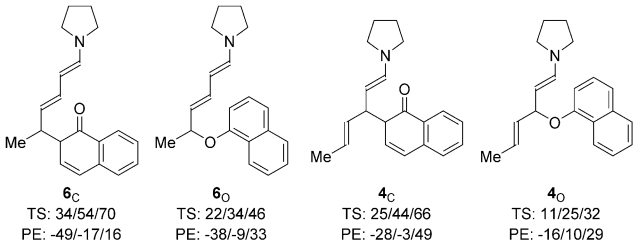
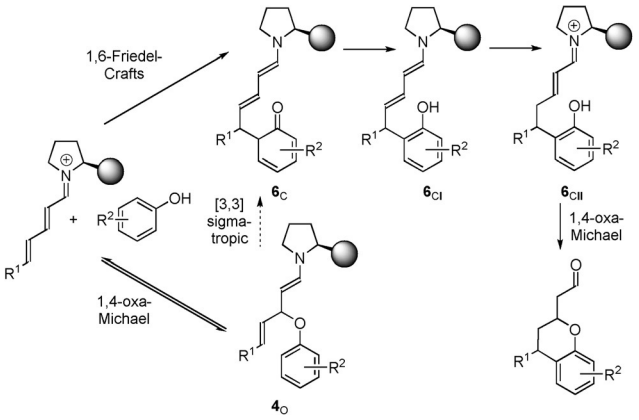


Figure 2. Transition-state (TS) and product energies (PE) (kJ mol^{-1}) for addition of 1-naphtholate, 1-naphtholate-1-naphthol, and 1-naphthol-DABCO to the vinylogous iminium-ion.

$\mathbf{4}_O$, while the highest is for the 1,6-Friedel–Crafts reaction leading to $\mathbf{6}_C$. The kinetic preference for the nucleophilic attack at C4 is in agreement with this carbon atom having both the highest positive charge and LUMO coefficient in the vinylogous iminium-ion intermediate. The relative energies of the products formed by these four different nucleophilic attacks show that the most stable intermediate is $\mathbf{6}_C$ followed by $\mathbf{6}_O$ and $\mathbf{4}_C$/$\mathbf{4}_O$. The higher stability of $\mathbf{6}_C$/$\mathbf{6}_O$ relative to $\mathbf{4}_C$/$\mathbf{4}_O$ is due to conjugation of the double bonds in the former class of products.

The energetics in Figure 2 show that activation energies decrease and product stabilities increase as the nucleophilicity of 1-naphthol is increased by complexation with DABCO or conversion into the naphtolate. All four addition reactions are predicted to be reversible under the reaction conditions, and $\mathbf{6}_C$ will thus be formed preferentially. Keto–enol tautomerization of $\mathbf{6}_C$ is calculated to be exothermic by 27 kJ mol^{-1}, thus leading to a dienamine-trapped intermediate $\mathbf{6}_{CI}$, and this effectively traps the first formed product corresponding to a 1,6-Friedel–Crafts reaction (Scheme 4). Upon protonation



Scheme 4. Proposed mechanism with intermediates.

at the γ-position of the intermediate $\mathbf{6}_{CI}$ the corresponding iminium-ion intermediate $\mathbf{6}_{CII}$ is generated. Once $\mathbf{6}_{CII}$ is formed it immediately undergoes the 1,4-oxa-Michael addition, thus leading to the observed product. The proposed overall mechanism is shown in Scheme 4. It should also be noted that no transition-state energy for the [3,3]-sigmatropic rearrangement of $\mathbf{4}_O$ leading to $\mathbf{6}_C$ was found, hence this pathway might result in higher energies than the dissociation energy of $\mathbf{4}_O$.

In summary, the first asymmetric organocatalytic 1,6-Friedel–Crafts/1,4–oxa-Michael cascade by reaction of hydroxyarenes with 2,4-dienals for the construction of chromans is described. The reaction proceeds with excellent regio- and enantioselectivities, thus giving optically active chromans in high yields and 94–99 % *ee*. The potential of the reaction concept developed is demonstrated with a series of transformations, including the formation of an optically active macrocyclic lactam. Computational studies point to a reaction sequence, involving a number of intermediates, driven by thermodynamic control of the Friedel–Crafts reaction step.

Keywords: asymmetric synthesis · heterocycles · Michael addition · organocatalysis · synthetic methods

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