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Treball Final de Grau

Fluoride-triggered homoallylic trifluoromethylation of allyl fluorides with *gem*-difluoroalkenes.

Trifluorometilació homoalílica de fluorurs d'alil amb difluoroalquens geminals promoguda per fluorurs.

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B:KC Barcelona Knowledge Campus
Campus d'Excel·lència Internacional

Vull expressar el meu sincer agraïment al Dr. Xavier Companyó per la seva excepcional comprensió i dedicació al llarg de tot el meu treball i estada al laboratori. També m'agradaria agrair especialment l'ajuda del Jordi Duran, qui m'ha ensenyat, guiat i donat suport en tot el que he necessitat. Així mateix, vull apreciar la col·laboració de la Paula Rodríguez, el Martí Gisbert, el Ward Vermeer i l'Enric Ponzano.

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REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (SDG)

This TFG project tackles the development of a new transition-metal free method for the installation of trifluoromethyl groups at homoallylic position triggered by a catalytic amount of a fluoride salt. Organocatalytic reactions are fundamental in green chemistry, as they avoid the use of transition metals, which are generally toxic, hazardous, and expensive. Further, the fluoride promoter/leaving group is recycled due to its incorporation into the final product to forge the trifluoromethyl group, allowing the development of a complete atom economical reaction.

Therefore, this TFG project aligns with different Sustainable Development Goals (SDGs) due to its commitment to scientific advancements as well as to increase sustainability and responsible development in chemical processes.

Specifically, this work tackles the **Goal 8: Decent work and Economic Growth** by developing a new sustainable methodology that may contribute to the advancement of industries, influencing a positive impact on green economic growth. Further, the project also contributes to the **Goal 9: Industry, Innovation, and Infrastructure** as it emphasizes the need to promote inclusive and sustainable industrialization and faster innovation. Finally, the **Goal 12: Responsible Consumption and Production** is also pursued as the work focuses on promoting more responsible production approaches by developing sustainable alternatives to existing methods.

CONTENTS

1. SUMMARY

Asymmetric allylic alkylations (AAA) enable the catalytic construction of new C-C and C-X bonds at allylic positions in a stereoselective manner. Around 1970, Trost discovered the first AAA catalysed by transition metals (TM). More recently, Lewis-base catalysed AAA reactions have been developed using Morita-Baylis-Hilman (MBH) adducts, that depending on different parameters can proceed either via S_N2'- S_N2' for γ-alkylations or via S_N2'-S_N2 for α-alkylations.

The aim of this TFG is the development of a new homoallylic trifluoromethylation reaction between MBH fluorides and *gem*-difluoroalkenes promoted by catalytic amounts of a fluoride salt. Firstly, fluoride adds to the *gem*-difluoroalkene to in situ generate the nucleophile. Subsequently, this fleeting nucleophile attacks the α-position of the MBH fluoride to form the new C-C bond while releasing fluoride as leaving group. Hence, fluoride ion plays a dual role as a catalytic promoter and as leaving group. As it is continuously regenerated and incorporated to the final product as trifluoromethyl group, the reaction becomes highly atom economic. Overall, this new methodology permits the synthesis of trifluoromethylated alkenes with good regioselectivities and perfect E/Z diastereoselectivity.

This TFG thesis has involved the synthesis of the starting materials, the optimisation of the reaction using diverse spectroscopic and chromatographic techniques to assess the selectivity, the conversion, the yield, and the characterisation of the final products.

Keywords: Morita-Baylis-Hillman fluorides, α-alkylation, *gem*-difluoroalkenes, atom economy, trifluoromethylated alkenes, regioselectivity, E/Z diastereoselectivity, NMR, GC

2. RESUM

Les alquilacions al·líliques asimètriques (AAA) permeten la construcció catalítica de nous enllaços C-C i C-X en posicions al·líliques de forma estereoselectiva. Al voltant de 1970, Trost va descobrir la primera AAA catalitzada per metalls de transició (TM). Més recentment, s'han desenvolupat AAA catalitzades per bases de lewis utilitzant adductes Morita-Baylis-Hilman (MBH), que depenent de diferents paràmetres poden procedir via S_N2'- S_N2' per a γ-alquilacions o mitjançant S_N2'-S_N2 per a α-alquilacions.

L'objectiu d'aquest TFG és el desenvolupament d'una nova reacció de trifluorometilació homoal·lílica entre fluorurs de MBH i difluoroalquens geminals promoguda per quantitats catalítiques de fluorur. En primer lloc, el fluorur ataca al difluoroalquè geminal per generar in situ el nucleòfil. Posteriorment, aquest nucleòfil ataca la posició α del fluorur MBH per formar el nou enllaç C-C alhora que allibera un fluorur com a grup sortint. Per tant, l'ió fluorur juga un doble paper com a promotor catalític i com a grup sortint. Com es regenera contínuament i s'incorpora al producte final com a grup trifluorometil, la reacció esdevé altament econòmica atòmicament. En conjunt, aquesta nova metodologia permet la síntesi d'alquens trifluorometilats amb bones regioselectivitats i una perfecta diastereoselectivitat E/Z.

Aquest TFG ha implicat la síntesi dels materials de partida, l'optimització de la reacció mitjançant diverses tècniques espectroscòpiques i cromatogràfiques per avaluar la selectivitat, la conversió, el rendiment, i la caracterització dels productes finals.

Paraules clau: Fluorurs de Morita-Baylis-Hillman, α-alquilació, difluoroalquens geminals, economia atòmica, alquens trifluorometilats, regioselectivitat, diastereoselectivitat E/Z, RMN, GC

3. INTRODUCTION

3.1. ASYMMETRIC ALLYLIC ALKYLATIONS

Asymmetric allylic alkylations (AAA) are amongst the most powerful and studied reactions in asymmetric catalysis, as they allow the catalytic construction of new C-C and C-X bonds at allylic positions in stereoselective manner. AAA reaction can be broadly classified in function of the nature of the catalyst between transition-metal[1] (TM) and Lewis base[2] (LB) catalysed transformations.

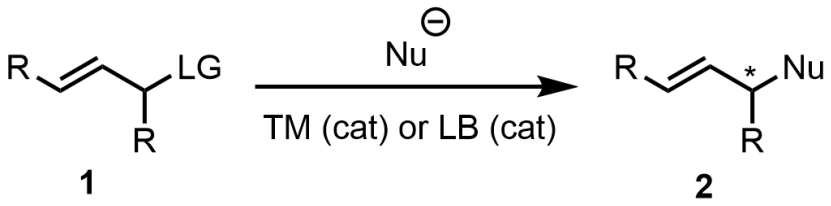


Figure 1. General asymmetric allylic alkylation reaction.

3.1.1. Transition-metal catalysed asymmetric allylic alkylations

In the 1970s, Trost developed the first AAA methodology catalysed by palladium complexes.[3] The general catalytic cycle of Tsuji-Trost starts with the coordination of Pd(0) with the chiral ligands (Figure 2). Consecutively, this metallic centre is coordinated with the substrate **1** to produce the η^2-π-allyl complex **3**. Then the leaving group (LG) is ionised and a η^3-π-allyl complex **4** is formed. Subsequently the nucleophile attacks the electrophilic centre **4** and is introduced in the allylic position creating a new C-C bond in molecule **5**. Finally, the palladium complex is reduced, regenerating its initial oxidation, and releasing the final product **2**.

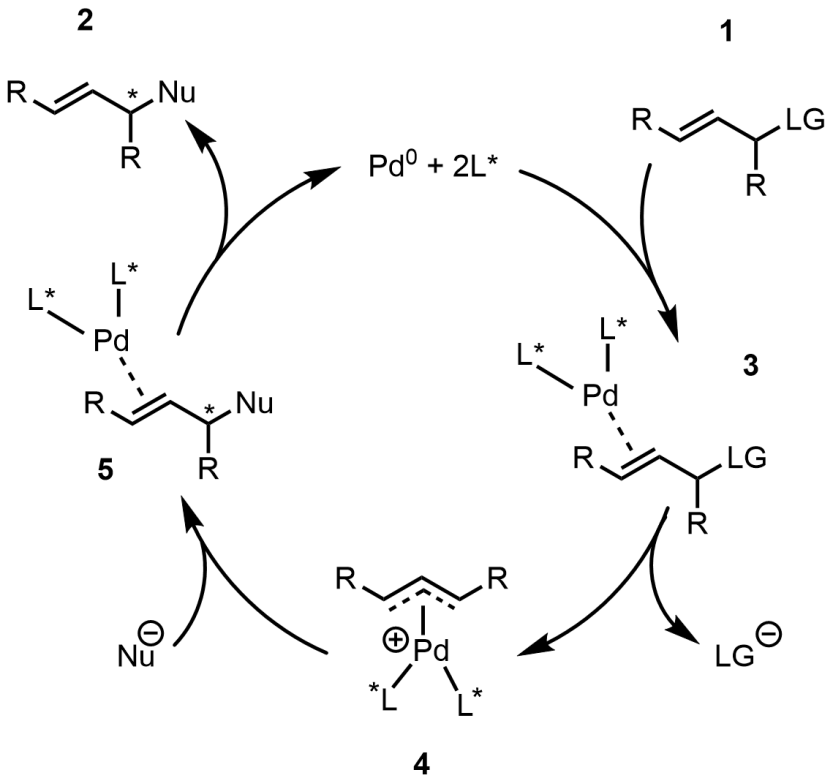


Figure 2. Catalytic cycle of Tsuji-Trost reaction.

After this pioneering discovery, a myriad of different synthetic transformations has been developed. Therefore, AAA reactions constitute one of the most powerful catalytic strategies for the stereoselective construction of C-C bonds.

3.1.2. Organocatalytic asymmetric allylic alkylations with Morita-Baylis-Hillman adducts

In 2004, Kim and Lu reported the first organocatalysed AAA reaction using Morita-Baylis-Hillman (MBH) carbonates **7** (LG = OBoc) and acetates (LG = OAc) as electrophiles with various stabilised pronucleophiles using chiral Lewis bases **6** as nucleophilic catalysts.[4]

The general mechanism for this organocatalytic process is shown in Figure 3. MBH adduct **7** is attacked by the nucleophilic catalyst (**6**) via a S_N2' process, ionising the leaving group **8** and generating an electrophilic intermediate **10**. Successively, a second S_N2' by the nucleophile **9** at the intermediate **10** results in the formation of the γ-alkylated product **11** via S_N2'- S_N2' mechanism. The reaction can also proceed via an alternative pathway comprising S_N2 attack of the nucleophile **9** to intermediate **10** to afford the α-alkylated product **12**. Therefore, this type of reactivity can be performed in regiodivergent manner towards α or γ-alkylation, depending on several reaction parameters such as catalyst, nucleophile, nature of the leaving group, solvent, temperature, etc.

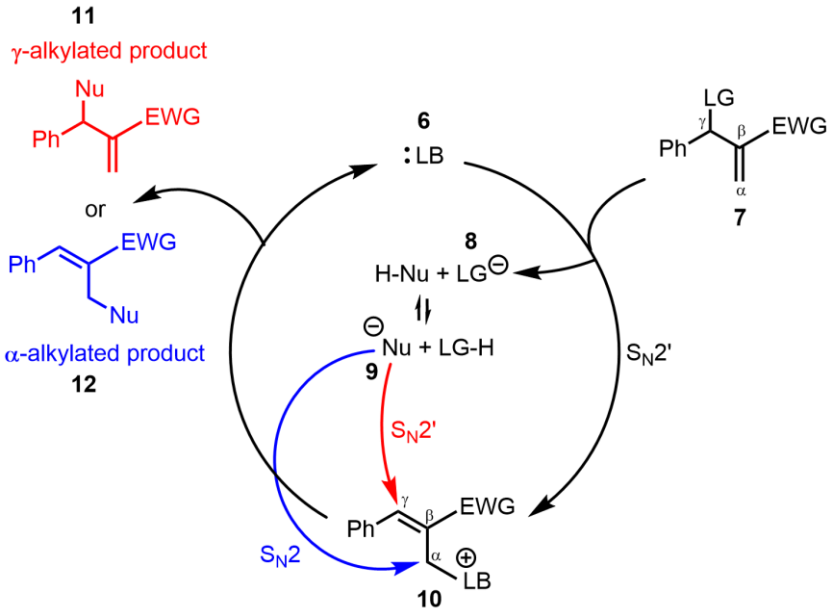


Figure 3. General mechanism for the organocatalytic asymmetric allylic alkylation reaction allowing either α or the γ-alkylation.

3.1.3. α-Alkylation of Morita-Baylis-Hillman adducts

As mentioned above, alkylation in the α position is generally caused by an S_N2' followed by an S_N2. The challenge of this process lies in the competition with the S_N2'-S_N2', which leads to alkylation in the γ position (see Figure 3, conventional reactivity). Generally, to achieve α-alkylation, bifunctional catalysis is used comprising a chiral Lewis basic site, which forms the catalytic electrophilic intermediate (see intermediate 10 in Figure 3), and an acidic Lewis site such as thiourea to enhance selectivity and impart stereocontrol. Some important reactions with MBH substrates are commented below and detailed in Figure 4.

In 2012, Lu and colleagues reported the α-alkylation of MBH carbonates **13** with nitroalkanes **14** catalysed by thiourea derived from quinine **15**.[5] They produced enantiomerically enriched nitroalkane **16** with good yields and enantiomeric excess (Figure 4A). Later, in 2014, Mukherjee and co-workers reported a related process but this time using a nucleophile with two nitro groups **17** and the catalyst **18** (Figure 4B).[6] The final products **19** were formed in slightly lower yields but with two neighbouring stereo centres with better enantiomeric excess. In 2016, Wang and his group achieved selectively the α/γ-alkylation of MBH carbonates **20** with oxazolones **21** (Figure 4C).[7] With a quinine-derived catalyst the reaction selectively forms the γ-alkylated product (not shown), while using the bifunctional tertiary amine-urea catalyst **22** the reaction affords the α-alkylated oxazolone product **23** with quite good yields and the best enantiomeric excess presented in Figure 4.

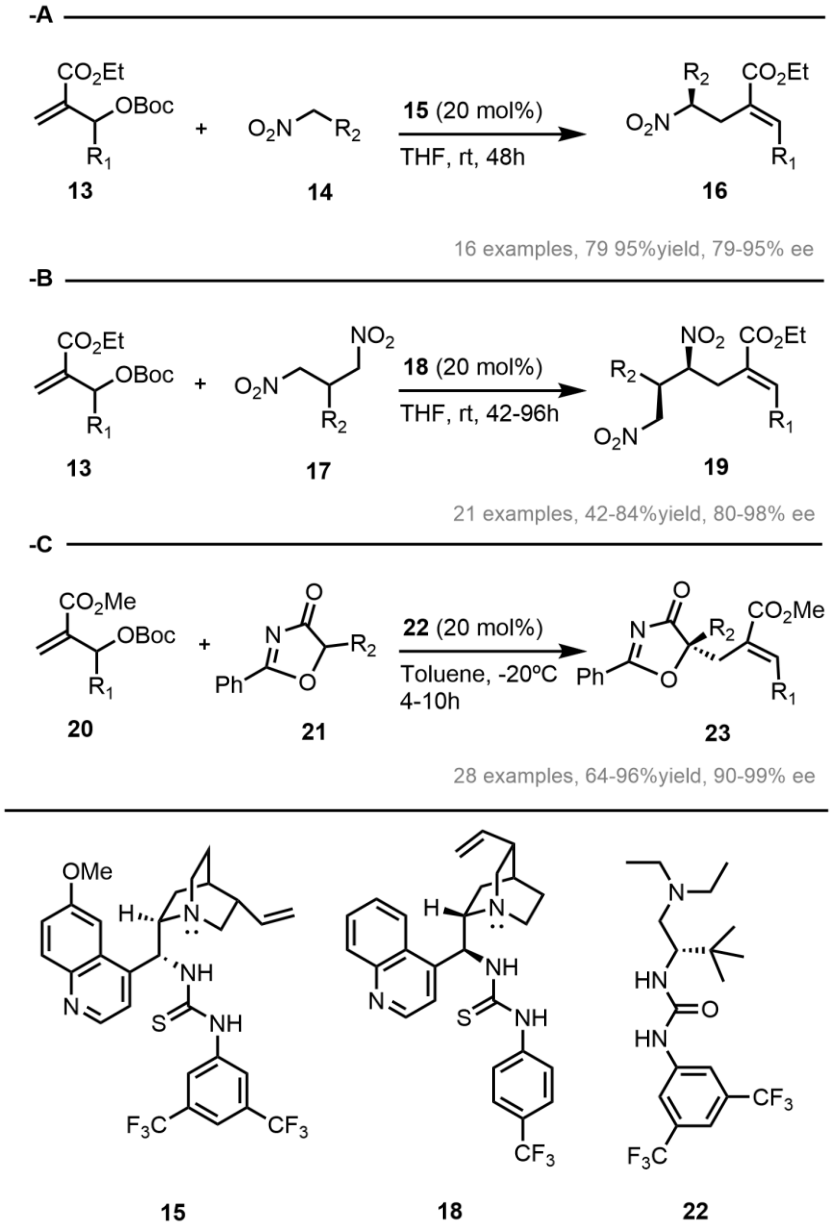


Figure 4. Relevant precedents in the α-alkylations of MBH adducts.

3.1.4. Asymmetric allylic alkylations with Morita-Baylis-Hillman fluorides

Recently, some publications have proposed the use of fluoride as unconventional leaving group in MBH substrates.[8] Although fluoride is a worst leaving group compared with the conventional acetates and carbonates, it can be used to activate silylated pronucleophiles through Si–F interaction and thus perform innovative and unprecedented AAA in the γ position. The most important reactions with Morita-Baylis-Hillman fluorides (MBHF) are shown Figure 5.

In 2014, Shibata and co-workers reported the first defluorinative AAA reaction (Figure 5A).[9] This pioneering work tackles the kinetic resolution of allyl fluorides **24** via asymmetric allylic trifluoromethylation catalysed by $(DHQD)_2PHAL$ **26**. This type of reaction begins with a C–F bond activation of **24** by coordination with the silicon atom of **25** through Si–F interaction to form a Lewis acid/base complex. Then, attack of the catalyst **26** generates an electrophilic intermediate and a trifluoromethyl carbanion through an S_N2' process, with concomitant formation of Me_3Si-F. Finally, a second S_N2' addition of carbanion to produce the trifluoromethylated product **27** and releases catalyst **26**. These authors continued studying the reactivity of MBHF in more detail, discovering the ability of the trifluoromethyl carbanion to activate the C-H bonds of chloroforms, alkynes, arenes, indenes and fluorobisphenylsulphonylmethane, to act as nucleophiles.[10]

In 2023, Companyó and co-workers developed an asymmetric defluorinative allylation of α-substituted silyl enol ethers (SEE) **28** with allyl fluorides **24** under Lewis-base catalysis, representing the first defluorinative AAA able to forge more than one stereogenic carbon in a single catalytic event (Figure 5B).[11]

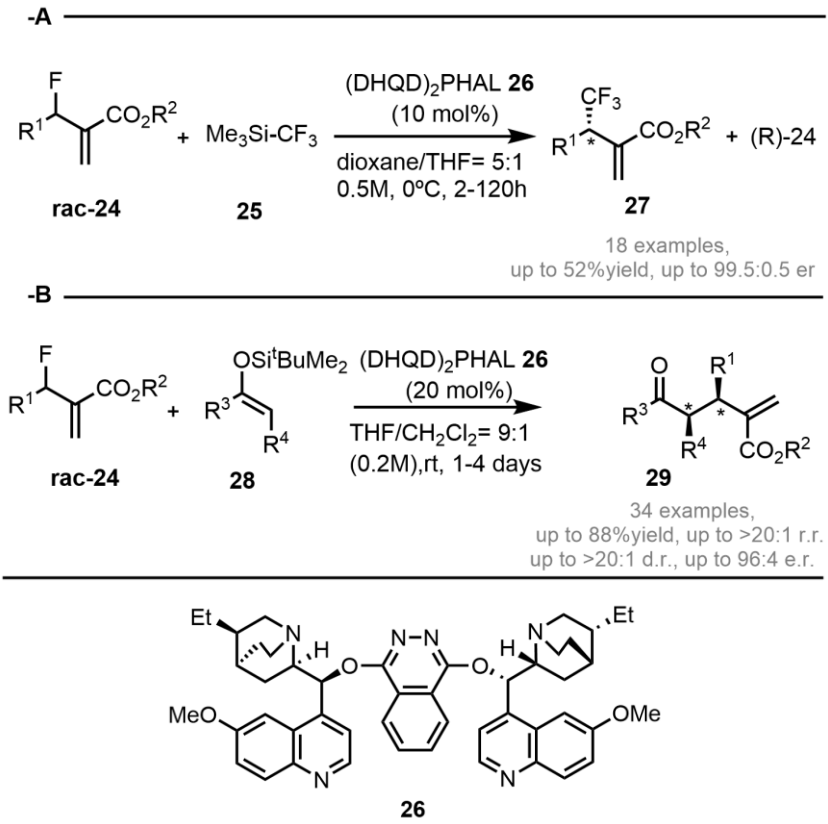


Figure 5. Relevant Asymmetric Allylic Alkylations with Morita-Baylis-Hillman fluorides

In all these precedents, the leaving group (fluoride) is used as a Lewis base to activate pronucleophiles via Si-F interaction. It should be noted that in all these cases the fluoride is never incorporated in the final product but instead, it is lost as TMS-F or TBS-F. This fact diminishes the atom economy of these transformations as not all the atoms involved in the reaction end up in the final product and hence the leaving group is “wasted”.

3.2. Principles of Green Chemistry

The Twelve Principles of Green Chemistry were introduced in 1998 by Paul Anastas and John Warner, including the following key concepts.[12]

- Prevention over Correction: It is more advantageous to prevent environmental harm than to rectify issues after they occur.
- Safer Substances: Use or produce substances that are safe and non-toxic to humans and the environment. Real-time monitoring of reactions is crucial to avoid the formation of unexpected hazardous by-products.
- Minimize Auxiliary Substances: Use as few auxiliary and derivative compounds as possible. Prefer the use of catalysts (preferably selective) over stoichiometric reagents.
- Consider Environmental and Economic Impact: Factor in both environmental and economic considerations. Conduct reactions at ambient temperature and pressure whenever feasible.
- Designed for Breakdown: Chemical products should be designed to break down after fulfilling their intended function, avoiding persistence in the environment.
- Atom Economy: Maximize the incorporation of all materials used in a reaction into the final product to minimize waste. The atom economy of a reaction can be measured by considering the molecular weights of the reactants and the final product (Figure 6). It is expressed as a percentage from 0 to 100%, considering that if the sum of the weights of the reactants is the same as the product, a 100% atom economy is achieved.

$$Atom\ Economy\ (\%) = \frac{MW\ of\ the\ product}{MW\ of\ all\ the\ reagents\ used}\ x\ 100\ ;\ \ 0 < AE(\%) \leq 100$$

Figure 6. Atom economy equation.

Therefore, this concept is crucial for evaluating the sustainability of a reaction, as more atoms of the starting material are incorporated into the final product, there is a reduction in the overall generation of residue in the reaction. Organocatalytic reactions are especially relevant in green chemistry, as they avoid the use of transition metals, which, according to the principles mentioned above, should be minimized due to their costly, hazardous, and toxic nature. In their place, organic catalysts are employed which are cheaper and significantly less polluting. This not only addresses

environmental concerns, but it also enhances the economic viability of sustainable catalytic processes.

3.3. Prevalence and relevance of fluorinated organic compounds

C-F bond is considered the stronger single bond that carbon forms.[13] This bond exhibits a relatively short length of approximately 1.3 Å due to its partially ionic nature. The high electronegativity of fluorine contributes to the strength of the bond, creating a negative charge density on fluorine and a positive charge density on carbon. The average bond energy for the C-F bond is around 500 kJ/mol. This high energy is one of the reasons why organofluoride compounds are chemically and thermally stable.

Although organofluoride compounds are very stable, they do not occur naturally and must be synthesised by humans. These compounds play crucial roles in modern society, especially in the pharmaceutical industry, where more than 140 drugs with fluorine atoms are registered. The introduction of fluorine into molecules can improve metabolic stability and alter various properties, which significantly increases the biological activity of many substances.[14]

An example of a molecule used in medicine that contains fluorine is Ubrogepante (Figure 7), used for the treatment of acute migraine headaches in adults.[14] It is not intended to prevent migraines but rather to provide relief during an active episode. It blocks the activity of calcitonin gene-related peptide (CGRP) receptors. Another example is Perxidartinib (Figure 7), used in the treatment of non-carcinoid tumours present in joints, specifically for tenosynovial giant cell tumour (TGCT).[14] It is classified as a tyrosine kinase inhibitor, and it works by targeting specific enzymes involved in the growth and survival of tumour cells. Finally, Siponimod (Figure 7) is a medication used for the prevention of symptoms as well as the treatment of relapsing forms of multiple sclerosis in adults.[14] This drug helps to reduce the frequency of relapses, delay the progression of disability, and decrease the number of brain damage and spinal cord associated with this disease.

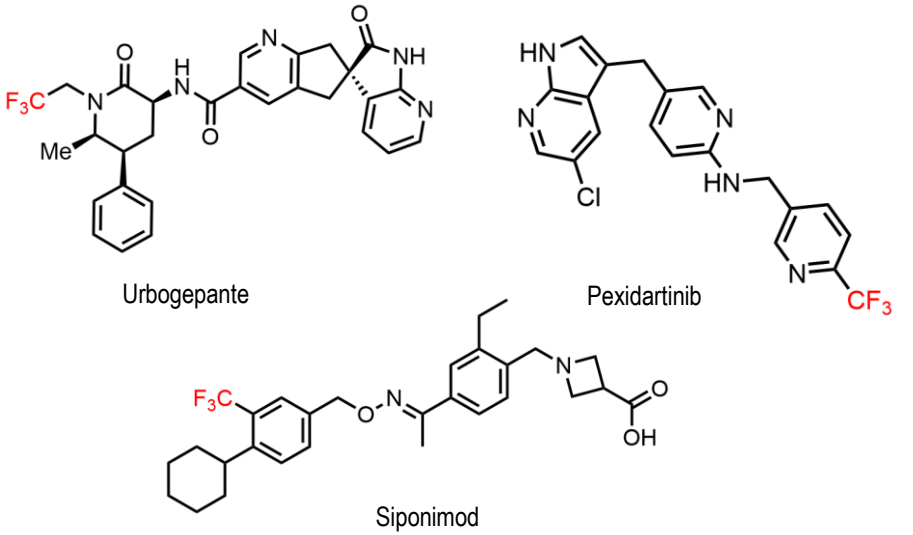


Figure 7. Relevant fluorinated pharmaceuticals.

4. OBJECTIVES

The aim of this TFG is the development of a new homoallylic trifluoromethylation reaction between MBHF and *gem*-difluoroalkenes triggered by catalytic amounts of a fluoride salt, representing a cross-electrophile coupling reaction.

The investigated reaction diverges from the conventional catalytic methods reported so far and shown above. It starts with the direct activation of *gem*-difluoroalkenes **31** using a catalytic amount of fluoride salt, creating a trifluoromethylated benzylic carbanion **31b** (see Figure 9), which has to be nucleophilic enough to attack the MBHF **30** and produce the α-alkylation of product **32** via S_N2' attack. In this process, a new atom of fluoride is generated that can successively attack a new molecule of the electrophile **31** to form the nucleophilic carbanion **31b** and a subsequent product **32**. This method exhibits high atom economy since all the atoms employed in the reaction, including the catalytic amounts of the fluoride salt required to initiate the reaction and the fluoride leaving group, are incorporated into the final product **32**.

Overall, the reaction (see figure 8) enables the synthesis of trifluoromethylated alkenes with high yields, regioselectivities, and perfect E/Z diastereoselectivity.

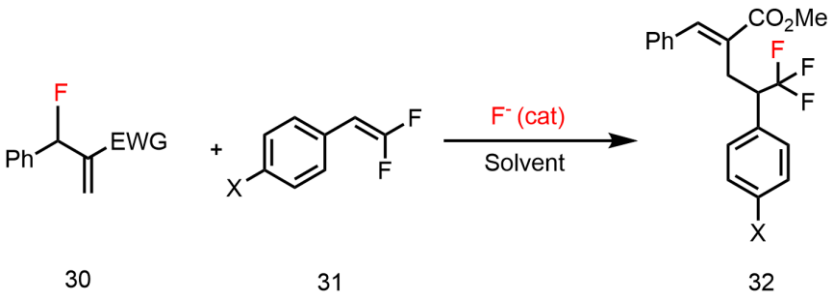


Figure 8. General scheme of the studied reaction.

As shown in Figure 9, the reaction does not proceed via a S_N2'-S_N2 mechanism (see section 3.1.3.) because the α-alkylation occurs at the same time as the release of the fluoride (S_N2').

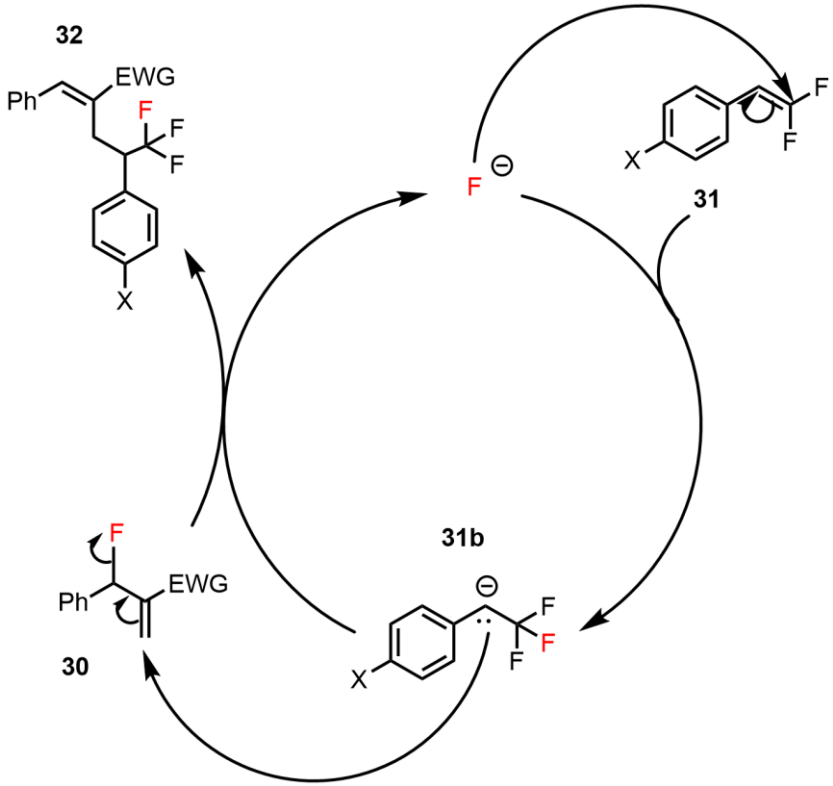


Figure 9. Mechanism of the studied cyclic reaction.

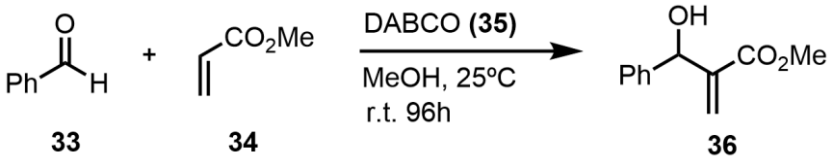
To optimise the reaction, the following objectives will be pursued:

- Synthesize the different starting materials.
- Find the ideal fluoride source; this will be a substance that could be dissolved in the chosen solvent and remain stable enough, so that, the entire promoter can attack the *gem*-difluoroalkenes **31** to produce the carbanion **31b**.
- Tested the reactivity with *gem*-difluoroalkenes bearing different substituents at the aryl ring. The formation and stability of the carbanion may depend directly on whether the X-substituent attached to the aromatic ring of the *gem*-difluoroalkenes **31** is an electron donor group (EDG) or electron-withdrawing group (EWG).
- Optimise the solvent and the ratio between reagents.

5. EXPERIMENTAL SECTION

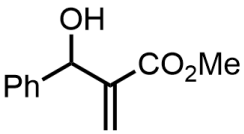
5.1. SYNTHESIS OF STARTING MATERIALS

5.1.1 Synthesis of Morita-Baylis-Hillman alcohol (methyl 3-hydroxy-2-methyldiene-3-phenylpropionate) 36



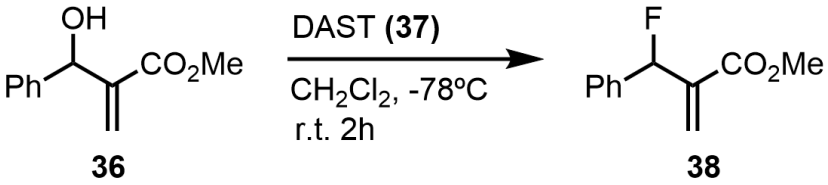
33 **34** **36**

To a round bottom flask containing MeOH (0.75 equiv.) and benzaldehyde **33** (1.0 equiv.) the corresponding acrylate **34** (1.2 equiv.) was added at room temperature. Then, triethylenediamine (DABCO) **35** (0.5 equiv.) was added, and the solution was stirred for 72-96h until the consumption of the starting material. The crude reaction mixture was purified by column chromatography using as eluent hexane/ethyl acetate in a ratio 3:1.



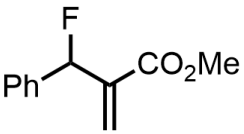
Yellowish oil. 80.9% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.29 (m, 5H), 6.33 (s, 1H), 5.83 (s, 1H), 5.56 (d, J = 5.6 Hz, 1H), 3.73 (s, 3H), 3.14 (d, J = 5.5 Hz, 1H) ppm. Chemical shifts match with those reported in the literature.[15]

5.1.2. Synthesis of Morita-Baylis-Hillman fluoride (methyl 2-[fluoro(phenyl)methyl]acrylate) 38



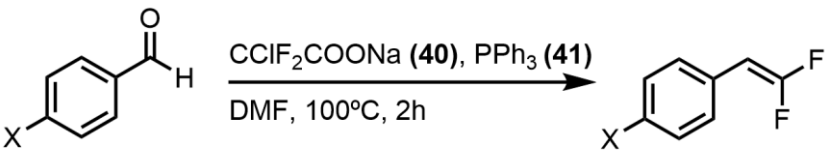
36 **38**

Into a two-necked round-bottom flask equipped with a magnetic stirring bar was added the MBH alcohol **36** (1.1 equiv.) in CH_2Cl_2 at -78 ºC under nitrogen atmosphere. To this solution, DAST **37** (1.0 equiv.) was added dropwise. The mixture was stirred for 2 hours at the same temperature and then quenched with saturated $NaHCO_3$ solution. The mixture was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **38** was purified by column chromatography using (Hexane/ CH_2Cl_2 =1:1).



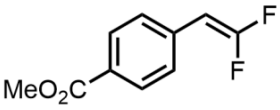
Light yellow oil. 40% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.32 (m, 5H), 6.45 (s, 1H), 6.29 (dt, JH-F = 46 Hz, 1H), 6.02 (s,1H), 3.71 (s, 3H). Chemical shifts match with those reported in the literature.[9]

5.1.3. Synthesis of *gem*-difluoroalkenes (methyl 4-(2,2-difluorovinyl)benzoate) 42

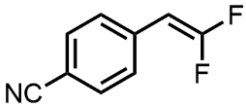


39 **42**

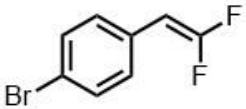
To a three-necked round-bottom flask equipped with a magnetic stirring bar and charged with a solution of aldehyde **39** (1.0 equiv.) in *N,N*-dimethylformamide (DMF) (0.5 M), PPh_3 **41** (1.2 equiv.) was added, and the mixture was heated until 100ºC. Then, a solution of sodium chlorodifluroroacetate **40** (1.5 equiv.) in DMF (1.4 M) was added dropwise for 15 minutes, due to the possible vigorous liberation of CO_2 gas. The reaction was heated at the same temperature for 90 minutes. After cooling the reaction mixture to 0 ºC, water was added, and the resulting solution was extracted with EtO_2. The combined organic phase was washed with water and then dried over $MgSO_4$. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography using hexane and ethyl acetate to obtain the *gem*-difluoroalkenes **42a-d**.



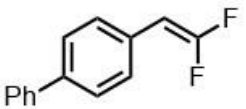
Methyl 4-(2,2-difluorovinyl)benzoate. **42-a** Colourless oil. 58% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.99 (AA'BB', 2H), 7.40-7.38 (AA'BB', 2H), 5.33 (dd, J_{H-F} = 26.0, 3.6 Hz, 1H), 3.92 (s, 3H) ppm. Chemical shifts match with those reported in the literature.[16]



4-(2,2-Difluorovinyl)benzonitrile. 42-b White solid. 43% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.61 (AA'BB', 2H), 7.43-7.41 (AA'BB', 2H), 5.34 (dd, J_{H-F} = 25.5, 3.6 Hz, 1H) ppm. Chemical shifts match with those reported in the literature.[16]

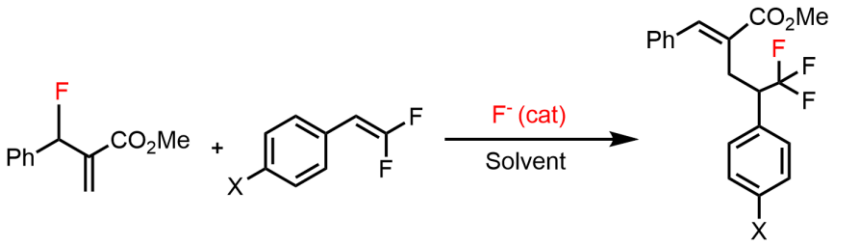


1-Bromo-4-(2,2-difluorovinyl)benzene. **42-c** Brown oil. 46% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.44 (AA'BB', 2H), 7.20-7.18 (AA'BB', 2H), 5.23 (dd, J_{H-F} = 26.0, 3.6 Hz, 1H) ppm. Chemical shifts match with those reported in the literature.[16]



4-(2,2-Difluorovinyl)-1,1'-biphenyl. **42-d** White solid. 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.32 (dd, J_{H-F} = 26.4, 3.7 Hz, 1H), 7.35 (tt, J_{H-H} = 7.4, 1.3 Hz, 1H), 7.48–7.38 (m, 4H), 7.62–7.55 (m, 4H) ppm. Chemical shifts match with those reported in the literature.[16]

5.2. General procedure to study the reactivity between Morita-Baylis-Hillman fluoride and *gem*-difluoroalkenes promoted by a fluoride source



38 **42** **43**

General procedure: The limiting reagent was weighed into a 4 mL vial equipped with a magnetic stirring bar. Subsequently, the necessary volume of solvent to create a 0.1 M was added, followed by the addition of the other reaction partner (the one in excess). The vial was purged with argon, catalytic amounts of the fluoride salt were added, and the resulting reaction mixture was stirred at a determined temperature during the specified reaction time.

5.3. Determination of the reaction outcome by means of ^{1}H-NMR

Conventional proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) was used to analyse the purity of the starting materials and to characterise the final products. To analyse the progress, conversion, and yield during the optimisation of the reaction, ^{1}H-NMR with an internal standard (IS) was used. Trimethoxybenzene is used as IS. The ratio between the integration of trimethoxybenzene, the limiting reagent and product **43**, allows to determine the conversion and yield of the reaction.

A solution of the internal standard was prepared with the same concentration as the solution of the studied reaction. In this way, equal and known volumes of the two solutions are placed in a vial, to put the same amount of mols. Then the solvent is evaporated to avoid interfering in the analysis of the crudes, and finally, it is dissolved in $CDCl_3$ and transferred to an NMR tube.

5.4. DETERMINATION OF THE REACTION OUTCOME BY MEANS OF GC

For some substrates the analysis of the crude ^{1}H NMR spectra was complex and was difficult to measure the conversion and reaction yield. Consequently, an alternative method was optimised involving gas chromatography (GC). Initial tests were carried out to find a method where the different species involved in the reaction were successfully separated. Subsequently, a calibration curve was built using both reactants, the studied product **43-a,** and an internal standard within the concentration range of 0.002M to 0.02M. Figure 10 shows the relation between the answers of the products and the internal standard (R_X/ R_{IS}) against the relation between the concentration of the products and the internal standard (C_X/C_{IS}).

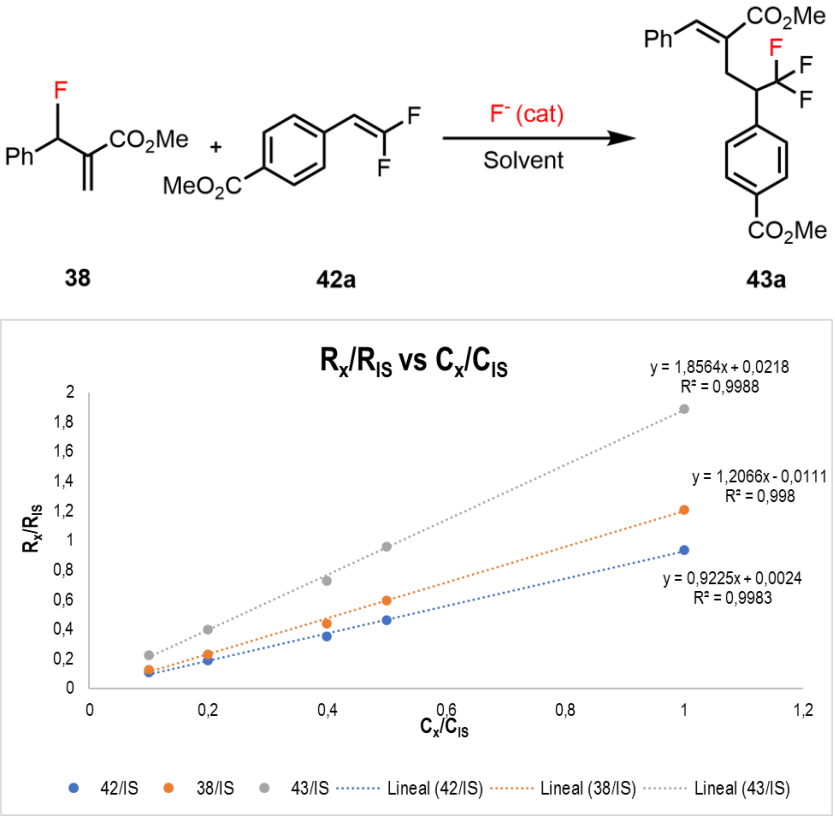
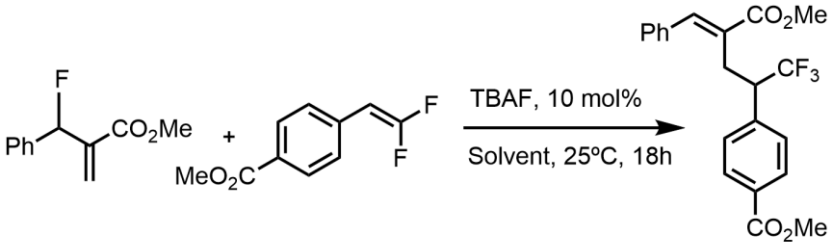


Figure 10. Graph relating the answers of the products against its concentration.

6. RESULTS, DISCUSSION AND CHARACTERIZATIONS OF NEW PRODUCTS

6.1. OPTIMISATION OF THE REACTION BETWEEN MORITA-BAYLIS-HILLMAN FLUORIDE 38 AND *GEM*-DIFLUOROALKENES 42 PROMOTED BY A FLUORIDE SOURCE

6.1.1. Solvent optimisation



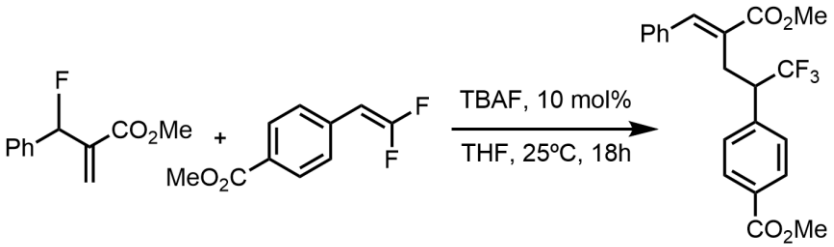
38 (1equiv.) **42a (2equiv)** **43a**

ENTRY	Solvent	Conversion (%)	NMR yield (%)
1	Toluene	42	4
2	THF	75	24
3	MeCN	39	2
4	CH_2Cl_2	12	0

Table 1. Solvent Optimisation.

Initially, the reaction between **38** and **42-a** was tested in four different solvents using a ratio between reagents **38/42-a**=1:2 and 10 mol% of tetrabutylammonium fluoride (TBAF) at room temperature for 18h. As shown in Table 1 entry 2, the best solvent is Tetrahydrofuran (THF), affording the final product **43-a** in 24% of NMR yield and 75% of conversion.

6.1.2. Ratio between reagents



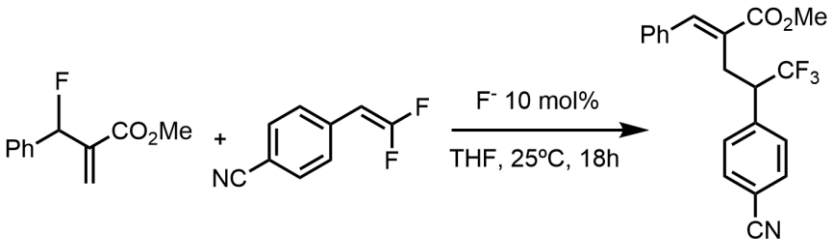
38 **42a** **43a**

ENTRY	Ratio (38:42a) (equiv.)	Conversion (%)	NMR yield (%)
1	1:2	40	17
2	1:3	6	5
3	3:1	100	36
4	2:1	100	42

Table 2. Ratio between reagents.

Secondly, the ratio of reagents was studied. The best results were obtained using **42-a** as the limiting reagent and the allyl fluoride **38** in excess in a ratio 2:1 (Table 2, entry 4), affording the final product **43-a** in 42% yield and full conversion after 18 hours reaction.

6.1.3. Nature of the fluoride source with Morita-Baylis-Hillman fluoride 38 and 4-(2,2-Difluorovinyl)benzonitrile 42-b



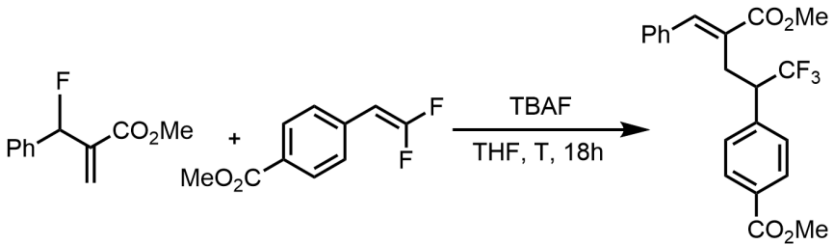
38 (2equiv.) **42b (1 equiv.)** **43b**

ENTRY	F^- 0,1 (equiv.)	Conversion (%)	NMR yield (%)
1	TBAF	100	96
2	CsF	20	0
3	$Et_3N{\cdot}3HF$	0	0

Table 3. Fluoride source.

Subsequently, the impact of the fluoride source was studied using the *gem*-difluoroalkene **42-b** instead of the **42-a**. I Selected three different fluoride sources: TBAF, CsF and $Et_3N{\cdot}3HF$. The best results were obtained with TBAF, achieving full conversion after 18 hours and affording the final product **42-b** with 96% yield (Table 3, entry 1). The other fluoride sources tested performed much worse, likely due to their poor solubility in THF.

6.1.4. Optimisation of the reaction between Morita-Baylis-Hillman fluoride 38 and methyl 4-(2,2-difluorovinyl)benzoate 42-a



38 **42a** **43a**

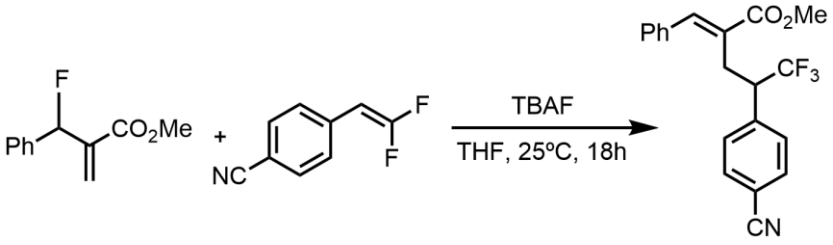
ENTRY	Ratio (38:42a)	TBAF (equiv.)	T (ºC)	Conversion (%)	NMR yield (%)
1	1:2	0,20	25	100	100
2	2:1	0,10	25	100	42
3	2:1	0,15	25	100	64
4	2:1	0,10	50	100	82

Table 4. Optimisation of the reaction between 38 and 42-a.

The most significant tests for *gem*-difluoroakene **42-a** are shown in Table 4. Entry 1 was performed with the initial ratio between reagents, and it enabled the isolation of the final product **43-a** in quantitative yield.

Subsequently, I tried to reduce the amount of promoter to see if the reaction could perform as well as in entry 1. I employed an excess of **38** with **42-a** as the limiting reagent (Table 4, entries 2-4), but with the lower amount of promoter, the yields of entries 2 and 3 decreased proportionally. Lastly, in Table 4, entry 4, I elevated the temperature while maintaining a controlled amount of fluoride (10 mol%) to investigate the impact of temperature. It was observed that the yield was doubled 82% compared to the one obtained at 25ºC, 42% (Table 4, entry 2).

6.1.5. Optimisation of the reaction between Morita-Baylis-Hillman fluoride 38 and 4-(2,2-difluorovinyl)benzonitrile 42-b



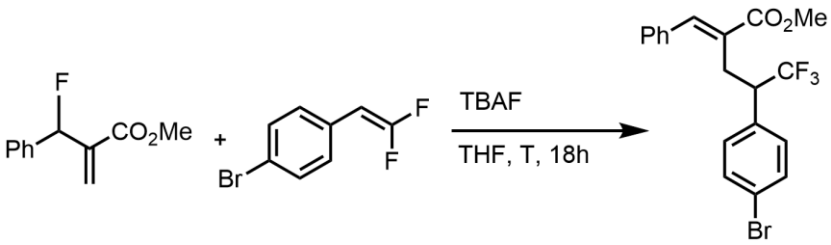
38 (2equiv.) **42b (1equiv.)** **43b**

ENTRY	TBAF (equiv.)	Conversion (%)	NMR yield (%)
1	0,1	100	96
2	0,05	100	100

Table 5. Optimisation of the reaction between 38 and 42-b.

42-b is the best *gem*-difluoroalkene tested. In Table 5, entry 2, with only 5% of promoter it already leads to the full conversion and the formation of the final product **43-b** in quantitative yield. This fact may indicate that nitrile is the group that better stabilizes the negative charge of the carbanion, making the subsequent attack to **38** and regeneration of the fluoride much more efficient.

6.1.6. Optimisation of the reaction between Morita-Baylis-Hillman fluoride 38 and 1-bromo-4-(2,2-difluorovinyl)benzene 42-c



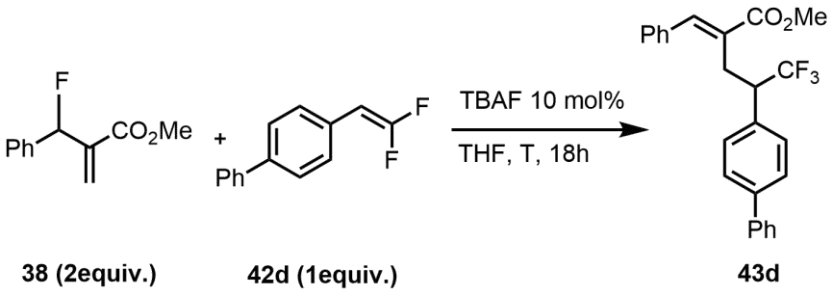
38 (2equiv.) **42c (1equiv.)** **43c**

ENTRY	TBAF (equiv.)	T (ºC)	Conversion (%)	NMR yield (%)
1	0,1	25	49	0
2	0,2	25	46	0
3	0,1	50	26	0
4	0,2	50	43	3

Table 6. Optimisation of the reaction between 38 and 42-c.

Subsequently, I tested the effect of other substituents in the aryl ring of **42**, such as bromide. The reaction with the *gem*-difluoroalkene **42-c** did not work, although I tried several conditions (Table 6). The result may be rationalised by the fact that bromine is not very EWG, and the stability of the corresponding carbanion is not efficient.

6.1.7. Optimisation of the reaction between Morita-Baylis-Hillman fluoride 38 and 4-(2,2-difluorovinyl)-1,1'-biphenyl 42-d



ENTRY	T (ºC)	Conversion (%)	NMR yield (%)
1	25	42	0
2	50	42	0

Table 7. Optimisation of the reaction between 38 and 42-d.

The reaction with *gem*-difluoroalkene **42-d** having another aromatic group did not work either. As can be seen in Table 7 entries 1-2, I tried to increase the temperature and it did not improve the results. In this case, it is worth mentioning a very relevant fact: analysing the ^{1}H NMR of the crude reaction, I detected the formation of regioisomer **44**.

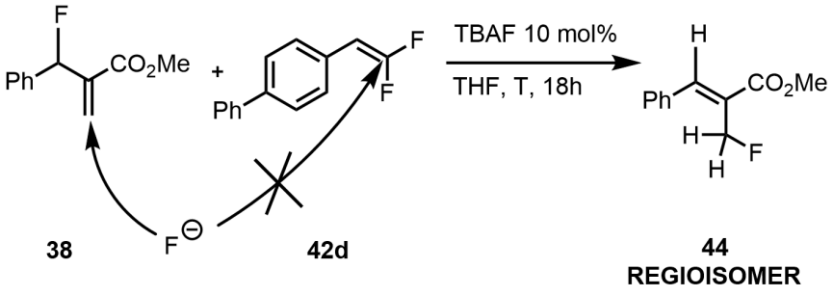
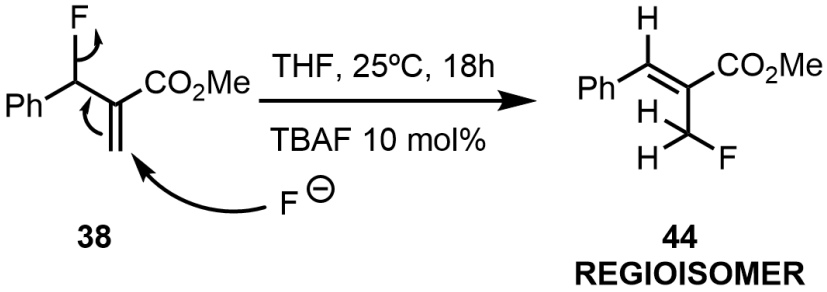


Figure 11. Outcome of the reaction between 38 and 42-d.

As can be seen in Figure 11, the fluoride anion prefers to attack the α-position of the MBHF **38** rather than the *gem*-difluoroalkene **42-d**. It may indicate that **42-d** is the one with the weakest

electrophilic carbon of all the *gem*-difluoroalkenes tested, because this regioisomer has never been observed for other substrates.

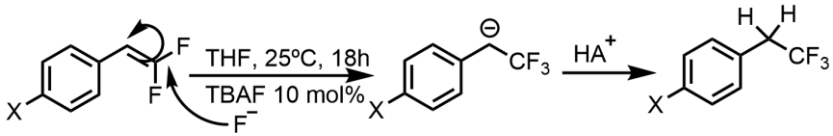
6.1.8. Control experiments



ENTRY	38 (equiv.)	TBAF (equiv.)	Conversion (%)	NMR yield (%)
1	1	0,1	78	56
2	1	0,05	45	44

Table 8. Control reaction between 38 and TBAF.

As shown in Table 8, in the absence of *gem*-difluoroalkene **42**, TBAF can directly attack the MBHF **38** and produce the regioisomer **44.**



42 (1 equiv.) **45** **46**

X=Br, Ph

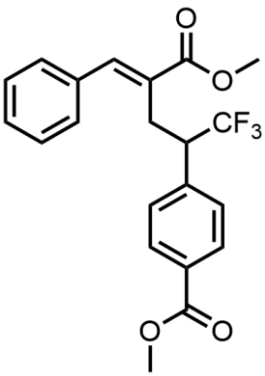
ENTRY	42 (type)	Conversion (%)	NMR yield (%)
1	c (Br)	50	6
2	d (Ph)	18	11

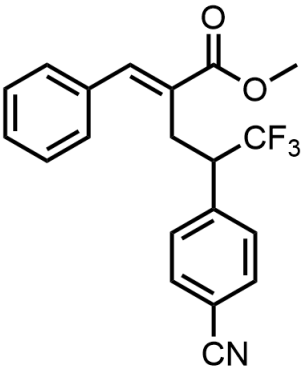
Table 9. Control reaction between 42 and TBAF.

I also studied the control reactions between two *gem*-difluoroalkenes **42-c** and **42-d** with weak EWG groups and TBAF in the absence of **38** to investigate if fluoride attack was taking place to form the reactive carbanion **45**. The yields refer to the product **46** arising from protonation of **45**. The reaction with **42-c** with a bromo has a significant 50% of conversion, but **46-c** was formed in 6% of yield (Table 9, entry 1). On the other hand, the reaction with **42-d** has a lower 18% conversion but product **46-d** was formed in 11% of yield (Table 9, entry 2).

6.2. CHARACTERIZATIONS OF NEW PRODUCTS

The products **43-a** and **43-b** have been successfully isolated and characterized using ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR.

	Methyl(E)-4-(1,1,1-trifluoro-4-(methoxycarbonyl)-5-phenylpent-4-en-2-yl)benzoate **43-a**. The product was synthesized following the general procedure explained in section 5.2 and purified by silica-gel column chromatography using a mixture of hexane/Et_2O=5:1, obtaining the final product **43-a** in 100% isolated yield . Colourless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.84-7.80 (d, J =8.43 Hz, 2H), 7.65 (s, 1H), 7.37-7.32 (m, 3H), 7.09-7.05 (m, 2H), 7.05-7.00 (d, J = 8.25 Hz, 2H), 3.91 (s, 3H), 3.83-3.765 (m, 1H), 3.765-3.75 (s, 3H), 3.30-3.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.75 (1C), 166.65 (1C), 142.60 (1C), 138.90 (1C), 134.93 (1C), 129.90 (2C), 129.55 (1C), 129.10 (1C), 128.60 (3C), 52.20 (1C), 48.70 (1C), 26.75 (1C). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -69.17 (d, JF-H = 9.12 Hz). High Resolution Mass Spectroscopy. HRMS (ESI^+) m/z 393.1319 (393.1319 calculated for $C_{21}H_{20}F_3O_4^+$, $[M+H]^+$). HPLC High Performance Liquid Chromatography (Appendix 3)



Methyl (E)-2-benzylidene-4-(4-cyanophenyl)-5,5,5-trifluoropentanoate **43-b**

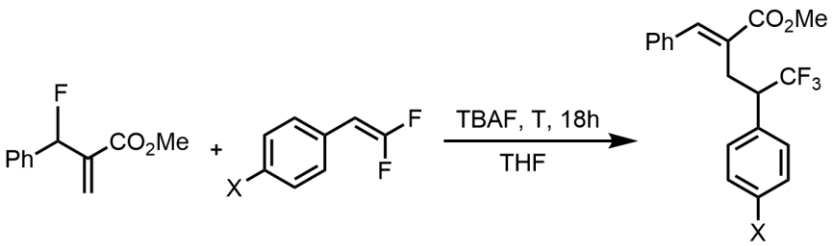
The product was synthesized following the general procedure explained in section 5.2 and purified by silica-gel column chromatography using a mixture of hexane/Et_2O =5:1, obtaining the final product **43-b** in 100% isolated yield.

White solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (s, 1H), 7.43-7.39 (d, J =8.84Hz, 2H), 7.38-7.34 (m, 3H), 7.07-7.02 (m, 4H), 3.79-3.76 (s, 3H), 3.83-3.75 (m, 1H), 3.32-3.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.6 (1C), 143.9 (1C), 139.1 (1C), 134.8 (1C), 131.9 (2C), 129.8 (1C), 128.7 (1C), 128.5 (3C), 52.3 (2C), 48.7 (1C)

^{19}F NMR ($CDCl_3$, 471 MHz): δ -69.18c (d, JF-H = 8.89 Hz).

6.3. DISCUSSION



38

X= CO_2Me **42a**
X= CN **42b**
X= Br **42c**
X= Ph **42d**

X= CO_2Me **43a**
X= CN **43b**
X= Br **43c**
X= Ph **43d**

Entry	Ratio (38:42)	42 (Type)	T (ºC)	TBAF (equiv.)	Conversion (%)	NMR yield (%)
1	2:1	b	25	0,05	100	100
2	2:1	a	25	0,15	100	64
3	1:2	a	25	0,2	100	100
4	2:1	a	25	0,1	100	42
5	2:1	a	50	0,1	100	82
6	1:2	d	25	0,1	64	6
7	2:1	c	25	0,1	49	0
8	2:1	c	50	0,2	43	3

Table 10. Summary of the best reactions.

Table 10 shows a summary of the most relevant results obtained in this TFG. **42-b** is the *gem*-difluoroalkene that has performed the best (Table 10, entry 1), achieving complete conversion and quantitative yield with only 5% fluoride at 25ºC. The superior performance of **42-b** can be attributed to both electronic and steric factors.

42-a did not perform as well as **42-b** but using a higher amount of fluoride (Table 10, Entry 3) also allowed the reaction to proceed with full conversion and quantitative yield of the corresponding product **43-a**. Raising the temperature with 10 mol% of TBAF is also an efficient strategy to accelerate reactivity (Table 10, Entry 5).

With the less electron-poor substrates **42-c and 42-d**, the reaction did not work. In the case of **42-d**, the fluoride preferred to attack the MBHF **38** to form regioisomer **44** rather than the

electrophile carbon of the **42-d**. This was evident in the two control experiments shown in section 6.1.8.

Finally, although the formation of the regioisomer **44** has never been observed in the reactions with **42-c**, the corresponding product **43-c** was never detected (Table 10, entries 7-8). This may be attributed to the fact that the intermediates are quenched, degraded, or simply not formed, as suggested in the control reactions of the *gem*-difluoroalkene in section 6.1.8. These results indicate that **42-c** is the least suitable substrate to work within this type of reactivity.

7. CONCLUSIONS

The main objectives set for this TFG thesis have been successfully achieved. First, the different starting materials have been synthesised and characterised. Their spectroscopic data matches with those reported in the literature.

The initial reactivity attempts already confirmed that the proposed fluoride-triggered activation and recycling strategy to activate the *gem*-difluoroalkene **42** and the corresponding attack to MBHF **38** to form the homoallylic trifluoromethylated group was successful. Optimisation and reactivity studies shown in section 6.3 and in Table 10 are consistent with the different steric and electronic nature of substrates **42**. Control experiments demonstrated why the less electron poor substrates **42-c** and **42-d** did not produce the expected product and instead, the regioisomer of MBHF **44** or the protonated trifluoromethylated carbanion **46** were detected.

Two different homoallylic trifluorometylated products **43-a** and **43-b** have been successfully isolated in racemic form and fully characterised by means of ^{1}H, ^{13}C and ^{19}F NMR, and HRMS.

It is also remarkable that a method for product quantification using gas chromatography has been developed, allowing reaction optimisation in a fast and precise way.

Future directions in this project would be: (i) to find general reaction conditions able to engage different *gem*-difluoroalkenes regardless its stereoelectronic nature (ii) use an asymmetric catalyst to control the absolute configuration of the newly formed chiral centre.

8. REFERENCES AND NOTES

1. For selected reviews on transition-metal catalysed AAA, see: (a) Trost, B. M. Metal Catalyzed Allylic Alkylation.*Tetrahedron*. **2015**, *71*, 5708. (b) Butt, N. A.; Zhang, W. Transition metal-catalyzed allylic substitution reactions with unactivated allylic substrates. *Chem. Soc. Rev.* **2015**, *44*, 7929. (c) Turnbull, B. W. H.; Evans, P. A. J. Asymmetric Rhodium-Catalyzed Allylic Substitution Reactions: Discovery, Development and Applications to Target-Directed Synthesis *Org. Chem.* **2018**, *83*, 11463. (d) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-catalyzed asymmetric allylic substitution reactions. *Chem. Rev*. **2019**, *119*, 1855. (e) Han, J.-F.; Guo, P.; Zhang, X.-G.; Liao, J.-B.; Ye, K.-Y. Recent advances in cobalt-catalyzed allylic functionalization. *Org. Biomol. Chem.* **2020**, *18*, 7740.
2. For selected reviews on Lewis-base catalysed AAA, see: (a) Rios, R. Organocatalytic enantioselective methodologies using Morita–Baylis–Hillman carbonates and acetates. *Catal. Sci. Technol.* **2012**, *2*, 267. (b) Liu, T.-Y.; Xie, M.; Chen, Y.-C. Organocatalytic asymmetric transformations of modified Morita–Baylis–Hillman adducts. *Chem. Soc. Rev.* **2012**, *41*, 4101.(c) Chen, Z.; Chen, Z.; Du, W.; Chen, Y. Transformations of Modified Morita-Baylis-Hillman Adducts from Isatins Catalyzed by Lewis Bases. *Chem. Rec.* **2020**, *20*, 541. (d) Calcatelli, A.; Cherubini-Celli, A.; Carletti, E.; Company., X. Unconventional Transformations of Morita–Baylis–Hillman Adducts. *Synthesis*. **2020**, *52*, 2922.
3. (a) Trost, B. M.; Dietsch, T. New synthetic reactions. Asymmetric induction in allylic alkylations. *J. Am. Chem. Soc*. **1973**, *95*, 8200. (b) Trost, B. M.; Strege, P. E. Asymmetric induction in catalytic allylic alkylation. *J. Am. Chem. Soc*. **1977**, *99*, 1649.
4. (a) Kim, J. N.; Lee, H. J.; Gong, J. H. Synthesis of enantiomerically enriched Baylis–Hillman alcohols from their acetates: combination of kinetic resolution during the salt formation with $(DHQD)_2PHAL$ and following asymmetric induction during hydrolysis with $NaHCO_3$ as a water surrogate. *Tetrahedron Lett.* **2002**, *43*, 9141. (b) Du, Y.; Han, X.; Lu, X. Alkaloids-catalysed regio-and enantioselective allylic nucleophilic substitution of tert-butyl carbonate of the Morita–Baylis–Hillman products. *Tetrahedron Lett.* **2004**, *45*, 4967.
5. Chen, G. Y.; Zhoung, F.; Lu, Y. Highly enantioselective and regioselective substitution of Morita–Baylis–Hillman Carbonates with Nitroalkanes. *Org. Let.* **2011**, *22*, 6070.
6. Singha Roy, S. J.; Mukherjee, S. Enantioselective desymmetrization of prochiral 1, 3-dinitropropanes via organocatalytic allylic alkylation. *Chem. Commun.* **2014**, *50*, 121.
7. Zhu, G.; Yang, J.; Bao, G.; Zhang, M.; Li, J.; Li, Y.; Sun, W.; Hong, L.; Wang, R. Catalyst-controlled switch of regioselectivity in the asymmetric allylic alkylation of oxazolones with MBHCs. *Chem. Commun.* **2016**, *52*, 7882.
8. Rodríguez, P.; Duran, J.; Gisbert, M.; Companyó, X.; Defluorinative Asymmetric Allylic Alkylations. *Synlett,* **2023**. *1*, 2

9. Nishimine, T.; Fukushi, K.; Shibata, N.; Taira, H.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. Kinetic Resolution of Allyl Fluorides by Enantioselective Allylic Trifluoromethylation Based on Silicon-Assisted C-F Bond Cleavage. *Angew. Chem. Int. Ed.* **2014**, *53*, 517.
10. Nishimine, T.; Taira, H.; Tokunaga, E.; Shiro, M.; Shibata, N.; Enantioselective Trichloromethylation of MBH-Fluorides with Chloroform Based on Silicon-assisted C-F Activation and Carbanion Exchange Induced by a RuppertPrakash Reagent. *Angew. Chem. Int. Ed Engl.* **2016**, *55*, 359.
11. Duran, J.; Mateos, J.; Moyano, A.; Companyó, X. *Chem. Sci.* **2023**, *14*, 7147.
12. Anastas, P.; Eghbali, N.; Green chemistry: principles and practice. *Chem. Soc. Rev*., **2010**, *39*, 301–312.
13. (a) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev*. **2008**, *37*, 308. (b) Luo, Y.-R. Comprehensive Handbook of Chemical Bond Energies; *CRC Press*, **2007**, *1,* 217.
14. (a) Inoue, M.; Sumii, Y.; Shibata, N.; Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS omega.* **2020.** *5, 19*, 10633–10640. (b) Shah, P.; Westwell, AD.; The role of fluorine in medicinal chemistry. *Journal of Enzyme Inhibition and Medicinal Chemistry*. **2007**, *22, 5*, 527–540. (c) Dodick, DW.; Goadsby, PJ.; Schwedt, TJ.; Lipton, RB.; Liu, C.; Lu, K.; Yu, SY.; Severt, L.; Finnegan, M.; Trugman, JM.; Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA. *Lancet.* **2023**. *16.* 2307-2316. (d) Cao, L.; Li, M.; Yao, L.; Yan, P.; Wang, X.; Yang, Z.; Lao, Y.; Li, H.; Yang, K.; Li, K.; Siponimod for multiple sclerosis. *Cochrane Database of Systematic Reviews.* **2021**, *11*. (e) Monestime, S.; Lazaridis, D.; Pexidartinib. The First FDA-Indicated Systemic Treatment for Tenosynovial Giant Cell Tumor. *Drugs R D*. **2020**. *20*. 189-195.
15. Santos, MS.; Coelho, F.; Oxidizing Morita–Baylis–Hillman adducts towards vicinal tricarbonyl compounds. *RSC advances.* **2012.** *2, 8,* 3237–3241.
16. Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M. J. A one-step synthesis of 1,1-difluoro olefins from aldehydes. *Org. Chem.* **1965**, *30*, 1027.

9. ACRONYMS

AAA: Asymmetric Allylic Alkylation

AE: Atom Economy

DABCO: Triethylenediamine

DAST: Diethylaminosulfur trifluoride

DMF: Dimethylformamide

EDG: Electron Donor Group

EWG: Electron Withdrawing Group

HPLC: High Performance Liquid Chromatography

HRMS: High Resolution Mass Spectroscopy

LB: Lewis Base

LG: Leaving Group

MBH: Morita-Baylis-Hillman

NMR: Nuclear Magnetic Resonance

SEE: Silyl enol ethers

S_N2: Bimolecular Nucleophilic Substitution

TBAF: Tetrabutylammonium fluoride

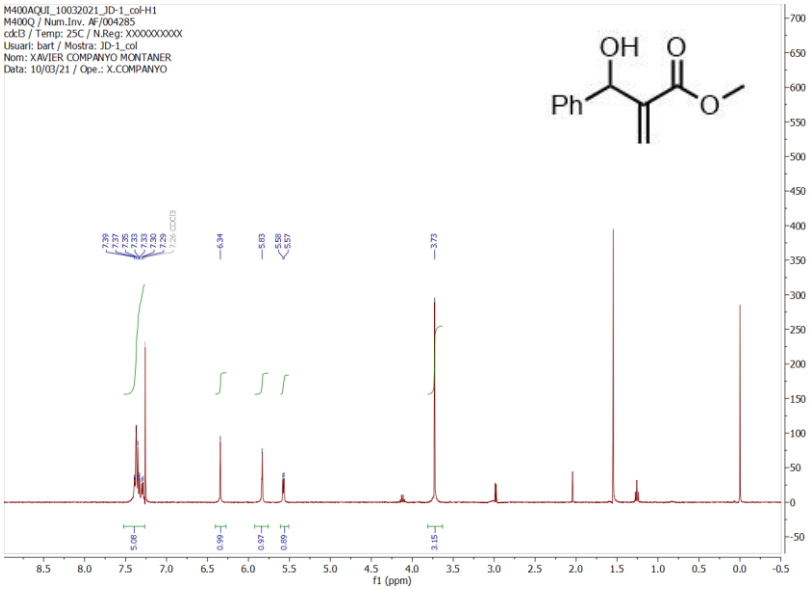
THF: Tetrahydrofuran

TM: Transition metal

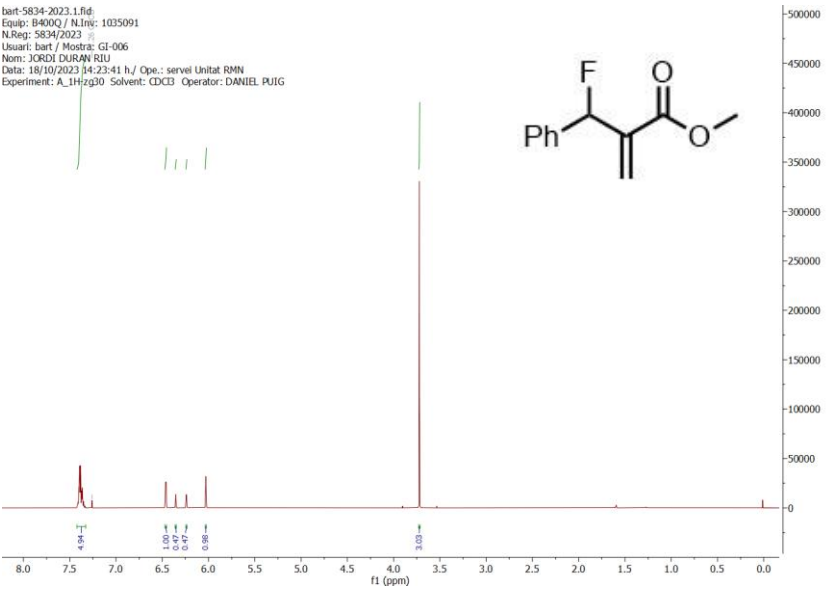
APPENDICES

APPENDIX 1: NMR SPECTRA OF STARTING MATERIALS

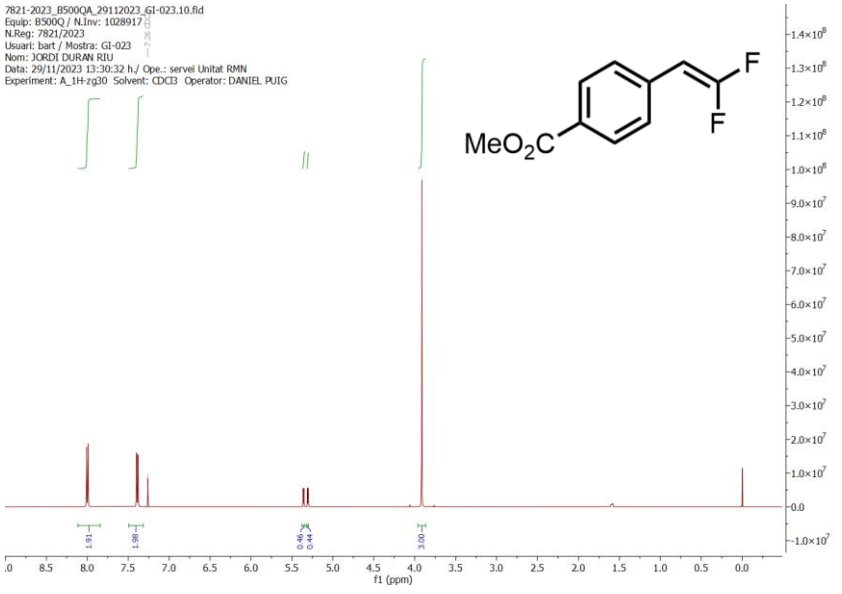
^{1}H-NMR Product 36



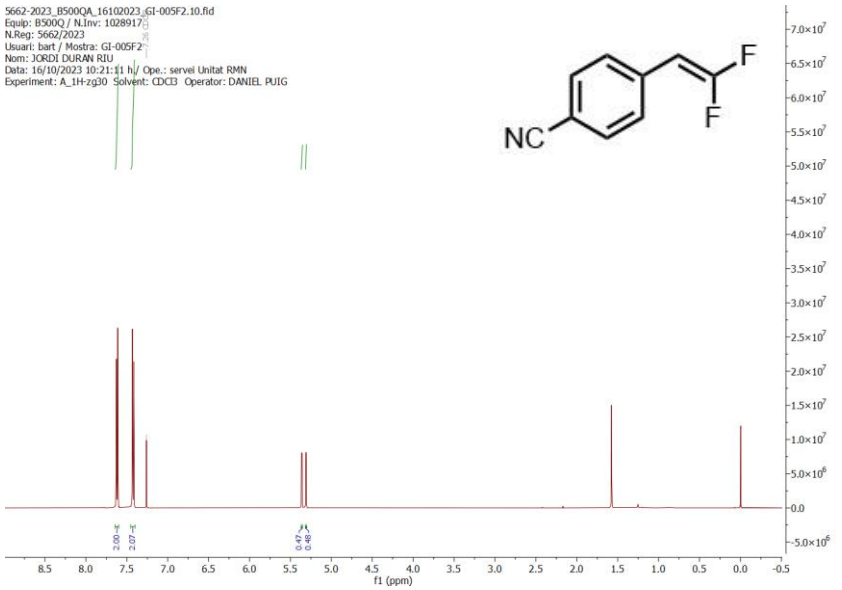
^{1}H-NMR Product 38



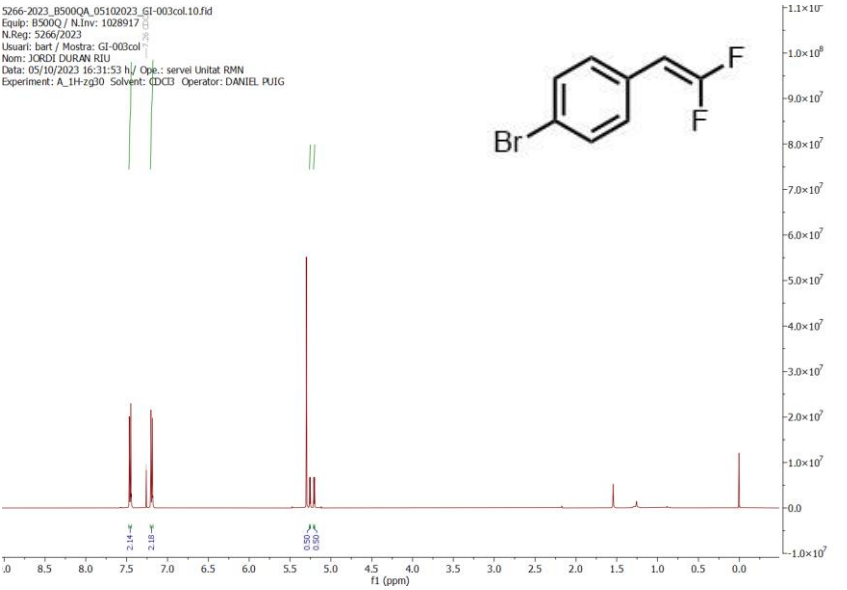
^{1}H-NMR Product 42-a



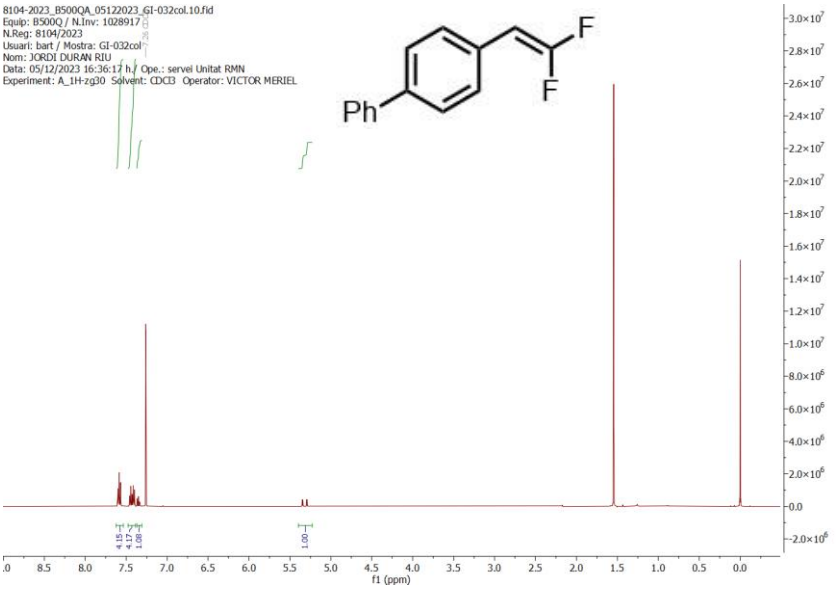
^{1}H-NMR Product 42-b



^{1}H-NMR Product 42-c

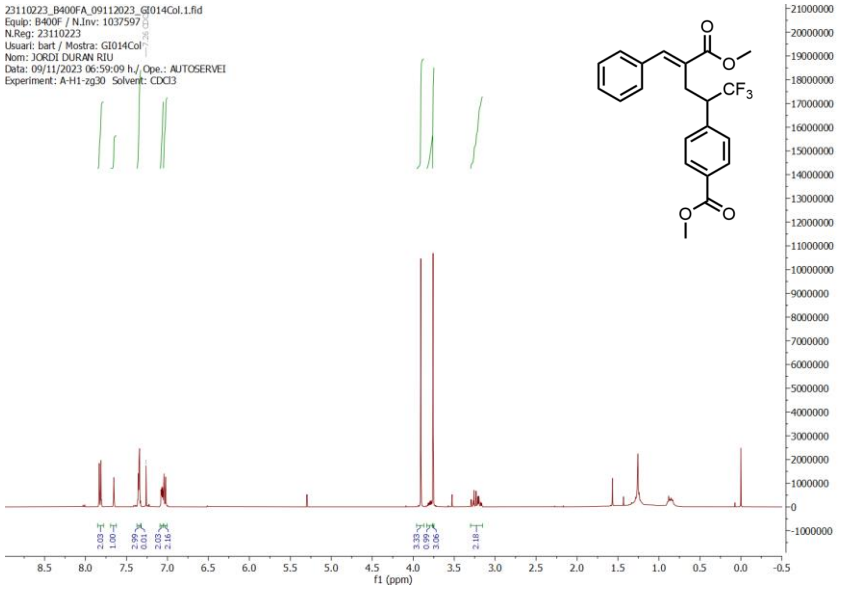


^{1}H-NMR Product 42-d

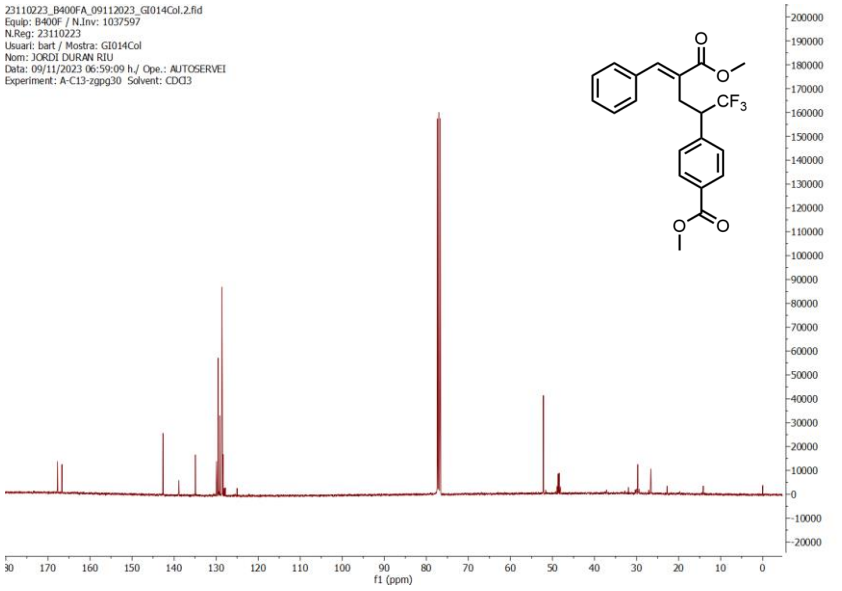


APPENDIX 2: NMR SPECTRA OF PRODUCTS 43-a AND 43-b

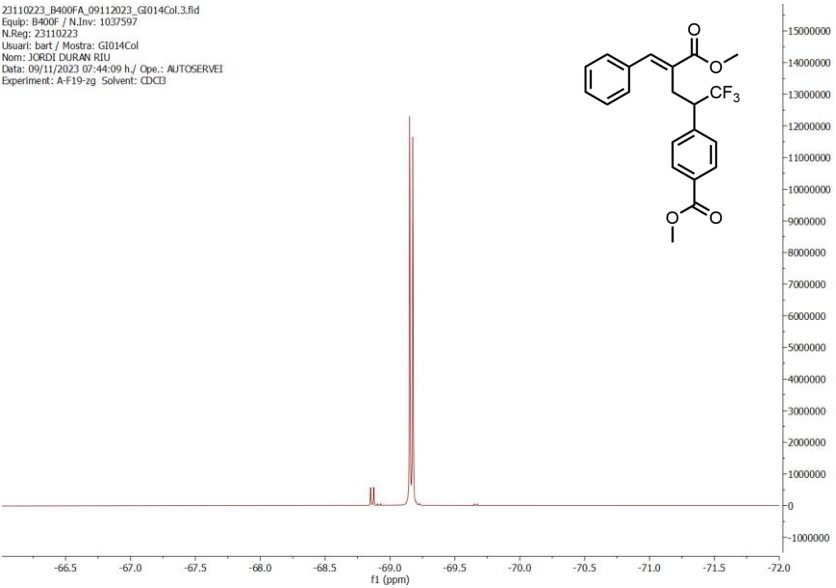
^{1}H-NMR Product 43-a



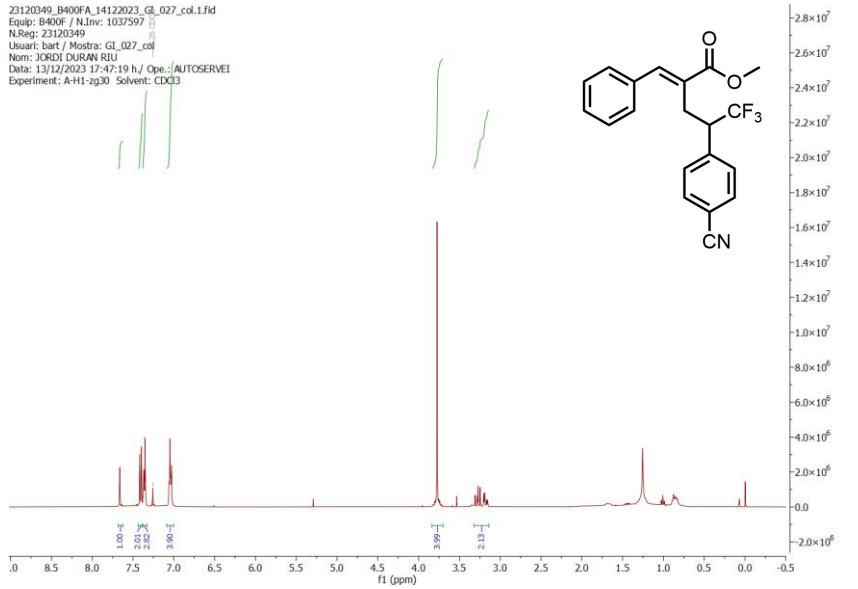
^{13}C-NMR Product 43-a



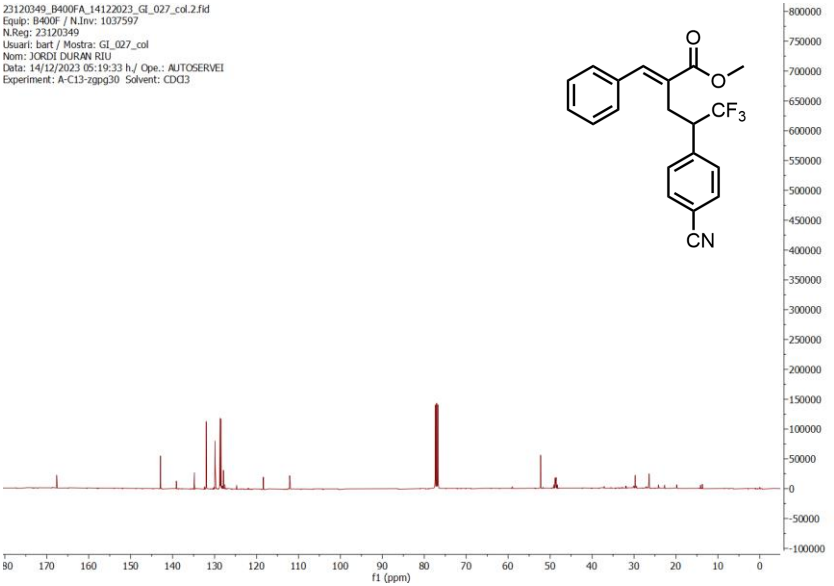
^{19}F-NMR Product 43-a



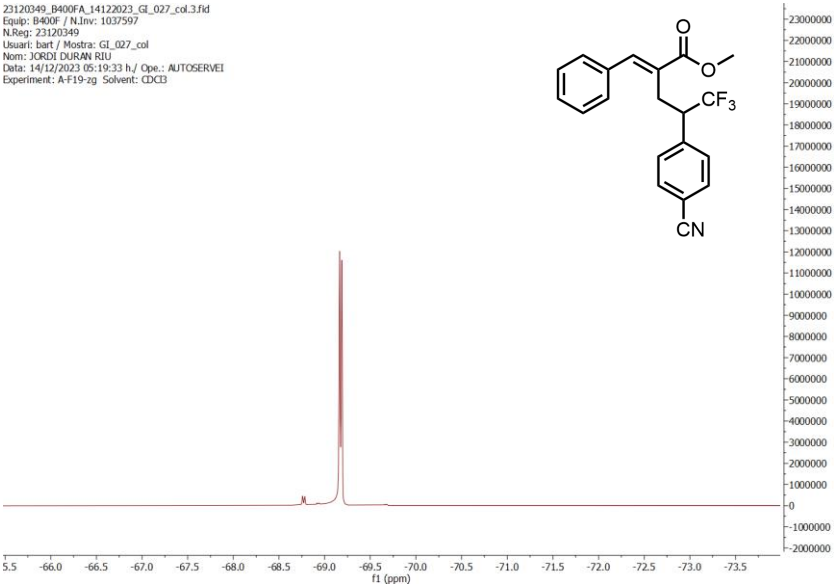
^{1}H-NMR Product 43-b



^{13}C-NMR Product 43-b



^{19}F-NMR Product 43-b



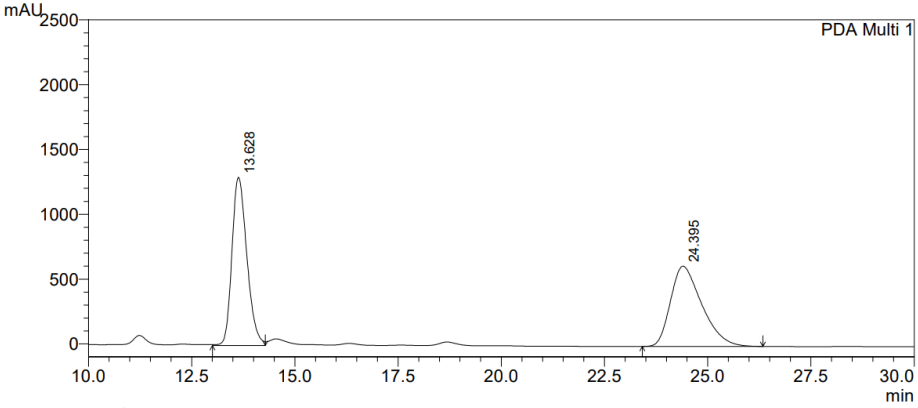
APPENDIX 3: HPLC CHROMATOGRAMS

The Chromatogram is a racemic mixture of **Product 43-a** and was recorded using:

- Column: Phenomenex Lux ® 5µm Cellulose-1, LC Column 250 x 4.6mm

- Mobile phase: 98% n-Hexane, 2% 2-Isopropanol

- Flow: 1 mL/min



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.628	32701779	1299040	50.070	67.721
2	24.395	32610815	619196	49.930	32.279
Total		65312594	1918235	100.000	100.000