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Stereoselective synthesis of conjugated trienamides

Bachelor's thesis

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1. Summary

1.1 English

A new stereoselective synthesis of conjugated trienamides by means of an anionic cascade reaction has been reported when testing the influence of the sterics of the anion-accelerated amino-Cope reaction. By the direct γ-selective union of a dienolate and a chiral conjugated sulfinyl imine containing bulky groups, a product containing a 3-double bonds conjugated system is obtained. This contrasts with the six-membered ring product obtained when the same reaction is performed with non-sterically hindered compounds. The same reaction was tested with chiral non-conjugated sulfinyl imines, and a 2-double bonds conjugated system product was obtained.

1.2 Catalan

Una nova síntesis estereoselectiva per sintetitzar trienamides conjugades a partir de una seqüència aniònica ha estat reportada quan s'ha analitzat l'influencia dels factors estèrics de la reacció amino-Cope accelerada per la presencia d'un anió. La unió directa amb selectivitat per la posició γ d'un dienolat amb una sulfinil imina quiral conjugada condueix a l'obtenció d'un producte que conté un sistema conjugat de 3 enllaços dobles. Això contrasta amb l'anell de 6 carbonis que es obtingut quan la mateixa reacció es realitzada amb compostos que no estan estèricament obstaculitzats. La mateixa reacció va ser duta a terme amb una sulfinil imina quiral no conjugada i un producte amb 2 enllaços dobles va ser obtingut.

2. Goal

The goal of this research work is to challenge the steric limitations of the anion-accelerated amino-Cope rearrangement, reaction previously studied by Dr. Jon T. Njardarson's group. By introducing bulky groups to the electrophile starting imine, the sterics of the reaction can be tested and the products generated can be studied. Sterically hindered starting materials are going to be synthesized and tested with the anion-accelerated amino-Cope conditions. Both starting materials synthesized, and products obtained after the reaction are going to be fully characterize by nuclear magnetic spectroscopy (NMR).

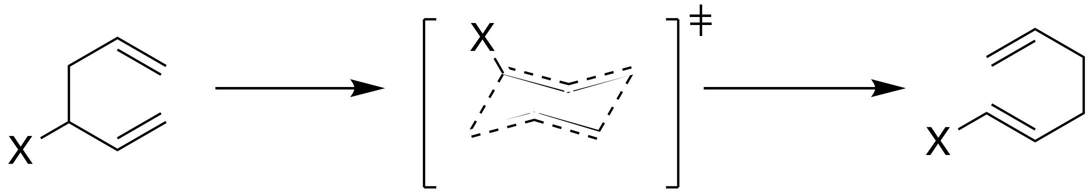
3. Introduction

This research work is developed in the context of previous work conducted at Dr. Jon T. Njardarson group[1] at the University of Arizona, in the area of synthetic organic chemistry. The research is focused on the development of useful new synthetic reactions as well as designing and executing creative efficient routes towards natural products with promising biological profiles. The natural products synthesized are mainly complex bridged bicyclic structures with unique architecture and reported biological activity. The group has three main research programs focused on the development of:

1) New catalytic ring expansions of strained heterocycles
2) New useful anionic cascade reactions
3) Oxidative deromatization strategies and reactions

The new stereoselective synthesis of trienes (the topic of my research work) corresponds to a project that is part of the "new useful anionic cascade reactions" research program. The present work follows the chemistry developed in four previously published papers. In 2017 the first paper[2] of the series was published in JACS (Journal of the American Chemical Society). In this paper, titled "New Class of Anion-Accelerated Amino-Cope Rearrangements as Gateway of Diverse Chiral Structures", a new lithium-assisted asymmetric anion-accelerated amino-Cope rearrangement cascade was reported.

The Cope rearrangement[3] is a type of [3,3]-sigmatropic rearrangement of 1,5-dienes and related compounds. The rearrangement proceeds through a six-membered ring transition state, usually in a chair conformation as shown in *Scheme 1*.

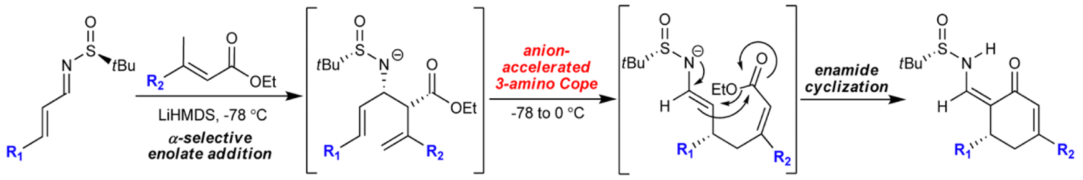


Scheme 1 - Cope-rearramgement[3]

A sigmatropic rearrangement is a "molecular rearrangement that involves the creation of a new σ-bond between atoms previously not directly linked and the breaking of an existing σ-bond". Usually there is a relocation of π-bonds in the molecule, without change of the total number of σ- nor π-bonds.

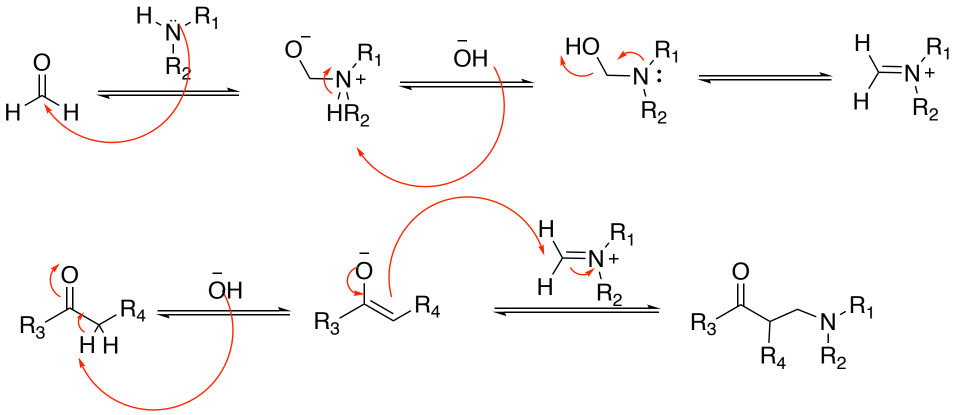
In comparison to the oxy-Cope rearrangement, in which the X substituent is a hydroxy or alkoxy group in the case of the anion-accelerated variant developed by Evans' group in 1975; the anion-accelerated amino-Cope is a neglected class of sigmatropic rearrangements in which the X substituent is a NR^-. Three different groups have investigated the anion-accelerated amino-Cope before to take advantage of the opportunities for designing asymmetric variants and the bond-forming potential of the resulting enamine products. Merck-Frosst's group[4] were the first ones to state that the anion-accelerated amino-Cope could indeed proceed at much lower temperatures than the anion-accelerated oxy-Cope giving lower yields, as well as a competing [1,3]-rearrangement product. Meyers and Houk[5] concluded that the reaction had to proceed through a stepwise mechanism in which the 3-amino-1,5-diene dissociates and then recombines. Allin's group[6] finally reported that chiral auxiliaries could be used for the anion-accelerated amino-Cope rearrangement. Allin's group[6] also reported that stereo-selectivity is not really good when chiral N-benzyl substituents are used.

From the previous statements, it is concluded that the anion-accelerated amino-Cope is feasible but there are some problems that have to be addressed. Computational and experimental data suggest a nonconcerted mechanism, where the amino-diene undergoes a heterolytic cleavage followed by reassembly either [3,3] or [1,3]-rearrangement. In order to avoid the [1,3]-rearrangement, Dr Jon T. Njardarson group used a chiral sulfinamide. Auxiliaries are used to form stable and inexpensive imines that, when treated with lithium bis-(trimethylsilyl)amide (LiHMDS) in presence of ethyl β-methyl cinnamate, promote the enolate α-addition (Mannich) followed by the anion-accelerated amino-Cope rearrangement. It was observed that the Cope product experiences an intramolecular 6-exo-trig cyclization wherein the chiral enamide is attacked by the Z-enoate to form a six-membered ring product. The whole mechanism can be found in *Scheme 2.*



Scheme 2 *- Anion-accelerated amino-cope rearrangement*[2]

The general Mannich reaction[7] proceeds with a compound containing a carbonyl group, formaldehyde and a 1^{ary} or 2^{ary} amine. The amine and the formaldehyde react under basic conditions to form an iminium ion, that is quite electron deficient and becomes a good electrophile. In a second step, the double bond of the enol resulting from the enolization of the carbonyl, attacks the iminium ion (nucleophilic attack) to finally form the Mannich product (*Scheme 3*). In the anion-accelerated amino-Cope, the imine is already formed, and this reacts with the ester to form the intermediate proceeding through a Mannich (specific α-enolate addition) to further undergo the Cope rearrangement and the final cyclization (*Scheme 2*).



Scheme 3 *- General Mannich reaction pathwaty under basic conditions.*

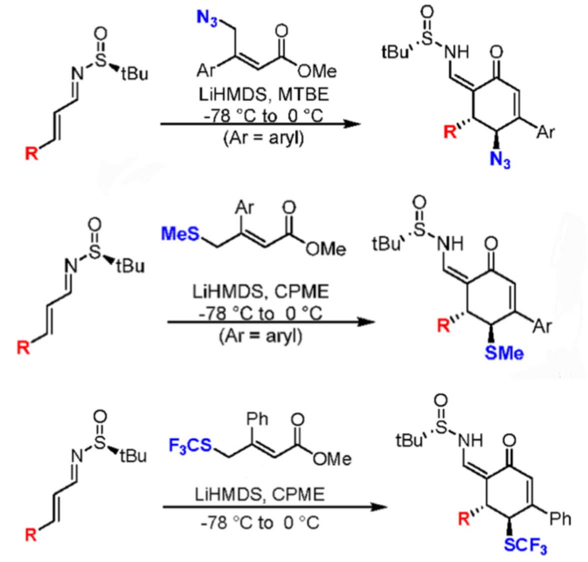
This new reaction is further developed by introducing more substituents to the starting materials, which would introduce one more stereocenter to the molecule. In the following papers of the series, the electronics of the anion-accelerated amino-Cope reaction were tested, with the introduction of either electron withdrawing (EWG) or electron donating groups (EDG). In the second paper[8] published in 2021, a dramatic effect on the product outcomes of the lithium ion enabled amino-Cope anionic asymmetric cascade was reported when different γ-dienolate heteroatom substituents were used. The γ-dienolate heteroatom substituents gave place to a range of different products besides the six-membered ring.

When the γ-dienolate heteroatom substituents were an azide, thiomethyl or trifluoromethylthiol the mechanism found in *Scheme 2* took place. When adding the substituents in the γ–positon of the dienolate, the product obtained contains two stereocenters that are found in *anti*-relationship (*Scheme 4*).

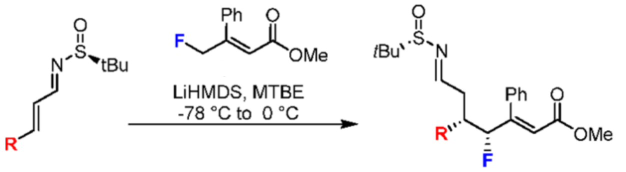
In contrast, when other substituents such as bromide, chloride, fluoride, or nitro group were used, other products were obtained. Fluoride-substituted nucleophiles gave a product containing two stereocenters with *syn*-relationship that results from the Mannich reaction between the dienolate, and the amino-diene followed by the amino-Cope rearrangement (*Scheme 5*).

Chloride or bromide-substituted nucleophiles also proceed through a Mannich followed by the amino-Cope rearrangement and a final 3-exo-tring cyclization that yields chiral cyclopropane products with five new stereocenters (*Scheme 6*).

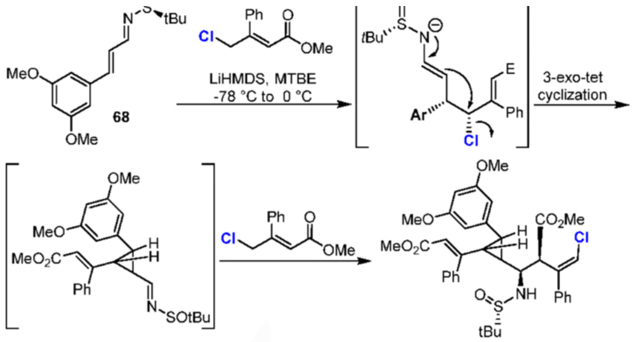
Nitro-substituted nucleophiles gave a β-lactam product instead of the amino-Cope rearrangement (*Scheme 7*).



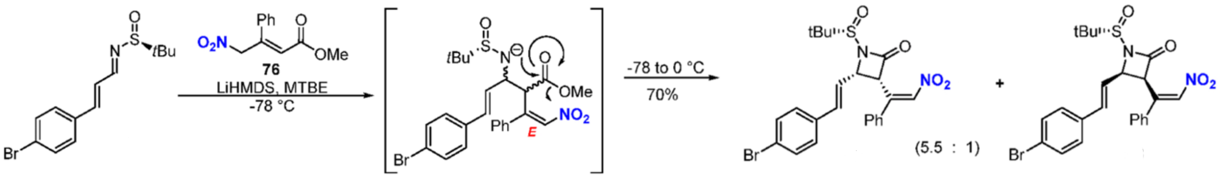
Scheme 4 - *Amino-Cope cascade with thiomethyl, azide and trifluoromethylthiol nucleophiles.*[8]



Scheme 5 - *Amino-Cope cascade with flourinated nucleophile.*[8]

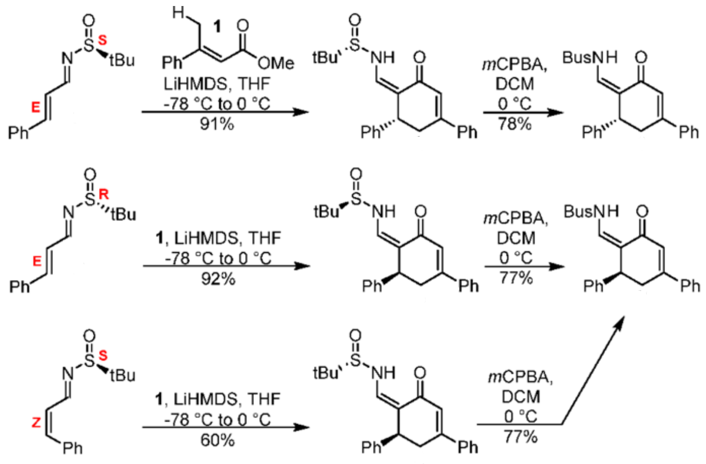


Scheme 6 - *Amino-Cope cascade with chloride and bromide nucleophiles. Cyclopropane products are formed.*[8]



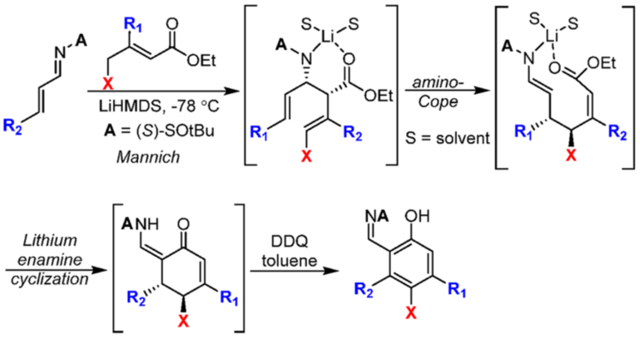
Scheme 7 - *Nitro-Substituted influence on the formation of β-Lactam.*[8]

Moreover, the anion-accelerated amino-Cope reaction reported in the paper[2] of 2017 has been tested with both enantiomers of the sulfonamide auxiliary imine electrophiles with *E*-double bond and the *S* enantiomer with *Z*-double bond. The same products with opposite stereochemistry were obtained for both enantiomers and for the two double bond configurations (*Scheme 8)*.



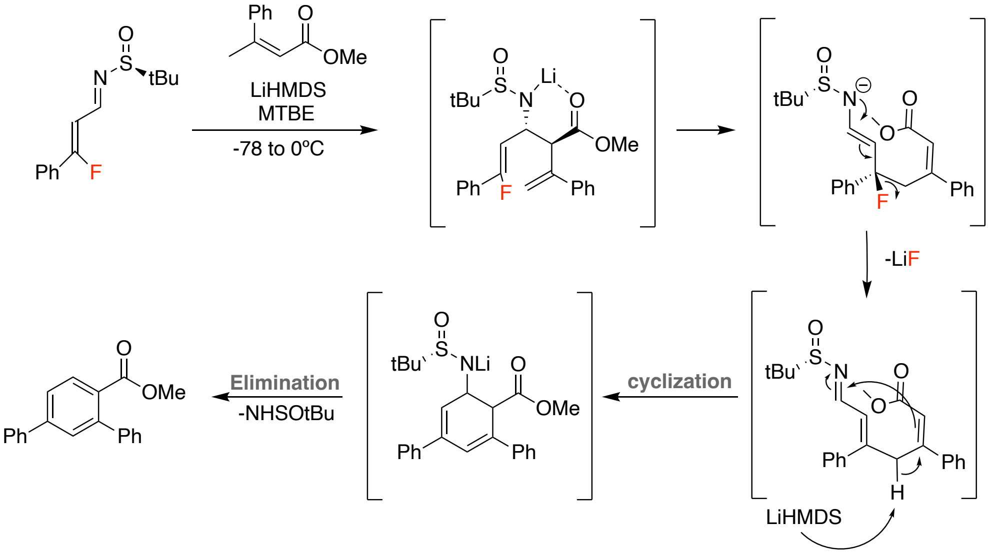
Scheme 8 - *Anion-accelerated amino-Cope rearrangement*[8]

The next paper of the series[9] was also published in 2021 describing the aromatization to phenols from the cyclohexanone product obtained in the anion-cascade union of an enoate and a conjugated imine. The cyclohexanone (amino-Cope product) is finally treated with DDQ to aromatize it (*Scheme 9*). The cyclohexanone products are also converted into enol triflates that through cross-coupling and aromatization steps can give diverse aromatic architectures.



Scheme 9 - *2-step anionic annulation-aromatization*[9]

Finally, the last paper[10] of the series was published in 2022 describing a new anionic cascade for assembling 2,4-substituted benzoate esters in one pot from racemic β-fluoro-substituted conjugate *tert*-butylsulfinyl imines and 3-substituted methyl 2-butenoates (*Scheme 10*). Following an initial reversible Mannich addition, an amino-Cope rearrangement proceeds, followed by rapid elimination of fluorine instead of a cyclization as observed previously. The acidic product of the resulting diene is abstracted by the base and then an intramolecular addition of an ester enolate to the sulfinyl imine occurs followed by the aromatization via elimination of NHSOtBu.



Scheme 10 - *New Amino-Cope Rearrangement Centered Anionic Cascade*[10]

Both papers published in 2021 and the one published at 2022 study the electronics of the anion-accelerated amino-cope rearrangement, and with the new project regarding my research work, the sterics of the reaction are also studied.

4. Experimental part

4.1 Reagents

All reagents used are commercially available and had not been submitted to further purifications. Sodium hydride (60% dispersion in oil; Flammable solid, corrosive), Pyridinium chlorochromate-PCC (Oxidizer, Health Hazard, Harmful, Enviromental hazard), triphenylphosphine-PPh_3 (99% purity; Health hazard, Corrosive, Harmful), (Trimethylsilyl)acetylene (98% purity; Flammable) and Rochelle salt-Sodium potassium tartrate (no hazard associated) were purchased from Oakwood chemicals.[11]

Lithium bis(trimethylsilyl)amide-LiHMDS (1.0 M in THF/Ethylbenzene, AcroSeal^{TM}; Flammable, Health hazard, Corrosive, Harmful), Diisobutylaluminum hydride-DIBAL (1M in heptane; Flammable, Corrosive), Titanium (IV) isopropoxide- $Ti(O\text{- }iPr)_4$ (98% purity; Flammable, Harmful), Oxalyl chloride-$(CoCl)_2$ (98% purity, Flammable, Acute toxic, Corrosive) Phosphorus tribromide-PBr_3 (99% prurity; Corrosive, Harmful), Methyl sulfoxide-DMSO (99,7% purity; no hazard associated), Dimethyl methylphosphonate (Health hazard, Harmful), CuI (Corrosive, Harmful, Enviromental hazard) and $CHCl_3$ (Acute toxic, Health hazard) were purchased from ACROS Organics.[12]

CSA (98% purity; Corrosive) was purchased from Matrix, AA Blocks and Ambeed.[13]

n-BuLi (2.5M in hexanes; Flammable, Health hazard, Corrosive, Harmful, Enviromental hazard) was purchased from both ACROS Organics[12] and Sigma Aldrich.[14]

Lithium Bromide-LiBr (99% purity; Harmful), Cyclohexanecarboxaldehyde (97% purity; Flammable, Harmful), Benzaldehyde (99% purity; Harmful) and Lindlar Catalyst (Flammable, Health hazard, Environmental hazard) were purchased from Alfa Aesar.[12]

Ethyl formate (98% purity; Flammable, Harmful), Triethylamine (99% purity; Flammable, Acute toxic, Corrosive) and Trimethyl phosphonoacetate (96% purity; no hazard associated) were purchased from TCI.[15]

Ethylmagnesium bromide-EtMgBr (3M in diethyl ether; Flammable, Corrosive, Harmful), Phenylacetylene (98% purity; Flammable, Health hazard, Harmful), Bis(triphenylphosphine)-palladium(II) chloride- $Pd(PPh_3)Cl_2$ (98% purity; Harmful), Paraformaldehyde (95% purity; Flammable, Health hazard, Corrosive, Harmful), Acetophenone (99% purity; Harmful), 4-methoxyacetophenone (99% purity; Harmful) were purchased from Sigma-Aldrich.[14]

4-bromoacetophenone (98% purity; Harmful) was purchased from Thermo Scientific.[12]

(S)-(-)-2-Methyl-2-propanesulfinamide (98% purity; no hazard associated) was purchased from FrontierSpecialityChemicals.[16]

Sodium sulfate (98% purity; no hazard associated) and magnesium sulfate (98% purity; no hazard associated) were purchased from EMD Millipore Corporation.[14]

4-Triflouromethylacetophenone (98% purity; Harmful) and Formylmethylentriphenylphosphoran (97% puriry; Harmful) were purchased from Ambeed.[13] Hexane (Flammable, Health hazard, Harmful, environmental hazard), Dichloromethane-CH_2Cl_2 (Health hazard, Harmful), Toluene (Flammable, Health hazard, Harmful) Ethyl acetate (Flammable, Harmful) and DMF (Flammable, Health hazard, Harmful) were purchased from Fischer scientific.[12]

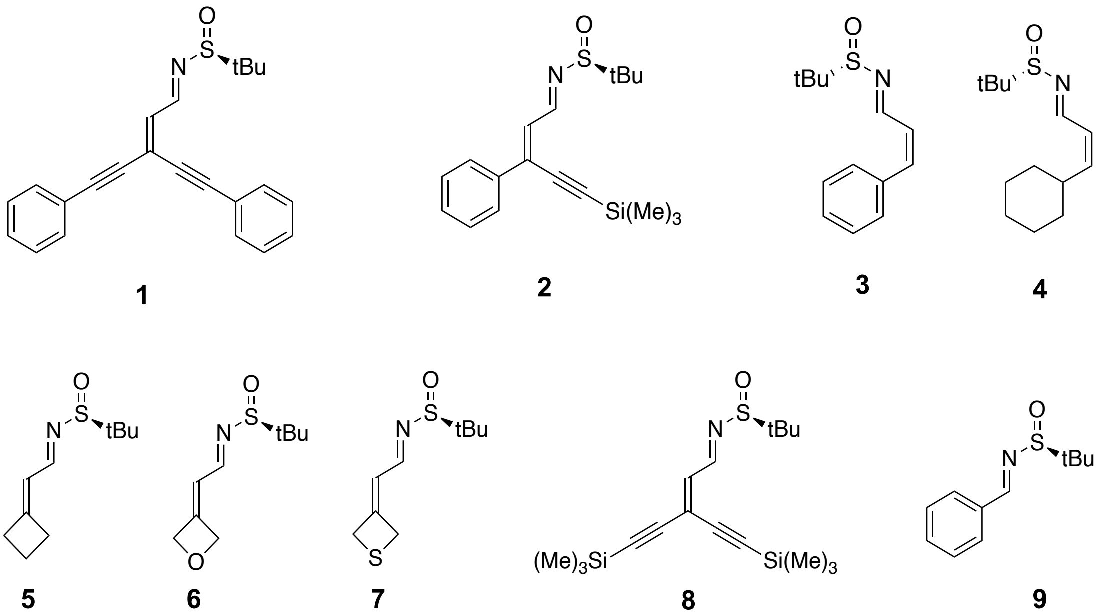
All reagents were handled using the appropriate PPE (Personal Protective Equipment). Flammable reagents had to be kept away from heat, hot surfaces, sparks, open flames, and other ignition sources. Corrosive materials had to be handled and stored under an inter gas and protected from moisture. All work is performed under the fume hood in order to avoid breathing dust, fume, gas, mist, vapors, or spray that could be a health hazard.

4.2 General experimental procedure

All glassware used were flame-dried under vacuum and all the reactions were performed under inert atmosphere (using a N_2 line) with dry solvents, unless otherwise stated. Dry tetrahydrofuran-THF (Flammable, Health hazard, Harmful) and dichloromethane-DCM (Health hazard, Harmful) were obtained by passing previously degassed solvents through activated alumina columns. The reactions were monitored by thin layer chromatography (TLC) carried out on Supelco 250µm silica gel 60-F254 plates. Plates were visualized using UV lamp, I_2 chamber and potassium permanganate stain followed by heat. All reactions were quenched with either water or saturated NH_4Cl solution, worked up doing an extraction with ethyl acetate (EtOAc) or dichloromethane (DCM) followed by washing of the extract with brine and drying over Na_2SO_4 or $MgSO_4$ or filtration using Celite® 281. Both extraction and filtration solutions are concentrated under reduced pressure and purified by Flash Chromatography with SiliaFlash® F60 (particle size 40-63µm). Dry loading of the sample into the chromatographic column was preferred over dry loading. All reactions performed at 0ºC were cooled down with an ice-water bath while all reactions performed at -78ºC were cooled down with a dry ice-acetone bath using a vacuum Dewar. Nuclear magnetic resonance spectroscopy was used to characterize the compound obtained in each of the steps. ^1H and spectra were obtained using AVIII 400 MHz and Bruker NEO 500 MHz instrument. Chemical shifts were referenced to residual $CHCl_3$ (δ 7.26 ppm) or TMS (δ 0.00 ppm) in $CDCl_3$. All the NMR data has been analyzed using MestreNova.

4.3 Synthesis of starting materials

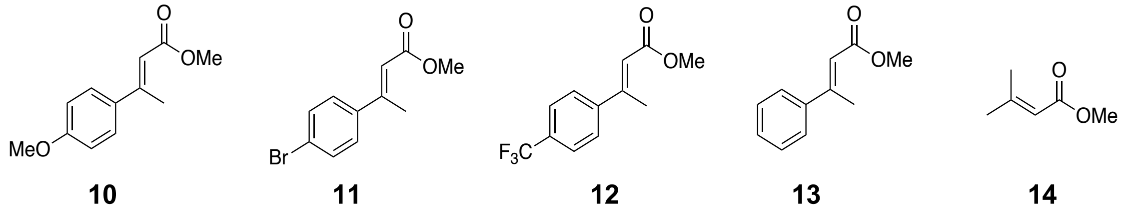
A number of starting materials, some of them being sterically hindered (*Figures 1* and *2*) wanted to be tested towards the anion-accelerated amino-Cope reaction. Most of the starting materials had to be synthesized, due to the fact that they were not commercially available.



1 **2** **3** **4**

5 **6** **7** **8** **9**

Figure 1 - Electrophiles used to test the sterics of the anion-accelerated amino-Cope rearrangement.



10 **11** **12** **13** **14**

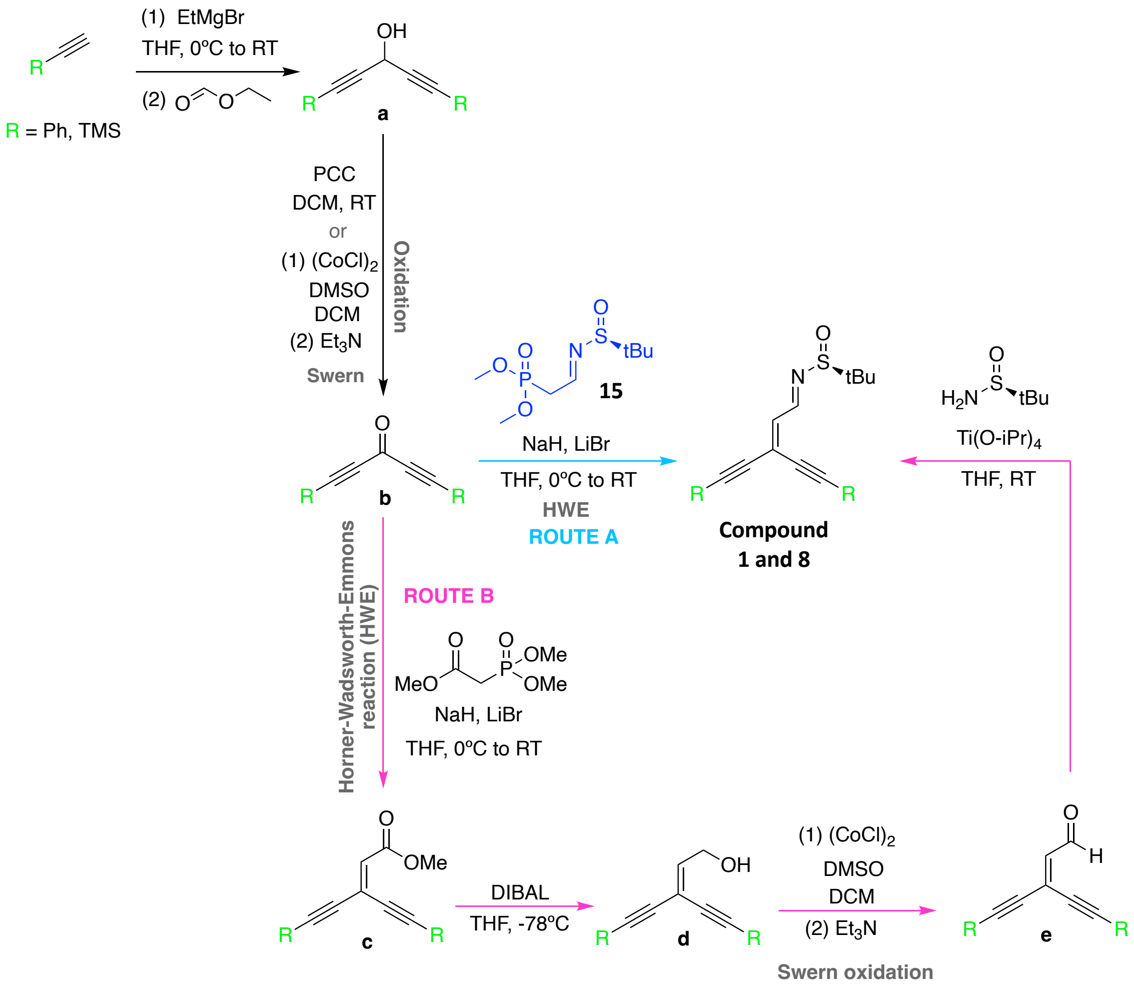
Figure 2 - Nucleeophiles used to test the sterics of the anion-accelerated amino-Cope rearrangement.

From the compounds above, only **14** is commercially available, so the rest had to be synthesized. Even though compounds **9** and **13** are not commercially available, these did not need to be synthesized because they were already synthesized by other members of the group.

The synthesis of all the compounds that are found above are described in the following sections.

4.3.1 Synthesis of compounds 1 and 8

Compounds **1** and **8** syntheses can be found in *Scheme 11*. Two different approaches were considered to obtain the two compounds: a 3-step (Route A) and a 6-step (Route B) synthesis in which the first two steps are common in both synthetic routes.



*Scheme 11 – Synthesis of compounds **1** and **8***

In the first step of both routes, commercially available phenylacetylene (2.2 equivalents) in THF is reacted with a Grignard reagent (2.2 equivalents) at 0 ºC letting it warm up to room temperature for an hour, following by addition of ethyl formate (1.0 equivalent) at 0 ºC. The reaction is then let to run overnight. The reaction is quenched with NH_4Cl and extracted with EtOAc. Separation by column chromatography is performed with 5% → 10% EtOAc/Hexanes eluent.

In the next step, the alcohol (compound **a**) is oxidized. Two different oxidations were tested, PCC and Swern oxidation. The oxidation using PCC is performed at room temperature. To a stirring solution of the alcohol (1.0 equivalent, 0.2M) in DCM, PCC (1.3 equivalents) is added, and the solution is let to run overnight. The resulting solution is filtered using Celite® 281, using DCM to wash the crude and separated through column using 5% → 10% EtOAc/Hexanes eluent. In the oxidation using the oxalyl chloride (the Swern oxidation), to the starting material (1.0 equivalent, 0.1M) in DCM is added to a solution of $(CoCl)_2$ (2.24 equivalents) in DCM (1/3 of the total amount) and DMSO (4.57 equivalents) at -78 ºC. After the solution has been stirred for an hour, triethylamine (5.0 equivalents) is added, and the solution is allowed to warm up to room temperature overnight. Solution is quenched with saturated NH_4Cl solution and extracted with EtOAc. Separation by column chromatography is performed with 5% → 15% EtOAc/Hexanes eluent.

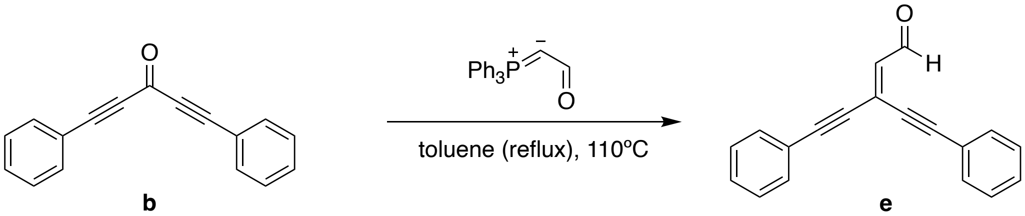
The next step in both synthetic routes consist of a Horner-Wadsworth-Emmons (HWE) reaction, with two different phosphonates. In the last step of route A, the HWE reaction is between compound **b** and **15** (species that already contains the sulfonamide auxiliary imine and that its synthesis[17] was also developed by Dr. Jon T. Njardarson group). This reaction between compound **b** and compound **15** would enable to obtain the desired product in just three steps, probably increasing the yield of the synthesis. In the case of route B, in the third step, trimethyl phosphonoacetate is used instead. To a stirred suspension of 60% NaH (2.4 equivalents) in THF at 0 ºC, the corresponding phosphonate (1.8 equivalents) is added dropwise. After being stirred at 0 ºC for around 0.5h, LiBr (1.6 equivalents) is added, and the solution is stirred until the stir bar moves without any problem. Finally, compound **b** is added (1 equivalent, 0.3M) and the reaction is stirred overnight. The solution is quenched with H_2O and extracted with EtOAc. Separation by column chromatography is performed with 5% → 15% EtOAc/Hexanes eluent.

The next step of route B consists of a reduction using DIBAL. To a solution of compound **c** (1 equivalent, 0.1M) in THF at -78 ºC DIBAL is added dropwise and after around an hour, when most of the starting material has been consumed, the solution is let to warm up to 0 ºC, diluted with EtOAc and quenched with H_2O. Then, a saturated solution of Rochelle salt (around the same amount as the volume of the reaction) is added and the solution is let to stir overnight. Solution is then extracted with EtOAc and the separation is performed using s 5% → 15% → 30% EtOAc/Hexanes eluent.

The alcohol obtained (**d**) is then oxidized to the corresponding aldehyde by performing a Swern oxidation. The eluent used for the separation is 5% → 15% EtOAc/Hexanes.

Finally, the aldehyde (**e**) is reacted with the sulfonamide auxiliary to form the desired product. Both starting materials, the aldehyde (**d**) (1 equivalent, 0.1M) and auxiliary (1.1 equivalents) are dissolved in THF and then the $Ti(O\text{-}iPr)_4$ (2.2 equivalents) is added and stirred overnight. Then, 0.5 mL of brine is added to the solution and the forming precipitate is filtered off using Celite® 281. The eluent used for the separation is once again 5% → 15% EtOAc/Hexanes.

Another reaction was also tested which would decrease the number of steps of route B synthesis from 6-steps to only 4 by converting the ketone (**b**) directly into the aldehyde (by performing a Wittig reaction) that is finally reacted with the auxiliary to form the desired product. As it is shown in *Scheme 12,* a solution of compound **b** in toluene is reacted with Formylmethylentriphenylphosphoran and the solution is let to be stirred at 110ºC in an oil bath overnight. The solution is then directly rotaevaporated and is separated using 5% → 15% EtOAc/Hexanes eluent.

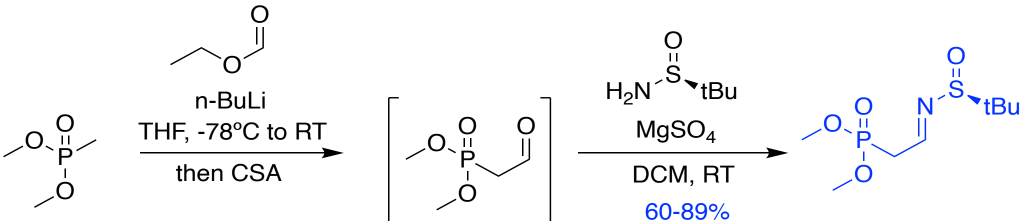


b

e

***Scheme 12** – The sequence of the Wittig reaction*

The one-pot synthesis of compound **15**, stated in the paper[17] of published in Organic letters in 2023 can be found in *Scheme 13.*



Compound 15

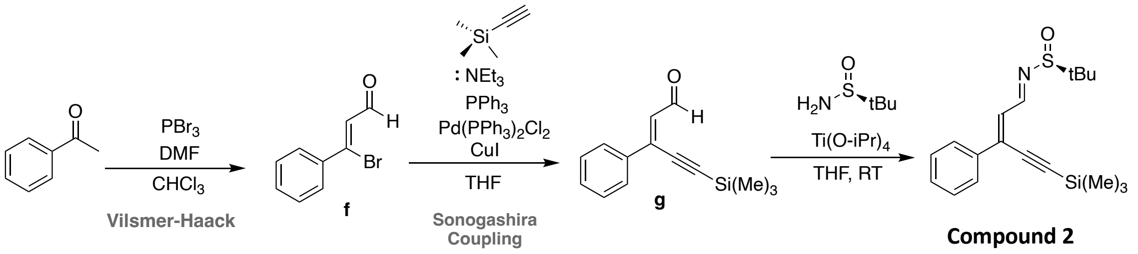
Scheme 13** – Synthesis of compound **14

To a flame-dried flask charged with a stir-bar dimethyl methyl phosphonate (1equivalent, 0.2M) is added followed by THF under inert atmosphere. The reaction mixture is cooled to -78 ºC and n-BuLi (0.95 equivalents) is then added. The reaction mixture is allowed to stir for 1h and then ethyl formate (2 equivalent) is added rapidly. The reaction mixture is allowed to warm up to room temperature slowly. CSA (1.2 equivalents) is then added and allowed to spin for 5 minutes before liberating from solvent under reduced pressure. To the resulting mixture (1.0M in DCM), the auxiliary (S)-tert-butylsulfinamide (1.2 equivalents) and $MgSO_4$ (2.5 equivalents) is added, followed by DCM. The resulting solution is allowed to stir overnight. The mixture is filtered over celite and liberated from solvent. Finally, it is purified by column using 40% Acetone/Hexanes solvent.

In this reaction, n-Buthyllithium is used, and this has to be titrated with DPAA to determine its accurate concentration. The titration is performed using a solution of 0,2 g of DPAA in 5 mL of THF. The supposed concentration of n-BuLi used is 3M, therefore 4 mL are needed to titrate the DPAA solution. Using an inert atmosphere, a syringe containing 0,8mL of n-BuLi is used to add it dropwise to the transparent DPAA solution. When the n-BuLi is added to the DPAA solution, a yellow color appears that rapidly fades away. The titration ends when the solution becomes yellowish, and the color does not disappear after 30 seconds. Before becoming yellowish, the solution becomes white and translucent. The volume of n-BuLi used has to be recorded in order to be able to finally calculate the accurate concentration. Concentration is calculated following *Equation 1*:

$$Concentration_{\,n-BuLi}\ (M) = \frac{mass\ DPAA\ (g) \cdot 1000}{MW\ DPAA \cdot V_{n-BuLI}\ (mL)} \qquad (Equation\ 1)$$

4.3.2 Synthesis of compound 2

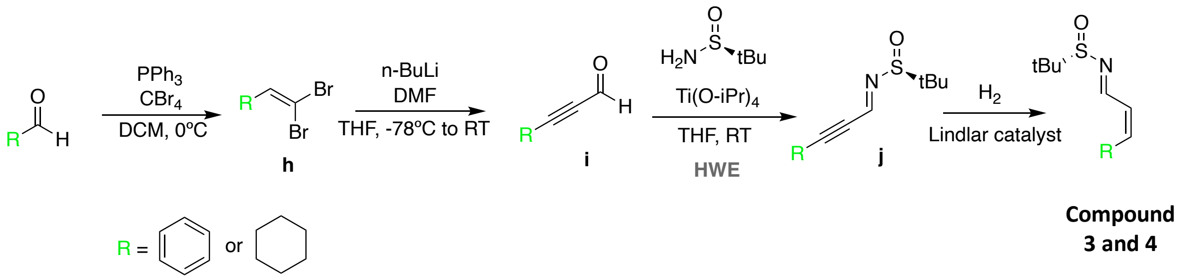


Scheme 14 – Synthesis of compound 2

In *Scheme 14*, the 3-step synthesis of Compound **2** is found. In the first step, commercially available acetophenone is reacted with PBr_3 through a Vilsmer-Haack reaction. To a mixture of DMF (3.6 equivalents) and Chloroform, PBr_3 (3.5 equivalents) is added dropwise at 0 ºC, and the mixture is stirred for 1h, before the addition of acetophenone (1 equivalent, 0,5M). The solution is stirred overnight before it is poured into water, neutralized with $NaHCO_3$ and extracted with DCM. The eluent used for the separation is 30% EtOAc/Hexanes. The next step of the reaction consists of a Sonogashira Coupling reaction. All solids, CuI (4% mol), PPh_3 (2% mol), $Pd(PPh_3)_2Cl_2$ (4% mol), and compound **f** (1 equivalent, 0.2M) are added to the reaction flask. THF and triethylamine (1.5 equivalent) are then added, and the solution is degassed (using either N_2 or Argon) and cooled down for 5 minutes. Finally, the alkyne (1.3 equivalents) is added, and the reaction is let to run overnight. The reaction mixture is filtered through celite and washed with $NaHCO_3$ and extracted with ethyl acetate. Finally, the same reaction from the last step of route B of Compound **1**, found in *Scheme 11,* is performed, following the same procedure found in 4.3.1 section.

4.3.3 Synthesis of compounds 3 and 4

The synthesis of both compounds **3** and **4** is the same, synthesis that can be found in *Scheme 15*. The synthesis consists of 4 steps.



Scheme 15- *Synthesis of compounds* ***3*** *and* ***4***

The first reaction of the synthesis is the Corey Fuchs reaction. The commercially available benzaldehyde or cyclohexanecarboxaldehyde (1 equivalent, 0.2M) are mixed with PPh$_3$ (3.3 equivalents), dissolved in DCM and cooled to 0 ºC. A solution of CBr$_4$ (2.2 equivalents) in DCM is then added over 10 minutes and the reaction is stirred for 1,5h at 0 ºC. Then, hexanes are added and the precipitate triphenylphosphine oxide is removed by filtration through silica gel. The solvent is removed in vacuo.

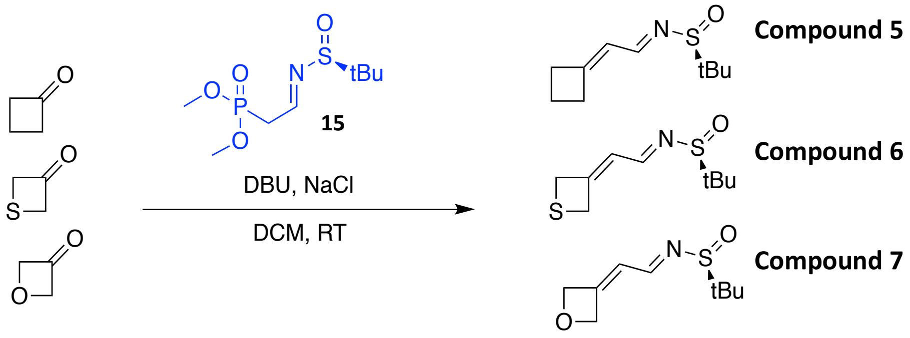
In the following step, to compound **h** (1 equivalent, 0.16M) in THF at -78 ºC, n-BuLi (2.2 equivalent) is added and stirred for an hour. After being warmed up to room temperature for another hour, DMF (1.6 equivalents) is added with 20% of the THF at -78 ºC and stirred overnight. The mixture is worked up with 1M HCl and extracted with EtOAc. The separation eluent used is 15%→30% EtOAc/Hexanes.

The next step is the same reaction as last step of route B from the synthesis of Compound **1**, found in *Scheme 11* and it is performed following the same procedure found in 4.3.1 section.

Finally, the resulting alkyne (**j**) is reduced by means of H$_2$ and Lindlar catalyst (hydrogenation reaction). The Lindlar catalyst is a heterogeneous catalyst that consists of 5% Pd in CaCO$_3$ which is poisoned with Pb(OCOCH$_3$)$_2$ and quinoline. To a solution of the alkyne (1 equivalent, 0.1M) in toluene, Lindlar catalyst (0.3 equivalents) is added at room temperature and a H$_2$ balloon is inserted through the septa. The reaction is stirred overnight and is filtered through Celite® and washed with ether. The separation eluent used is 10%→15% EtOAc/Hexanes.

4.3.4 Synthesis of compounds 5, 6 and 7

In order to obtain compounds **5**, **6** and **7**, a Horner-Wadsworth-Emmons reaction (HWE) reaction between the corresponding commercially available reagents and Compound **15**, as can be observed in *Scheme 16*.

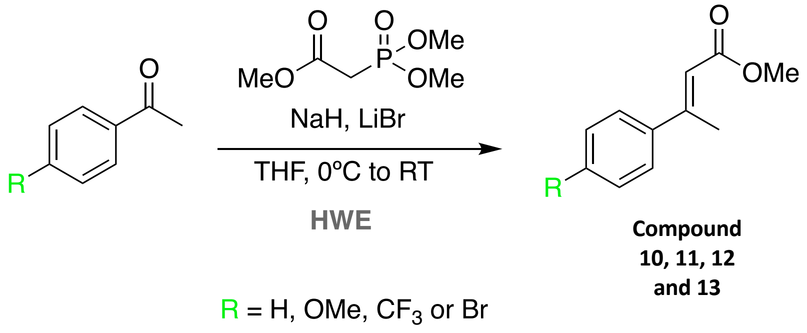


*Scheme 16- Synthesis of compounds **5**, **6** and **7***

To a flame-dried vial charged with a stir bar, the phosphonate is added. To this, powdered oven dried NaCl is added, and the vial is flushed with Argon using a balloon. DCM is then added to the reaction vessel. Then DBU followed by the ketone is added, and it is allowed to stir at room temperature overnight. The reaction mixture is then quenched with saturated NH_4Cl and extracted with DCM. The eluent used for the separation is 0% → 15% EtOAc/Hexanes.

4.3.5 Compound 10, 11, 12 and 13 syntheses

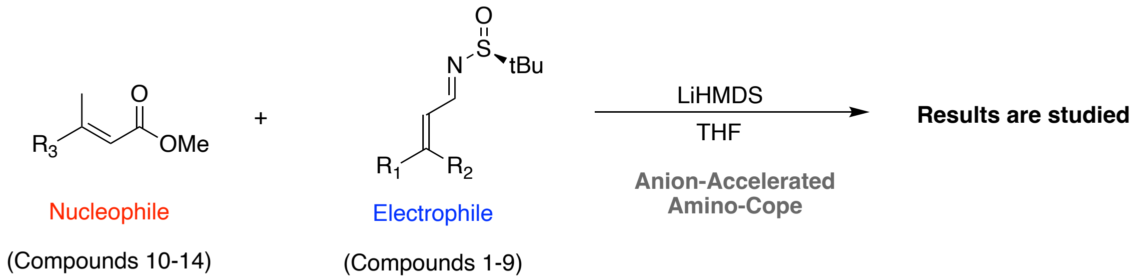
The synthesis of compounds **10**, **11**, **12** and **13** is common for all of them and can be found in *Scheme 17*. The synthesis is a HWE reaction with the corresponding commercially available starting materials 4-bromoacetophenone, 4-trifluoromethylacetophenone, 4-methoxyacetophenone and acetophenone with trimethyl phosphonoacetate. The procedure that has to be followed is the same one that is followed in the 3rd step on the route B synthesis of Compound **1** found in section 4.3.1.



*Scheme 17 – Synthesis of compounds **10**, **11**, **12** and **13***

4.4 Anionic cascade reaction

The compounds shown in *Figure 1* and *2* from section 4.3 have been reacted with the anion-accelerated amino-Cope reaction conditions in order to test de influence of the sterics in the reaction, by introducing bulky groups in the electrophile.



Scheme 18- Anion-Accelerated Amino-Cope reaction

To a stirring solution of the electrophile (1 equivalent, 0.1M) and nucleophile (1.5 equivalents) in THF, LiHMDS (3.0 equivalents) is added dropwise at -78ºC under inert atmosphere. This is then let to stir overnight. The solution is quenched with saturated NH_4Cl and extracted with EtOAc.

Different combination of the nucleophile and the electrophile have been performed and a range of different products have been obtained.

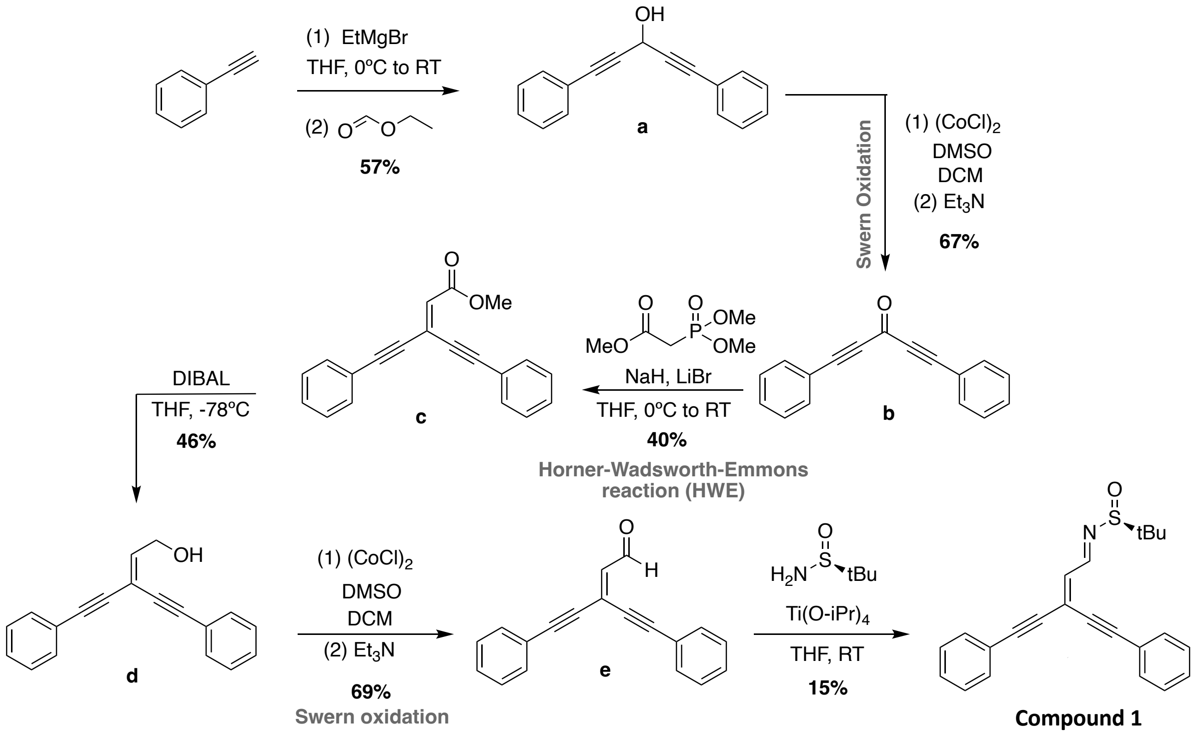
5. Results and discussion

5.1 Synthesis of starting materials

5.1.1 Compounds 1 and 8

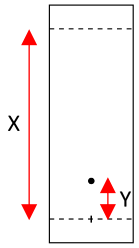
As stated in section 4.3.1, two different synthetic routes were considered to synthesized both compounds **1** and **8**. The last step of route A was not feasible, and the longer route B one had to be used instead. Due to having more steps, the final yields were lower. The last step of the 3-step synthesis (route A) was performed twice and in both cases the TLC performed after leaving the reaction overnight showed that no product had been formed, therefore, the reaction could not proceed. In the Horner-Wadsworth-Emmons (HWE), the phosphonate is previously deprotonated to form a phosphonate carbanion to then perform the attack to the carbonyl of the ketone or aldehyde (nucleophilic addition). In a second step, elimination of the oxaphosphonate takes place. The bulkiness of the electrophile in the reaction could not enable the phosphonate to attack the ketone and therefore obstructed the reaction to proceed.

- <u>Compound 1</u>



*Scheme 19 - Synthesis of Compound **1***

In the first reaction of the 6-step synthesis (route B), there has always been full conversion of the starting materials, as the TLC (in 10% EtOAc/Hexanes) performed before the workup showed. The Rf of the desired product, which is calculated from *Equation 2*, is 0.2.



$$Rf = \frac{Y}{X} \qquad (Equation\ 2)$$

Figure 3 *- TLC plate*

In the 2nd and 5th step of the synthesis, an oxidation is performed. Two different oxidation reagents were tested: PCC and Oxalyl chloride (Swern oxidation). PCC or Pyridinium chlorochromate, is a compound containing Cr^{6+} which is really toxic. Even though oxalyl chloride is also acute toxic, the Swern oxidation waste products are much less toxic than those resulting from the PCC oxidation. Moreover, when performing the PCC oxidation, a brown tar is formed which is really difficult to clean. For being safer to handle, cleaner and also giving better yields (as it is shown in *Table 1*), the Swern oxidation is preferred over the PCC one. When doing the filtration through celite as part of the work up of the PCC oxidation, both ethyl acetate and DCM were tested to wash the product. When ethyl acetate was used, filtration through celite was not clean enough and some lumps appeared in the filtered solution, but this did not restrain the separation. In both the 3rd and 5th steps, full conversion of the starting materials was obtained, as it could be seen in the TLC (10% and 15% EtOAc/Hexanes, respectively) before work up. The ketone resulting from the oxidation is much less polar than the starting alcohol, therefore it has higher Rf, which is 0.43 in both cases. Below, *Table 1* containing the yields of the two oxidation methods, can be found:

Table 1 *- Yields from the two types of oxidations*

Oxidation	**Yield (%)**
PCC	48%
Swern	67%

The 3rd step of the synthesis is an HWE. When the phosphonate is added to the stirred suspension of NaH, hydrogen gas is released, and a white foam is produced that does not allowed the stir bar to stir correctly. LiBr is used to help dissolve the enolate, as the Li coordinates to both the oxygens of P=O and C=O. All starting material is consumed.

In the reduction using DIBAL, 4th step of the synthesis, the starting material is not consumed completely as can be seen in the TLC, being the lower spot (with smaller Rf) the desired product. The product is easily separated.

The last reaction of the synthesis did not work very well. The reaction was carried out under dark conditions because it was suspected that the product could decompose with light, due to the very low yields that the reaction was giving (Around 15%). Even carrying out the reaction under dark conditions, the yield did not improve. The high conjugation of the compound made it to be really unstable and to decompose easily.

Finally, the reaction shown in *Scheme 12*, that would have decreased the number of steps of the synthesis, was also tested. Even though in the TLC performed before work up showed different spots, none of the spots ended up being the desired product and therefore route B could not be shortened.

The yield of each of the steps of the reactions and overall yield can be found in *Table 2.* The yield of a reaction is calculated according to *Equation 3.*

$$\%\, yield = \frac{actual\ yield}{theoretical\ yield} \cdot 100 \qquad (Equation\ 3)$$

Table 2 *-Yields of each of the steps of the synthesis of compound* ***1***

Steps	**Yield (%)**
1	57%
2	67%
3	40%
4	46%
5	69%
6	15%
Overall yield	1%

Despite the challenge in the synthesis, little amount of the compound has been able to be synthesized and characterized using NMR spectroscopy.

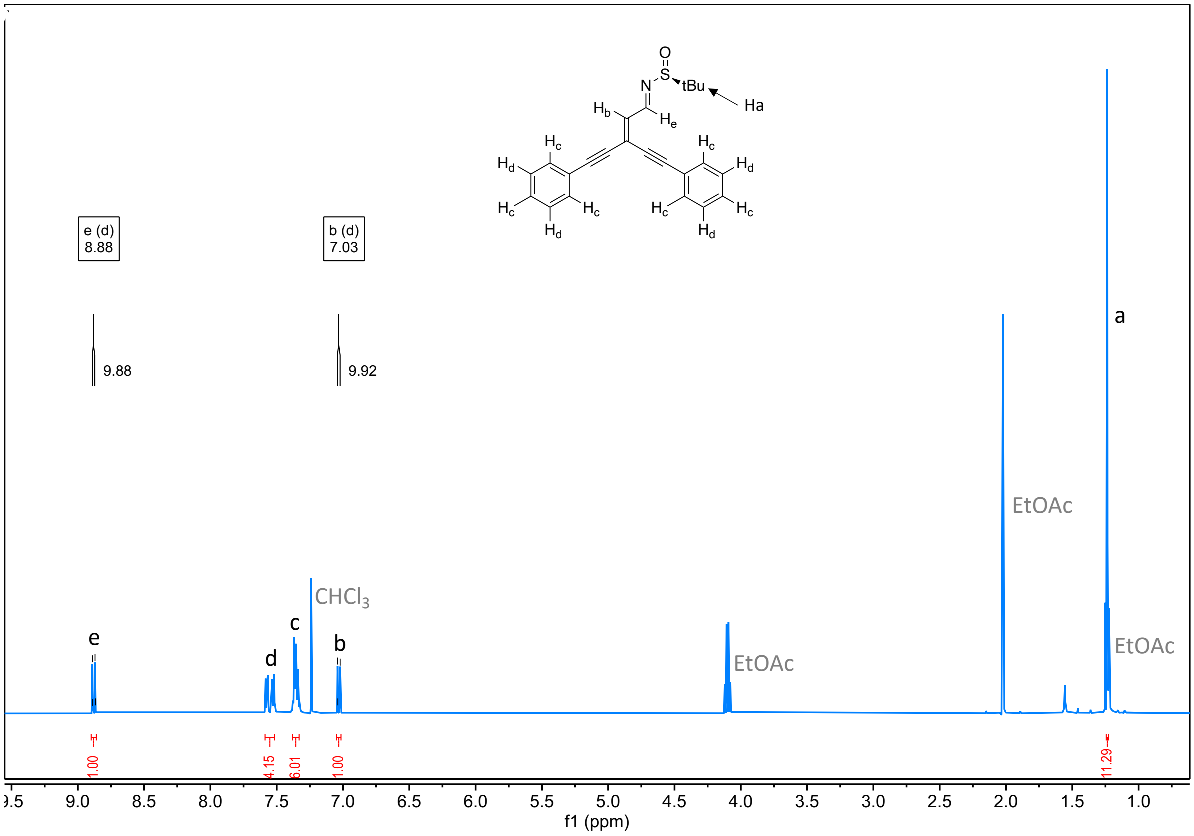


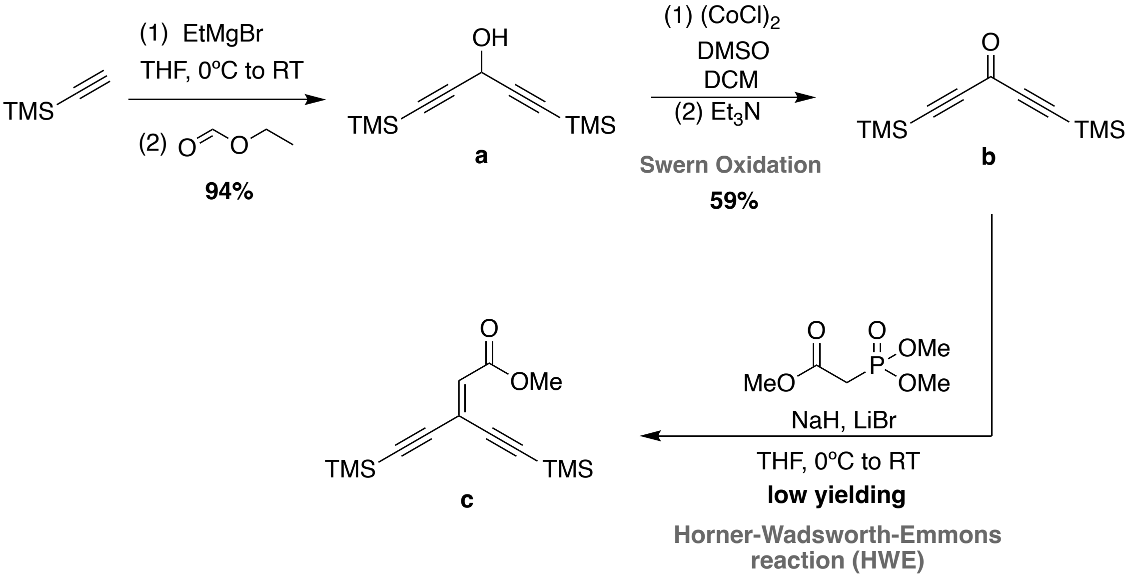
Figure 4** - ^1H NMR spectrum at 500MHz of compound **1

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.89 - 8.87 (d, 1H); 7.59-7.51 (m, 4H); 7.38-7.33 (m, 6H); 7.04 - 7.02 (d, 1H); 1.23 (s, 9H).

The singlet at 1.23 (*a*), even though it integrates up to 11H, corresponds to the protons of the *tert*-butyl group (9H). The reason behind this anomaly is that, within that same region, there are two different signals: one being the singlet corresponding to the protons of the *tert*-butyl group and another one, being a triplet that corresponds to the residual EtOAc. These two signals overlap and cannot be differentiated.

Signals *b* and *e* are the only signals that integrate to 1H and are coupled. One of the signals is more deshielded than the other one (higher ppm). These two signals can be assigned taking into account that the proton that is linked to the N (which is an EN atom) would be more deshielded (downfield) due to the inductive effect.

- Compound 8



Scheme 20 *- Synthesis of compound* ***8***

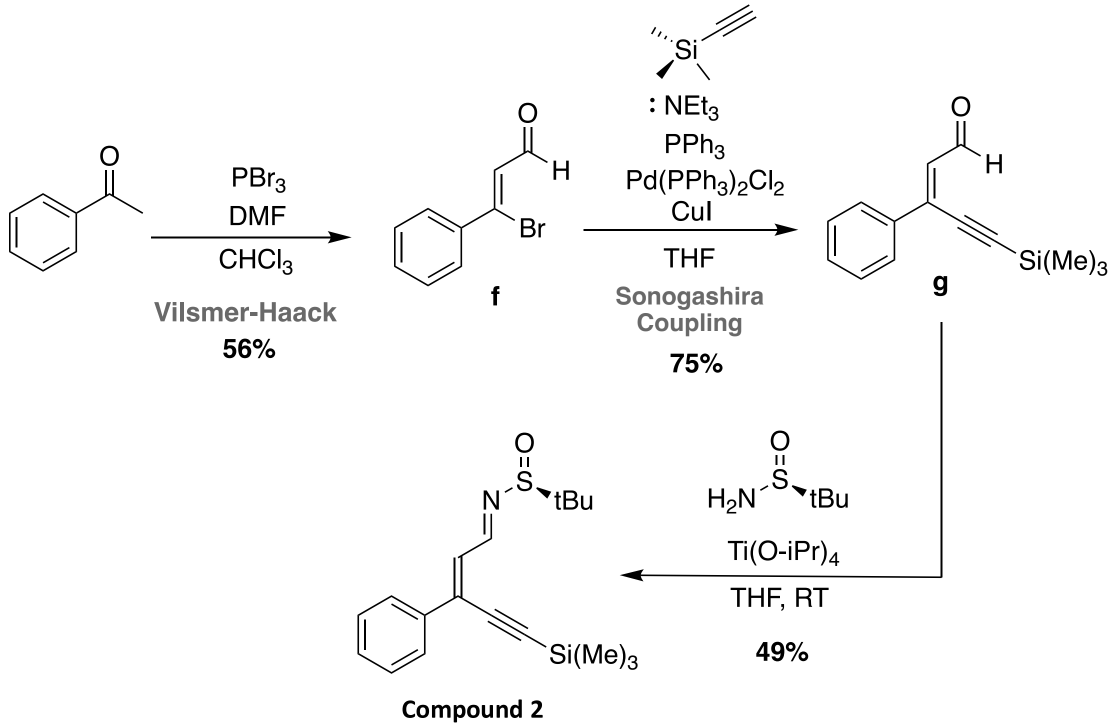
The first two reactions of the synthesis showed full conversion of the starting materials according to the TLC performed before the work up. The solution resulting from the 3rd step reaction from route B is really dark. The extraction is difficult, because the two phases cannot be easily differentiated. By using a flashlight to illuminate the solution, the two phases could be finally separated. The TLC after the work up showed 2 different spots with very similar Rf, that could be easily isolated.

As with compound **1**, because of the compound being so conjugated, it decomposed easily. Even though the yield of the first step of the synthesis is really high and the second step one is not too low, the third step is very low yielding. It seems like this compound is even less stable than compound **1** and could not be synthesized. In order to be able to proceed with the following steps of the synthesis, bigger scale reactions should have been performed.

Table 3 *- Yields (%) of each of the steps of compound's* ***8*** *synthesis*

Steps	Yield (%)
1	94%
2	59%
3	Low yielding

5.1.2 Compound 2



Scheme 21 - Synthesis of Compound 2

After the Vilsmer-Haack reaction (1st reaction of the synthesis), the TLC (performed at 30% EtOAc/Hexane), apart from showing full conversion of the starting materials also showed two spots, with different Rf (*Figure 5*).

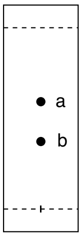


Figure 5 - TLC plate at 30% EtOAc/Hexanes

NMR spectroscopy has been used to determine which of the two spots corresponds to compound **f**. The NMR of both spots that were separated through flash chromatography were compared. The spectra looked different, but in both cases the aldehyde peak was present. *Spot a* spectrum sum of peaks integrated to more protons than what the final compound had. Moreover, as the alkene contains a Br, the proton of the alkene should be found very downfield, peak that is present around 6.7 ppm in *spot a* spectrum whereas in *spot b* spectrum is found at around 9.4 ppm. Also, taking a look at the aldehyde peak it has been observed that the aldehyde peak of *spot a* spectrum is a doublet, while in the *spot b* spectrum it is a singlet (*Figure 6*).

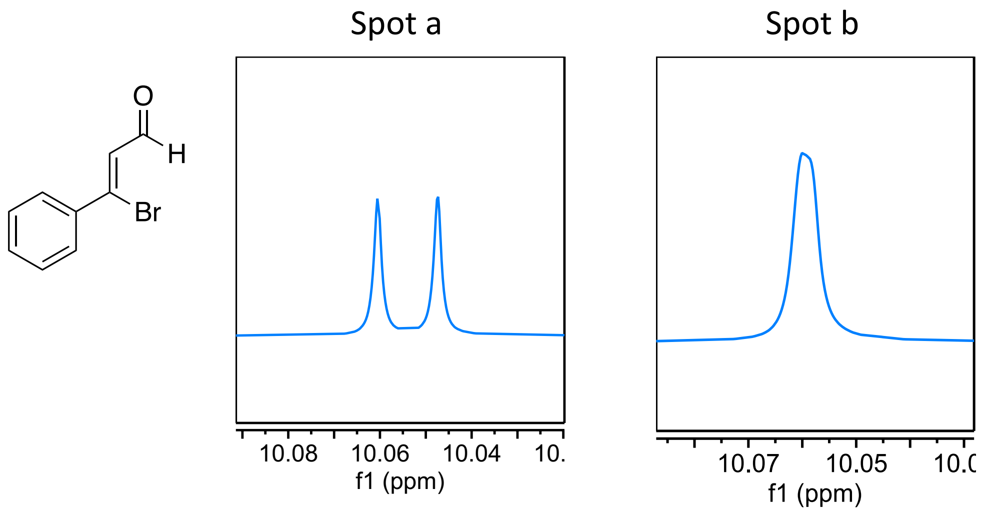


Figure 6 *- ^{1}H NMR spectrum 500MHz aldehyde peaks*

From all the information above stated, and knowing that the sum of peaks in *spot b* spectrum integrated to 7, it has been concluded that the desired product (**f**) was *spot b*. The structure from the other compound (*spot a*) is not determined because it was not needed. The yield of the Vilsmer-Haack reaction is 56%, as it can be seen in *Table 4*.

In the following steps of the synthesis, there was also full conversion of the starting materials, as both TLCs performed just before workup showed. The Sonogashira coupling reaction yield is the highest out of the three reactions, this being 75%. The last step of the synthesis is the lowest yielding one, with a yield of 49%. The overall yield of the synthesis as well as the synthesis of each of the steps can be found in *Table 4* found bellow.

Table 4 *- Yields (%) of each of the steps of compound's* ***2*** *synthesis*

Steps	Yield (%)
1	56%
2	75%
3	49%
Overall yield	21%

Compound **2** has been able to be characterized using NMR spectroscopy.

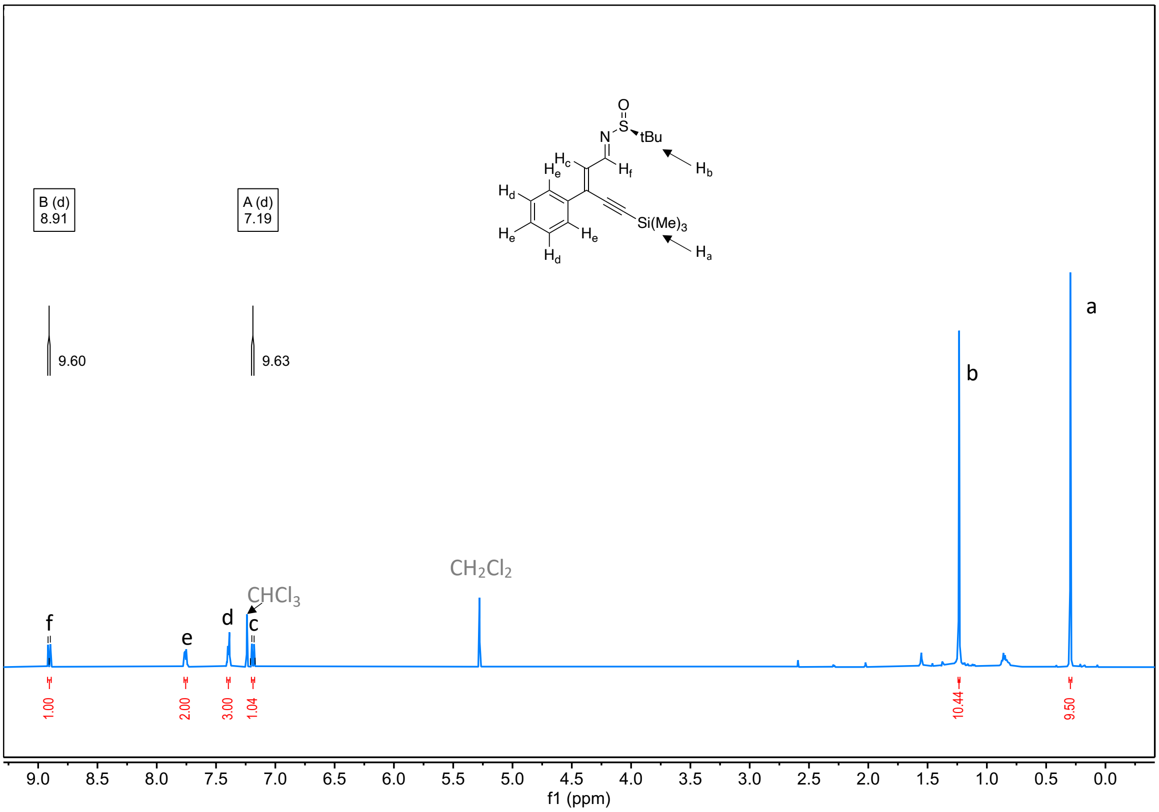


Figure 7** -^{1}H NMR spectrum 500MHz of compound **2

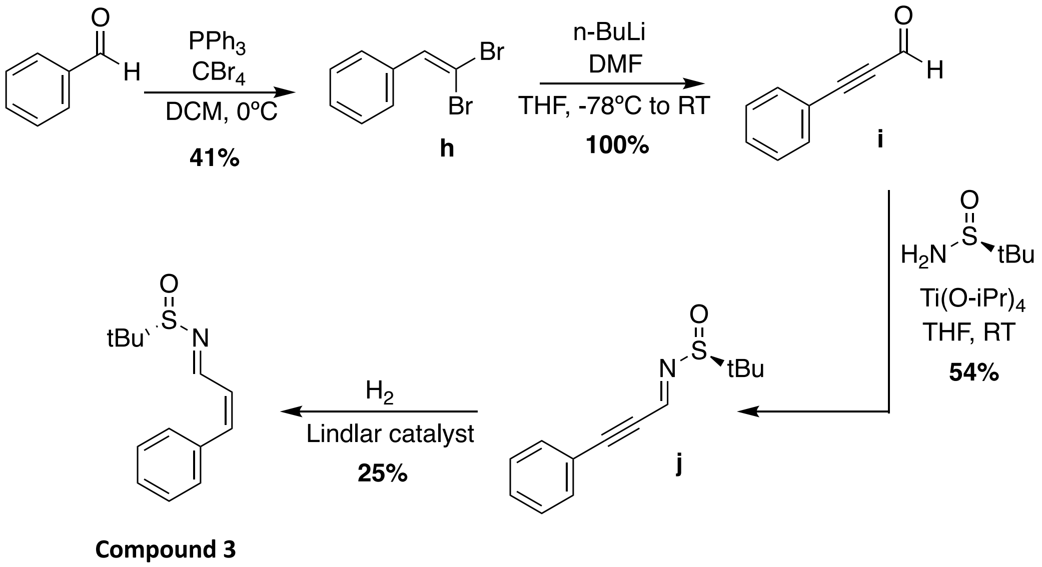
^{1}H NMR (CDCl$_3$, 500 MHz): δ = 8.92-8.89 (d, 1H); 7.77-7.74 (m, 2H); 7.41-7.38 (m, 3H); 7.21-7.17 (d, 1H); 7.25-7.22 (s, 9H); 0.31-0.28 (s, 9H)

There are two signals that are very shielded (downfield) in comparison with the rest of the signals. One of these integrates to 9H and the other one to 10H. These two signals correspond to the *tert*-butyl and TMS groups. The most shielded signal corresponds to the TMS group. In proton NMR TMS is the reference and the signal should appear at 0 ppm, but as this group is bonded to an alkyne becomes more deshielded and appears more downfield (higher ppm). The other signal, even though integrates for 10, corresponds to the *tert*-butyl group (9H). The anomaly might be due to grease that would have affected the baseline.

The rest of the signals are more deshielded. Signals *c* and *f* are the only signals that integrate to 1H and are coupled. One of the signals is more deshielded than the other one (higher ppm). The two signals can be assigned considering that the proton that is linked to the N (which is an EN atom) would be more deshielded due to the inductive effect.

5.1.3 Compounds 3 and 4

- Compound 3



*Scheme 22 - Synthesis of compound **3***

In the first step of the synthesis, when the CBr_4 is added, the transparent PPh_3 and starting material solution turns yellowish. Overtime it turns darker, and a precipitate is formed. The TLC performed just before work up showed full conversion of the starting materials. Only one product was obtained, and the yield of the reaction was 41%. In the following steps also full conversion of the starting materials was obtained.

The next step of the synthesis is a formilation reaction in which there is a lithium-halogen exchange between the bromides and the lithium of the n-BuLi, followed by an electrophilic quench with DMF. This reaction has a 100% yield. In the following step only one product is obtained, and the yield of the reaction is 54%.

The last step of the synthesis consists of a hydrogenation reaction. The hydrogenation reaction using the Lindlar catalyst, always gives the cis-alkene (*Z* steroisomer) because both hydrogens are added in the same side. The TLC performed after the reaction, just before the work up, showed only one spot. After the column, the TLC showed once again only one spot, but when the NMR was taken (*Figure 8*) it was observed that there was a mixture of products, which seem to be the two isomers.

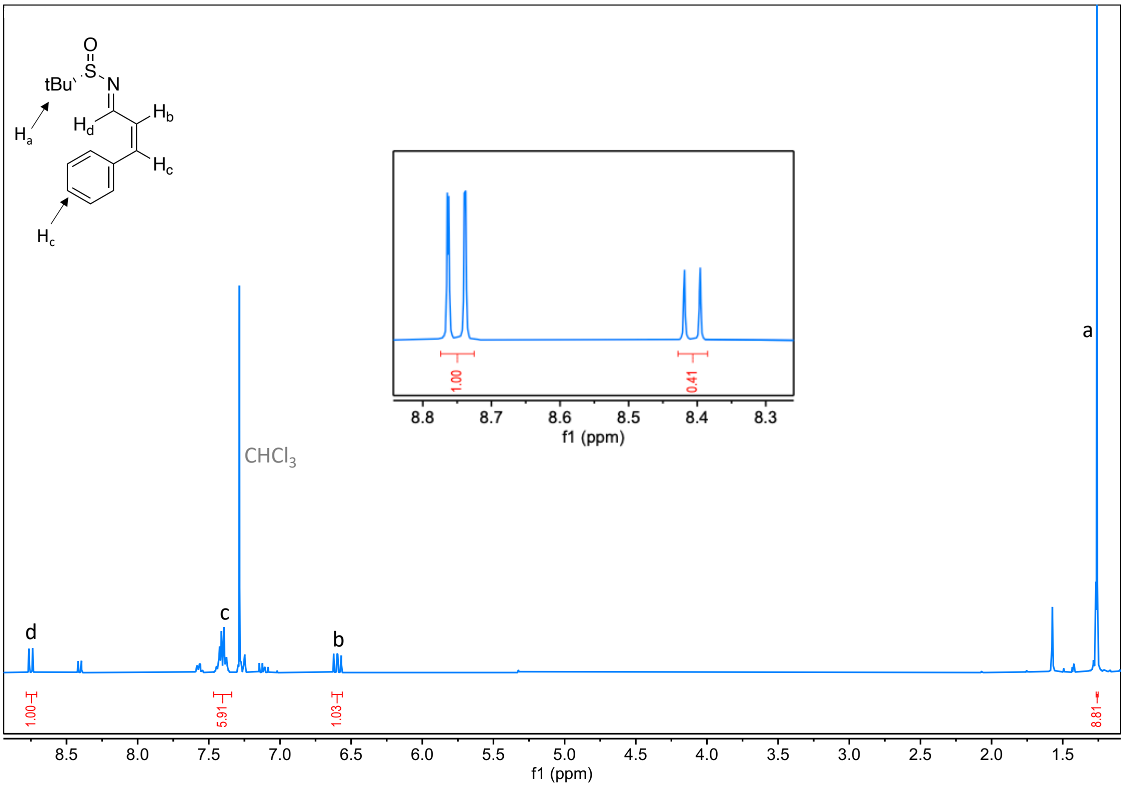


Figure 8 - ^1H NMR spectrum 400MHz of compound **3**

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.78-8.71 (d, 2H); 7.45-7.35 (m, 6H); 6.63-6.56 (dd, 1H); 1.27 (s, 9H)

As observed in *Figure 8*, there is a mixture of the two isomers, which is 70:30, being the major one the *Z* isomer (the one that is wanted). The acidic silica of the column isomerizes the resulting *Z* alkene; therefore, the column has to be neutralized before performing the separation. The silica gel, that is already saturated with hexanes, can be neutralized by first running a solution of 0.5% of triethylamine in hexanes through it, followed by EtOAc and finally with pure hexanes.

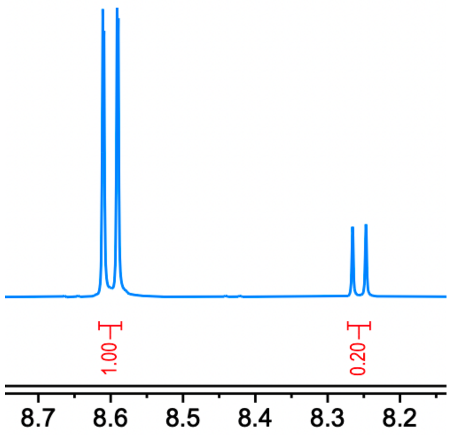
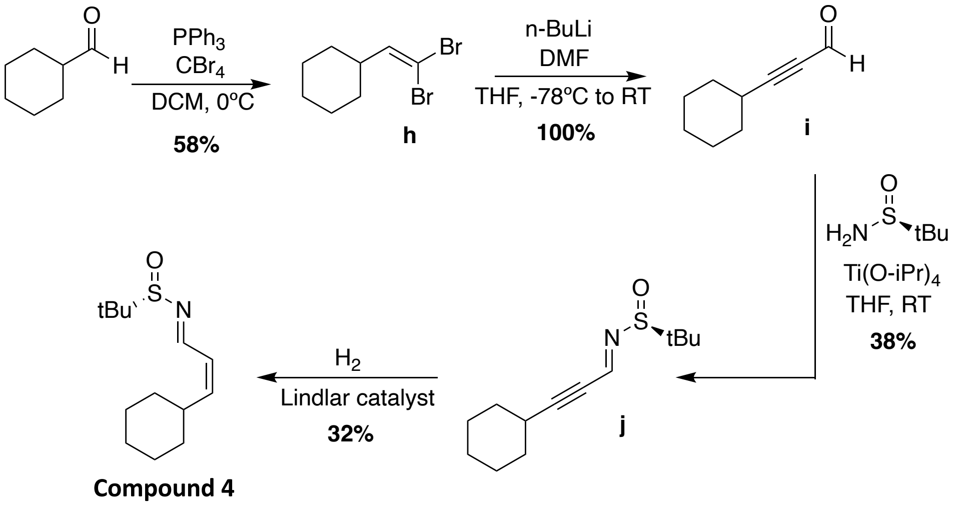


Figure 9 - ^1H NMR spectrum of the enamine peak of the two isomers of compound **3**

Once the column is neutralized, the sample to be separated can be loaded and the separation can be performed. As the two compounds seem to have the same Rf, the separation through column would be difficult. All fractions containing the mixture were collected and were separated in two. The purest of the two fractions is the one that is used to test the anion-accelerated amino-Cope rearrangement reaction. After the second separation using the neutralized column, the better fraction had an 86:14 (*Z* to *E*) isomer ration, as can be seen in *Figure 9*.

- Compound 4



Scheme 23 - Synthesis of compound 4

In the first step of the synthesis, as with compound 3, there is full conversion of the starting materials, but the yield is higher. The second step yield is 100% for both compounds, while the third step of the synthesis is lower yielding than compound's **3** one. The same problem encountered in the last step of the synthesis of compound **3** was also encountered in compound's **4** synthesis. The column was once again neutralized, and two fractions were separated.

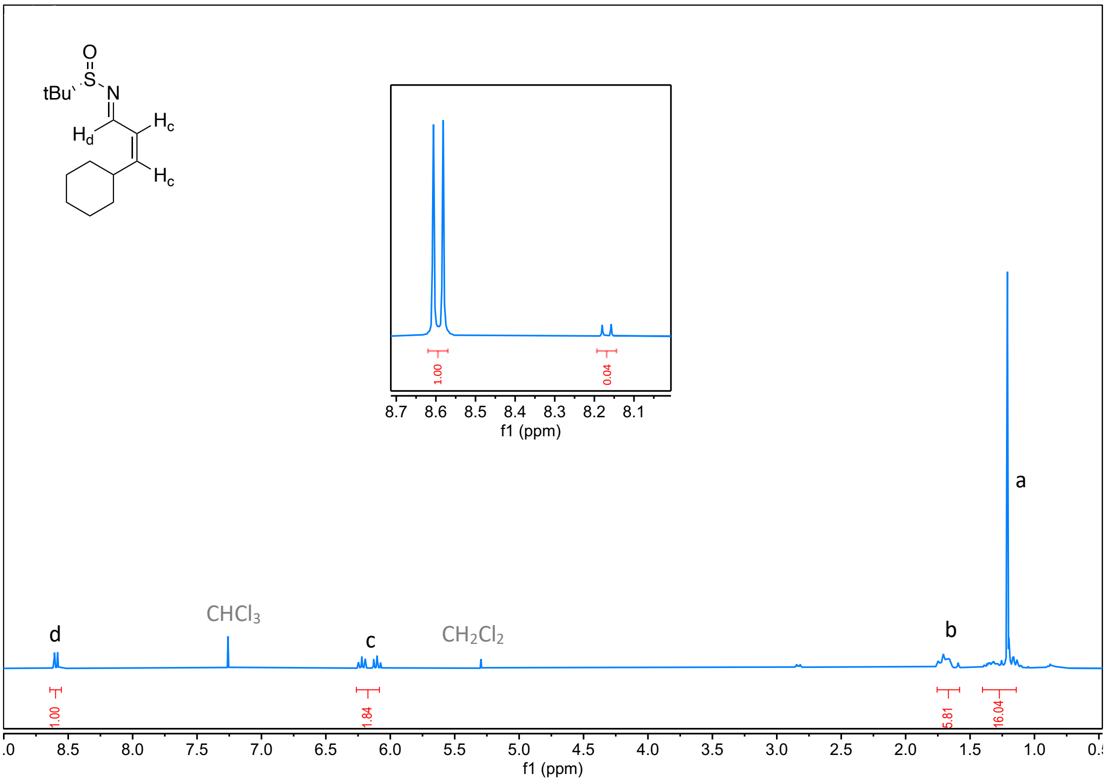


Figure 10 - ^{1}H NMR spectrum 400MHz of compound 4

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.61-8.58 (d,1H); 6.25-6.07 (m, 2H); 1.76-1.58 (m, 5H); 1.37-1.14 (m, 16H)

It is observed, that after the neutralized column, compound **4** is almost pure; 96:4 *Z* to *E* isomer.

Signals *a* and *b* correspond to the cyclohexane and *tert*-butyl protons. Signal *d*, which is a doublet and is the most deshielded signal, integrates to one proton and this is the one linked to the N atom. The other signal is a multiplet and corresponds to the 2 alkene protons.

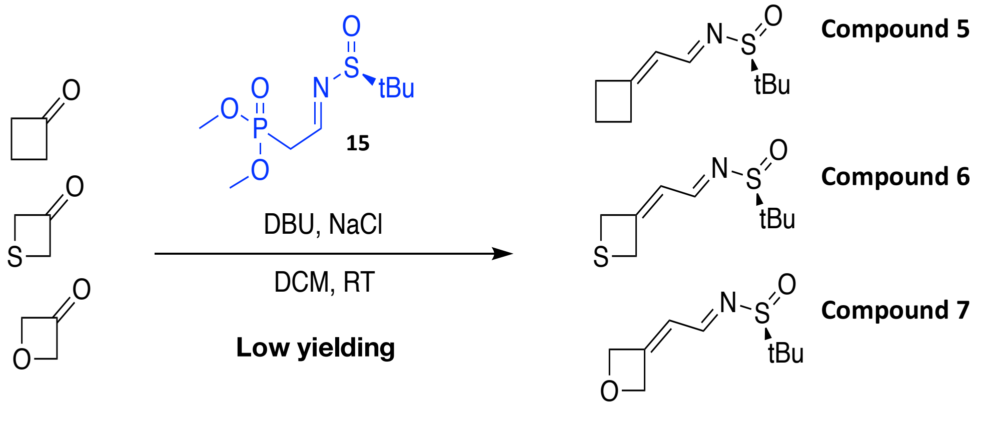
In *Table 5* the yield of each of the steps of the reactions for the synthesis of both compounds **3** and **4,** as well as the overall yield, can be found.

Table 5 - Compounds 3 and 4 yields

Steps	Compound 3 yield (%)	Compound 4 yield (%)
1	41%	58%
2	100%	100%
3	54%	38%
4	25%	32%
Overall yield (%)	6%	7%

The overall yields of compounds **3** and **4** are not very high, but enough product was synthesized for these reactions to be tested towards the anion-accelerated amino-Cope reaction. To improve the overall yield, the yield of the individual steps should be improved by optimizing each one of the reactions.

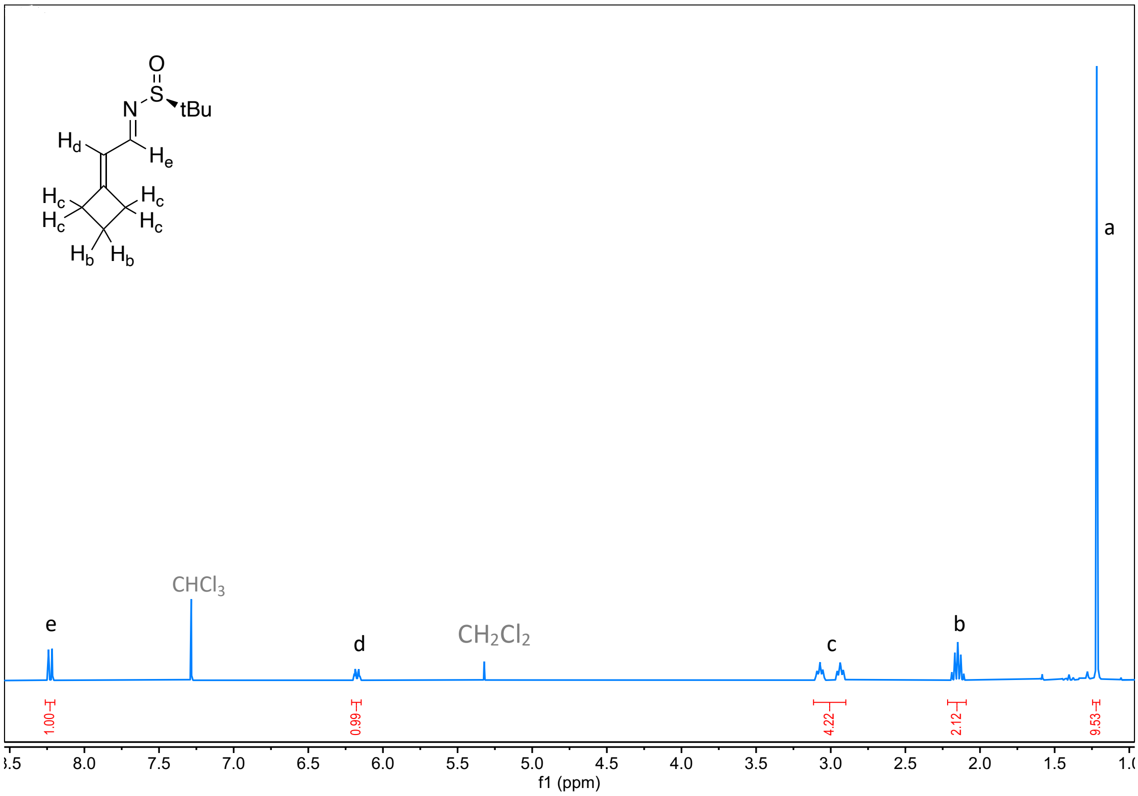
5.1.4 Compounds 5, 6 and 7



Scheme 24 *- Synthesis of compounds* ***5, 6*** *and* ***7***

The synthesis of compounds **5**, **6** and **7** consisted only of one reaction. The reaction is also a Horner-Wadsworth-Emmons (HWE) reaction, but the procedure is a bit different from the rest of the HWE reactions performed. In this case, the base used is DBU instead of NaH. It was proven before that the reaction gives better yields following this experimental procedure when the phosphonate compound **15** is used.

All the reactions are very low yielding reactions and therefore the compounds could not be tested towards the anionic cascade, because not enough compound was synthesized. Only compound **5** has been able to be characterized by NMR spectroscopy, spectrum of which can be found bellow.

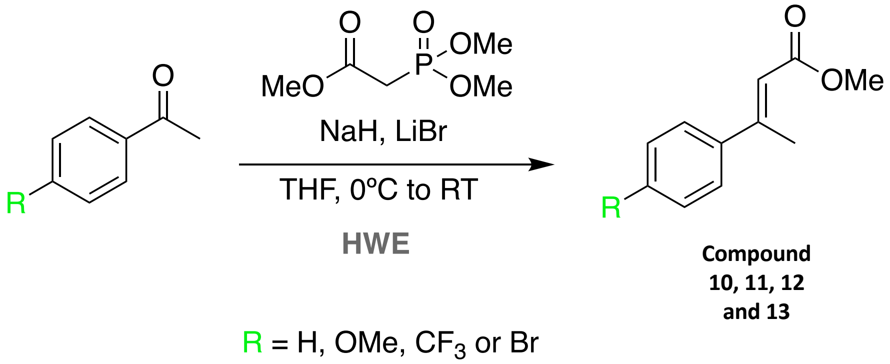


^{1}H NMR (CDCl$_3$, 500 MHz): δ = 8.26-8.21(d,1H); 6.19-6.14 (m, 1H); 3.11-2.90 (m, 4H); 2.20-2.09 (q, 2H); 1.24-1.19 (s, 9H)

Signal *a* corresponds to the *tert*-butyl group. Signals *b* and *c* correspond to the cyclobutane protons. Signal *b*, correspond to the protons of the cyclobutane carbon that is not bonded to the alkene, which couple with the other 4 protons of the cyclobutane. Signals *d* and *e* are the only signals that integrate to one proton, being signal *e* the one coming from the proton bonded to the N atom.

5.1.5 Compounds 10, 11, 12 and 13

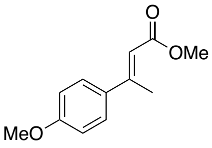
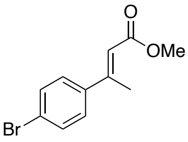
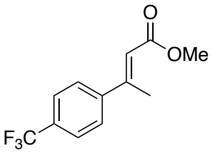
The synthesis of all the compounds (**10**, **11**, **12** and **13**) consisted only in one step in which there was full conversion of the starting materials in all cases, as the TLC just before separation showed. The TLC of compounds **10, 11** and **12** showed only one spot, but the NMR was not completely clean. Apart from the desired product, other compounds seem to be present in the samples, but in less amount, and these were not determined.



Scheme 25 *- Synthesis of compounds* ***10, 11, 12*** *and* ***13***

The yields of each of the HWE reactions for synthesizing compounds **10, 11** and **12** are found in *Table 6*:

Table 6 *- Compound's* ***10, 11*** *and* ***12*** *yields*

Compounds	Yield (%)
 **Compound 10**	38%
 **Compound 11**	42%
 **Compound 12**	35%

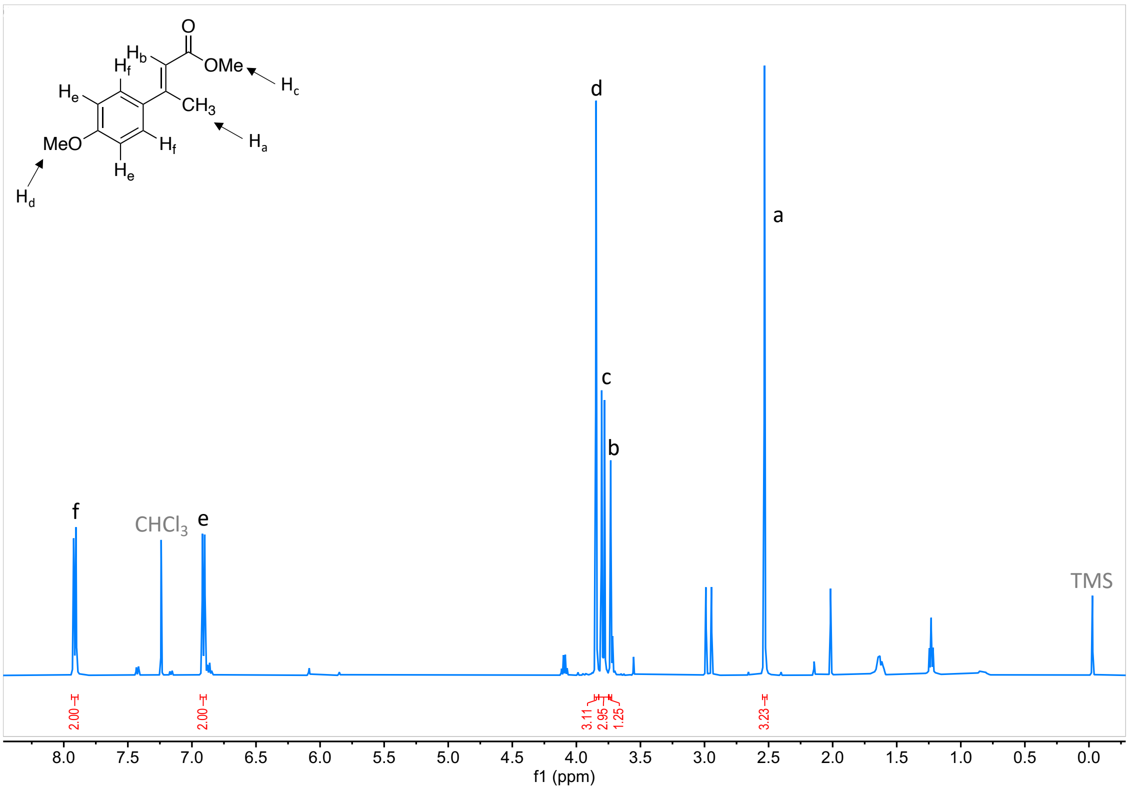


Figure 12 *- ^{1}H NMR spectrum 500MHz of compound **10***

^{1}H NMR (CDCl$_3$, 500 MHz): δ = 7.94-7.88 (d, 2H); 6.94-6.89 (d, 2H); 3.85 (s, 3H); 3.82-3.77 (d, 3H); 3.73 (s, 1H); 2.53 (s, 3H)

As it can be observed in *Figure 12,* apart from the peaks coming from the signals of the protons of compound **10**, there are some other signals in the spectrum, that correspond to signals from another species present in the sample, found in less abundance (as can be concluded from their intensity, because they are much less intense than the signals coming from compound **10**). There are three signals that integrate for three protons, two of them corresponding to the methoxy and methyl ester groups and another one to the methyl group bonded to the alkene. The methoxy and methyl ester protons signals will be found more downfield because the protons are bounded to O (which is an electronegative atom), and through inductive effect they become more deshielded. According to that, signal *a* corresponds to the methyl group bonded to the alkene. The other two signals are found close in the spectrum but considering that the inductive effect generated by the methoxy group is greater than the one generated by the ester, the methoxy protons will be found more downfield. The last two signals correspond to the aromatic protons. The methoxy group acts as an electron donating group when found at ortho or para position, whereas acts as electron withdrawing when it is found at meta position. The protons that are at ortho-postion respect to the methoxy are more shielded, and therefore are found more upfield (signal *e*), while the protons at meta position respect to the methoxy are deshielded and found more downfield (signal *f*).

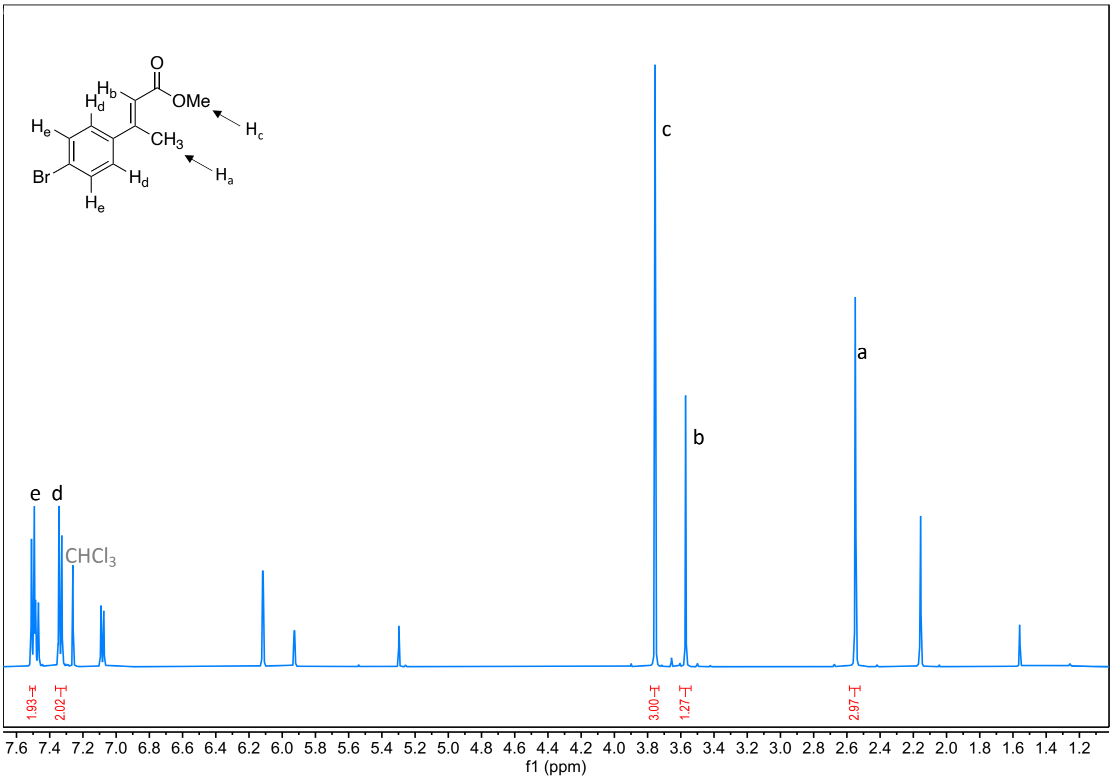


Figure 13**- ^{1}H NMR spectrum 500Mz Compound **11

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.52-7.48 (m, 2H); 7.35-7.32 (m, 2H); 3.76 (s, 3H); 3.57 (s, 1H), 2.55 (s, 3H)

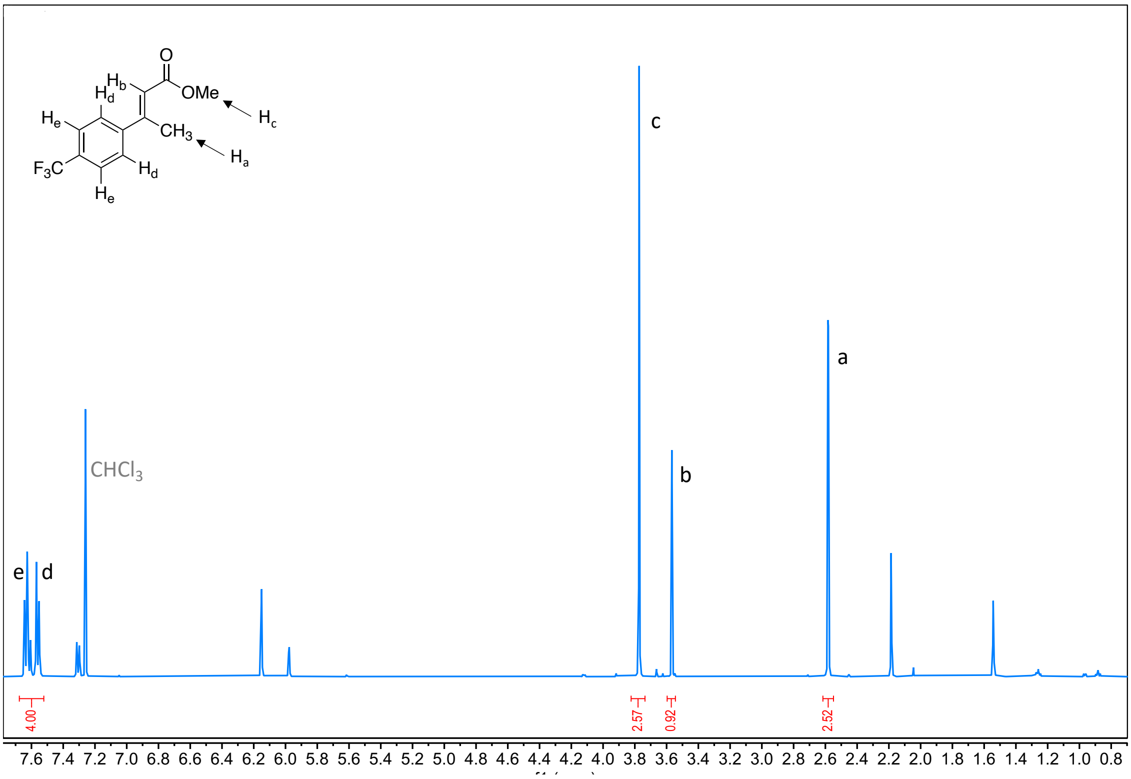


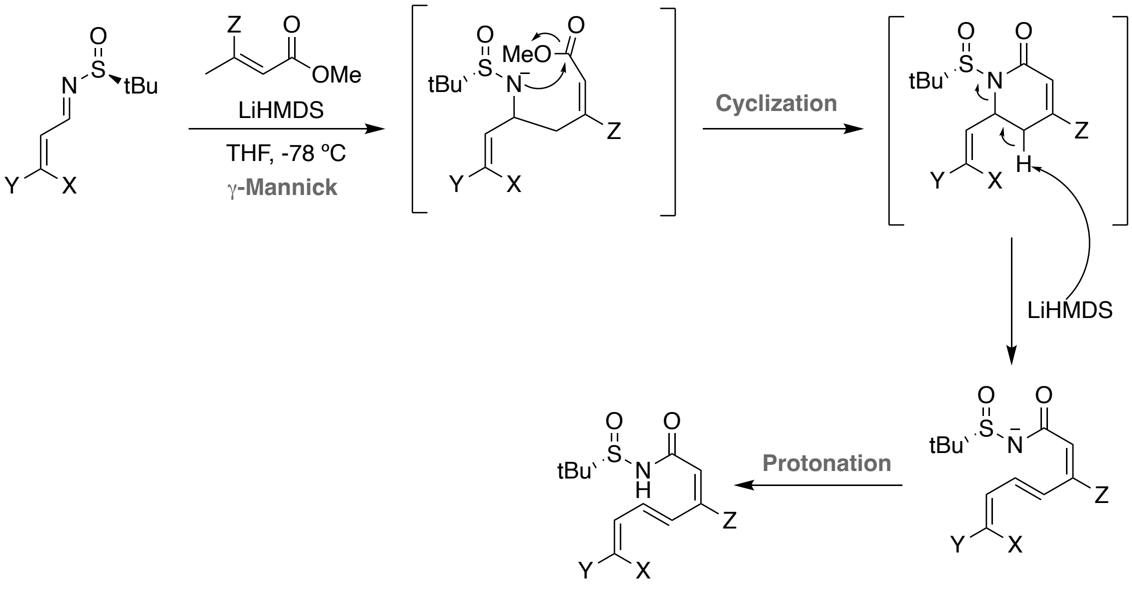
Figure 14** - ^{1}H NMR 500MHz spectrum compound **12

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.61-7.65 (m, 2H); 7.54-7.58 (d, 2H); 3.78 (s, 3H); 3.57 (s, 1H); 2.59 (s, 3H).

The reasoning behind the assignation of signals *a*, *b* and *c* on compounds **11** and **12** is the same reasoning previously stated with compound **10**. Signals *d* and *e* correspond to the aromatic protons. Both bromide and trifluoromethyl are electron withdrawing groups, therefore the protons next to it (in ortho-position respect that substituent) are more deshielded (higher ppm), while the other two protons (meta position respect the substituent) are found more upfield, not that deshielded.

5.2 Anionic cascade reaction

When reacting the nucleophiles and the electrophiles containing bulky substituents towards the anion-accelerated amino-Cope reaction, a new trienamide compound was obtained. The bulky groups diverted the dienolate nucleophile from the α-Mannich addition pathway to a selective γ-Mannich addition/cyclization resulting in the formation of an intermediate 5,6-dihydropyridin-2(1H)-one, which then presumably undergoes a second deprotonation of a γ-proton of the N-heterocycle to break the C-N bond and form the trienamide with the last double bond selectively formed as *E*-isomer. (Scheme 26)



Scheme 26 - New stereoselective synthesis of trienes mechanism

This new reaction, in which trienamides are obtained, is said to be stereoselective, due to the fact that only the *E* isomer (of the double bond that is formed) is obtained. When the reaction is carried out with chiral non-conjugated imines instead of the conjugated imines, dienamide products are obtained.

5.2.1 Products

Not all the starting materials found in *Figures 1* and *2* could be tested towards the anion-accelerated amino-Cope reaction. Compounds **1** and **8**, are really unstable. Compound **8** could not be even synthesized. Even though compound **1** could be synthesized, the yield was really low and not enough compound was obtained for this to be tested towards the anionic cascade.
The same problem was encountered with compounds **5**, **6** and **7**. All of these three compounds could be synthesized, but the yield was really low.

Different combinations of the sterically hindered Compound **2** and the nucleophiles were tested, and the following results were obtained. The compounds obtained from this new stereoselective synthesis of trienes were fully characterized using NMR spectroscopy.

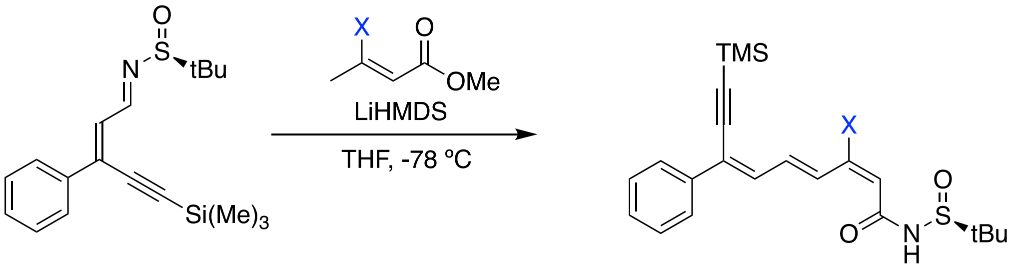
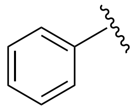
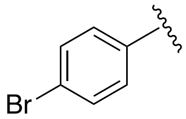
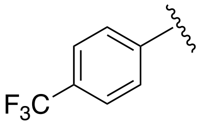
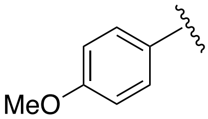


***Table** 7 - Scope of anionic cascade for conjugated tri-substituted sulfinyl imines*

X	**Yield (%)**
 **(16)**	65%
 Br **(17)**	42%
 F3C **(18)**	34%
 MeO **(19)**	Could not be tested

In *Table 7* it can be observed that the highest yield is obtained when the phenyl substituent is not substituted. When electron-withdrawing groups (EWG) were placed in the para-position of the phenyl group, the reaction did proceed but the yield decreased. It is also observed that the yield is also affected by the strength of the electron withdrawing group that is found in the para-position of the phenyl group. When stronger of an EWG, lower the yield of the reaction. (CF_3 is better of an electron-withdrawing group than Br). Using an electron-donating group in the para-position of the phenyl group wanted to be tested as well, but this could not be done by lack of time.

All the compounds synthesized have been characterized using NMR spectroscopy. Bellow, the ^{1}H NMR spectrum of Compound **16** can be found. The spectrum has been compared to the predicted ^{1}H spectrum (*Figure 18* in the Annexes section) built with ChemDraw program. The spectra obtained using the ChemDraw function are just used to have an idea of how the spectra of the compound should look, but sometimes the program does some mistakes and the spectra obtained are far from what is really obtained experimentally. Because of the fact that these compounds haven't been synthesized before, there is a higher possibility of the spectrum built by ChemDraw to be wrong, but it is useful enough to give an idea about the position of some of the peaks.

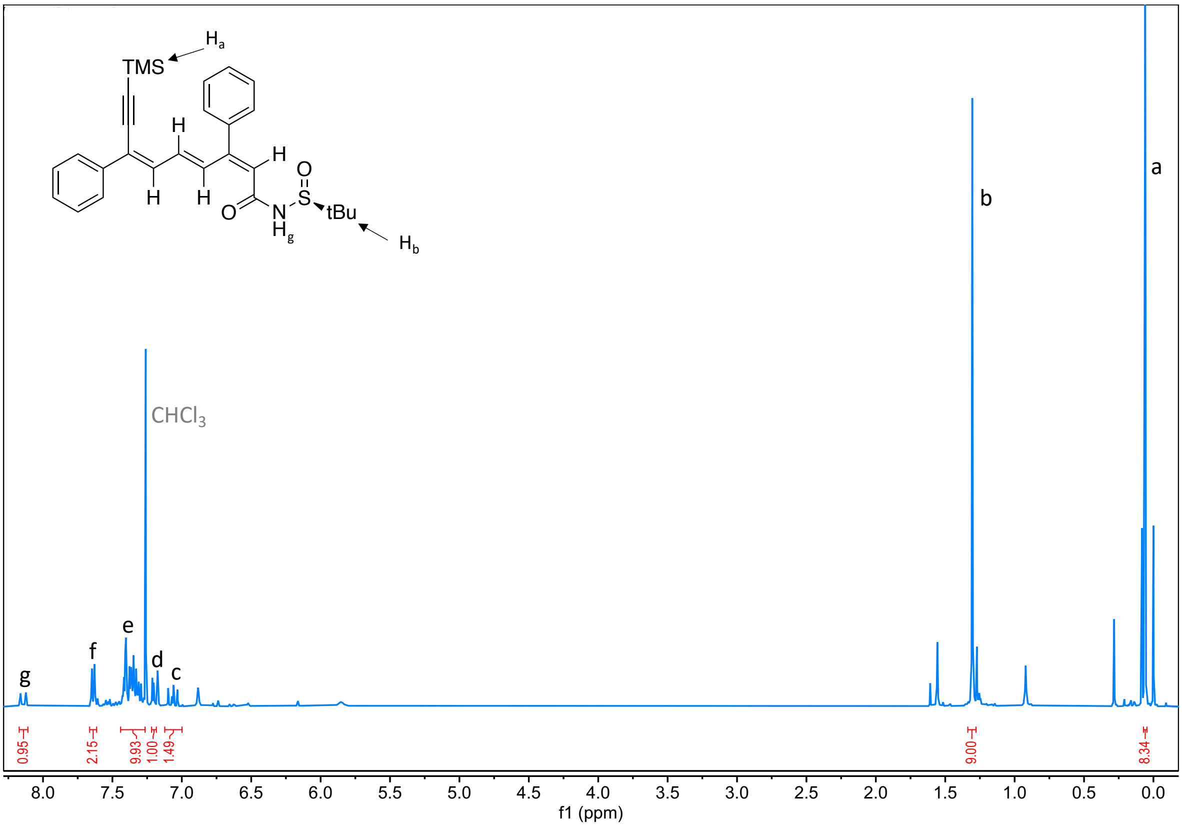


Figure 15 *- 1H NMR 400MHz Compound 16*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.18-8.11 (d, 1H); 7.67-7.62(m, 2H); 7.44-7.28(m, 10H); 7.23-7.20 (d, 1H); 7.1-7.01 (t, 1H); 1.30 (s, 9H); 0.06 (s, 3H).

Signal *a* integrates for 8 protons, but in reality, corresponds to the TMS signal and the anomaly is due to an overlap with another signal. Signal *b* corresponds to the *tert*-butyl signal. In the predicted spectrum (*Figure 18* in the Annexes section) these are the only two signals that have been predicted correctly.

As it can be seen in the spectrum (*Figure 15*), there are a lot of peaks in the aromatic region that overlap and are difficult to distinguish. The assignation of each of the peaks to every proton is then difficult to performed. Signal *e* (which is the region in which most of the peaks are overlapping) integrates for ten protons, and this corresponds to the aromatic protons. The rest of the signals in this region correspond to the alkene protons, signals that have not been assigned.

Signal *g* is the most downfield of the signals, that integrates for a proton. This signal probably corresponds to the amide proton, because of this proton being directly bonded to an electronegative atom, that through inductive effect makes this proton to be more deshielded. In the predicted spectrum (*Figure 18* in the Annexes section) this signal is found around 12.5 ppm and is a singlet, while this same signal appears at around 8.2 ppm and is a doublet in *Figure 15*.

Some of the electrophiles synthesized (specifically compounds **3** and **4**) were not specially sterically hindered but contained a bulky substituent. When these compounds were reacted with the nucleophile (compound **13**), a mixture of the Cope and the trienamide products was obtained.

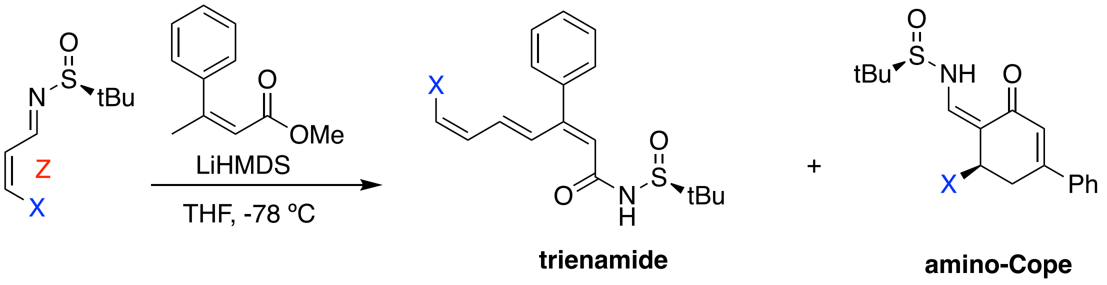
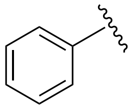
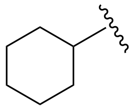


Table 8 - Impact of the substituent size of Z-sulfinyl imines on ratio of amino-Cope vs. trienamide products

X	Trienamide Yield (%)	Amino-Cope Yield (%)
 **(20)**	Not observed	60%
 **(21)**	40%	15%

As it can be observed in *Table 8,* when the X substituent is a phenyl group, no trieanamide is observed and only the Cope product is obtained, while when the X substituent is a cyclohexane, both products are obtained, being the trienamide the major one. It is known that when there is a steric hindrance, the anionic cascade is diverted towards this new stereoselective synthesis of trienes. Phenyl is planar, while cyclohexane adopts a chair structure, being the latter one a bulkier substituent. It seems like the phenyl group is not bulky enough to divert the synthesis while cyclohexane, which is not planar, is and therefore can divert the synthesis to the formation of the trienamide but also allowing some minor formation of the Cope product.

Compound **21** has been characterized using NMR spectroscopy and its spectrum can be found bellow.

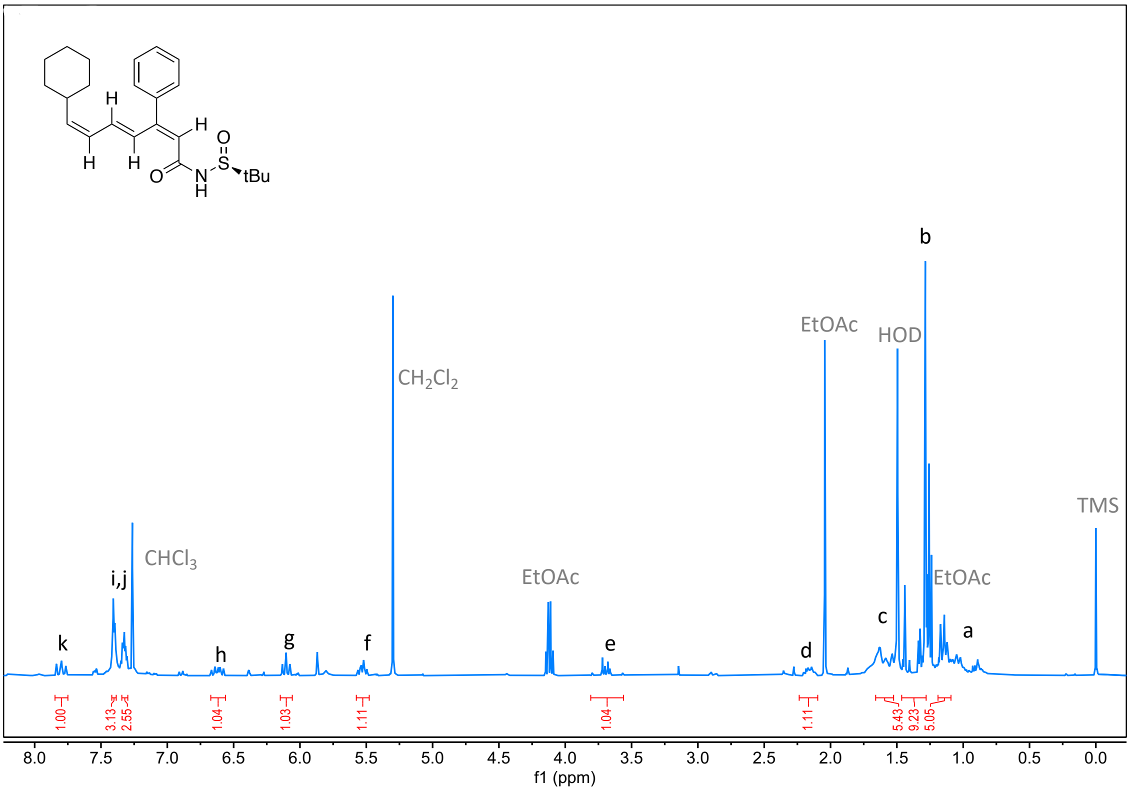


Figure 16 *- 1H NMR 400Mz Compound 21*

^{1}H NMR (CDCl$_3$, 500 MHz): δ = 7.84- 7.75 (t, 1H); 7.44-7.36 (m, 3H); 7.35-7.30 (m, 2H); 6.67-6.67-6.58 (m, 1H); 6.15-6.06 (t, 1H); 5.57-5.49 (m, 1H); 3.72-3.67 (m, 1H); 2.22- 2.10 (m, 1H); 1.68-1.53 (m, 5H); 1.28 (s, 9H); 1.20-1.09 (m, 5H).

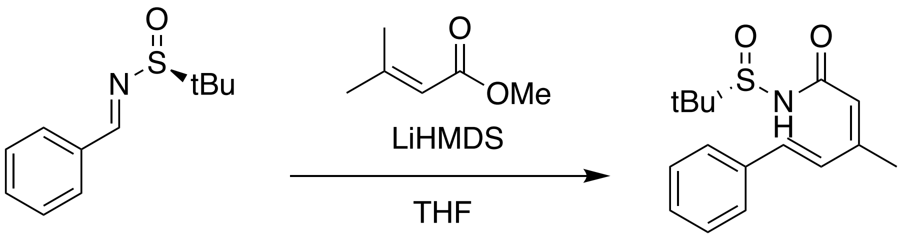
The spectrum is not really clean, there are a lot of residual solvent peaks. Signal *b* corresponds to the *tert*-butyl group protons and signals *a*, *c* and *d* correspond to the cyclohexane protons, being the latter one the one corresponding to the proton of the carbon of the cyclohexyl group bonded to the alkyl chain. In this region, there is also some signals coming from the EtOAc and from the grease (that affects the baseline). There are two signals that integrate for two and three protons (signals *i* and *j*) that correspond to the aromatic protons. The rest of the signals only integrate for one proton and correspond to the alkene and the amide protons. Considering that the amide proton is bonded to an electronegative atom (N) and should be more deshielded, the amide signal should be signal *k*. The rest of the signals are not assigned to each of the protons.

The spectrum obtained is compared to the predicted ^{1}H NMR spectrum from ChemDraw (*Figure 19 in the Annexes section*). Signals *a*, *b*, *c* and *d* more or less coincide with the prediction, wheareas the rest of the signals do not. The amide proton is once again found around 12 ppm in the predicted spectrum, but no signal is found in that region in the experimental spectrum.

5.2.2 Optimization

The reaction temperature and base equivalents for the new stereoselective dienolate γ-Mannich addition route to synthesize di- and trienamides had to be optimized, due to the fact that the conditions to obtain the desired products and good yields might differ from the asymmetric anionic amino-Cope ones.

The same reaction was performed to do all the optimizations, in which electrophile **9** and commercially available nucleophile **14** were used (from *Figures 1* and *2* in section 4.3). The reaction between the chiral non-conjugated sulfinyl imine and the ester is found in *Scheme 27*. The product of the reaction is a dienamide, instead of the trienamide that is obtained when chiral conjugated imines are used.



Scheme 27 - *Stereoselective synthesis of diamines*

Before doing the optimizations, the reaction was tested doing a 200 mg scale reaction (*Scheme 27*). The reaction was performed at -78 ºC, with 3.0 equivalents of the base and 1.5 equivalents of the nucleophile. The reaction was monitored by Thin Layer Chromatography (TLC) each hour the first three hours and then was let to run overnight. As it is observed in *Figure 17*, the starting materials are not still completely consumed after 3 hours. After one hour what it seems to be the intermediate is present in the mixture and is still being formed after 3 hours. No product is found after 1 hour but is present after 2 hours. After 2 hours there is the formation of a compound with higher Rf than the intermediate and product of the reaction but lower Rf than the starting materials which was not isolated because it was not of interest in that moment.

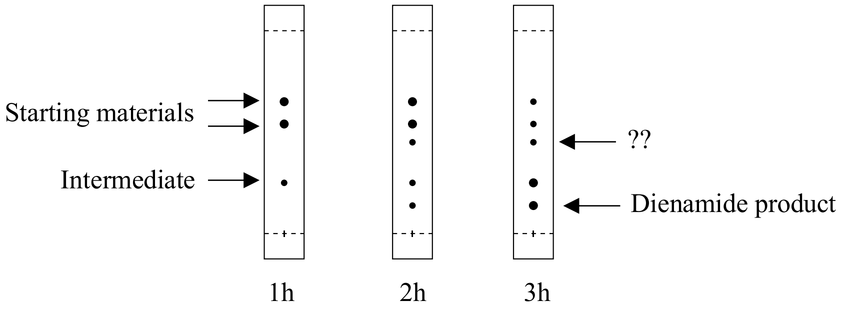


Figure 17 *- TLC performed at 30% EtOAc/Hexanes*

From the postulated mechanism of the reaction shown in *Scheme 26*, at least 2 equivalents of the base must be used for the reaction to procced. The optimization of the base was performed by carrying out four different reactions of 20 mg scale of the electrophile, simultaneously, with the same conditions, but with different equivalents of base added (1.0, 2.0, 3.0 and 4.0 equivalents of base). The reactions were run at -78 ºC, overnight and using 1.5 equivalents of the nucleophile. The reactions were then quenched with saturated NH_4Cl and extracted with EtOAc. As the scale of the reactions is very small, the total amount of each of the starting materials to perform the four reactions was weighted together, dissolved in the corresponding amount of THF (0.1M of the electrophile) and these solutions were distributed equally to each of the vials that had been already flame-dried and contained a stirbar inside. In the *Table 9* the volumes of LiHMDS that had been added to each of the reactions are found.

Table 9 *- Base equivalent optimization*

Base equivalents	Volume LiHMDS (mL)
1.0	0.10
2.0	0.19
3.0	0.29
4.0	0.38

Something that was not considered while performing this optimization was that the LiHMDS volume was not trivial and would influence the concentration of the electrophile in the solution. Even though, the NMRs of the four reactions could be compared and it was concluded that at least 3 equivalents of the base were needed for the desired product to be present in the final solution. For future optimizations, this should be considered. The NMRs of the products of each of the reactions can be found in the Annexes section. The samples used to measure the NMR were the products obtained just after the reaction, without performing any type of separation (crude NMR).

Once the base equivalents were optimized, the temperature, as well as the time of the reaction were optimized. Once again, 20 mg scale (of the electrophile) reactions were set up. The reactions were carried out in THF (0.1M of the electrophile in THF) and 1.5 equivalents of the nucleophile and 3.0 equivalents of the base were added. The reactions were prepared following the same procedure as for the optimization of the equivalents of the base.

In *Table 10* the conditions of each of the five reactions that have been set up can be found.

Table 10 *- Temperature and Time optimization*

Reaction	Temperature	Time
1	-78ºC	overnight
2	-78ºC	3h
3	-78ºC	6h
4	0ºC	3h
5	Prepare at 0ºC then RT	3h

The NMR of the compounds are compared, and it is concluded that the better conditions for obtaining the trienamide (in which the spectrum obtained was cleaner) it is by carrying out the reaction at 0ºC and let it run for 3 hours (*reaction 4* conditions). The NMRs of each of the reactions are found in the Annexes section. The samples used to measure the NMR were the products obtained just after the reaction, without performing any type of separation (crude NMR).

Moreover, the order in which the base and the nucleophile were added to the reaction were also tested. Two reactions with the same conditions were set up and the order in which the nucleophile and the base were added was reversed. The yields of both reactions were pretty similar, but a bit better yield was obtained when the nucleophile was added first.

6. Conclusions

6.1 English

The main goal of this research work was to test the influence of the sterics of the anion-accelerated amino-Cope. It was observed that when using conjugated chiral sulfinyl imines and nucleophiles that are sterically hindered, a trienamide product was obtained instead of the Cope-product and therefore a new stereoselective synthesis of trienes was reported. The same reaction was also tested with quiral non-conjugated sulfinyl imnes and dienamide products were obtained.

A series of starting materials were proposed to test the Anion-acccelerated amino-Cope reaction. Most of the starting materials proposed were not commercially available and had to be synthesized. Some of the compounds could not be isolated because they were not stable enough. Some other materials had very low yields which did not enable them to be tested towards the Cope reaction. If those compounds would like to be tested, either larger scale reactions would be needed to perform or those reactions would have to be optimized in order to obtain enough compound to run the Cope reaction. From the eight not commercially available electrophiles proposed only three could be synthesized and tested, while only one of the four not commercially available nucleophiles that were synthesized could not be tested because of lack of time.

A range of products were obtained when reacting the synthesized electrophiles and nucleophiles and these were characterized using NMR spectroscopy. The yield of the synthesis changed depending on the combination of starting materials.

Reaction conditions, such as time, temperature and base equivalents were optimized in order to improve the yield and diminish the side-products formed.

6.2 Catalan

El objectiu principal de la tesis era analitzar la influencia dels factors estèrics dels reactius en la reacció amino-Cope accelerada per la presència d'un anió. Es va observar que quan una sulfinil imina quiral conjugada reacciona amb electròfils que estan estèricament obstaculitzats, una trienamide es obtinguda en canvi del producte de la reacció Cope. Aquest descobriment ha permès reportar una nova síntesi esteroselectiva per sintetitzar triens. La mateixa reacció també es va provar amb sulfinil imines quirals no-conjugades i dienamides es van obtenir com a producte.

Una sèrie de reactius es van proposar per tal d'analitzar els factors estèrics la reacció amino-Cope accelerada per la presència d'un anió . La gran majoria dels reactius proposats no estaven disponibles online i per tant van haver de ser sintetitzats. Alguns dels compostos no van poder ser sintetitzats ja que no eren suficientment estables. Altres tenien síntesis amb molt poc rendiment que no va permetre que s'utilitzessin en la reacció amino-Cope. Per tal de poder utilitzar aquests darrers compostos, reaccions de major escala s'haurien de dur a terme o les síntesis s'haurien d'optimitzar, per així aconseguir suficient compost per dur a terme l'amino-Cope. Dels vuit electròfils proposats que necessitaven ser sintetitzats, només tres es van poder utilitzar. En canvi, tots els nucleòfils que s'havien proposat es van poder sintetitzar, però un no es va poder utilitzar per falta de temps.

Un conjunt de productes es van obtenir en reaccionar els nucleòfils i electròfils que s'havien sintetitzat, productes que es van caracteritzar utilitzant espectroscòpia RMN. El rendiment de les síntesis es diferent depenent de la combinació de reactius utilitzats.

Les condicions de la reacció, com ara el temps, temperatura i equivalents de la base utilitzats de la nova reacció van ser optimitzats, per tal de poder obtenir un rendiment màxim i minimitzar el nombre de productes no desitjats.

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8. Appendix

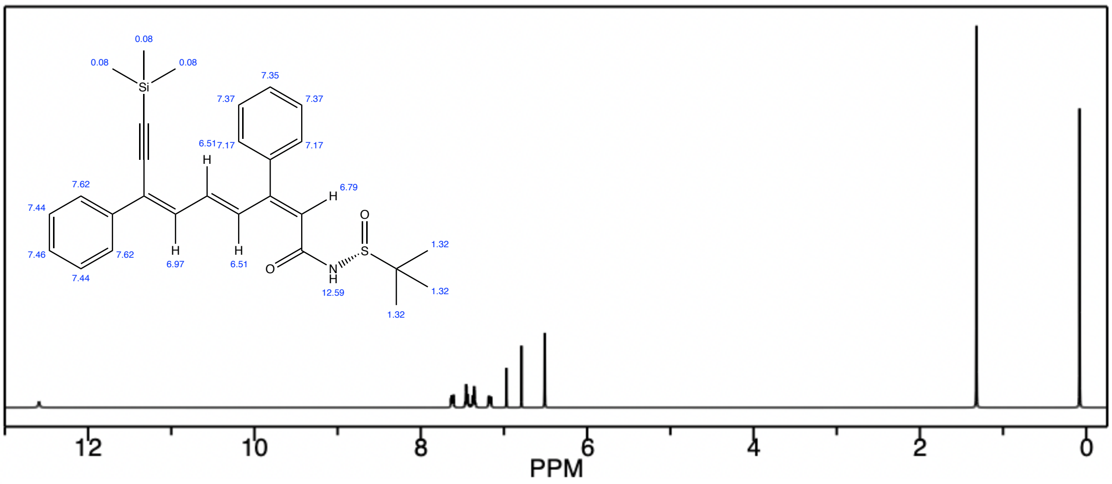

Figure 18 - *Predicted ^{1}H NMR Compound* ***16***

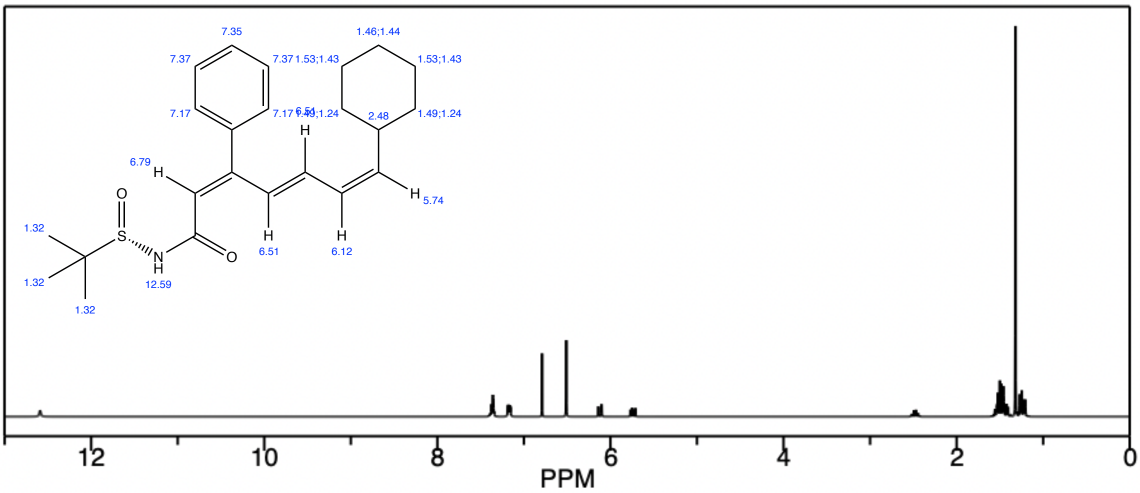

Figure 19 - *Predicted ^{1}H NMR Compound* ***21***

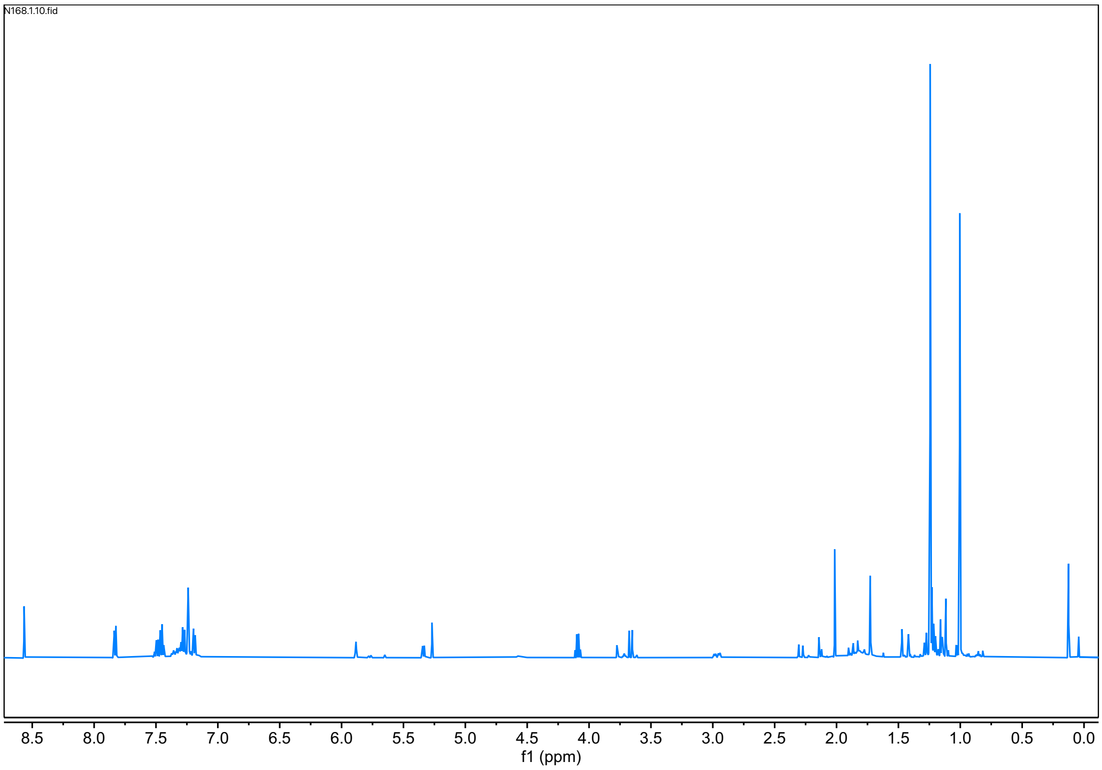

Figure 20 *– Base equivalents optimization (1.0 equivalents)*

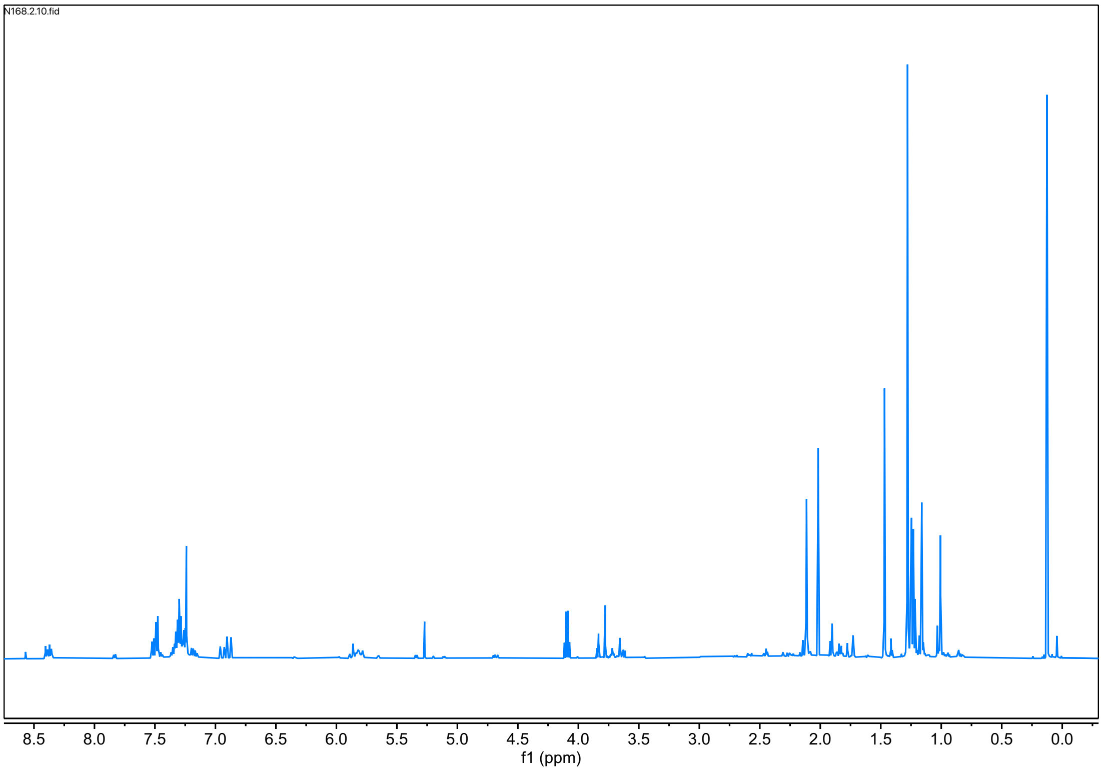

Figure 21 *- Base equivalents optimization (2.0 equivalents)*

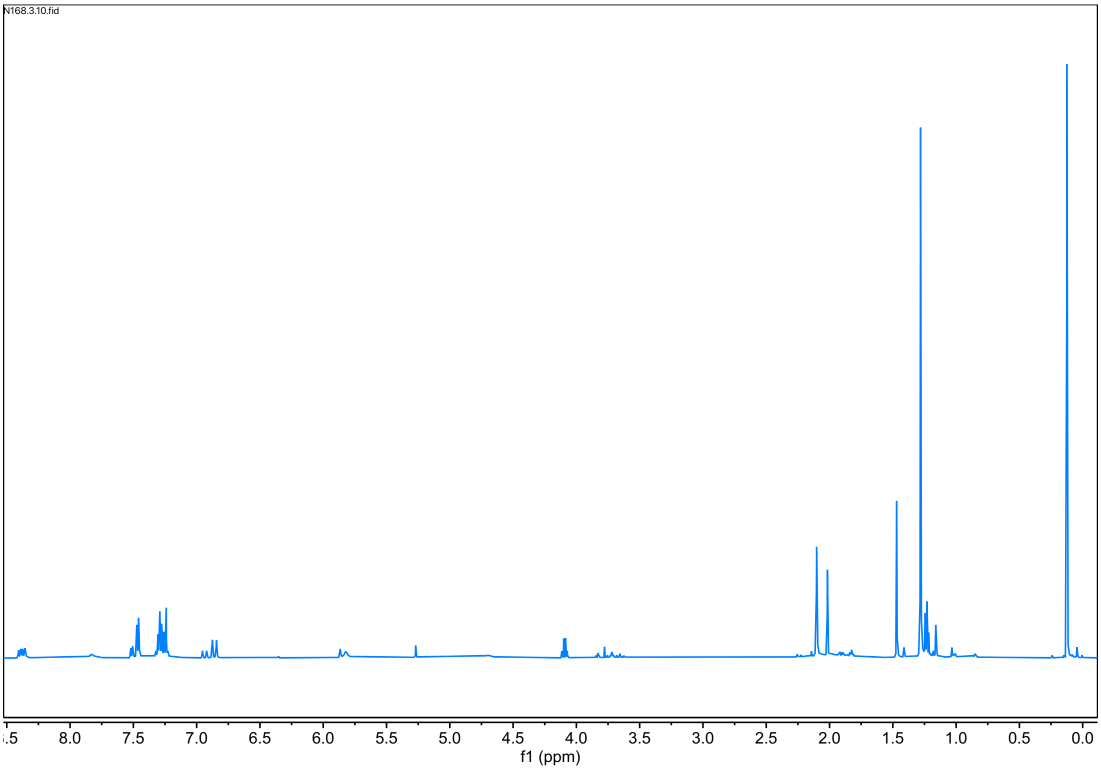

Figure 22 *- Base equivalents optimization (3.0 equivalents)*

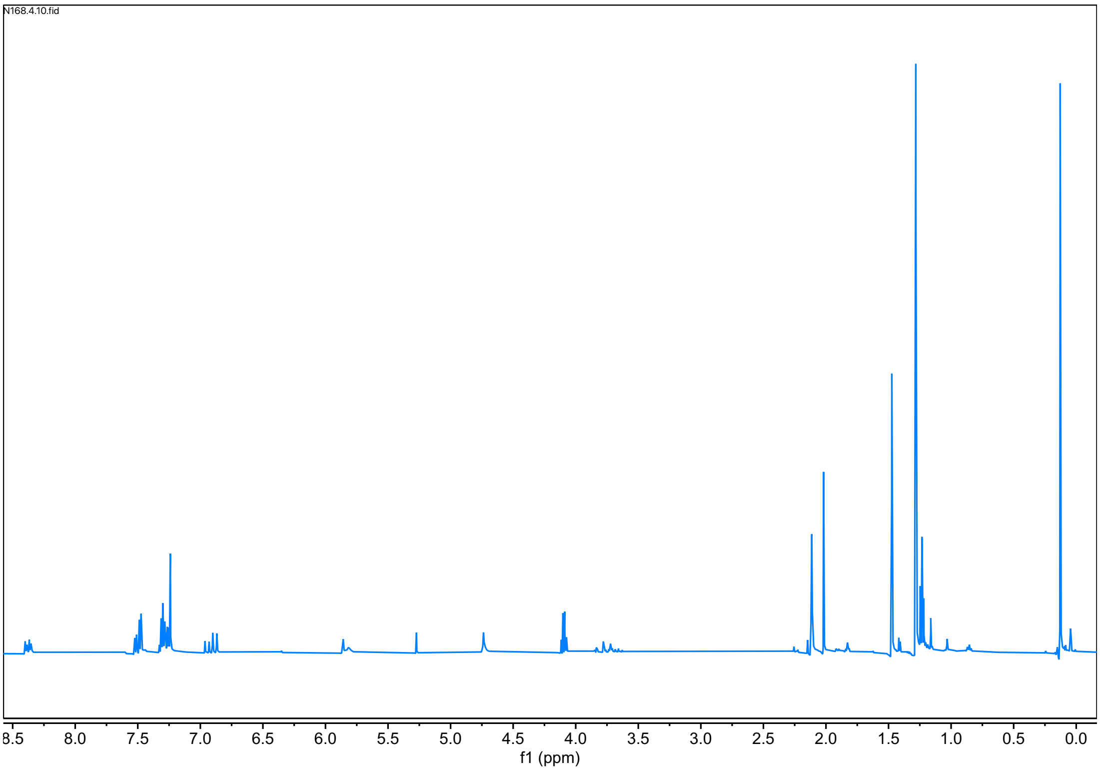

Figure 23 *- Base equivalents optimization (4.0 equivalents)*

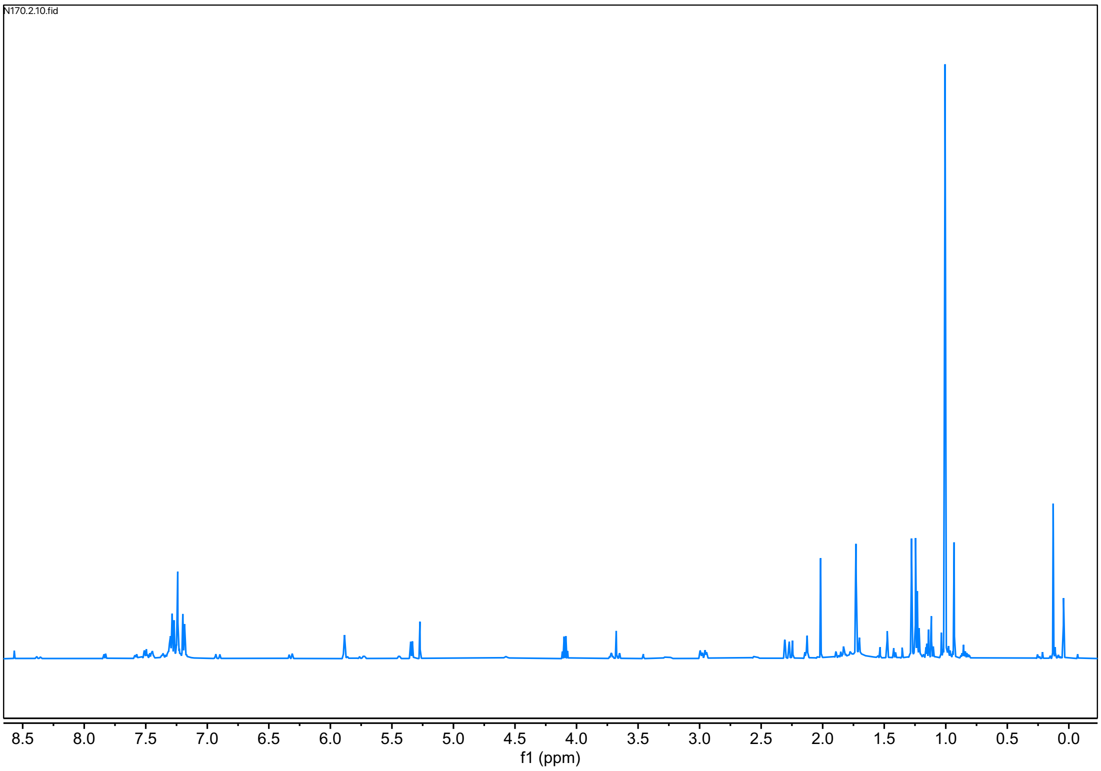

Figure 24 *- Temperature and time optimization (-78ºC for 3h)*

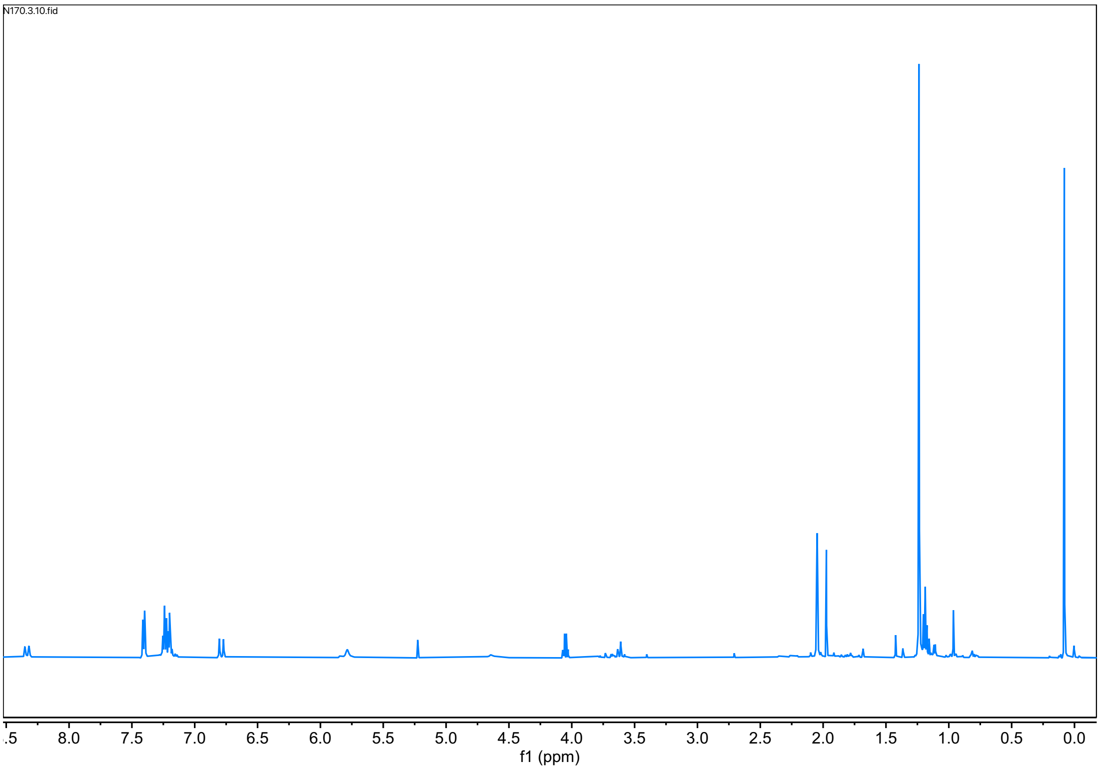

Figure 25 *- Temperature and time optimization (0ºC for 3h)*

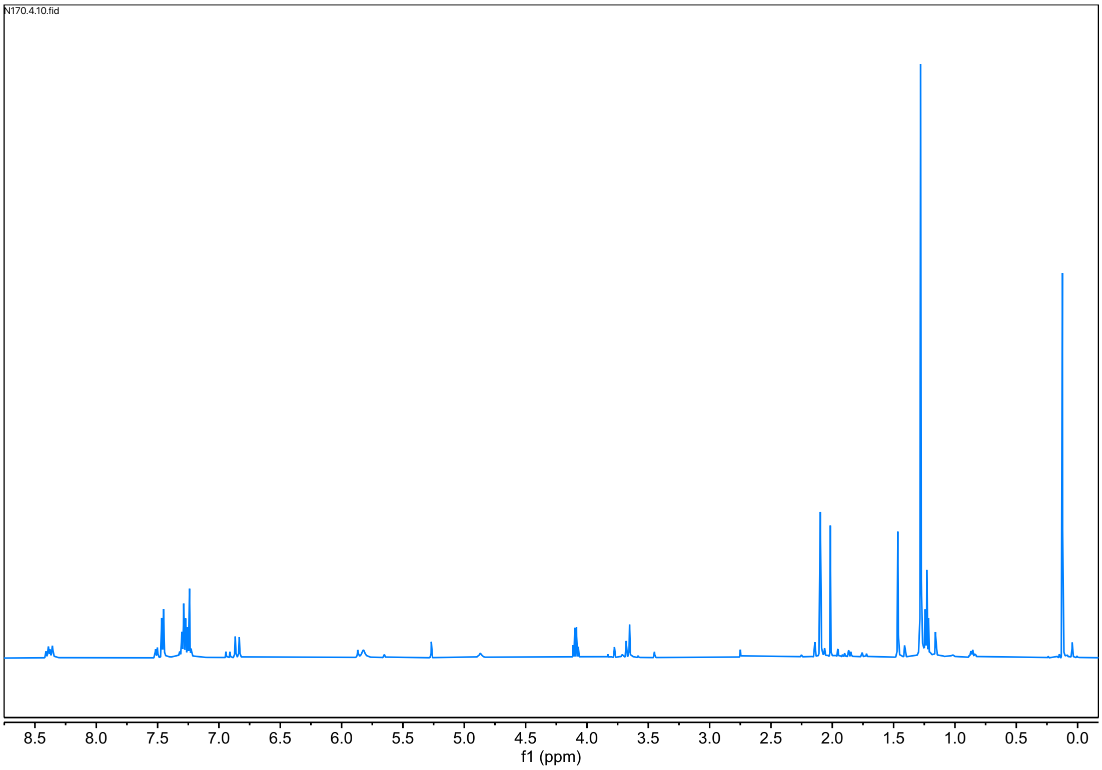

Figure 26 *- Temperature and time optimization (Prepared at 0ºC then RT for 3h)*