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Grau de Química

Treball Final de Grau

Development of new asymmetric allylic alkylations with Morita-Baylis-Hillman fluorides and difluoroalkenes

Desenvolupament de noves reaccions d'alquilació al·líliques asimètriques entre fluorurs de Morita-Baylis-Hillman i difluoroalquens

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Vull agrair al Dr. Xavier Companyó la seva comprensió i dedicació durant tot el treball. Ha sigut realment important per a poder realitzar tota aquesta feina en un semestre tan atapeït. També agrair l'ajuda del Prof. Albert Moyano i el suport d'en Pol Torres, l'Ana Martínez i la Laura Roldán durant l'estada al laboratori.

REPORT

Contents

1. SUMMARY

Asymmetric catalysis has been one of the main topics in organic chemistry in the last 50 years. Traditionally, asymmetric allylic alkylation reactions (AAA) were based on transition-metal-catalysed reactions. Recently, the organocatalytic AAA has been developed where small organic molecules, such as chiral tertiary amines and phosphines, are used as catalysts instead of transition metals.

The objective of the TFG has been the development of a new asymmetric allylic alkylation reaction (AAA) using Morita-Baylis-Hillman (MBH) fluorides and nucleophiles activated by the fluoride anion (difluoroalkenes). The leaving group of the MBH adduct activates the nucleophile, and it is incorporated in the final product as a trifluoromethyl group, this is the distinguishing aspect of the reaction. The products are interesting because of its trifluoromethyl group, a singular group in organic chemistry which is commonly used in pharmaceutical industry. The reactivity has been tested using chiral tertiary amines as catalyst, such as β-isocupreidine, a compound derived from quinine, to synthesise the corresponding enantioenriched products.

The characterisation of the products has been performed by spectroscopic and chromatographic methods such as NMR and chiral HPLC, respectively.

Keywords: Asymmetric catalysis, asymmetric allylic alkylation, organocatalysis, chiral Lewis bases, trifluoromethyl group, NMR spectroscopy, chiral HPLC.

2. RESUM

La catàlisi asimètrica ha estat un dels aspectes més importants dels últims 50 anys en la química orgànica. Tradicionalment, les alquilacions al·líliques asimètriques (AAA) han estat basades en reaccions catalitzades per metalls de transició. Recentment, les AAA organocatalítiques s'han desenvolupat amb molècules orgàniques petites, com ara amines terciàries o fosfines quirals, que són usades com a catalitzadors, en lloc de metalls de transició.

L'objectiu del TFG ha estat el desenvolupament de noves reaccions d'alquilació al·líliques asimètriques (AAA) emprant adductes fluorats dels alcohols de Morita-Baylis-Hillman (MBH) i nucleòfils activats a través de l'anió fluorur (difluoroalquens). La particularitat d'aquesta reacció és que el grup sortint de l'adducte de MBH és el que activa el nucleòfil, que és incorporat al producte final com un grup trifluorometil. Els productes són interessants, ja que contenen un grup trifluorometil, grup singular en química orgànica que sol ser important en la indústria farmacèutica. La reactivitat ha estat provada utilitzant catalitzadors com ara la β-isocupreidina, un derivat de la quinina, per sintetitzar productes d'alquilació al·lílica enantioenriquits.

L'anàlisi de l'estructura i puresa dels productes obtinguts s'ha aconseguit mitjançant mètodes espectroscòpics i cromatogràfics com ara RMN i HPLC quiral.

Paraules clau: Catàlisi asimètrica, alquilació al·lílica asimètrica, organocatàlisi, bases de Lewis quirals, grup trifluorometil, espectroscòpia RMN, HPLC quiral.

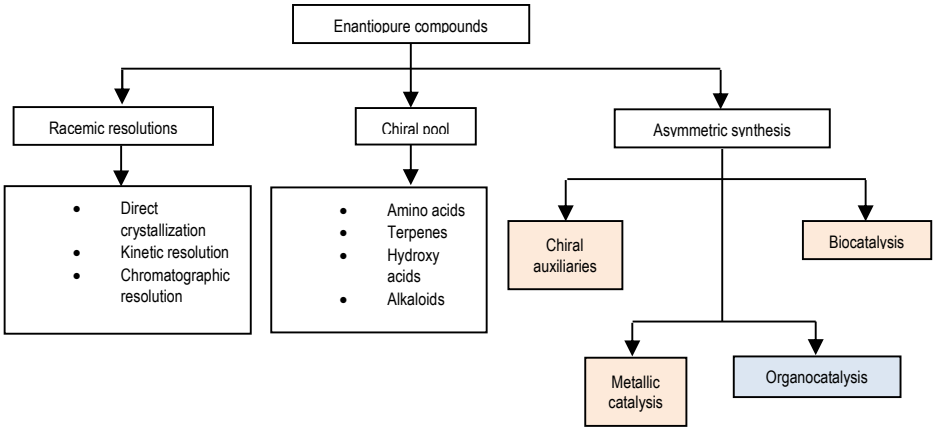
3. INTRODUCTION

3.1. ASYMMETRIC CATALYSIS

3.1.1. SYNTHESIS OF ENANTIOPURE COMPOUNDS

Asymmetric synthesis is one of the main topics in organic chemistry in the last 50 years. The obtention of chiral molecules in a pure enantiomeric form has been studied until our recent days. Since the end of 19th century, the enantioselective synthesis of chiral molecules has attracted the attention of chemists, who have responded with brilliance and cleverness.

Scheme 1 shows the main strategies to obtain enantioenriched chiral compounds.



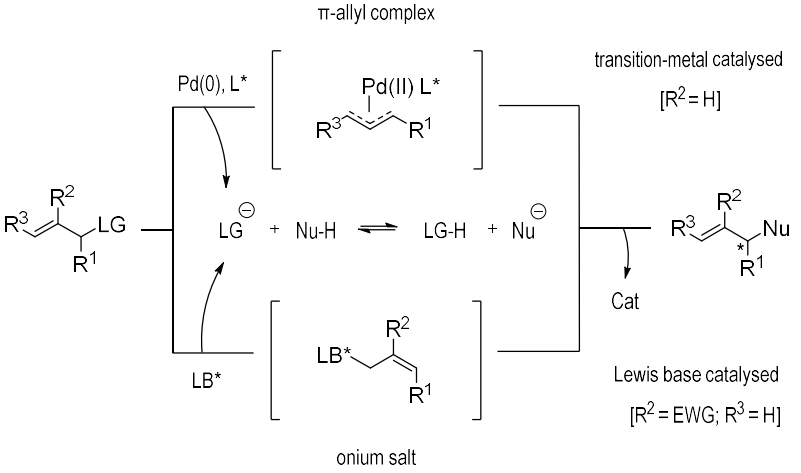
Scheme 1. Different strategies for the obtention of enantioenriched chiral compounds[1]

As it is shown in the conceptual map, there are three main methods to obtain enantioenriched compounds. The resolution of racemic compounds; the use of the chiral pool; and asymmetric synthesis[1]. On the one hand, racemic resolutions are based on the separation of the two enantiomers of a racemic product using different methodologies. Consequently, only half of the initial material is converted in the desired enantiomer. On the other hand, chiral pool relies on a collection of abundant enantiopure buildings blocks provided by nature, such as amino acids, terpenes or alkaloids. This fact provides an intrinsic limitation. Moreover, it is difficult to perform it on a large scale. Therefore, asymmetric synthesis is the most interesting method because it is the most efficient.

Asymmetric synthesis can be further classified into three different groups[1]. One of them is the utilization of chiral auxiliaries, which are chiral groups or units that are temporarily incorporated into an organic compound to control the stereochemical outcome of the synthesis. Another one is biocatalysis, which is the catalysis carried out by chiral molecules from biological origin, such as enzymes. And the last one, asymmetric catalysis, is the most interesting because of its versatility and it can be organometallic catalysis and organocatalysis. We will consider organometallic catalysis if the catalyst has a transition metal[1]. On the other hand, we define organocatalysis as the acceleration of organic reactions using exclusively organic molecules as catalysts. Both include asymmetric allylic alkylations, which are the studied reactions in this project. Aside from asymmetric allylic alkylations, other classic organic reactions such as aldolic reaction, Mannich reaction or Michael reaction have been developed under both organometallic and organocatalytic versions[2].

3.1.2. ASYMMETRIC ALLYLIC ALKYLATION

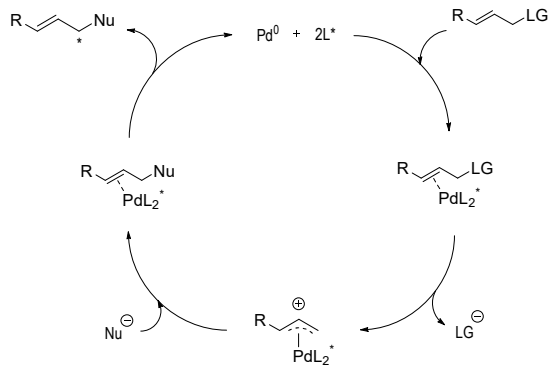
Asymmetric allylic alkylations (AAA) are amongst the most powerful transformations in modern chemistry. They enable the stereoselective generation of new C-C, C-N, C-O, C-S or C-P bonds in allylic positions, so it is a fundamental method to functionalise organic molecules in a stereoselective manner.



Scheme 2. Transition-metal and organocatalytic asymmetric allylic alkylation[2]

3.1.3. HISTORY OF AAA

In the 1970s, Trost developed the first asymmetric allylic alkylation methodologies catalysed by palladium complexes[3]. They mechanism is based on the initially oxidative addition of the catalyst to the allylic substrate to form a π-allyl complex (Scheme 3). The chiral ligand bonded to the metal centre are the responsibly of the asymmetric induction. In Scheme 3 it is shown the catalytic cycle of the Tsuji-Trost reaction. Palladium activates the substrate ionising the leaving group (LG), so it is oxidised to Pd (II) and incorporates two ligands (L_2) to generate the chiral π-allyl complex. This electrophilic complex is then attacked by a nucleophile with negative charge, creating the new bond between the nucleophile and the substrate, and the palladium is restored to its metallic form (Pd^0)[3].



Scheme 3. Mechanism of Tsuji-Trost reaction

At the beginning of the 21st century, Kim and Lu reported[4] a method to perform asymmetric allylic alkylations using organic chiral Lewis bases, as a nucleophilic catalyst such as tertiary amines or phosphines.

3.1.4. MBH ADDUCTS

Specifically, Kim and Lu reported[4] the transition-metal-free AAA of racemic Morita-Baylis-Hillman (MBH) adducts, catalysed by chiral organic bases.

MBH adducts are molecules synthesized from MBH alcohols. They are molecules synthesized by the Baylis-Hillman reaction, a carbon-carbon bond forming reaction between the α-position of an activated alkene (with an electron withdrawing group (EWG)) and a carbon

electrophile such as an aldehyde. The reaction is catalysed by a nucleophile such as a tertiary amine or a phosphine. The most used is DABCO (Fig. 1), because of its increased nucleophilic properties compared with other tertiary amine.

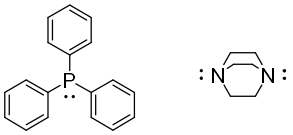


Figure 1. Triphenylphosphine and DABCO structures

MBH adducts are formed upon alcohol protection of MBH alcohols. They have an electron withdrawing group (EWG) from MBH alcohol in β-position and a leaving group (LG) in their α-position if it is considered the following structure (Fig. 2). The most common LGs are carbonates (OBoc) or acetates (OAc).

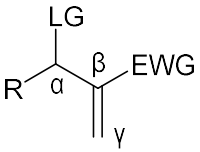
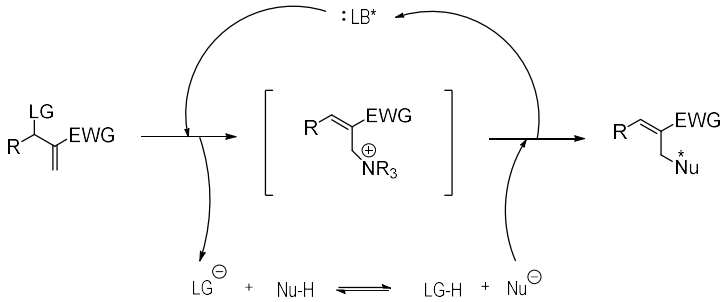


Figure 2. MBH carbon nomenclature

These MBH adducts are susceptible to be attacked by nucleophilic catalysts via a S_N2' process (Scheme 2). As described in Scheme 2, the catalyst binds to the adduct removing the leaving group and forming an electrophilic onium intermediate[2]. Then, a nucleophile can attack the onium salt via another S_N2' mechanism, so it means attacking the α-carbon (α-alkylation, Scheme 2), or via S_N2, so attacking the γ-carbon (γ-alkylation, Scheme 4). In Scheme 4 is represented γ-alkylation of MBH adducts. Depending on different reaction parameters including the solvent, the temperature, the leaving group, the starting materials or the catalyst, the reaction can go through α or γ alkylation, so it can be regiodivergent.



Scheme 4. AAA through a γ-alkylation mechanism[2]

Recently, it has been published some articles[5] about the use of MBH fluorides where the LG is a fluorine atom, alternatively to acetates and carbonates. This ionized leaving group (fluoride) can activate pronucleophiles with C-Si bonds, affording the corresponding products in good yields and enantiomeric excesses[5].

3.1.5. GREEN CHEMISTRY

In recent years, global warming, is one of the biggest problems in our actual society. It is a challenge for the humanity to preserve the planet where we live in the best possible situation for future generations. That is why chemistry cannot stay behind the transition to a more sustainable world. Chemist must provide the necessary tools to achieve this change such as finding new ways to create better batteries in order to avoid processes that release CO_2.

Between the end of the last century and the beginning of the 21st century, Anastas and Warner settled the bases of green chemistry[6]. Green chemistry is the utilization of a set of principles that reduces the use or generation of hazardous substances in the design manufacture and application of chemical products. In 1998, they defined "The Twelve Principles of Green Chemistry" and amongst them there is the Atom Economy principle[6].

This concept defines how much starting material is necessary in a process compared to the produced product. It considers the molecular weights of the reagents and the desired product, and its definition is shown in the following formula. It is expressed in a percentage, so it goes from 0 to a 100 % if all the atoms of the staring materials end up in the final product[6].

$$Atom\ economy\ (\%) = \frac{MW\ of\ desired\ product}{MW\ of\ all\ reagents\ used} \times 100$$

$$0 < AE\ (\%) \leq 100$$

Therefore, atom economy is a good indicator of the sustainability of a reaction, because the more atoms of starting material are incorporated in the product the less residue is generated.

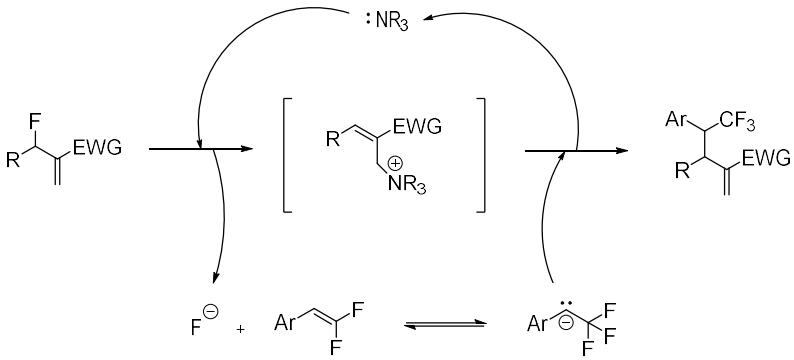
Continuing with organocatalytic reactions, they also represent a giant step in sustainable catalysis because they avoid the use of transition metals. As mentioned before, in Tsuji-Trost reaction, the common catalytic used is palladium, which it is an expensive metal, owing to its shortage in the earth's crust, so it hinders its utilization and it can be a reason for deciding not to investigate it further.

In addition, wastes generated are strongly regulated by the actual environmental legislation, so using heavy transition metals which have a high toxicity and carcinogenicity, such as palladium, can be a disadvantage and is not clearly a future model to follow.

For the last reasons is why organocatalysis performed a fundamental change in the last two decades. In organocatalysis, the catalysts are purely organic molecules, which are much less toxic than transition metals. Moreover, these organic catalysts have a considerably lower cost compared with their metallic equivalents, because of its inexpensive and easy synthesis.

3.1.6. NEW ASYMMETRIC ALLYLIC ALKYLATION BETWEEN MBH FLUORIDES AND DIFLUOROALKENES

Having exposed the most relevant transformations of MBH adducts, the approach of the project is to develop a new asymmetric allylic alkylation using organocatalysis. Specifically, fluoride adducts of MBH alcohols will be investigated. Normally, the leaving group in MBH carbonates or acetates are not useful anymore and hence are considered waste of the reaction, remaining in solution as the protonated counterparts ^{t}BuOH or AcOH. One of the proposals of this project is to reuse the leaving group (fluoride) to activate the nucleophile and subsequently be incorporated in the final product. This activated nucleophile is going to attack the onium salt (electrophile) liberating the catalyst and creating a new C-C bond, so forming a bigger molecule which is the addition of the two starting molecules. The reaction is described in Scheme 5.



Scheme 5. Designed reaction

The designed reaction (Scheme 5) consists of three important steps. An initial S_N2' reaction, followed by a nucleophile activation that concludes in another S_N2'.

As reported previously[2], MBH adducts have been investigated to achieve asymmetric allylic alkylations, but the reuse of the leaving group after the nucleophilic attack is unknown. In this case, the intention is to design a novel reaction which the two steps involucrate only the two starting molecules and the catalyst. Moreover, in the activation of the nucleophile, there is not a loss of mass, because the fluoride is integrated into the nucleophile, generating a trifluoromethylated molecule. Finally, the trifluoromethyl nucleophile is going to attack the onium salt, generating once again a very efficient transformation. That is why the global reaction is so interesting.

First of all, the reaction can be stereoselective if a chiral catalyst is used. Secondly, it is transition-metal-free reaction, so it is less dangerous for the environment. Besides, organocatalysts are much cheaper than metallic catalysts. It cannot be forgotten that it is a good way to create new C-C bonds in stereoselective manner. And one of the best aspects of the proposed reaction is that its atom economy is perfectly at 100%.

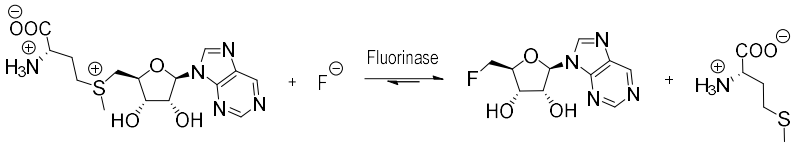
$$Atom\ Economy\ (\%) = \frac{392.1235}{194.0743 + 198.0492} \times 100 = 100\%$$

It means that all the atoms of the starting material end up constituting the product.

3.2. ORGANOFLUORINE CHEMISTRY

3.2.1. HISTORICAL PERSPECTIVE

Organofluorine chemistry began in the 19th century when it started the organic chemistry development. The first organofluorine compounds were chlorofluorocarbons (CCl_3F and CCl_2F_2), developed in the 1920s. Electrochemical fluorination was discovered in 1930s to create highly stable fluorinated materials, which allowed the synthesis of C-F bonds without using elemental fluorine. In 1957, it was designed and described one of the first fluorinated drugs[7]. Years later, it was discovered the contribution of CFCs in atmospheric ozone destruction, and this study showed to the world the consequences of these compounds in the planet. In 21st century, one of the most relevant studies was the discovery of the first C-F bond-forming enzyme, called fluorinase, which is able to fluorinate 5'-deoxyadenosine in carbon 5 (Scheme 6). It is the only known enzyme that can catalyse the formation of a C-F bond[7].



Scheme 6. Fluorinase enzymatic reaction

3.2.2. C-F BONDS AND F PROPERTIES

Carbon-fluorine bond length is about 1.3 Å. It is shorter than other carbon bonds with other atoms as it is shown in Table 1.

C-R Single Bond	Bond Length (Å)	Bond Energy (D) (kJ/mol)
C-H	1.09	414
C-C	1.54	347
C-N	1.47	305
C-O	1.43	358
C-F	1.35	485
C-Cl	1.77	327
C-Br	1.94	285
C-I	2.14	213

Table 1. Bond lengths and bond energies of different C-X bonds[8]

C-F bond is the shortest carbon bond with another atom after the C-H bond. Moreover, C-F is the shortest carbon-halogen bond.

Fluorine is a small atom compared to the rest of the halogens that are much bigger as the atomic number increases in the 17th group (Table 2). But even compared with all the periodic table, it is an element with a very small atomic radius, because it has the fourth shortest radius of all the periodic table, just over Ne, He and H.

Element	Atomic Radii (pm)		
	Empirical	Calculated	Van der Waals
H	25	53	120
F	50	42	147
Cl	100	79	175
Br	115	94	185
I	140	115	198

Table 2. Atomic Radii of different elements[9, 10, 11]

If the atomic radius of hydrogen is compared with the fluorine one, they are not much different. This is a fact in periodic table when atomic number (Z) increases in a unit every element in the right, so electrons are strongly attracted to the nucleus, decreasing the radius.

For this reason, fluorine is an atom sterically similar to hydrogen, but with very different chemical properties. Only by looking the electronegativity, fluorine is the most electronegative element in the periodic table and compared with hydrogen it presents almost 2 units of difference in Pauling scale.

As a consequence, C-F bonds are one of the strongest single bonds, and sometimes are considered as the strongest ones in organic chemistry (Table 1). It is a certainly short bond because of its partial ionic character. The fluorine electronegativity makes the bond very strong, with a negative charge density on F and a positive charge density on C (Fig. 3). It has an average bond energy of 485 kJ/mol. It is a higher value compared with other carbon-halogen bonds (C-X) in Table 1 and this is one of the reasons why organofluorine compounds are chemically and thermally stable.

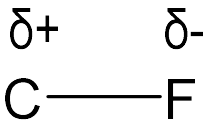


Figure 3. Partially polarized C-F bond

3.2.3. PHARMACEUTICAL PROPERTIES AND BIOLOGICAL ROLE OF FLUORINATED COMPOUNDS

Although organofluorine compounds are so stable, they cannot be found in nature. It means that all the fluorinated compounds must be synthesised by humans. Fluorinated compounds have an important role in current society such as food security, new materials, energy generation or drug industry. The last one is paramount importance. Nowadays, in pharmaceutical industry, over 140 drugs containing a fluorine atom are registered. The first one was a fluorocorticosteroid drug approved in 1956 for the FDA[12]. Some examples of currently fluorinated drugs are shown in the Figure 4.

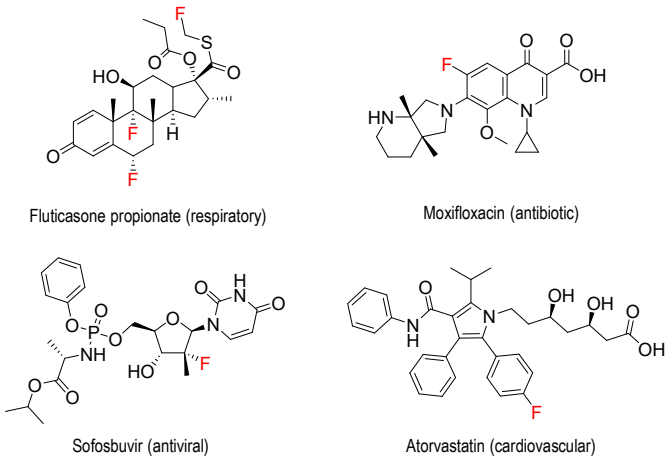


Figure 4. Relevant fluorinated pharmaceuticals[12]

Approximately 20% of new pharmaceuticals contain at least one fluorine atom in their structures, because many pharmaceutical companies, one of the first things they do when are trying to develop a new drug is to start fluorinating the molecules[12]. As previously mentioned,

fluorine has a similar radius than hydrogen, so a hydrogen atom can be substituted by a fluorine with no affection in its steric properties, in other words, maintaining the same "molecule volume", but with a massive impact in its electronic properties.

Metabolic stability is a determinant of the bioavailability of compounds, so substitutions with fluorine at metabolic attack site can be interesting due to the attack resistance of C-F bond compared with C-H one. The introduction of a fluorine can also change inductive and resonance effects as well as conformational and electrostatic behaviour of a molecule. Moreover, pK_a, dipole moment and even reactivity of other functional groups can be altered. In some cases, fluorine can reduce the basicity properties of some compounds, which can penetrate better in a membrane[12].

In general, the fluorination of a molecule highly increases its biological activity compared with their non-fluorine equivalent.

Besides the extended medical use of organofluorines, they are also used in food security. Many agrochemicals, herbicides, insecticides and fungicides containing fluorine atoms have been developed. Some of them are shown in Figure 5.

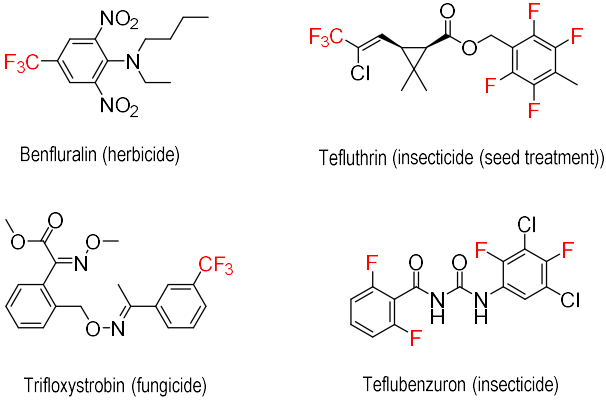


Figure 5. Relevant fluorinated agrochemicals[12]

4. OBJECTIVES

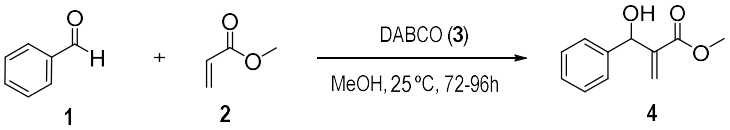
The aim of the TFG is the development of a new asymmetric allylic alkylation reaction between fluorinated Morita-Baylis-Hillman adducts and nucleophiles activated by the fluoride anion (difluoroalkenes) catalysed by chiral organic Lewis bases. Organocatalysis is going to be used, since it is a fundamental tool in sustainable asymmetric synthesis. Therefore, during this TFG, the main methodology of an organic chemistry laboratory will be learned and applied, including the synthesis of different starting materials and the following optimization of the catalytic transformations. Finally, the analysis of the reaction outcome along with the regio, stereo and enantioselectivity of the products obtained in the reactions attempted will be the main objective for this project.

5. EXPERIMENTAL SECTION

5.1. SYNTESIS OF STARTING MATERIAL

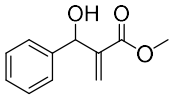
^{1}H-NMR spectra of the previously characterized compounds were recorded on VARIAN MERCURY 400 MHz NMR apparatus.

5.1.1. Synthesis of MBH alcohol (methyl 3-hydroxy-2-methyldiene-3-phenylpropionate (4))



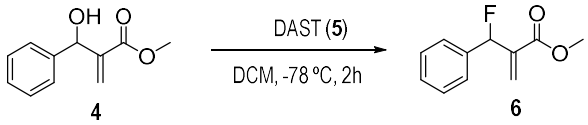
1 2 4

To a round bottom flask charged with MeOH (0.75 equiv.) was added benzaldehyde **1** (1.0 equiv.) and subsequently methyl acrylate **2** (1.2 equiv.). Finally, DABCO **3** (0.5 equiv.) was added and the solution was stirred for 72-96 h until the consumption of the starting material. The crude reaction mixture was purified by column chromatography using hexane and ethyl acetate in a 3:1 ratio.



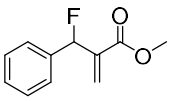
Yellowish oil. > 90% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.41-7.27 (m, 5H), 6.34 (s, 1H), 5.83 (s, 1H), 5.57 (d, J = 5.6 Hz, 1H), 3.73 (s, 3H). Chemical shifts match with those reported in the literature[13].

5.1.2. Synthesis of MBH fluoride (methyl 2-[fluoro(phenyl)methyl]acrylate (6))



4 6

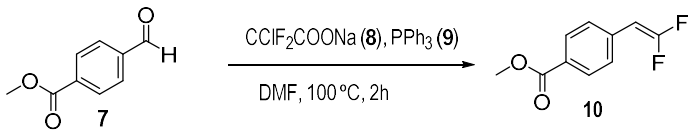
To a two-necked round-bottom flask equipped with a magnetic stir bar was added the MBH alcohol **5** (1.1 equiv.) in dichloromethane (DCM) at -78 ºC. To this solution, a solution of DAST **4** (1.0 equiv.) in DCM was added dropwise. (The final concentration of MBH in DCM had to be 0.33 M, so half of the DCM was used to dissolve reagent **5** and the other half was used for the solution of the alcohol). The mixture was stirred for 2 h and then quenched with saturated $NaHCO_3$ solution. The mixture was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **6** was purified by column chromatography using hexane and DCM mixtures.



Light yellow oil. 43% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.41-7.34 (m, 5H), 6.45 (s, 1H), 6.29 (d, J_{H-F} = 45.9 Hz, 1H), 6.02 (s, 1H), 3.72 (s, 3H).

Chemical shifts match with those reported in the literature[14].

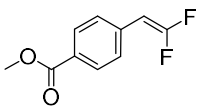
5.1.3. Synthesis of gem-difluoroalkene (methyl 4-(2,2-difluorovinyl)benzoate (10))



7 10

To a tree-necked round-bottom flask equipped with a magnetic stir bar and charged with a solution of aldehyde **7** (1.0 equiv.) in DMF (0.5 M for **7**) was added PPh_3 **9** (1.2 equiv.) and heated until 100 ºC. Then, a solution of carboxylate **8** (1.5 equiv.) in DMF (2 M) was added dropwise during 30 min, paying attention in the first additions because of the CO_2 liberation.

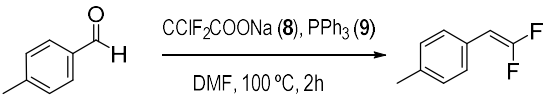
After the addition, the reaction was heated at the same temperature for 1 h 30 min. After cooling to 0 ºC, water was added to the reaction mixture and the resulting solution was extracted with EtO_2. The combined organic phase was washed with water and brine and then dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography using hexane and ethyl acetate in a 20:1 ratio to obtain the gem-difluoroalkene **10**.



Colourless oil. 77% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.01-7.99 (AA'BB', 2H), 7.40-7.38 (AA'BB', 2H), 5.33 (dd, J_{H-F} = 26.0, 3.6 Hz, 1H), 3.91 (s, 3H).

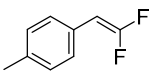
Chemical shifts match with those reported in the literature[15].

5.1.4. Preparation of gem-difluoroalkene (1-(2,2-difluorovinyl)-4-methylbenzene (12))



11 12

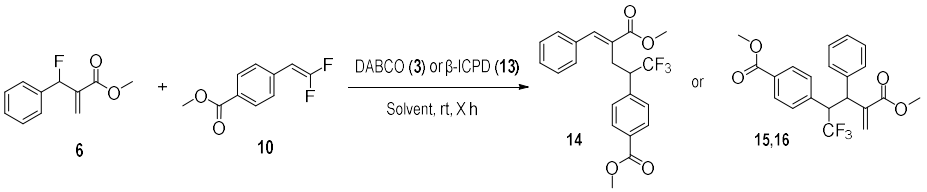
To a tree-necked round-bottom flask equipped with a magnetic stir bar and charged with a solution of aldehyde **11** (1.0 equiv.) in DMF (0.5 M for **11**) was added PPh_3 **9** (1.2 equiv.) and heated until 120 ºC. Then, a solution of carboxylate **8** (1.5 equiv.) in DMF (2 M) was added dropwise during 30 min, paying attention in the first additions because of the CO_2 liberation. After the addition, the reaction was heated at the same temperature for 2 h. After cooling to 0 ºC, water was added to the reaction mixture and the resulting solution was extracted with EtO_2. The combined organic phase was washed with water and brine and then dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography using hexane and ethyl acetate in a 50:1 ratio to obtain the gem-difluoroalkene **12**.



Pale yellow oil. 20% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.23-7.13 (m, 4H), 5.24 (dd, J_{H-F} = 26.4, 3.9 Hz, 1H), 2.34 (s, 3H).

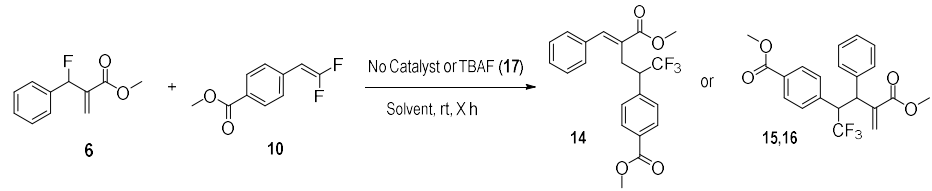
Chemical shifts match with those reported in the literature[15].

5.2. STUDY OF THE REACTIVITY OF MBH FLUORIDE AND GEM-DIFLUOROALKENE CATALYSED BY DABCO OR β-ICPD IN DIFFERENT ORGANIC SOLVENTS



Compound **10** was weighted into a 4 mL vial equipped with a magnetic stirring bar. Then, the necessary volume of solvent to create a 0.1 M solution of the limiting reagent was added, followed by compound **6**, and 20 mol % of catalyst **3** or **13** (0.2 equiv.). The resulting solution was stirred at room temperature during the specified reaction time.

5.3. STUDY OF THE NON-CATALYSED AND FLUORIDE-CATALYSED REACTION

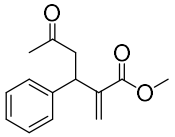
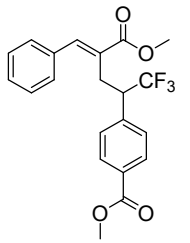
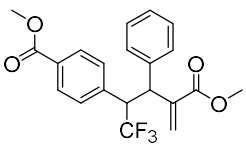
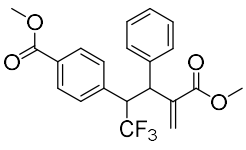


To study the non-catalysed reaction, it was followed the same experimental procedure as described by the catalysed reaction, without adding the catalyst in the final step.

To study the fluoride-catalysed reaction, it was followed the same experimental procedure, adding 10 mol % (0.1 equiv.) TBAF **17** (tetrabutylammonium fluoride) (1.0 M solution in THF) instead of the catalyst.

5.4. CHARACTERISATION OF NEW PRODUCTS

^{1}H-NMR, ^{19}F-NMR and ^{13}C-NMR spectra of the new synthesised compounds were recorded on BRUKER 500 MHz NMR apparatus.

 **18**	Colourless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.30-7.17 (m, 5H), δ 6.29 (s, 1H), δ 5.58 (s, 1H), δ 4.47 (t, J = 7.6 Hz, 1H), δ 3.69 (s, 3H), δ 3.06-2.91 (m, 2H), δ 2.09 (s, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 205.33 (1C), 165.87 (1C), 141.63 (1C), 140.43 (1C), 127.52 (2C), 126,83 (2C), 125.77 (1C), 123.64 (1C), 50.93 (1C), 47.39 (1C), 40.86 (1C), 29.21 (1C). **HRMS (ESI$^+$)** m/z 233.1174 (233.1174 calculated for $C_{14}H_{17}O_3^+$, $[M+H]^+$).
 **14**	Colourless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.84-7.80 (d, J = 8.43 Hz, 2H), 7.66 (s, 1H), 7.37-7.33 (m, 3H), 7.09-7.05 (m, 2H), 7.05-7.01 (d, J = 8.25 Hz, 2H), 3.91 (s, 3H), 3.83-3.765 (m, 1H), 3.765-3.75 (s, 3H), 3.30-3.15 (m, 2H). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 167.89 (1C), 166.80 (1C), 142.74 (1C), 139.02 (1C), 135.07 (1C), 129.67 (2C), 129.27 (1C), 128.76 (1C), 128.73 (3C), 52.29 (2C), 48.77 (1C), 26.74 (1C). **^{19}F NMR** ($CDCl_3$, 471 MHz): δ -69.16 (d, J_{F-H} = 9.19 Hz). **HRMS (ESI$^+$)** m/z 393.1319 (393.1319 calculated for $C_{21}H_{20}F_3O_4^+$, $[M+H]^+$).
 **15**	Colourless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.01-8.00 (d, J = 8.39 Hz, 2H), 7.45 (ddd, J = 11.2, 7.6, 1.8 Hz, 4H), 7.37-7.30 (m, 2H), 7.29-7.26 (m, 1H), 6.02 (s, 1H), 5.58 (s, 1H), 4.66 (d, J = 12.20 Hz, 1H), 4.35 (dq, J_{H-F} = 12.2, 8.2 Hz, 1H), 3.92 (s, 3H), 3.58 (s, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 166.78 (1C), 166.37 (1C), 140.44 (1C), 139.71 (1C), 139.37 (1C), 129.96 (2C), 129.80 (3C), 128.71 (2C) 128.62 (2C), 127.13 (1C), 52.93 (m, 1C), 52.14 (2C), 48.19 (1C). **^{19}F NMR** ($CDCl_3$, 471 MHz): δ -64.25 (d, J_{F-H} = 8.21 Hz). **HRMS (ESI$^+$)** m/z 393.1312 (393.1312 calculated for $C_{21}H_{20}F_3O_4^+$, $[M+H]^+$).
 **16**	Colourless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.87-7.82 (d, J = 8.16 Hz, 2H), 7.32-7.29 (m, 3H), 7.18-7.11 (m, 2H), 7.06 (ddt, J = 9.8, 7.6, 2.3 Hz, 3H), 6.31 (s, 1H), 5.97 (s, 1H), 4.68 (dq, J_{H-F} = 11.9, 8.5, 1H), 4.5 (d, J = 12.0 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 166.73 (1C), 166.45 (1C), 166.29

	(1C), 140.88 (1C), 139.86 (1C), 139.40 (1C), 129.79 (2C), 129.68, (2C), 129.28 (1C), 128.99 (2C), 128.40 (1C), 127.31 (1C), 126.98 (1C) 51.72 (m, 1C), 52.18 (2C), 49.83 (1C). **^{19}F NMR** ($CDCl_3$, 471 MHz): δ -64.81 (d, J_{F-H} = 8.49 Hz). **HRMS (ESI$^+$)** m/z 393.1312 (393.1312 calculated for $C_{21}H_{20}F_3O_4^+$, $[M+H]^+$).

It was done a preparative TLC to firstly characterise and identify the previously mentioned products.

5.5. METHOD TO DETERMINE REACTION OUTCOME

^{1}H-NMR spectroscopy was used to determine conversion, regioselectivity, diastereoselectivity and yield of the reaction. A 0.1 mL aliquot of the reaction crude was taken from the vial and the solvent was evaporated using the vacuum line. The evaporated crude was diluted into an NMR tube with 0.5 mL of $CDCl_3$ and pyrazine as internal standard.

The standard pyrazine solution was 0.0025 M. It was weighted 20 mg of pyrazine and diluted in a 10 mL volumetric flask to create a 0.025 solution. With a Hamilton syringe, it was taken 1 mL of the solution and diluted in a 10 mL volumetric flask again, to obtain the 0.0025 M final internal solution. In the ^{1}H-NMR spectrum, pyrazine appears as a single peak at δ = 8.6, so there is not overlap between pyrazine and other signals of the crude reaction. Thus, its integration can be done successfully. Pyrazine concentration is 4 times lower respect the concentration of the theoretical product supposing a 100 % of yield, because it has 4 equivalent protons. Therefore, the integration ratio between a proton of a theoretical product (**14**, **15** or **16**) with 100% yield and the pyrazine protons must be 1:1.

Chiral HPLC was used to determine enantiomeric excess of the products. When the crude was injected directly, it appeared different peaks making difficult to discern which one was corresponded to each compound. Therefore, a preparative TLC of the reaction crude was done, to quickly purify the products and evaluate their enantiomeric excesses.

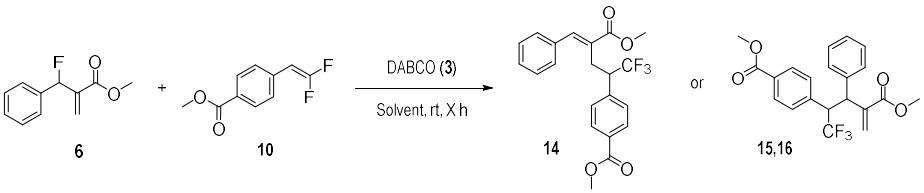
6. RESULTS AND DISCUSSION

6.1. FIRST REACTION ATTEMPTS

To have an initial qualitative screening of suitable conditions, the reaction was first tested with DABCO **3**. DABCO is more nucleophilic than other tertiary amines since its lone pairs are more available (see structure Fig. 1).

It was also tried a phosphine, specifically PPh_3 **9**, but the TLCs of some reactions demonstrated that it is less reactive than DABCO **3**, so the study of the solvents was done with catalyst **3**. A possible explanation why **9** is less reactive than **3** is that in **9** phenyls are shielding the phosphorus lone pair.

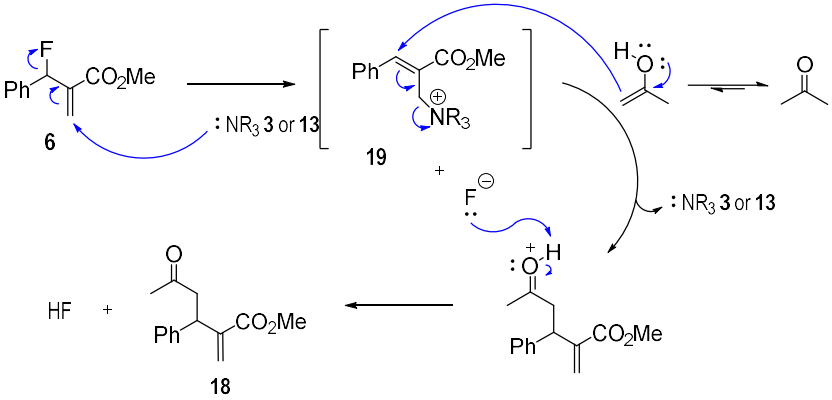
The 3 main groups of organic solvents were tested, and the results are shown in Table 3.



Solvent Polarity	Solvent	Conversion	Speed	Products		
				α-alkylation (15 and 16)	γ-alkylation (14)	Acetone product (18)
Non-polar solvents	Toluene	Bad	Very slow	No	No	No
Aprotic polar solvents	DCM	Bad	Very slow	No	No	No
	MTBE	Good	Slow	Yes	Yes	No
	THF	Good	Fast	Yes	Yes	No
	Acetone	Good	Fast	Yes	Yes	Yes
	DMSO	Good	Very fast	No	Yes	No
	DMF	Good	Very fast	No	Yes	No
	MeCN	Good	Very fast	No	Yes	No
Protic polar solvents	MeOH	No reaction	No reaction	No	No	No

Table 3. Qualitative description by TLC of compounds **6** and **10** reaction catalysed by catalyst **3** in different organic solvents

As shown in Table 3, there is a correlation between the polarity of the solvent and the product obtained. Moreover, the reaction speed can also be conditioned by the polarity of the solvent. Using a non-polar solvent, for example toluene, the reaction is very slow and there are no traces of any product. Using an aprotic polar solvent, the possibilities are wider. It seems that reactions with less polar solvents such as dichloromethane or tert-butyl methyl ether (MTBE) are slower than the ones using more polar solvents such as DMSO, DMF or acetonitrile. Besides, the most polar solvents reactions produce the γ-alkylation product **14**, while less polar solvents such acetone or tetrahydrofuran generate a diastereomeric mixture of the α-alkylation product **15** and **16**. In addition, with acetone, it is generated a different product **18** (Scheme 7). About reactions in acetone and THF, they are faster than in DCM or in MTBE. Finally, a protic polar solvent was tested too. With methanol, there was no reaction. A possible explanation could be that protic solvents can solvate the leaving fluoride after ionisation, so it cannot attack compound **10** to generate nucleophile **21**. If the nucleophile is not formed, the reaction is not working.



Scheme 7. Proposed mechanism for the formation of product **18** in acetone

6.2. OPTIMISATION AND PROBLEMS WITH Γ-ALKYLATION REACTION

Having studied this wide variety of solvents, the first objective was to optimise γ-alkylation reaction, because it generates only product **14** with one stereogenic carbon, while α-alkylation generates a mixture of two diastereomers **15** and **16**. The chosen solvent was DMF and I tested two chiral bases to start the optimisation, which were quinine (**20**) and β-isocupreidine (**13**) (Fig. 6). The catalyst **20** reaction was too slow, but the catalyst **13** generated product **14**. As it can be

seen in Scheme 7, catalyst **13** is a derivative of **20** in which its alcohol has been linked to the ring through an ether bond. This makes the molecule more reactive than molecule **20** because the molecule has a more strained structure.

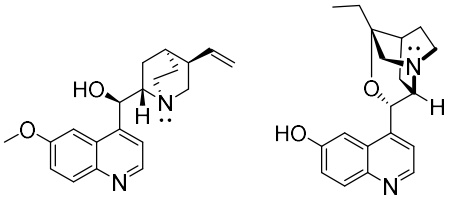
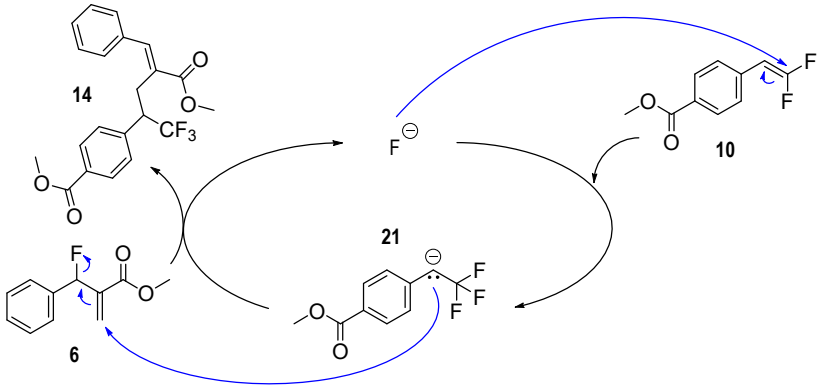


Figure 6. Quinine (**20**) and β-isocupreidine (**13**) structures

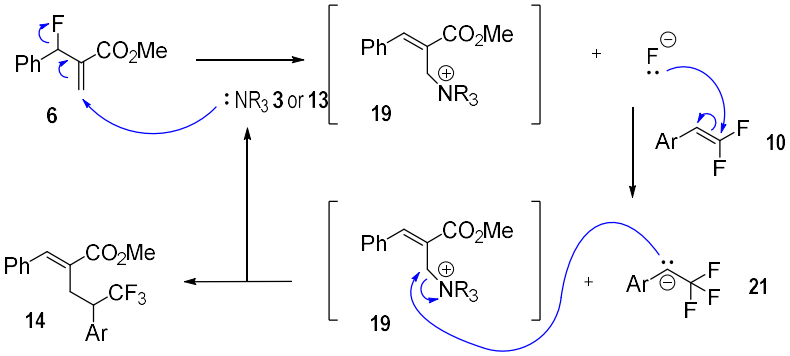
To determine the enantiomeric excess, product **14** was purified by flash column chromatography. The enantiomeric excess was practically 0% despite the use of a chiral tertiary amine. In order to explain this result, I subsequently studied potential background reactions.

The reaction in the absence of catalyst did not work, because the reagents were still in the solution a day after. Contrary from this one, the reaction in the presence of 10 mol % of compound **17** was very reactive, because just adding the fluoride solution to the vial, the reaction colour changed rapidly with a very high intensity. After 24h, all the starting material was consumed and the product **14** was formed. With the addition of fluoride, a proposed mechanism for the reaction is the following one (scheme 8).



Scheme 8. γ-alkylation promoted by fluoride

As it can be seen in Scheme 8, a tertiary amine catalyst is no necessary to produce product **14**. This means that is very difficult to make this reaction enantioselective, because it is not mediated by a Lewis base, as it was thought initially (Scheme 9).

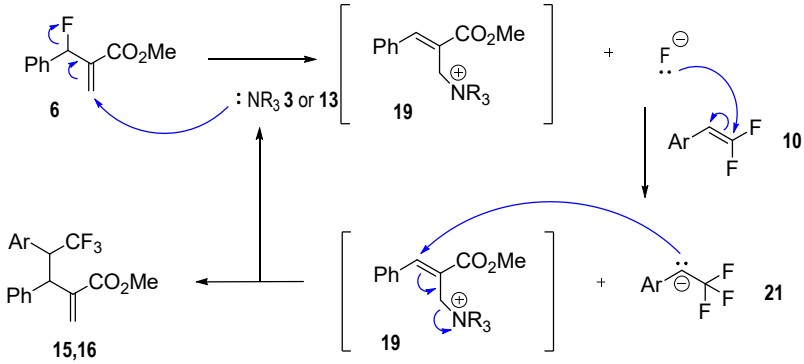


Scheme 9. γ-alkylation mechanism via S_N2'-S_N2

Therefore, in the reactions with catalysts which gave product **14**, the function of the tertiary amine catalyst was to generate catalytic amounts of fluoride attacking compound **6**. Then, the fluoride activates difluoroalkene **10**, to subsequently attack compound **6** to afford product **14** and generate new fluoride. Remarkably, the only product formed is the *E* diastereomer because it is more stable than the *Z* diastereomer.

6.3. OPTIMISATION OF A-ALKYLATION REACTION

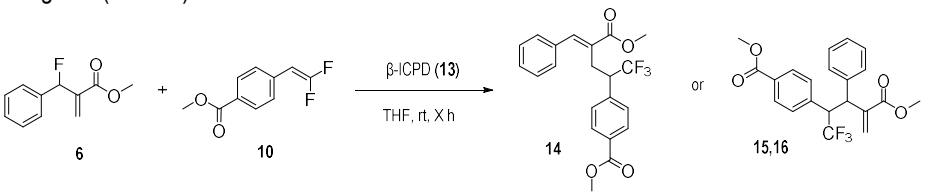
Subsequently, I started to optimise the α-alkylation reaction, because mechanistically, this cannot proceed in the absence of the Lewis-base catalyst (Scheme 10).



Scheme 10. α-alkylation mechanism via S_N2'-S_N2'

A main problem of all the project was the difficulty to know the conversion, regioselectivity, stereoselectivity and yield of the reaction to create a table to control all these parameters in every reaction. The routine NMR instrument had not enough resolution to calculate peak integrations accurately of a crude. However, the solution is described in experimental section (5.5) and finally, it was found a method to determine all the parameters correctly.

Having stablished the method, 7 reactions with THF as a solvent and catalyst **13** were investigated (Table 4).



#	Catalyst	Reag. 6:10	C (M)	Solvent	T	t (h)	Conversion (%)	^{1}H-NMR yield (%)	RR 14:(15 +16)	DR	ER	ee (%)
1	β-ICPD	1:1	0,1	THF	rt	24	66	26	6.4:1	1.4:1	71:29	43
											ND	ND
2	β-ICPD	1:3	0,1	THF	rt	24	80	ND	0:1	1.5:1	ND	ND
3	β-ICPD	3:1	0,1	THF	rt	24	100	ND	2.9:1	1.3:1	ND	ND
4	β-ICPD	1:3	0,1	THF	rt	48	100	70	0:1	1.5:1	68:32	36
											54:46	8
5	β-ICPD	3:1	0,1	THF	rt	48	100	80	1:2	1.6:1	68:32	36
											54:46	8
6	DABCO	1:3[a]	0,1	THF	rt	24	-	-	-	-	-	-
7	β-ICPD	1:3[a]	0,1	THF	rt	24	-	-	-	-	-	-

(a) Difluoroalkene **12** was used instead of **10**.

(b) Conversion and yield determined by ^{1}H-NMR.

(c) rt: standard conditions; RR: regiomeric ratio; DR: diastereomeric ratio; ER: enantiomeric ratio; ee: enantiomeric excess; ND: Not Determined.

Table 4. Optimisation table

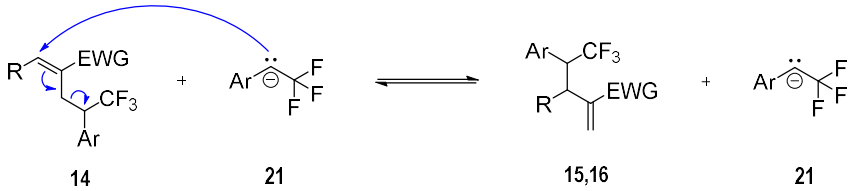
What table shows is that with an excess of compound **6**, the reaction is clearly gone through an α-alkylation mechanism (Entry 2, Table 4), while with an excess of compound **10**, the

reaction at 24h goes through a γ-alkylation mechanism (Entry 3, Table 4). However, after 24 h, the proportion of regioisomers changed, being products **15** and **16** majority (Entry 5, Table 4).

Regarding the conversion, the reaction with catalyst **13** in THF at standard conditions gives a satisfactory conversion and NMR yield (Entries 1, 4, 5; Table 4).

The proportions of two diastereomers **15** and **16** from α-alkylation, are very similar in all the reactions, because it is believed that the two molecules are in equilibrium and the ratio at the equilibrium is 1.6:1.

Enantiomeric ratio was determined only in the 48 h reactions, because in the first day it was tried to directly analyse the crude. Too many peaks appeared, so it was impossible to identify which peak corresponded to each product. Then, it was decided to do a preparative TLC to purify the products and analyse them separately. In the case of 1:1 first reaction, it was only determined the enantiomeric excess of a diastereomer, because the crude was purified by flash column chromatography, and it was the only diastereomer that could be purified and analysed properly in HPLC. A possible reason for the low enantiomeric excesses is the existence of a detrimental equilibrium (Scheme 11) after the catalytic reaction. This equilibrium is generating products **15** and **16** from product **14**, so the formation of new products **15** and **16** is not mediated by the catalyst and therefore is formed without stereocontrol. In conclusion, reactions after 2 days had changed their diastereomeric ratio, so their enantiomeric excesses had decreased.



14 21 15,16 21

Scheme 11. Non-catalysed equilibria between 14 and 15,16

To reduce or, if possible, avoid the detrimental equilibrium of the products (Scheme 11), it was tried a different gem-difluoroalkene **12** (Entries 6 and 7, Table 4). Instead of the substituted in para with an ester group, it was used a substrate substituted with a methyl in the aryl ring. With methyl in para position, nucleophile **21** would be less stable, because the negative charge

is not as stabilised as in the one with an ester, which is more electron withdrawing than the methyl. Thereby, nucleophile **21** would be a worst leaving group, so the equilibrium would be reduced.

Initial attempts with compound **12** did not work. The only product obtained was a dimer of compound **6**.

7. CONCLUSIONS

In conclusion, the TFG has supposed an important step to initiate in organic chemistry and asymmetric catalysis. It has been important to learn the working methodologies of a research lab. Also, the experience of being in a research group with other people is a key point.

This TFG has been the beginning of a big project which could not be finished. It has permitted to have a general vision of the reagent's reactivity to carry on in the study of the reaction deeply. It makes easier the posterior study in front of other chiral catalysts, new solvents, other conditions, etc. Owing a limited time to develop the project, it was also not possible to try other substituted reagents, because they require a previous preparation, and some of them need various steps. Although it was difficult to stablish a useful method to determine all the reaction results such as regiomeric, diastereomeric and enantiomeric ratio, it was finally found a valid methodology, overcoming the routine NMR limitations. It should be noticed that the reaction under study is very challenging, because it can produce different products complicated to purify. However, with more time in hand, it could have been deduced more solid conclusions.

Nevertheless, the project has been satisfactory, because I have been able to demonstrate that asymmetric allylic alkylations can be done reusing the leaving group after the nucleophilic attack. The negative part is that so far, the reaction is not very regio and stereoselective. That is why the project is not finished and it must be further investigated.

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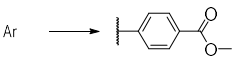
20. In all the previously suggested mechanisms blue arrows represent an electron pair movement, and the abbreviation “Ar” means:



9. ACRONYMS

AAA: Asymmetric Allylic Alkylation

L: Ligand

LG: Leaving Group

MBH: Morita-Bailys-Hillman

EWG: Electron withdrawing group

DABCO: 1,4-diazabicyclo[2.2.2]octane or Triethylenediamine

S_N2: Bimolecular Nucleophilic Substitution

AE: Atom Economy

MW: Molecular Weight

CFCs: Chlorofluorocarbons

FDA: Food and Drug Administration

β-ICPD: β-Isocupreidine

TBAF: Tetrabutylammonium fluoride

THF: Tetrahydrofuran

DCM: Dichloromethane

DMF: Dimethylformamide

DMSO: Dimethyl sulfoxide

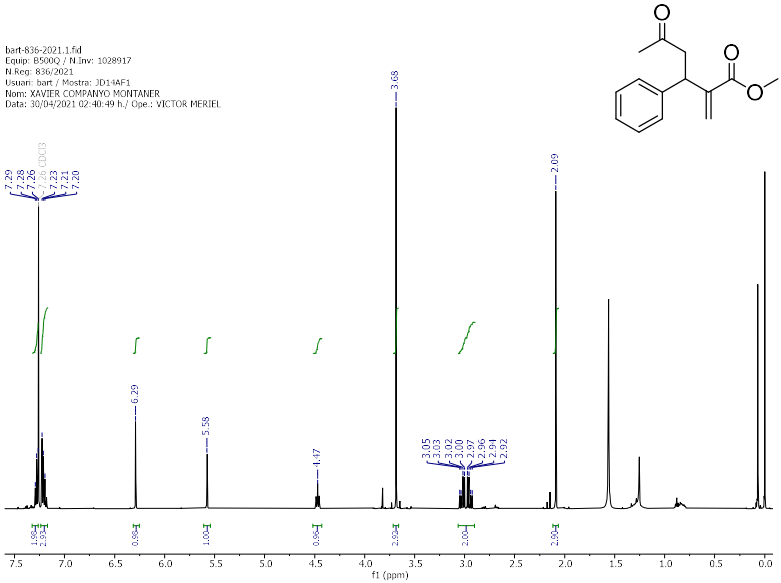
MTBE: Methyl tert-butyl ether

ND: Not determined

APPENDICES

Appendix 1: NMR Spectra

^{1}H-NMR Product 18



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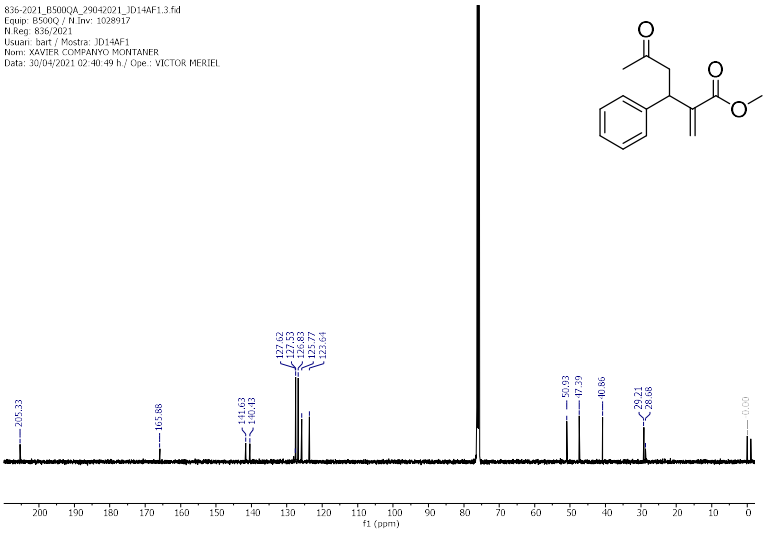

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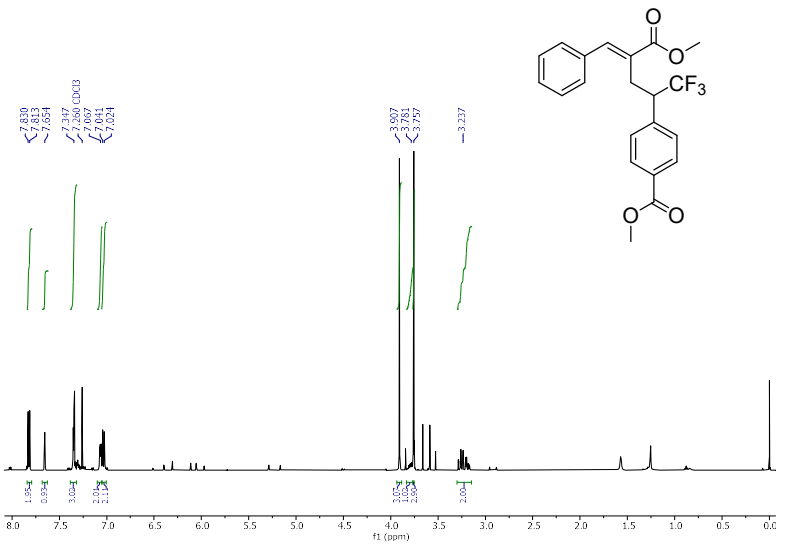

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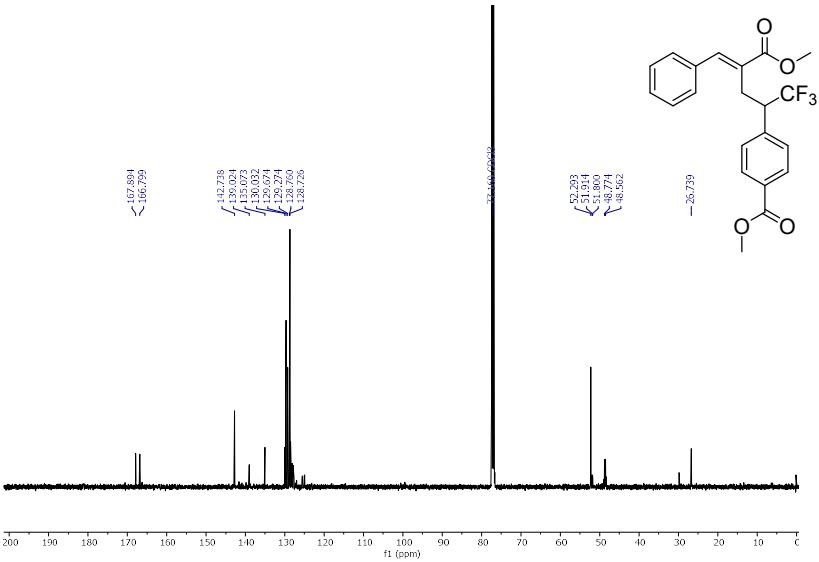

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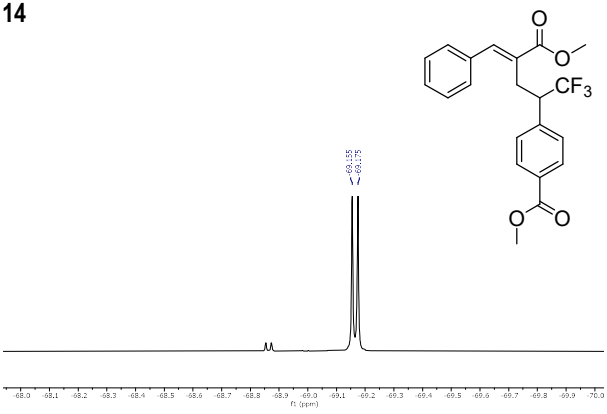

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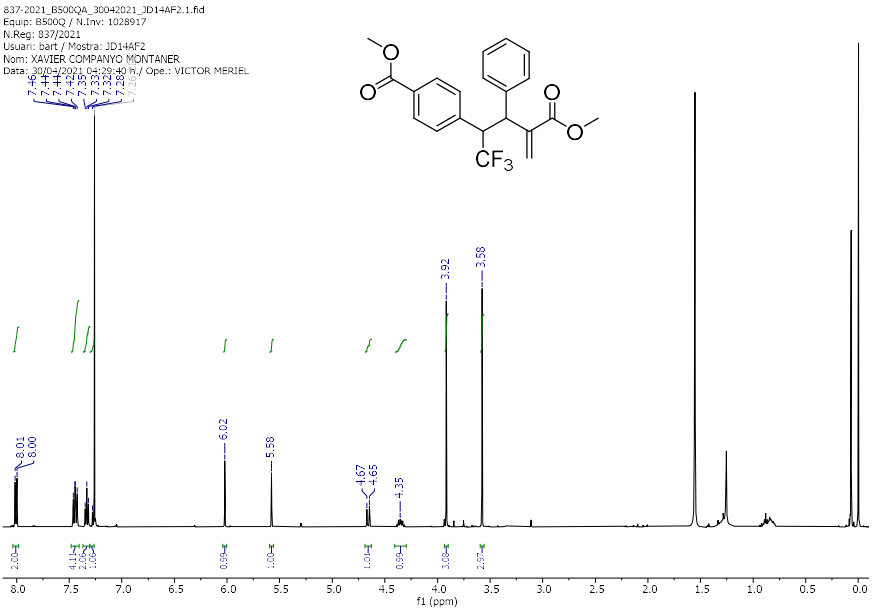

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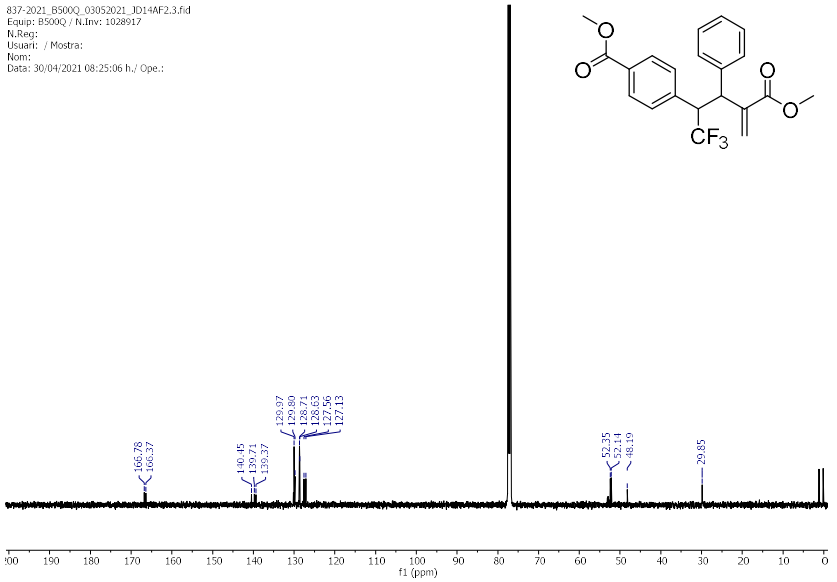

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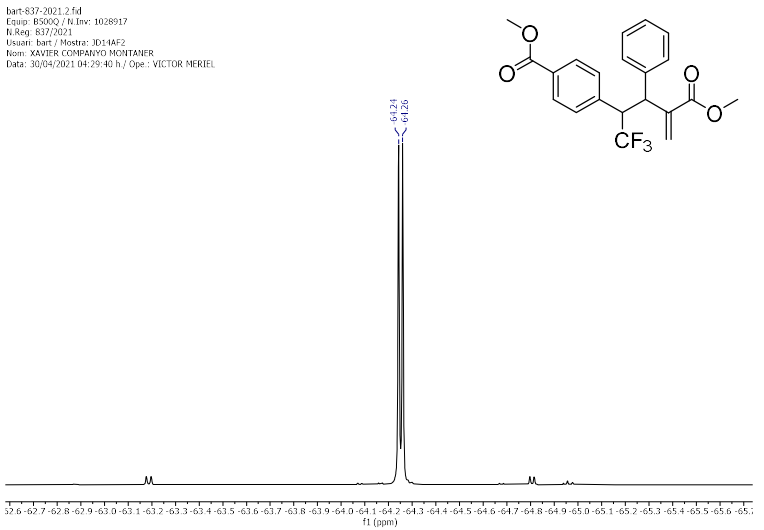

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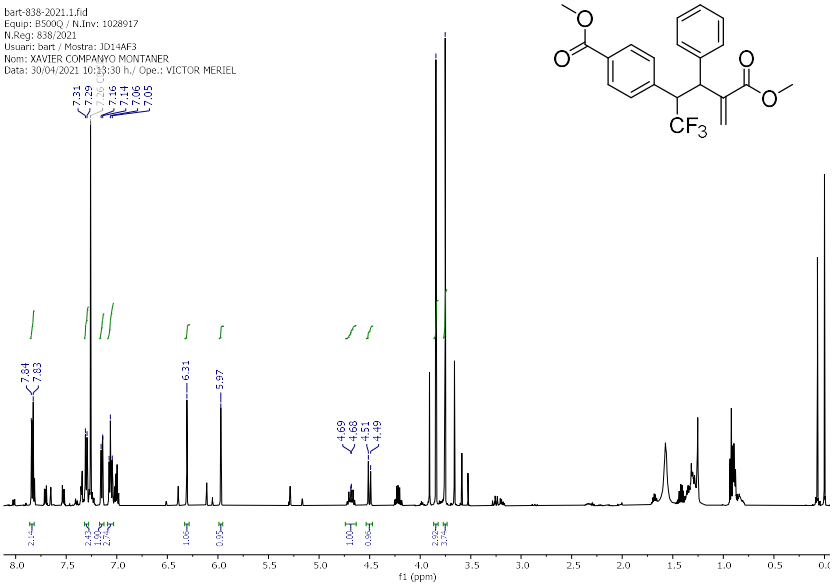

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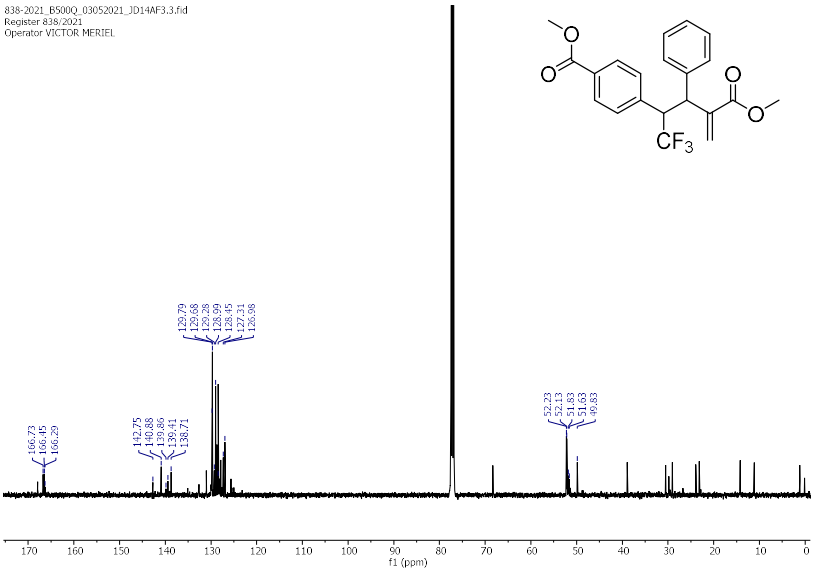

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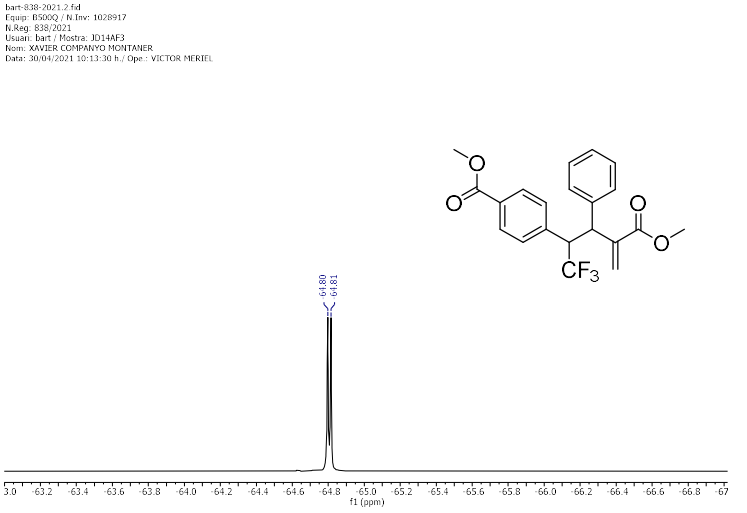

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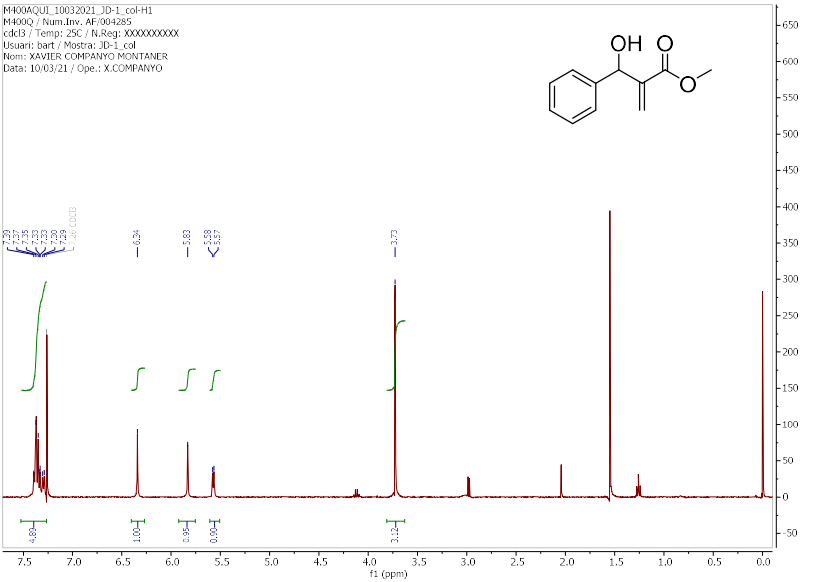

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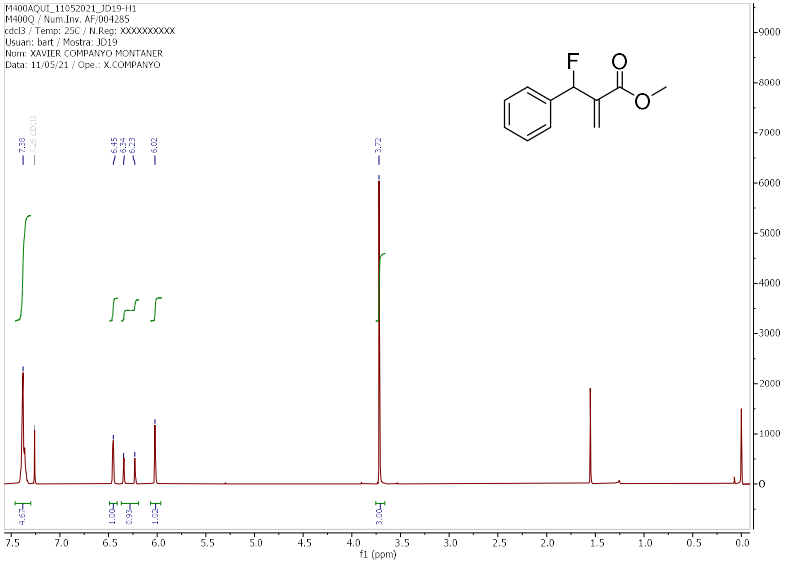

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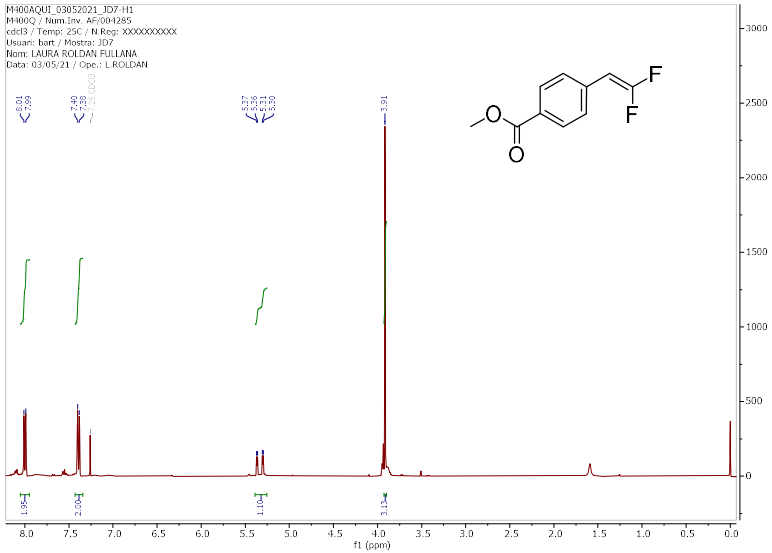

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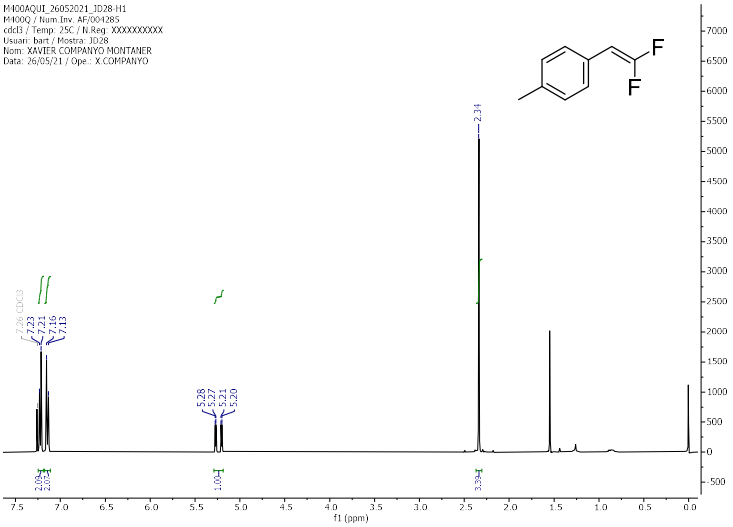
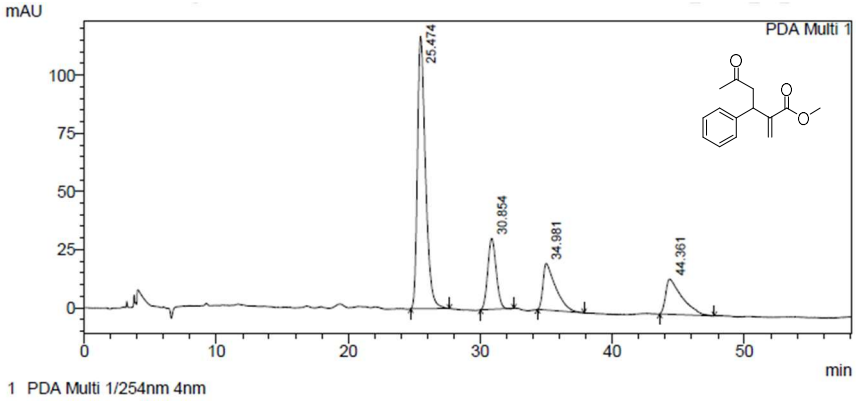


Appendix 2: HPLC Chromatograms

All the chromatograms are racemic mixtures recorded using:

- Column: Phenomenex Lux ® 5µm Cellulose-1, LC Column 250 x 4.6mm
- Mobile phase: 99% n-Hexane, 1% 2-Propanol
- Flow: 1 mL/min

Product 18

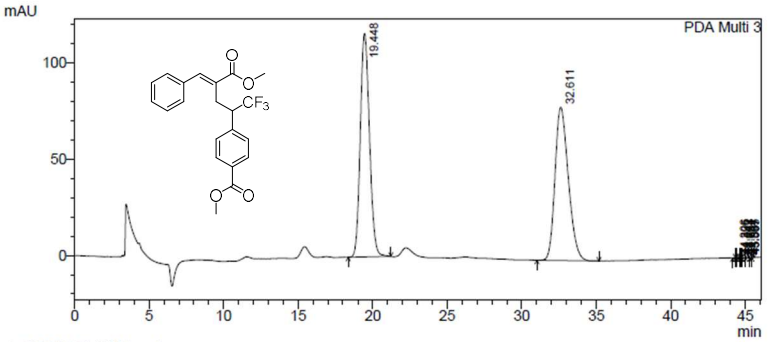


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	25.474	4940431	117097	55.429	64.080
2	30.854	1350016	30496	15.146	16.689
3	34.981	1329552	20042	14.917	10.968
4	44.361	1293074	15101	14.508	8.264
Total		8913073	182737	100.000	100.000

Product 14



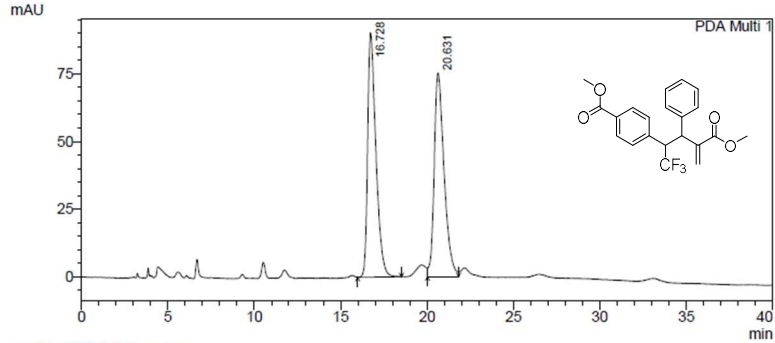
1 PDA Multi 1/254nm 4nm
2 PDA Multi 2/220nm 4nm
3 PDA Multi 3/270nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.447	4676148	111140	49.891	59.248
2	32.611	4696663	76445	50.109	40.752
Total		9372812	187585	100.000	100.000

Product 15



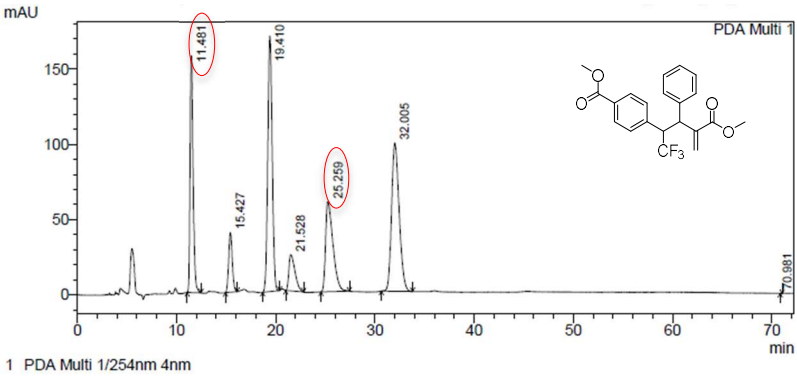
1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.728	2996661	90339	50.024	54.560
2	20.631	2993757	75237	49.976	45.440
Total		5990418	165576	100.000	100.000

Product 16



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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2	15.427	1000660	39714	5.298	7.210
3	19.410	5228030	169910	27.680	30.848
4	21.528	1028570	24149	5.446	4.384
5	25.259	3094206	60411	16.382	10.968
6	32.005	5229886	98558	27.690	17.894
7	70.981	1062	152	0.006	0.028
Total		18887268	550790	100.000	100.000