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Green solvents for the hydroaminomethylation of estragole

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Green solvents for the hydroaminomethylation of estragole

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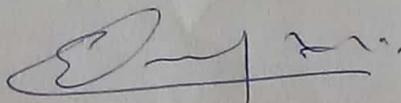
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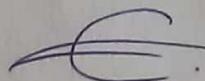
## "Green Solvents for the Hydroaminomethylation of Estragole"

**Maria Gabriela Paredes Gutierrez**

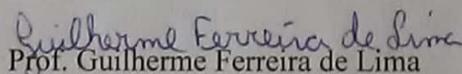
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## ***Abstract***

Hydroaminomethylation (HAM) is a simple route to synthesize amines through a highly atom-economic reaction of alkene with syngas (carbon monoxide/hydrogen mixture) and a primary or secondary amine. HAM consists of three successive steps occurring in the same reactor: hydroformylation, condensation of the aldehyde with the amine, and hydrogenation. Both hydroformylation and hydrogenation are catalyzed by transition metal complexes. In this work, a series of novel amines with potential bioactivity was obtained in excellent yields. Some eco-friendly solvents were employed for the first time in this reaction. *p*-Cymene, anisole and ethanol proved to be excellent greener alternatives for toluene, the solvent conventionally used for hydroaminomethylation. The performance of *p*-Cymene and anisole was similar to that of toluene; whereas the reactions in ethanol solutions showed better yields and selectivity for the products. Propyl anisole was also tested, but the results were not as good as the others solvents, as significant amounts of enamines were not hydrogenated.

The regioselectivity varied with the amine counterpart: the  $\beta/\gamma$  ratio was 40/60 in the reactions with di-*n*-butylamine vs. 50/50 in those with 4-methylpiperidine. Thus, the nature of the amine counterpart seems to affect the reactivity of rhodium species operating in the hydroformylation step of the HAM process. The reactions with morpholine gave excellent yields of main products, with their isomeric composition being dependent on the solvent nature. In toluene, *p*-Cymene, anisole and propyl anisole, the substrate isomerization and the hydroformylation of the resulting anethole were significant. In ethanol, the isomerization of estragole was much less significant. HAM of estragole with 2,6-dimethylmorpholine, gave excellent yields in all solvents, except propyl anisole where the last step (hydrogenation) was not favourable, and enamine intermediate remained in significant amounts.

*Keywords:* green solvents, biorenewables, estragole, hydroaminomethylation

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### ***List of abbreviations***

HAM	Hydroaminomethylation
REACH	"Registration, Evaluation, Authorization, and Restriction of Chemical"
DCM	Dichloromethane
EHS	Influential two-level assessment of the environment, health, safety and energy demand
CED	The net cumulative energy demand of the solvent production
GSK	GlaxoSmithKline guide
COD	1,5-cyclooctadiene
R	Alkyl group
PPh <sub>3</sub>	Triphenylphosphine
TBPP	tris(2,4-di- <i>tert</i> -butylphenyl) phosphite
GC	Gas chromatography
FID	Flame ionization detector
<sup>1</sup> H NMR	Nuclear magnetic resonance
DEPT	Distortionless Enhancement by Polarization Transfer

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## **1. Introduction**

### **1.1 Green chemistry and catalysis**

It is now widely recognized that there is a growing need to generate more environmentally friendly processes in the chemical industry where large amounts of waste are generated every day such as inorganic salts, highly explosive hydrocarbons, halogenated compounds, alcohols, and phenols, among many others. The conventional procedures in the chemical industry that generate toxic waste are increasingly being replaced by more efficient alternative processes, enabling chemists to be key players in the reduction of toxic wastes (TANG; SMITH; POLIAKOFF, 2005)

Thus, the Green Chemistry principles aim to the efficient use of raw materials, preferably renewable, minimization of waste and the substitution of toxic reagents and solvents by less hazardous materials in the manufacture of chemicals. (SHELDON; ARENDS; HANEFELD, 2007)

Catalysis is in accordance with the principles of green chemistry because it can have benefits for the environment, among which we can mention the reduction of energy consumption, better yields, selectivities, increase efficiency and decrease the number of steps in chemicals reactions. (CENTI; PERATHONER, 2003)

### **1.2 Green solvents**

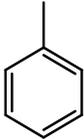
Driven by great concern for environmental problems, the establishment of green solvents for extractions, separations, formulations and chemical reactions has become an increasingly important area of research.(HÄCKL; KUNZ, 2018)

The indiscriminate use of toxic solvents in various chemical processes is related to the beneficial attributes of these solvents, but these benefits are often counterbalanced by drawbacks. For instance, the volatility of the solvents allows their recovery and purification by distillation, but also creates unwanted air emissions that can cause risk of exposure to workers. Other examples are amide solvents, which have the high polarity required to dissolve a wide range of compounds, but

are considerably toxic. (ASHCROFT *et al.*, 2015). Apolar solvents such as hydrocarbons provide the ability to dissolve oils in extractions and help to perform separations (SICAIRE *et al.*, 2015), but they are highly combustible and have a low water solubility, which is related to bioaccumulation and aquatic toxicity (GISSI *et al.*, 2015). In efforts to eliminate unwanted solvents, replacement strategies are based on finding structurally related compounds that are not yet qualified as not allowed by legislative and regulatory measures. Therefore, benzene, since its formal recognition as a carcinogen in the mid-twentieth century, is usually replaced by toluene (ORGANIZATION, 1971).

However, in the last years the European regulation concerning the "Registration, Evaluation, Authorization, and Restriction of Chemical" (REACH) has introduced a restriction on toluene, chloroform, and dichloromethane with specific conditions. In Table 1 it can be observed the controls that REACH put on the import and use of a wide range of chemical products in Europe. Any product that does not meet the requirements established in REACH is withdrawn from the market through the information system "rapid alert system for non-food dangerous products" (RAPEX). An example of this is in 2015 the banned products included glues containing toluene, chloroform or benzene (BYRNE, F. *et al.*, 2016)

Table 1. REACH restriction on the solvents toluene, DCM and chloroform with hazard codes also provided (UNITED NATIONS. ECONOMIC COMMISSION FOR EUROPE. INLAND TRANSPORT COMMITTEE., 2008)

Solvent	Condition <sup>a</sup>	Hazards <sup>b</sup>
	"Shall not be placed on the market or used, as a substance or in mixtures in a concentration equal to or greater than 0.1% by weight where the substance or mixture is used in adhesives or spray paints intended for supply to the general public"	May be fatal If swallowed and enters airways (H304). Suspected of damaging the unborn child (H361d). May cause damage to organs through prolonged or repeated exposure (H373).
CH <sub>2</sub> Cl <sub>2</sub> DCM	"paint strippers containing dichloromethane in a concentration equal to or greater than 0.1 % by weight shall not be placed on the market"	Suspected of causing cancer (H351)
CHCl <sub>3</sub> Chloroform	"Shall not be placed on the market or used, as a substance, as constituents of others substances, or in mixtures in concentration equal to or greater than 0.1 % by weight, where the substance or mixture is intended for supply to the general public and/or is intended diffusive of applications such as in surface cleaning and cleaning of fabric"	Suspected of causing cancer (H351)

<sup>A</sup> Conditions abbreviated and/or paraphrased from the full text found in Regulation (EC) No 1907/2006 (REACH) ref 21-23  
<sup>b</sup> Hazard codes defined according to Regulation (EC) No 1272/2008 (CLP) ref 29

According to (Fischer et al., 2007) and, looking to answer "What is a green solvent", conducted a series of studies evaluating different factors to classify a solvent as green. The response is a two-level assessment of the environment, health, safety (EHS) and energy demand (CAPELLO; FISCHER; HUNGERBÜHLER, 2007). By understanding the energy required to produce a solvent, and the options available at the end of its useful life to recover part of that energy, the net cumulative energy demand (CED) of the solvent production can be calculated. Both the EHS and CED combine to complete a numerical rating system. In Figure 1, it can be observed that low scores indicate greener solvents. The results show that alcohols and esters (not shown) are greener than hydrocarbons (BYRNE, F. *et al.*, 2016)

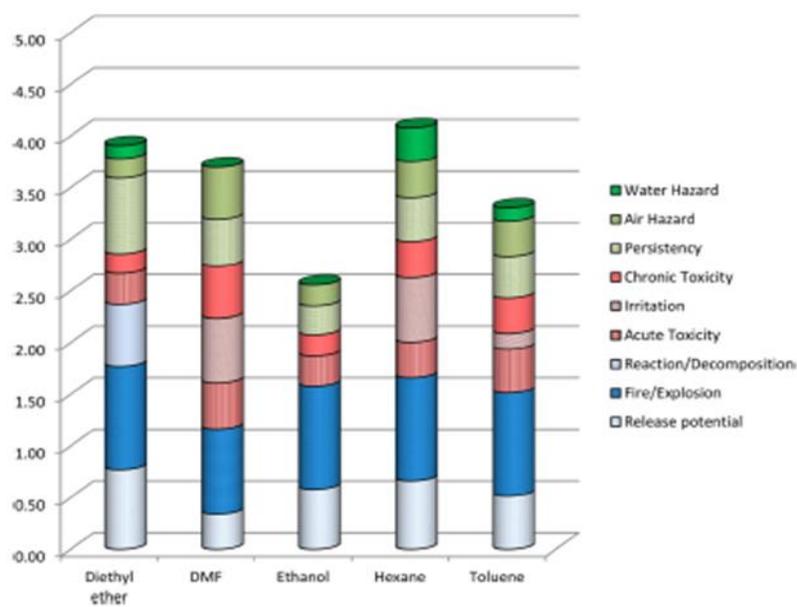


Figure 1. Environmental health and safety rankings for the representative solvents(BYRNE, F. et al., 2016)

### 1.3 Hydroaminomethylation reaction (HAM)

Amines are one of the most important chemical compounds that have been used on the chemical industry to have access to dyes, solvent, and functional materials; with a production of a million-ton scale annually. Secondary amines are important functionalities in new drugs such as Sensipar, NPS 467, NPS 568, and Strattera., shown in Figure 2 (ARAVA; GORENTLA; DUBEY, 2012).

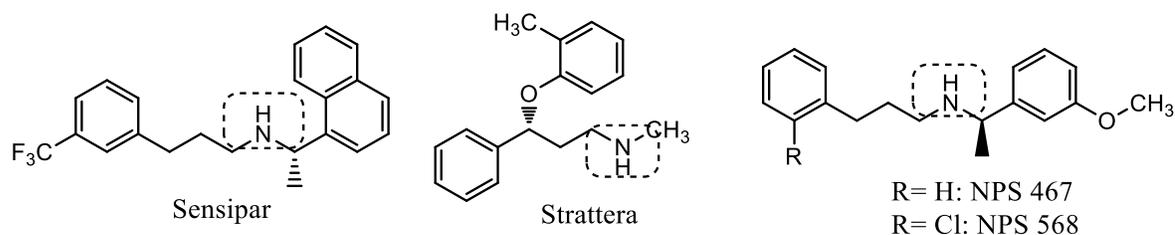


Figure 2. Sensipar, Strattera, NPS 467and NPS 568

Those substances are traditionally synthesized through classical methods as the reduction of amides, reduction of nitriles and reductive amination of carbonyl

compounds which required large amounts of reagents and long reaction times. (CHEN, C.; DONG; ZHANG, 2016) Nowadays, a highly effective catalytic method for the synthesis of this type of compounds is known: the HAM.

HAM arose in the decade of 1940, when Reppe discovered the reaction between carbon monoxide and acetylenic compounds in the presence of water and ammonia, which required harsh conditions ( $T > 300\text{ }^{\circ}\text{C}$ , pressure up to 150 bar) in stoichiometric amounts of  $\text{Fe}(\text{CO})_5$  (REPPE, 1949). HAM uses  $\text{CO}/\text{H}_2$  (synthesis gas) and consists of three successive steps, hydroformylation, condensation of the aldehyde with the amine and hydrogenation. Both hydroformylation and hydrogenation are catalyzed by transition metal complexes (Figure 3) (CROZET; URRUTIGOÏTY; KALCK, 2011).

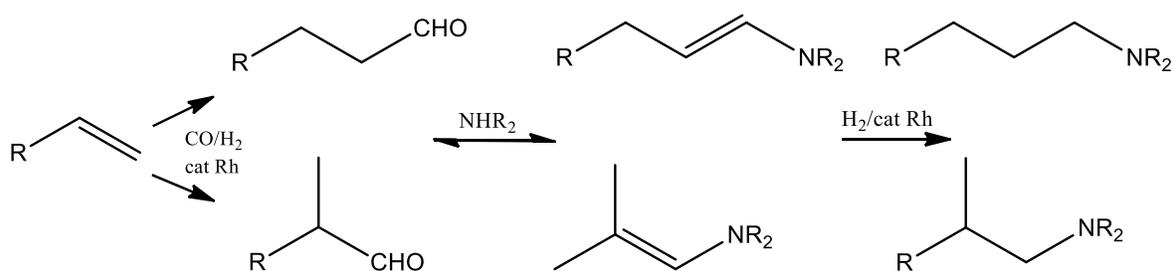


Figure 3. Hydroaminomethylation reaction

Iqbal in 1971 reported the first rhodium-catalyzed hydroaminomethylation. This catalyst was used in the *HAM* of cyclohexene, and it was determined that rhodium was much better than the iron catalyst used by Reppe (CHEN, C.; DONG; ZHANG, 2016). In the last years rhodium dimers  $[\text{Rh}(\text{COD})\text{L}_2]$ , where L is a bridging ligand, have been used in this type of reaction for the synthesis of a large variety of amines, since it has numerous advantages such as: easy synthesis and air stability, (KRANEMANN; EILBRACHT, 2000). An example of this type of catalyst is shown in the figure 4

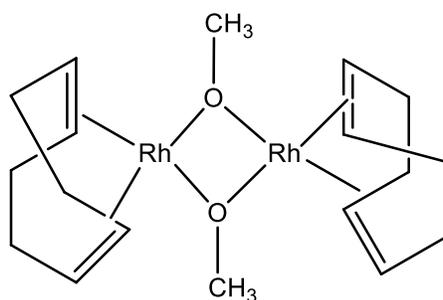


Figure 4. Structure of the catalytic precursor di- $\mu$ -methoxy-bis[(1,5-cyclooctadiene)rhodium(I)]

Although known since 1940s, only recently has HAM gained importance in the synthesis of more complex molecules and fine chemicals (OLIVEIRA *et al.*, 2015). From the works of Beller, hydroaminomethylation has become a versatile, selective tool for the synthesis of a range of organic compounds, including the synthesis of amines from esters of unsaturated fatty acids, and synthesis of pharmaceutical compounds (AHMED *et al.*, 2006). Besides, HAM is an efficient environment-friendly method to produce amines, concerning to atom economy (CROZET; URRUTIGOÏTY; KALCK, 2011).

As described before, HAM is a reaction that involves two different catalytic cycles in the same reactor. Thus is considered a tandem process, i.e., the catalyst precursor and reagents are in the same reactor, and the sequential transformation of the substrate occurs via two mechanistically distinct processes.(FOGG; DOS SANTOS, 2004). The steps of HAM will be detailed in sequence.

#### **1.4 Hydroformylation**

Hydroformylation is the first transformation that occurs in the hydroaminomethylation reaction; this reaction consists in the carbonylation of the alkene with carbon monoxide and hydrogen (CO/H<sub>2</sub>) catalyzed by transition-metal complexes (see Figure 5). The most commonly metal used for this transformation are cobalt, rhodium and ruthenium (BÖRNER, A., FRANKE, R. 2016).

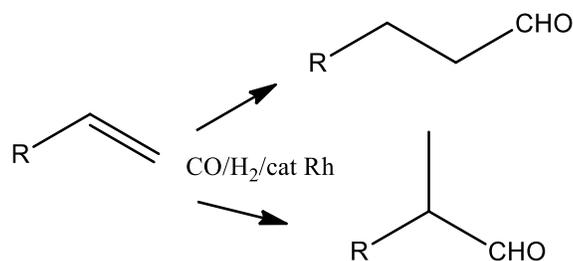


Figure 5. Hydroformylation reaction

Hydroformylation reaction represents one of the most powerful tools for synthesis of organic compounds. This process allows the transformation of cheap raw material in high added value products (aldehydes), which are used as building blocks for numerous chemical products. Beside, a synthesis of branched aldehydes is important to the synthesis of pharmaceuticals and fine chemicals because of the potential formation of a stereogenic center (POSPECH *et al.*, 2013).

In 1938, Otto Roelen accidentally discovered that the reaction of ethylene with CO and H<sub>2</sub> in the presence of a catalyst of rhodium, cobalt, and magnesium oxide yields not only alkanes but also diethyl ketone and propionaldehyde. Nowadays, more than 10 million tons of aldehydes are produced yearly. A study between 2010 and 2015 shows that a hydroformylation process is still an important tool for industrial research. (Table 2)(BÖRNER, A., FRANKE, R. 2016)

Table 2. Patents and publications connected with hydroformylation between 2010 and 2015

	2010	2011	2012	2013	2014	2015
Patents	81	80	79	82	109	48
Journal, Letters, Reports	192	153	163	195	162	106
Reviews	38	31	29	26	1	8

The first mechanism for the hydroformylation was proposed in 1961, using cobalt catalyst [HCo(CO)<sub>4</sub>]. Nevertheless, this catalyst present low regio- and chemoselectivity and undesired side products like alkanes are formed (HECK; BREWSLOW, 1961).

Later in 1965, it was proposed a mechanism that used a rhodium complex [RhH(PPh<sub>3</sub>)<sub>2</sub>(CO)<sub>2</sub>] to catalyzed hydroformylation of alkenes under mild conditions, which presented better regio- and chemoselectivity than of cobalt complex. The

proposition involved two mechanisms; a dissociative (Figure 6) and an associative (not shown). The dissociative mechanism is more accepted because involved the loss of one CO ligand to generate a square planar complex, which is more susceptible to the attack of the olefinic substrate than a hexacoordinated complex in the associative mechanism (EVANS; OSBORN; WILKINSON, 1968).

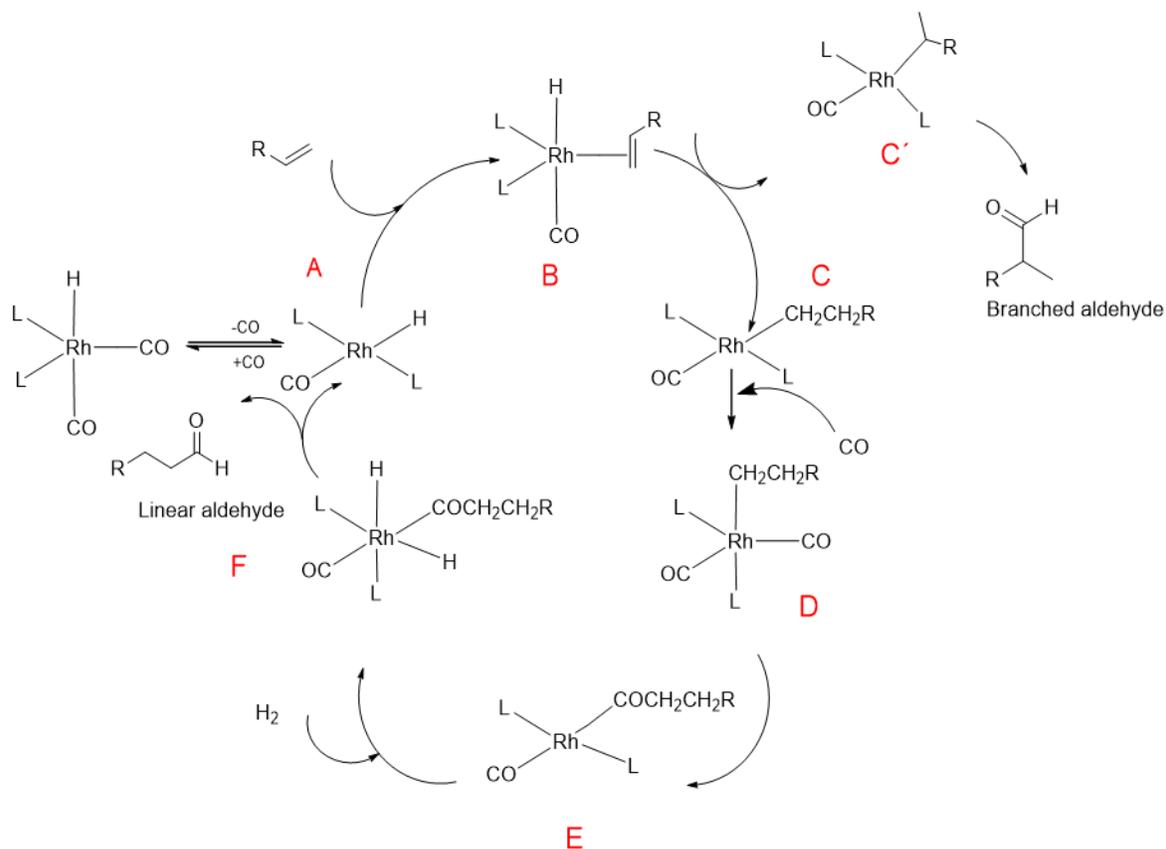


Figure 6. The mechanism for the hydroformylation of alkenes, using rhodium catalyst

The first step is a dissociation of one carbonyl (CO) ligand to generate a square planar complex of 16 electrons (A), this step allows the coordination of the alkene to form the complex (B). Subsequent transfer of hydrogen to one of the carbons of the olefin produces an alkyl complex. In this step, the regioselectivity of the product is defined. If the transfer of the hydrogen occurs in the most substituted carbon, the branched intermediate will be obtained (C'). Conversely, if the transfer of H occurs in the least substituted carbon, the linear intermediate will be formed (C). Also, regioselectivity can be influenced depending on the nature of ligand L. If L is bulky, orientation results in a linear aldehyde, because it occupies less space in the sphere

of coordination of the complex than the branched intermediary(CROZET; URRUTIGOITY; KALCK, 2011).

The coordination of carbonyl ligand results in an intermediate (D) that can suffer two reactions:  $\beta$ -hydride elimination, resulting in the isomerization of the substrate, or migratory insertion of CO to form (E). It was reported that with lower CO pressure,  $\beta$ -hydride elimination is favored over CO coordination. Thus, it is possible to have two competing reaction: alkene isomerization or migratory insertion of CO. While maintaining high syngas pressure, CO coordinate is facilitated by promoting linear aldehyde formation (OCTOBER; MAPOLIE, 2017). Finally, complex (E) suffers oxidative addition to forms (F), which is accompanied to the liberation of the final product.

### **1.5 Phosphite ligands**

In the early 1990s, phosphites emerged as suitable ligands for asymmetric Rh-catalyzed hydroformylation. These ligands are attractive for catalysis since they possess electronic and steric properties that have the ability to change the characteristics of the catalytic species, and consequently, influence the selectivity and reaction activity of the hydroformylation. Another advantage of these ligands is that they are less sensitive to air and other oxidizing agents than phosphines (LEEUWEN *et al.*, 2011).

Phosphorus ligands can easily coordinate to the metal center, due to the combination of  $\sigma$  interactions where the phosphorus atom donates a pair of electrons to the metal and  $\pi$  interactions, in which the metal gives electrons for ligand orbitals with adequate symmetry by a process called backbonding (CROZET; URRUTIGOITY; KALCK, 2011)(Figure 7).

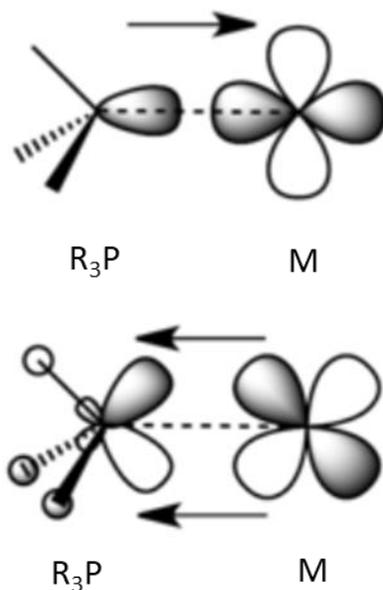


Figure 7. backbonding effect

### 1.6 Condensation of the aldehyde with an amine

Condensation of the aldehyde is the second step in the HAM reaction; the combination of the aldehyde with a primary amine produces an imine and with a secondary amine produces enamine. Figure 8 shows the mechanism to form an enamine (MORRISON; BOYD, 1998).

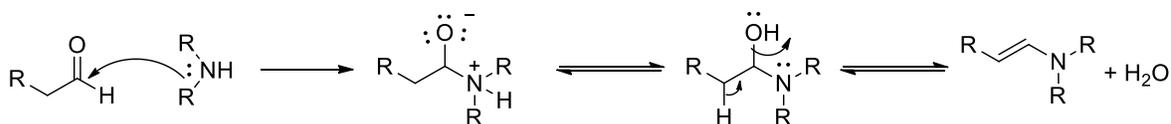


Figure 8. Mechanism of formation enamine

### 1.7 Hydrogenation

Hydrogenation of the enamine formed in the condensation of aldehyde is the last step in the HAM. This reaction is one of the backbones of the chemical industry, because of its broad range application in the synthesis of many products such as fine chemicals, pharmaceuticals, food, dyes and perfumery (CHEN, Z.; CHEN; LI, 2017). Another important application of the hydrogenation reaction is the asymmetric hydrogenation of olefins by BINAP-Ruthenium complexes that was implemented by

the Takasago industry to obtain Menthol which is used as an aroma (NOYORI, 2002).

Hydrogenation consists in the addition of molecular hydrogen ( $H_2$ ) to unsaturated organic compounds, usually in the presence of a catalyst such a nickel, ruthenium or rhodium. This process is employed to reduce double or triple bonds in organic compounds (VILÉ *et al.*, 2016) (see figure 9).

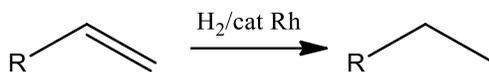


Figure 9. Hydrogenation reaction

The Wilkinson catalyst  $[RhCl(PPh_3)_3]$  is now the most widely used for hydrogenation of a variety of unsaturated substrates, at pressures of hydrogen close to 1 atm or less at room temperature (TAKAYA; NOYORI, 1991). In 1912, the Nobel Prize in chemistry was awarded to Paul Sabatier "for his method of hydrogenation of organic compounds in the presence of finely divided metals, He observed that the reaction between nickel and ethylene at 300 °C the system became white-hot and gas was formed. Analysis of the white gas showed high amounts of ethane and not hydrogen as believed by Sabatier. The conclusion was that hydrogen generated in the partial decomposition of ethylene was transferred to the double bond of ethylene thanks to the presence of the metal (RIDEAL; M.A.; D.SC, 1951)

The first cycle of the hydrogenation of alkenes by Wilkinson's catalyst is shown in the Figure 10. It involves the oxidative addition of  $H_2$  in the 16 electrons complex (A) to form an 18 electrons complex (B), followed by the loss of  $PPh_3$  ligand to obtain coordinately unsaturated complex (C), which allows the insertion of the olefin (D). Hydrogen transfer yields the alkyl complex, thus (E) takes a phosphine ligand and forms (F), the last step is hydrogen migration to carbon results in the reductive elimination of the alkane and the reformation of (A).

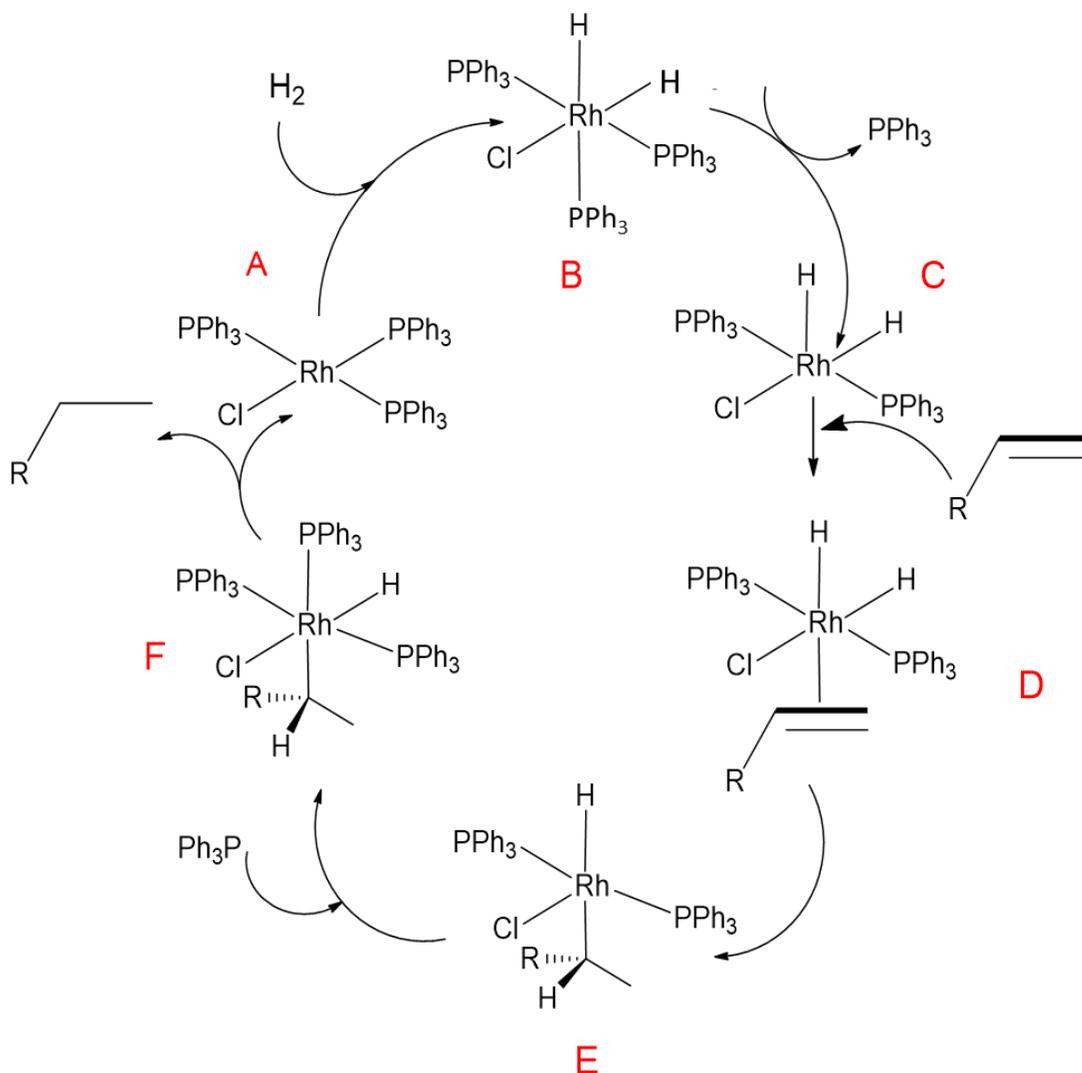


Figure 10. The catalytic cycle for the hydrogenation of terminal alkenes by Wilkinson's catalyst

### 1.8 Important aspects in the hydroaminomethylation reaction

For the HAM reaction to be successful regarding excellent yields and good selectivities, it is important to have control of different parameters such as temperature, CO/H<sub>2</sub> pressure, nature of the solvent, and ligand.

To achieve good yields in synthesizing amines, the HAM reaction is usually done at 90-130°C temperature and 30-60 bar of CO/H<sub>2</sub>, considered as medium pressure. These experimental conditions are somewhat more severe than the used for the hydroformylation reaction alone, but are consistent with a step determinant of the

speed in the hydrogenation reaction of the imines/enamines. The composition of CO/H<sub>2</sub> mixture depends on the experimental procedures and generally varies from 1:1 to 1:5. The use of ligands, mainly phosphorus-containing ligands, in the coordination sphere of metal has significant effects on the selectivity of the reaction (KALCK; URRUTIGOÏTY, 2018).

The catalytic phosphine-containing rhodium systems are well known to be efficient in the hydroformylation reaction (FRANKE; SELENT; BÖRNER, 2012). Some ligands widely used in this type of reaction are: Naphos, Iphos, Xantphos, and di-*t*-Bu-Xantphenoxaphos, see Figure 11. The steric hindrance of the ligands also allows converting an internal alkene into large amounts of the terminal aldehyde (l/b = 96:4) due to the isomerization reaction of the carbon-carbon double bond. The succession of the hydride transfers to the coordinated internal C=C double bond and the β-H elimination produces mainly the linear alkyl-rhodium, which is further carbonylated into the terminal aldehyde. Thus, these catalytic systems have been examined in the HAM reaction to provide attractive regioselectivity in linear amines up to 99:1% for terminal alkenes (SEAYAD et al., 2002) (AHMED et al., 2006).

The conventional systems of solvents used in the HAM reaction are being replaced to be in tune with sustainable chemistry, regarding to environmental. The most common alternatives reported in the literature are: 1- the biphasic systems and 2- the use of ionic liquids (KALCK; URRUTIGOÏTY, 2018).

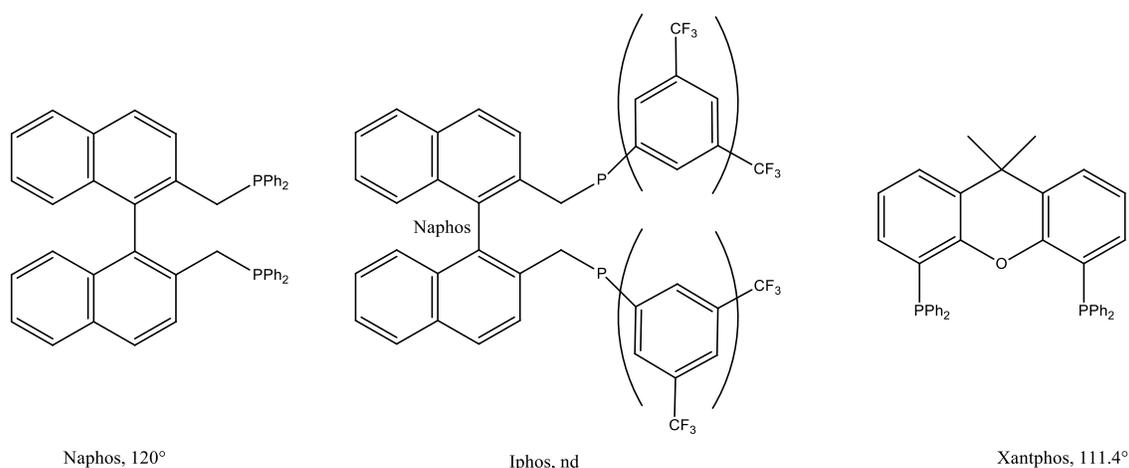


Figure 11. structure of the ligands commonly used in the hydroaminomethylation reactions

## **2. Objective**

The general objective of this project is to synthesize primary or secondary amines with potential bioactivity using estragole as a starting material, through the reaction of hydroaminomethylation, employing environmentally friendly solvents.

More specifically, the HAM of estragole will be studied with the following amine counterparts: di-n-butylamine, 4-methylpiperidine, morpholine, 2,6-dimethylmorpholine under various reaction conditions. Toluene will be employed as a benchmark solvent for HAM, and the results will be compared with greener solvents: ethanol, anisole, propyl anisole, *p*-cymene (figure 13).

### **3. Methodology**

#### **3.1 Commercial reagents**

Estragole (4-Allylanisole  $\geq 98\%$ ) Sigma Aldrich

p-Xylene (1,4-Dimethylbenzene for HPLC,  $\geq 99\%$ ) Sigma Aldrich

tris(2,4-di-*tert*-butylphenyl) phosphite (TBPP) Sigma Aldrich

Toluene anhydrous, 99.8% Sigma Aldrich

Ethanol  $\geq 99.8\%$  NEON

Anisole anhydrous, 99.7% Sigma Aldrich

Propyl anisole  $\geq 99\%$  Sigma Aldrich

*p*-Cymene  $\geq 99\%$  Sigma Aldrich

di-N-butylamine 98% VETEC

Morpholine 99% VETEC

4-Methylpiperidine 96% Sigma Aldrich

2,6-Dimethylmorpholine 97% Sigma Aldrich

The ligand used was the tris(2,4-di-*tert*-butylphenyl) phosphite (TBPP, see figure 15) from Sigma Aldrich. The TBPP remained stored under Argon atmosphere within a Glove Box type chamber (Model LabMaster, MBRAUN).

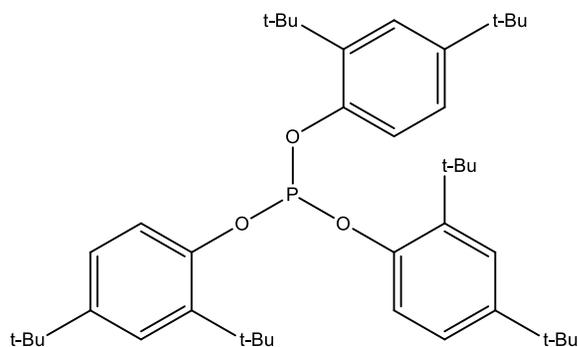


Figure 12. tris(2,4-di-tert-butylphenyl) phosphite (TBPP)

### **3.2 Treatment of reagents and solvents**

All solvents were previously treated and/or distilled according to (ARMAREGO, W. CHAI, C.,2003) and stored under inert atmosphere.

Propyl anisole and estragole were refluxed with magnesol/celite for 1 hour, followed by distillation under argon atmosphere in a kugelrohr apparatus.

Toluene was refluxed with sodium/benzophenone during 6 hours and distilled over inert argon atmosphere.

p-Cymene was refluxed with magnesol for 3 hours and then distilled in a kugelrohr apparatus

Ethanol was treated under reflux and in the presence of magnesium (5.0 g) and iodine (0.5 g), until all of the Mg turnings disappeared and the gray solution is formed (approximately three hours). After the formation of gray precipitate in solution, was refluxed for 3 hours, collected and transferred via cannula to a Kontes flask under argon.

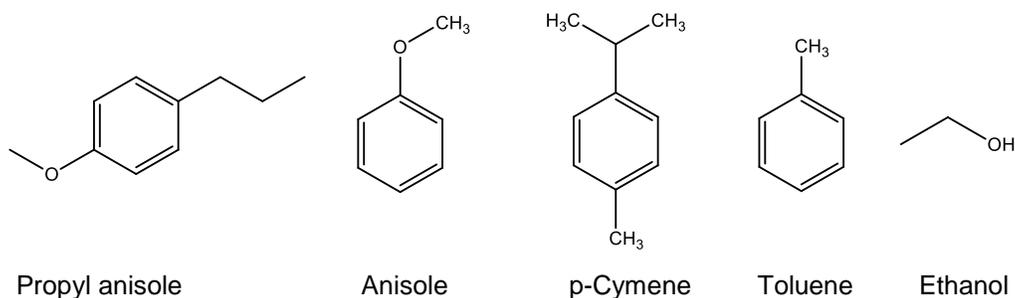


Figure 13. structure of reagents and solvent used in the HAM reactions

### 3.3 Structure of amines

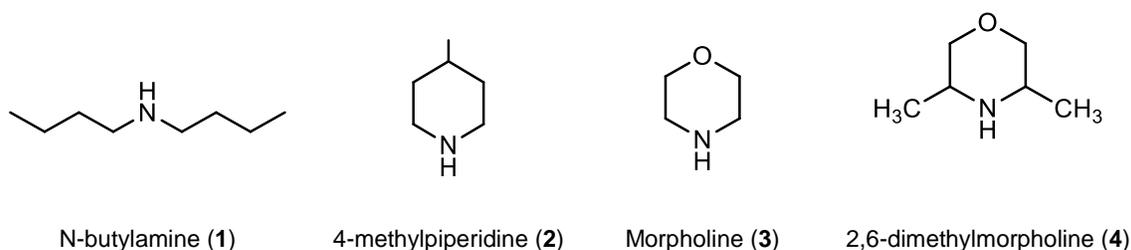


Figure 14 amines used in the HAM reactions

### 3.4 Synthesized reagents

#### **Synthesis of the bis[( $\mu$ -chloride)(1,5-cyclooctadiene) rhodium (I)] [Rh(cod)(Cl)]<sub>2</sub>**

The synthesis of the complex [Rh(cod)(Cl)]<sub>2</sub> was carried out following the process reported in literature (GIORDANO, G. CRABTREE, 1990). In a 100 mL Schlenk, under an inert argon atmosphere, containing a magnetic stirrer, 20 mL of a solution was added (5:1), 3 mL of 1,5-cyclooctadiene and 2.0 g of RhCl<sub>3</sub>·H<sub>2</sub>O (weighed in a glove box). A reflux condenser was coupled to the Schlenk, and connected to the Argon line. The reaction was allowed to reflux under magnetic stirring for 18 hours at a constant temperature of 80 °C, in an oil bath. At the end of the procedure, the Schlenk was cooled and the solid obtained was filtered in a sintered plate funnel, the Schlenk was washed with 5 mL portions of pentane. The solid in the funnel was washed with 3 portions of 10 mL of pentane and 5 mL portions of a cooled mixture of methanol-water (1:5) until no more chloride ions were detected in the filtrate through the test with a silver nitrate solution. Finally, the solid was dried in a vacuum desiccator for 24 hours. 85% yield was obtained.

### ***Synthesis of the bis[( $\mu$ - methoxyl)(1,5-cyclooctadiene) rhodium (I)] [Rh(cod)(OMe)]<sub>2</sub>***

Synthesis of rhodium catalyst [Rh(cod)(OMe)]<sub>2</sub> was made following the literature procedure (USON; ORO; CABEZA, 1985). 175 mg of [Rh(cod)(Cl)]<sub>2</sub> and 15 mL of dichloromethane were added to a 50 mL round bottom flask containing magnetic stirrer. The mixture was stirred until the solid dissolved. Then, a solution of 40 mg of potassium hydroxide in 15 mL of methanol was added to the balloon, which was sealed with a rubber septum and the system remained under stirring for 30 minutes at room temperature. The solvents were evaporated under vacuum and the solid formed was washed with 15.0 mL of water and 10.0 mL of methanol and separated with sintered glass funnel under vacuum. The solid in the funnel was washed with 10 portions of 5 mL of water, dried in a vacuum desiccator for 24 hours and recrystallized from a dichloromethane / hexane solution. The yield reached was 95%.

### ***3.5 Catalytic runs***

#### ***Hydroaminomethylation***

In a stainless steel bomb, pre-catalyst [Rh(cod)(OMe)]<sub>2</sub> (0.005 mmol), ligand TBPP (50 mmol) and a PTFE-covered magnetic stirring bar, were placed. The bomb was sealed, followed by three cycles of vacuum and argon. Then, the amine (11 mmol), estragole (10 mmol), *p*-xylene (5 mmol) and solvent (20 mL) were placed in a Schlenk under argon. Finally, all the solution was transferred from a Schlenk to the steel bomb by a syringe over inert argon atmosphere. The steel bomb was pressurized with 40 bar of CO/H<sub>2</sub> (1:3). The reaction proceeded with magnetic stirring and heating (80°C for the amines (1), (2) and 120°C for (3), (4) for 24h. Aliquots of 0.5 mL were taken periodically. Finally, at the end of the reaction the reactor was depressurized and the products were analyzed by gas chromatography.

### ***3.6 Treatment of data***

The conversion and product distributions calculations were made based on the peak area of the internal standard as shown in the equations below:

$$\text{conversion (\%)} = \frac{S_o - \left(\frac{P_o \times S}{P}\right) \times 100}{S_o} \quad \mathbf{eq(1)}$$

Where  $S_o$  and  $P_o$  are, respectively, the area the substrate and the area of the internal standard in the aliquot 0h.  $S$  and  $P$  are, respectively, the area of the substrate and the area of the internal standard in the aliquot to be calculated.

$$\text{product distribution} = \frac{A_i}{\sum_j A_{ij}} \times 100 \quad \mathbf{eq(2)}$$

Where  $A_i$  is the area of product  $i$  the chromatogram and  $\sum A_{ij}$  is the sum of all the products.

### **3.7 Gas chromatography**

The products were quantitatively analyzed by gas chromatography (GC) using a Shimadzu GC2010 instrument equipped with a split/splitless injection port (320 °C), flame ionization detector (320 °C) (FID).

5% phenylmethylsilicone Restek Rtx-5MS apolar capillary column (25 m x 0.25mm x 0.25 μm), using the followed conditions:

- Initial temperature: 50 °C for 3 min,
- Heating ramp: 20 °C/min up to 180 °C
- Heating ramp: 10 °C/min up to 250 °C
- Heating ramp 20 °C/min up to 310 °C for 5min
- Injector temperature: 320 °C
- Detector temperature: 320 °C
- Total pressure: 66KPa
- Split: 50, H<sub>2</sub> as flow gas

Polyethylene glycol (PEG) Restek polar capillary column (25 m x 0.25mm x 0.25 μm), using the followed conditions:

- Initial temperature: 80 °C for 3 min
- Heating ramp: 10 °C/min up to 220 °C for 20 min

- Injector temperature: 250 °C
- Detector temperature: 250 °C
- Total pressure: 70.6 KPa
- Split: 50, H<sub>2</sub> as flow gas

Qualitative analysis was made by GC fitted with a Restek RTX-5 MS capillary column (30 m x 0.25 mm x 0.25 μm) coupled with a mass spectrometer in a Shimadzu GC2010/QP2010, working at 70 eV.

### **3.8. Isolation of the products**

The separation of the products (amines) from the other components (substrate, internal standard, catalyst, ligand and solvent) was carried out through an acidic base extraction. To a separatory funnel were added the mixture and 3 portions of 50 mL of 0.1 mol L<sup>-1</sup> HCl solution at each extraction. In the aqueous phase was then basified with sodium bicarbonate and the amines were extracted with dichloromethane. The products from the di-butylamine, morpholine, and 4-methylpiperidine were isolated using a centrifugal thin layer chromatograph, (Chromatotron, Model 7924T) with a mixture of 90% DCM: 5% acetone: 5% MeOH (10% NH<sub>4</sub>OH) as a mobile phase.

### **3.9. Nuclear magnetic resonance spectroscopy**

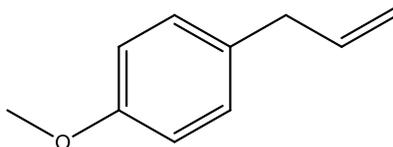
NMR spectra <sup>1</sup>H, <sup>13</sup>C and DEPT were obtained on a BRUCKER DRX-400 Avance spectrometer belonging to the Resonance Laboratory Nuclear Magnetic - LAREMAR, Department of Chemistry / UFMG. To perform the experiments, CDCl<sub>3</sub> was used as the deuterated solvent.

#### 4. Results and discussion

##### ***Hydroaminomethylation of estragole catalyzed by rhodium complex, using green solvents.***

Natural products among them, the terpenes play an essential role in human health about the prevention and treatment of inflammatory conditions. They are the most abundant and most widespread class of secondary metabolites. They are found in plants, mosses, algae, lichens, in insects, microbes or marine organisms. Some terpenes have been used for therapeutic purposes for centuries, as antibacterial, anti-inflammatory and antitumor agents. In recent decades the research in the clinical activity of these class of compounds has continuously increased as a source of pharmacologically interesting agents (HERAS; HORTELANO, 2009). It has been suggested that this type of phytotherapeutic compounds are anti-inflammatory because they can inhibit the production of TNF- $\alpha$  and IL-2, which are proteins from the group of cytokines released by the cells of the immune system involved in processes of inflammation and joint destruction secondary to rheumatoid arthritis, as well as in other pathologies (GONZÁLEZ-FLORES; RODRÍGUEZ; PARIENTE, 2014)

Estragole belongs to the family of monoterpenes, it is the constituent of essential oils of aromatic plants. It has been used for flavorings, and pharmaceutical formulations. This essential oil has relaxing properties, anticonvulsant, anesthetic, bradycardic, vasoactive, antioxidant and antimicrobial. (PONTE *et al.*, 2012) This compound has a terminal C=C double-bond in its structure, susceptible to be hydroformylated (first stage in the HAM) which makes it an attractive substrate for the HAM reactions.



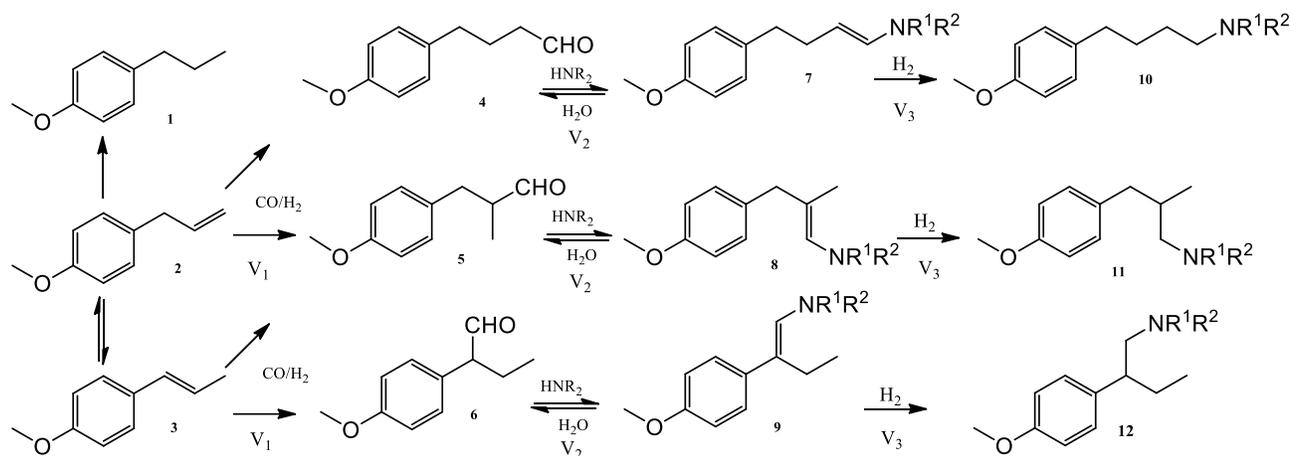
Structure of estragole

In the literature, only one report is found on the HAM of estragole catalyzed by rhodium complexes. The HAM reaction involving phosphohole ligands and di-butylamine, results in the formation of the linear and branched amines, almost

without double bond isomerization (OLIVEIRA *et al.*, 2015). The reaction was carried out in toluene, which is the typical solvent in this type of reaction.

In this work, alternative solvents will be employed on the HAM reaction of estragole with secondary amines with the purpose of replacing toluene, a solvent qualified as toxic according to REACH, by more environmentally friendly solvents such as ethanol, *p*-Cymene, anisole, and propyl anisole.

To extend the scope of the hydroaminomethylation reaction of estragole, the system studied is presented below, figure 15. In the reactions three isomeric amines were obtained **10**, **11** and **12** as final products, which were formed from the aldehydes with the formyl group in  $\gamma$ -,  $\beta$ - and  $\alpha$ -positions, respectively (**4,5** and **6** in Scheme 1) through intermediates enamines (**7-9**). Side products as alcohols were also observed.



7a-12a:  $R^1=R^2=-(CH_2)_3CH_3$

7b-12b:  $R^1=R^2=-(CH_2)_2CH(CH_3)(CH_2)_2-$

7c-12c:  $R^1=R^2=-(CH_2)_2O(CH_2)_2-$

7c-12c:  $R^1=R^2=-(CH_2)_2O(CH_2)_2.(CH_3)_2-$

Figure 15. Hydroaminomethylation of estragole with secondary amines

#### 4.1. The solvent effect in the hydroaminomethylation of estragole

According to GlaxoSmithKline (GSK) guide, ethanol, anisole, and *p*-Cymene are presented as good alternatives for chemicals processes (PRAT *et al.*, 2016). Propyl anisole has not reported so far as a solvent in the HAM reaction.

*p*-Cymene is a natural compound, present in essential oils, mainly in the genus *Thymus*, and is considered non-toxic. Today, the large-scale production of *p*-Cymene is based on petrochemicals, but it is recently recognized its potential as a renewable solvent once it can be easily obtained from renewable sources also available on a large scale (CLARK; MACQUARRIE; SHERWOOD, 2013). The aromatization of *d*-limonene obtained from the citrus industry produces *p*-Cymene in high yields, which can reach 500 000 tons per year. Therefore, *p*-Cymene has a good potential to be a sustainable alternative to aromatic solvents such as benzene or toluene, and it is expected to increase its production using renewable starting materials.

Anisole is also recommended as a green solvent by the GSK guide. It is present in essential oils such as *Tagetes parryi* (LV; YANG, 2012)

Propyl anisole is not ranked in recent guides as a solvent, but considering that it can be obtained from natural sources, e.g., in the essential oil *Pimpinella anisum*, or by hydrogenation of estragole, it was also examined in this study. Both anisole and propyl anisole can be obtained from lignin, a stream of low-value residual biomass that is generated in the manufacture of pulp and cellulosic ethanol plants (TIAN *et al.*, 2017).

Finally, ethanol has many advantages to be used as a solvent in this type of reactions. One of them is due to the easy obtainment from the renewable raw material such as sugar cane, through fermentation. This compound is produced globally on a large scale and low cost. The leading world producers are the United States and Brazil with 58% and 28% respectively (“Industry Statistics – Renewable Fuels Association”, 2017). According to the chem21 solvent guide, ethanol is recommended as a green solvent with a score close to that of water (PRAT *et al.*, 2016).

#### **4.2. Hydroaminomethylation of estragole with di-n-butylamine**

The results of the HAM of estragole with di-n-butylamine are present in Table 3. The yields of amines **10a** and **11a** in ethanol 83% and *p*-Cymene 87% were better than in toluene 75%. On the other hand, in anisole 63% and propyl anisole 71% the yields were lower than in toluene. Besides, the reactions in toluene, anisole, *p*-Cymene and propyl anisole presented alcohols in significant amounts (Table 3, runs 1-4). This can be attributed to the fact that original di-n-butylamine was partially decomposed to give the nonreactive (toward the aldehydes) tri-n-butylamine and decreased the selectivity for HAM products. In this runs, according to the GC analysis, no more di-n-butylamine was left in these solvents after 2 hours. Thus, the remaining aldehydes did not react with the di-n-butylamine to follow the HAM direction, but instead were hydrogenated to corresponding alcohols.

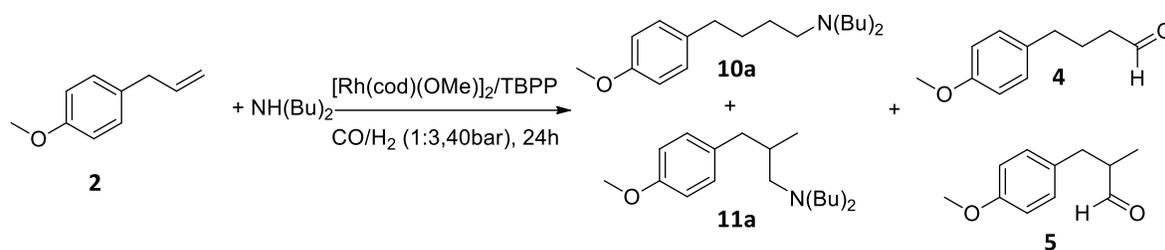


Table 3. Solvent effect in the hydroaminomethylation of estragole **2** with di-*n*-butylamine,

Run	Solvent	Aldehydes (%)	Enamine (%)	Alcohols (%)	Amines (%)		
		<b>5</b>	<b>9a</b>		<b>10a</b>	<b>11a</b>	<b>Total</b>
<b>1</b>	Toluene	0	0	25	58	17	75
<b>2</b>	<i>p</i> -Cymene	0	0	13	65	22	87
<b>3</b>	Anisole	0	4	28	45	18	63
<b>4</b>	Propyl anisole	0	5	24	50	21	71
<b>5</b>	Ethanol	17	0	0	58	25	83

Conditions: **2** ( $10 \cdot 10^{-3}$  mol); di-*n*-butylamine ( $11 \cdot 10^{-3}$  mol);  $[\text{Rh}(\text{cod})(\text{OMe})_2]_2$  ( $5 \cdot 10^{-6}$  mol); TBPP ( $5 \cdot 10^{-5}$  mol); solvent (20 mL); 40 bar ( $\text{CO}/\text{H}_2$  1:3); 80 °C, 24 h. Conversion: >99%

The decomposition of di-*n*-butylamine was minimized in ethanol. First, the decomposition of di-*n*-butylamine into tri-*n*-butylamine was not observed even after 24 hours of reaction. Second, no formation of undesired alcohols was observed, although the concentration of aldehydes was higher in ethanol than in other solvents at the same reaction time (Table 3, run 5). Therefore, in this solvent classified as the greenest among those tested, there are two beneficial factors: the stability of the original amine and the aldehydes under the reaction conditions ensured excellent selectivity for the HAM products in ethanol. It is also important that no concomitant formation of diethyl acetals has been observed in ethanol solutions under the conditions employed. The formation of diethyl acetals has already been observed in previous hydroformylation studies of our research group. Indeed, the aldehydes were stable in ethanol solutions to both in relation to the acetalization by the solvent and the hydrogenation catalyzed by Rh. The last step of HAM, the hydrogenation reaction was not completed in anisole and propyl anisole, because 4% and 5% respectively of enamines remained even after 24 h of reaction.

Also, the effect of the solvent for the HAM was studied through the kinetic curves that are presented in Figure 17. It is observed that the hydroformylation step was fast in the five solvents. At the first 30 minutes the transformation of all substrate was nearly complete in toluene, anisole and propyl anisole, 63% in *p*-Cymene and 85% in ethanol. The hydroformylation must be fast (stage one), to avoid the isomerization of the substrate (**2**), which is confirmed by the formation of aldehydes **4** and **5** as main reaction products in all cases. As expected, the branched aldehyde is more challenging to condensate with the amine, due to the higher steric hindrance as compared to the linear aldehyde. The intermediate enamines **7a** and **8a** were detected in the five experiments in small amounts. However, the combination between the primarily formed aldehydes with di-*n*-butylamine was the slowest step of the whole HAM process in all the solvents tested. This observation disagrees to what is reported in literature, where they report that the slow step of the reaction is the hydrogenation (last stage in HAM) of the enamine intermediates. (KALCK; URRUTIGOITY, 2018). Comparing *p*-Cymene figure (b) with toluene (a), the kinetics of the reaction for obtaining the main products was faster in *p*-Cymene than toluene. In toluene, in the first 30 minutes the yield for the aldehyde **5** was twice that of *p*-Cymene, indicating that  $V_2$ , (condensation of amine) is faster in *p*-Cymene. In toluene after 6 hours of reaction, the reduction of aldehydes to alcohols was the double of that in *p*-Cymene. In *p*-Cymene after 2 hours the maximum yield for the amines **10a** and **11a** was reached. This is a promising result since the use of *p*-Cymene as a solvent in HAM reactions is not reported in the literature.

The tendency of estragole to the double bond isomerization was also dependent on the solvent nature. Relatively high concentrations of anethole 15% were detected and anisole solutions at short reaction times. Nevertheless, the amine derived from  $\alpha$ -aldehyde **5** (compound **12a** in Scheme 1) was observed only in anisole solutions and only in small amounts. Therefore, the primarily formed anethole was mainly consumed through the conversion back to estragole, rather than through the direct hydroformylation which would give aldehydes **4** and **5**.

According to the literature, the use of bulky ancillary ligands avoids secondary reactions such as isomerization of the substrate, due to steric hindrance (BÖRNER, A., FRANKE, R. 2016). A suggestion to explain the isomerization of the substrate with this solvent is that anisole can be coordinated to the metal center through a  $\eta^6$  bond (RICHTER-ADDO; HUNTER; WICHROWSKA, 1990), and compete with the ligand TBPP, because anisole has a lower steric hindrance, affecting active sites of the catalyst and discourages the migratory insertion of the CO molecules. Thus favoring the  $\beta$ -elimination of the hydride, and forming the isomer anethole, (see Figure 16). In the first 6 hours, all the intermediaries are observed. After 24 hours, the yields for the amines of interest **10a** and **11a** were 63%. In the reaction in anisole it is possible to see the enamine intermediate, showing that  $V_3$ , hydrogenation step was slower than in toluene, because 4% branched enamine remained in solution.

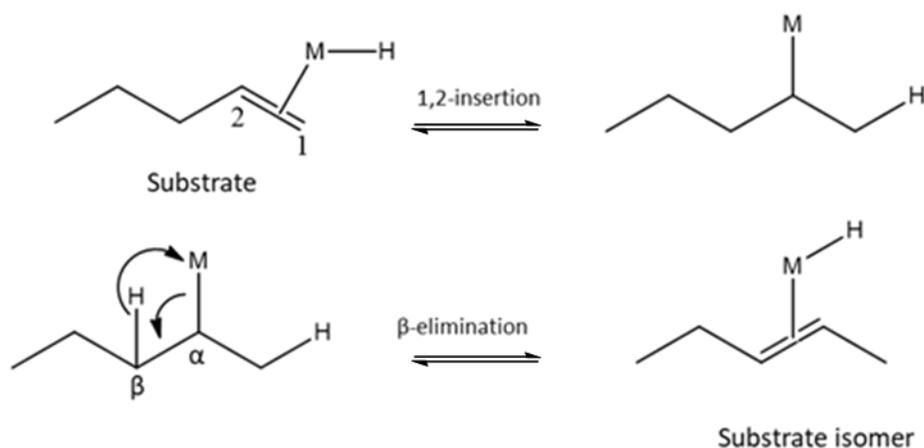


Figure 16. Mechanism of isomerization of substrate

In the case of the propyl anisole, it was observed that in the first 30 minutes the formation of alcohols was favored 20%. Also, the linear aldehyde **4** reacted slower in this solvent than toluene, as it had not been consumed, even after 6 hours of reaction.

In the case of ethanol, the branched **5** and linear **4** aldehydes were obtained in a 1:1 ratio, a fact that was not observed in any of the other solvents. This indicates that  $V_2$ , the condensation reaction of these with di-*n*-butylamine is slower in this solvent. Besides, the presence of all intermediates is observed, even in 6 hours of reaction. Thus, the reaction is slower in ethanol than in toluene and although the rate of the

aldehyde consumption (the second step of the HAM process) was lower than in other solvents, the aldehydes were converted exclusively to the desired amines, and the decomposition of di-n-butylamine and the reduction of the aldehydes to the corresponding alcohols were avoided. In this sense, ethanol represents a potential substitute for toluene in hydroaminomethylation reactions. First, because it is classified as the greenest, and also recommended to use as an alternative solvent according to a recent guide (PRAT *et al.*, 2016). Another significant advantage is that the ethanol is produced on a large scale from the renewable raw material such as sugarcane (“Industry Statistics – Renewable Fuels Association”, 2017)

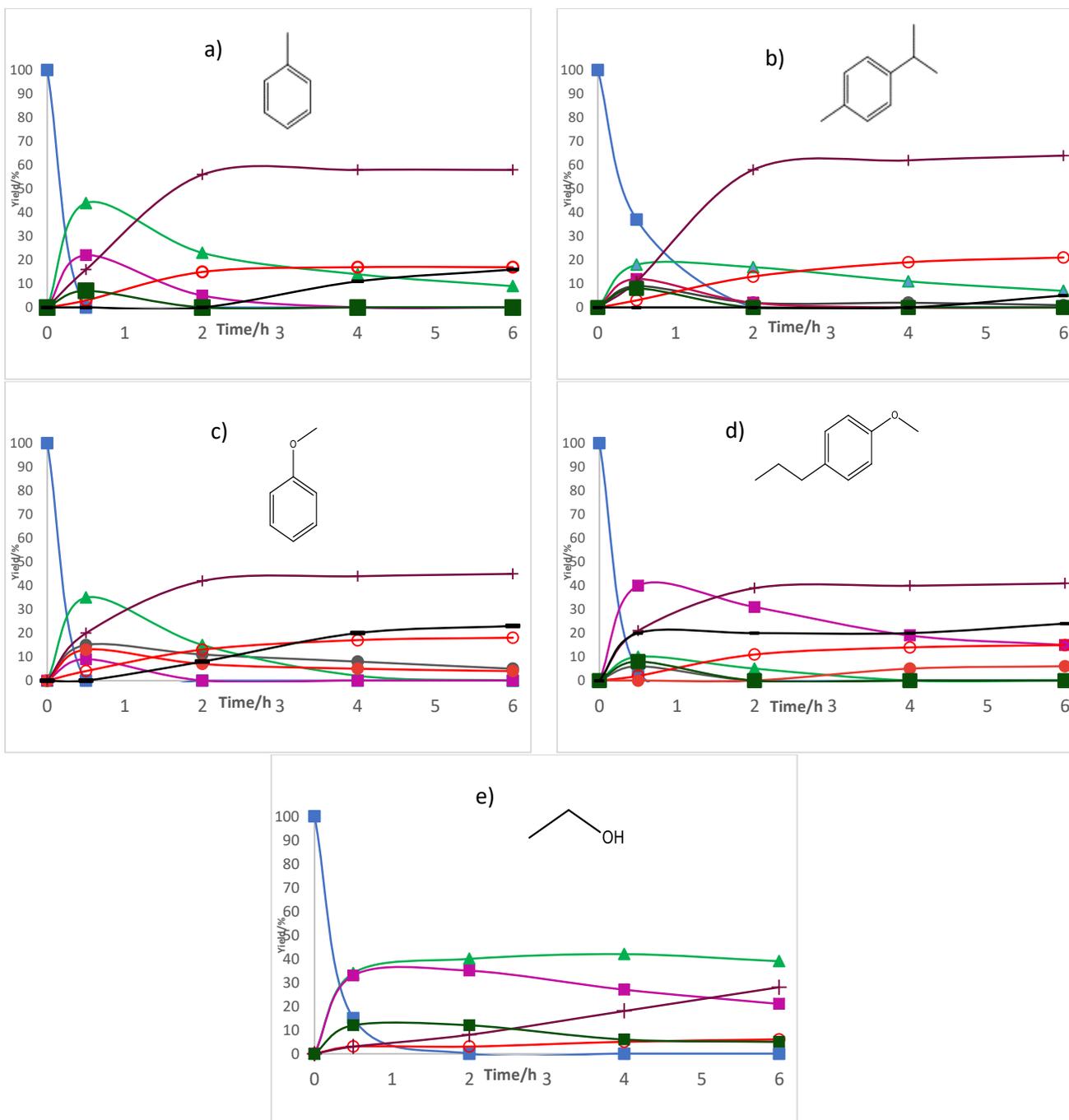


Figure 17. Kinetic curves for the HAM of estragole with di-butylamine a) Toluene, b) p-cymene, c) Anisole, d) Propyl-anisole, e) Ethanol

—■— Estragole(2) —●— Anethole(3) —■— Aldehyde  $\gamma$ (4) —▲— Aldehyde  $\beta$ (5) —+— Amine  $\gamma$ (10a) —○— Amine  $\beta$ (11a) —■— Enamine  $\gamma$ (7a) —●— Enamine  $\beta$ (8a) —— Alcohols

### 4.3. Hydroaminomethylation of estragole with 4-methylpiperidine

The HAM of estragole with 4-methylpiperidine gave excellent yields of novel amines **10b** and **11b** (Table 4, runs 1-5). All the solvents tested, *p*-Cymene, anisole, propyl anisole, and ethanol, proved to be excellent green alternatives to the conventional toluene. *p*-Cymene and anisole presented a performance better to that of toluene. The reduction of aldehydes to alcohols was only observed in toluene 10% and *p*-Cymene 4%. The reactions in ethanol showed important benefits for the reaction selectivity due to the lower activity of the rhodium catalyst in the undesirable isomerization of the substrate and the hydrogenation of the intermediate aldehyde. One challenge of these reactions is the regioselectivity control to reach a specific amine at the end of the reaction. Due to the similar physical properties of the isomeric products, it is difficult to separate and purify them. As is well known, the regioselectivity of products in the HAM reactions is determined at the first step, hydroformylation, which is mainly governed by the ligand influence, and in most cases, the linear product predominates (CROZET; URRUTIGOÏTY; KALCK, 2011). Nevertheless, the ratio observed with 4-methyl-piperidine for **10b** and **11b** was almost 50:50 for all solvents studied (Table 4, runs 1-5).

This contrast with previous works employing other amines, where the regioselectivity for the products linear and branched were 70:30 respectively (AHMED *et al.*, 2006)(OLIVEIRA *et al.*, 2015). Unlike reactions with di-*n*-butylamine (Figure 17) it was possible to observe high concentrations of the corresponding enamines in the intermediate reaction stages, indicating that the hydrogenation of enamines derived from 4-methylpiperidine it happened slowly.

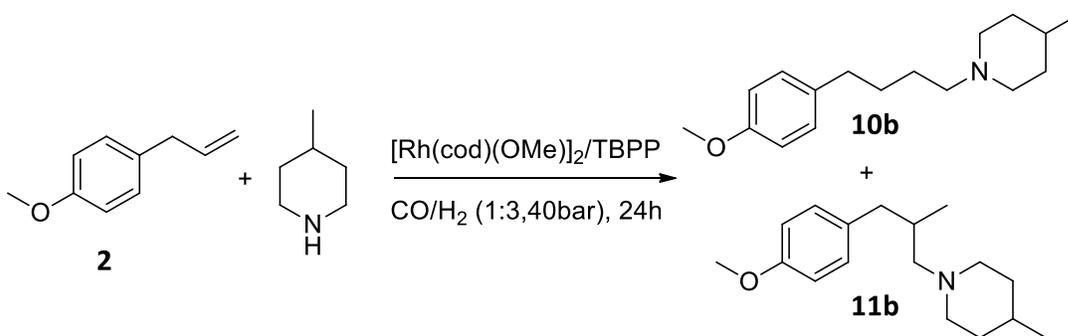


Table 4. Solvent influence in the hydroaminomethylation of estragole **2** with 4-methylpiperidine

Run	Solvent	Alcohols(%)	Amines(%)		
			<b>10b</b>	<b>11b</b>	total
1	Toluene	10	45	42	87
2	<i>p</i> -Cymene	0	47	48	95
3	Anisole	4	52	44	96
4	Propil anisole	0	51	41	92
5	Ethanol	0	51	46	97

Conditions: **2** ( $10 \cdot 10^{-3}$  mol); 4-methylpiperidine ( $11 \cdot 10^{-3}$  mol);  $[\text{Rh}(\text{cod})(\text{OMe})]_2$  ( $5 \cdot 10^{-6}$  mol); TBPP ( $5 \cdot 10^{-5}$  mol); solvent (20mL); 40 bar ( $\text{CO}/\text{H}_2$  1:3); 80 C; 24h. Conversion: >99%

In Figure 18 the kinetic curves were compared with four alternative solvents. Comparing *p*-Cymene with toluene, it is clearly observed that the total consumption of estragole (**2**) happened in the first 2 hours in both cases. In the first 30 minutes of reaction, the formation of the main intermediates is observed. The consumption of the branched aldehyde **5** is slow in both solvents as expected, due to its steric hindrance.

The linear enamine **7b** is converted to its corresponding amine **10b** at a low speed in *p*-Cymene, since this is the limiting stage of the HAM reaction (KALCK; URRUTIGOÏTY, 2018). For the others intermediates, the behavior was similar in both solvents. For toluene and *p*-Cymene, in 24 hours, all intermediates were consumed, and the maximum yield for the amines **10b** and **11b** was greater than 90%, in a ratio of almost 50:50 for linear and branched amines in both cases.

Comparing anisole (c) with toluene (a), it is observed that the hydrogenation of the linear enamine **7b** intermediate is faster in anisole. Accordingly, the maximum yield 52% for the amine **10b** was obtained in a shorter time, 6 hours, while in toluene, after 6 hours of reaction, only 36% of **10b** was formed. Thus, anisole showed to be a better solvent for this couple of reactants.

In propyl anisole, the consumption of linear enamine **7b** was faster than in toluene, what is reflected in the rate of formation of amine **10b**. In 2 hours of reaction, 25% of the amine **10b** was obtained in propyl anisole, while in toluene only 9% of **10b** was formed. The formation of the branched amine is slow in both solvents, as expected. The maximum yield was achieved only at 24 hours of reaction in both solvents.

In ethanol (e), it was observed that the consumption rate of the linear aldehyde **4** was lower than in toluene (18% in ethanol vz. 4% in toluene in 30 min of reaction), showing that amine condensation is slower in ethanol.

In general, the activity and selectivity of the catalyst to synthesize the amines **10b** and **11b** was better in the four alternative solvents than in toluene. This is a promising result since it opens up the possibilities of hydroaminomethylation reactions in more environmentally friendly solvents.

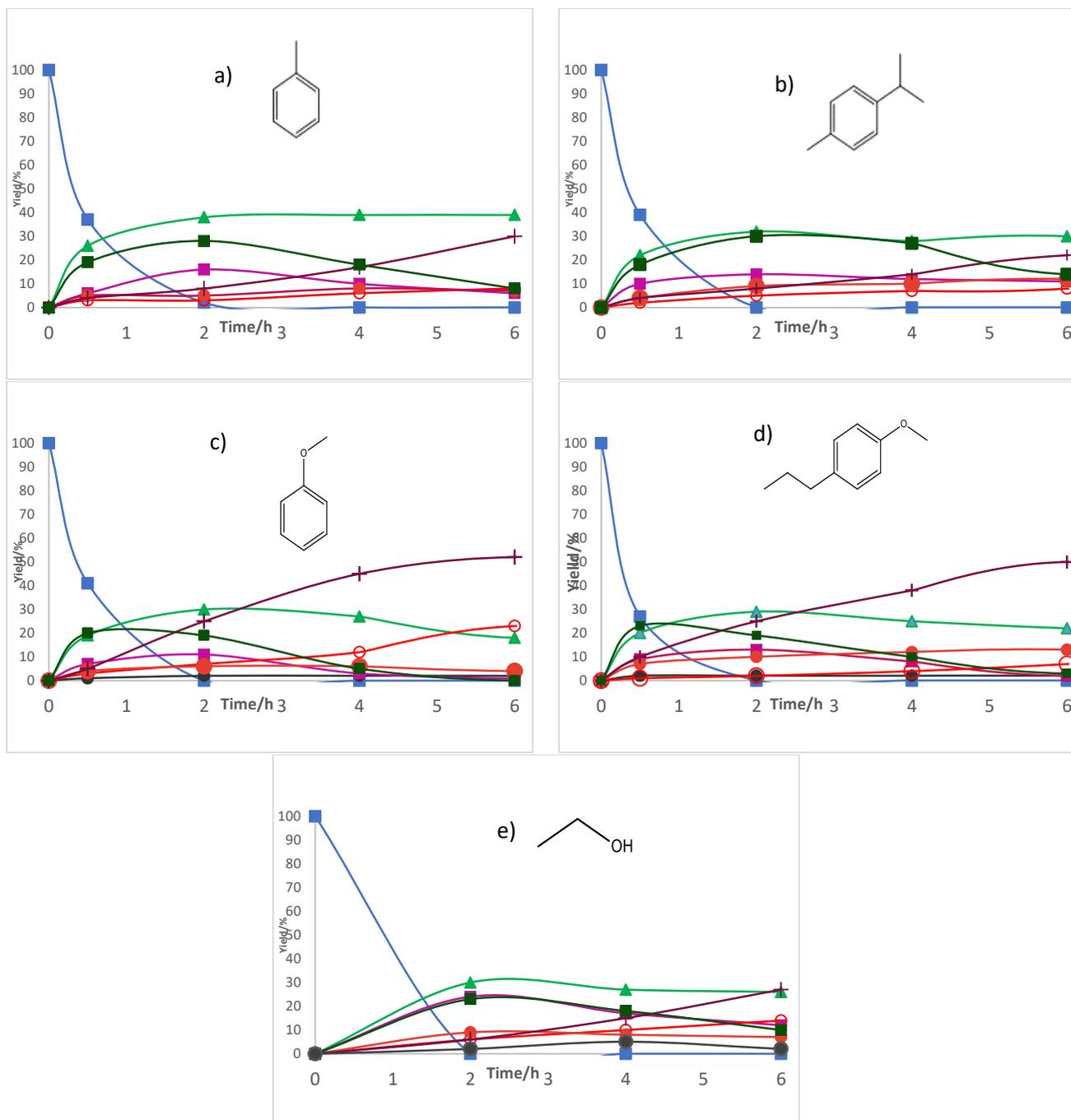


Figure 18. Kinetic curves for the HAM of estragole with 4-methylpiperidine a) Toluene, b) p-cymene, c) Anisole, d) Propyl-anisole, e) Ethanol

—■— Estragole(2) —●— Anethole(3) —■— Aldehyde  $\gamma$ (4) —▲— Aldehyde  $\beta$ (5) —+— Amine  $\gamma$ (10a) —○— Amine  $\beta$ (11a) —■— Enamine  $\gamma$ (7a) —●— Enamine  $\beta$ (8a) ——— Alcohols

#### 4.4. Hydroaminomethylation of estragole with morpholine

Temperature plays an important role in the conversion rate of the substrate. In general, it can be suggested that the rate of a reaction increases with increasing temperature (the increase of 10 degrees in temperature essentially doubles the rate of the reaction, according to Arrhenius equation). Higher temperature increases the average energy of the molecules, therefore increasing the number of collisions among them and allowing that the molecules can reach the activation energy necessary for the reaction takes place (SCHWAAB; PINTO, 2007). In this sense, the influence of temperature on the HAM of estragole with morpholine was studied, since at 80 °C (temperature established for previous experiences of our research group) (OLIVEIRA *et al.*, 2015) the reaction was too slow. In Table 5, runs 1-3, the results with temperature variation from 80 °C to 120 °C are shown. At 80 °C, the yields for the amines of interest **10c** and **11c** was low 21% and 43% of aldehydes remained. Also, 21% of enamine was not hydrogenated. At 100 °C, the yield was favored for the amines 89%, however, 11% of aldehyde remained. To increase the yield of the products of interest, the reaction was tested at 120 °C, which improved the yield from 84%

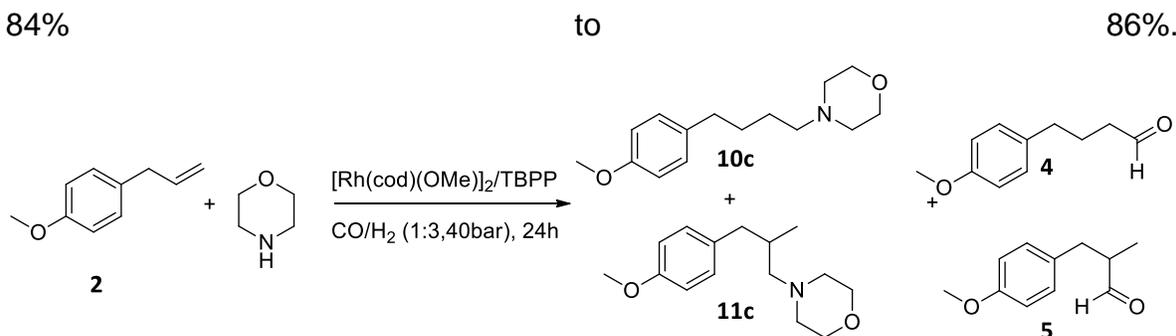


Table 5. Temperature influence in the hydroaminomethylation of estragole 2 with morpholine

Run	Temperature (°C)	Aldehydes (%)		Enamine (%)	Amine (%)		
		<b>4</b>	<b>5</b>	<b>(7+9)c</b>	<b>10c</b>	<b>11c</b>	<b>total</b>
1	80	22	36	21	15	6	21
2	100	0	14	0	54	30	84
3	120	0	12	0	58	28	86

Conditions: **2** ( $10 \cdot 10^{-3}$  mol); morpholine ( $11 \cdot 10^{-3}$  mol);  $[\text{Rh}(\text{cod})(\text{OMe})_2]$  ( $5 \cdot 10^{-6}$  mol); TPPB ( $5 \cdot 10^{-5}$  mol); ethanol(20mL); 40 bar (CO/H<sub>2</sub> 1:3); 24h. Conversion:>99%

Observing the Figure 17, it is clear that the conversion of the substrate is rapid: in the first 30 min, it was completely consumed. However, at 80 °C the stages of amine condensation with aldehyde (V<sub>2</sub>) and the hydrogenation of the enamine (V<sub>3</sub>) intermediates were slow. At 100 °C, the three steps of the HAM were faster. However, the maximum yield for the products of interest (**10c-11c**) was only reached after 24 hours and 14% of aldehydes remained unreacted.

At 120 °C, the reaction is much faster. The consumption of the enamine intermediate (V<sub>3</sub>) was completed in 2 hour. Also, the maximum yield for the amines of interest was reached in 4 hours. In this sense, 120 °C was chosen to perform the reactions for the solvent study with morpholine and 2,6-dimethylmorpholine.

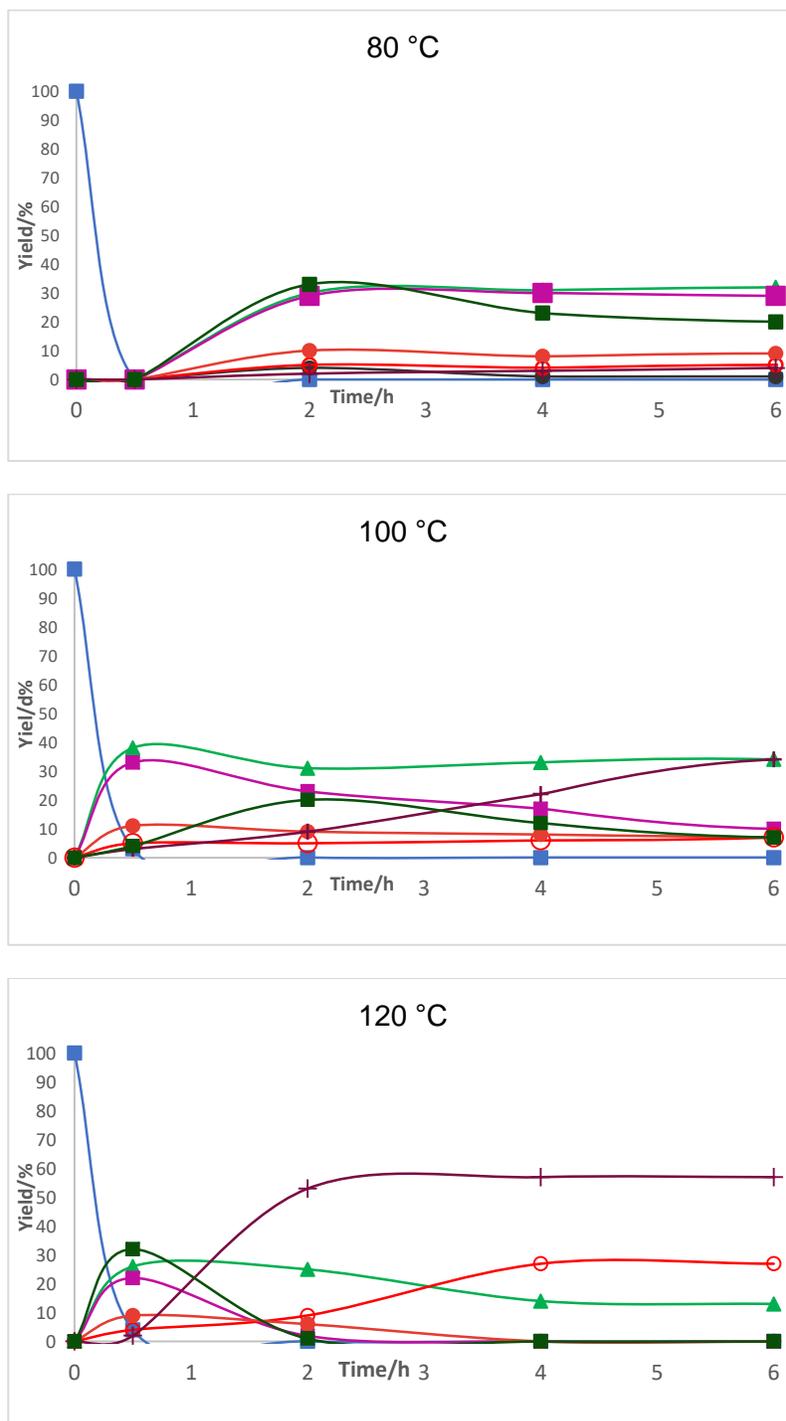


Figure 19. Temperature influence for the HAM of estragole with morpholine (a) 80 °C, (b) 100 °C, (c) 120 °C

—■— Estragole(2) —●— Anethole(3) —■— Aldehyde  $\gamma$ (4) —▲— Aldehyde  $\beta$ (5) —+— Amine  $\gamma$ (10a) —○— Amine  $\beta$ (11a) —■— Enamine  $\gamma$ (7a) —●— Enamine  $\beta$ (8a) —— Alcohols

The reactions with morpholine were performed at 120 °C to ensure the efficient hydrogenation of the corresponding enamines (Table 6, runs 1-5). In all the solvents

tested, excellent combined yields of amines were obtained, with their isomeric composition being dependent on the solvent nature. In toluene and anisole, the substrate isomerization followed by the hydroformylation of anethole was significant (Table 6, runs 1,3).

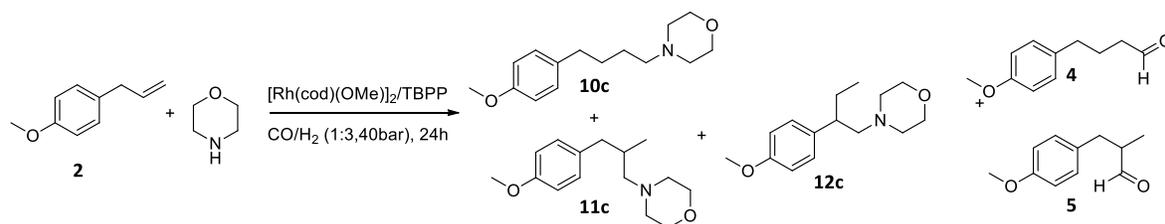


Table 6. Solvent influence in the hydroaminomethylation of estragole 2 with morpholine

Run	Solvent	Aldehydes (%)		Enamine (%)	Alcohols (%)	Aminas(%)			Total
		4	5			10c	11c	12c	
1	Toluene	5	3	0	7	49	28	4	81
2	<i>p</i> -Cymene	1	5	0	0	60	29	0	89
3	Anisole	0	5	0	5	45	29	9	83
4	Propyl anisole	0	0	33	0	35	30	0	65
5	Ethanol	0	12	0	0	58	28	1	87

Conditions: **2** ( $10 \cdot 10^{-3}$  mol); morpholine ( $11 \cdot 10^{-3}$  mol);  $[\text{Rh}(\text{cod})(\text{OMe})_2]_2$  ( $5 \cdot 10^{-6}$  mol); TPPB ( $5 \cdot 10^{-5}$  mol); solvent (20 mL); 40 bar (CO/H<sub>2</sub> 1:3); 120 °C; 24h. Conversion: >99%

As a result, the contribution of branched amines **11c** and **12c** increased, which was not observed in any of the previous experiments. On the other hand, in *p*-Cymene, propyl anisole and ethanol the isomerization of estragole was much less significant so that the amine product was largely consisted of only two compounds: **10c** and **11c** (Table 6, runs 2,4 and 5). Also, In ethanol 87% and *p*-Cymene 89% the yield for the amines **10c** and **11c** was better than in toluene 81%. The formation of side products such as alcohols was only observed in toluene 7% and anisole 5%.

Using propyl anisole as solvent a lower yield 65% was obtained for the amines **10c** and **11c**, in contrast with toluene 82%. Also, 33% of the enamine was not hydrogenated. Besides, it was observed that aldehydes remained in all solvents. This is attributed to the fact that the quantity of amine was not enough to react with

all the aldehyde and form the corresponding enamine, because this was consumed quickly in the first two hours of reaction.

The kinetics of the reactions are presented in Figure 18. Total substrate consumption was reached in the first 30 minutes in all solvents. In the case of *p*-Cymene (b), the reaction is faster than in toluene (a), since it was not possible to see the set of intermediates. Only a small amount of branched 5% and linear 8% aldehydes were observed after 24 hours of reaction. Besides, no enamine was observed, which confirm that all the reduction of enamine is fast. In toluene, in the first two hours all the reaction intermediaries were observed. In both cases, the maximum yield of the products of interest was reached in 2 hours.

In anisole (c), it was also observed that the reaction is faster than in toluene because only small amounts of intermediaries was observed. These are produced and consumed so quickly in this solvent, that only 5% branched aldehyde and 8% linear were observed. The formation of the anethole isomer was favored in the first 30 min of the reaction 30%, which was consumed quickly after 2 hours. The maximum yield for the amines **10c** ,**11c** ,**12c** was achieved in 2 hours in anisole and toluene.

In propyl anisole, the formation of the anethole isomer was favored in the first 30 min of reaction. The amine condensation stage was faster than in toluene, because intermediate aldehydes were not observed in this solvent. However, the hydrogenation of the linear enamine **7c** intermediate was not favored, with 33% of this remaining. After 4 hours the maximum yield of the amines of interest **10c** and **11c** was achieved. A suggestion for this observation is that the catalyst in this solvent is deactivated because after 4 hours no change in the product distribution was observed. There was no increase in the yield of the products, nor was the linear enamine hydrogenated.

As described for the other amines, in ethanol, the kinetics of the reaction in the first hours is slower than in toluene. It is possible to see all the intermediates (aldehydes and enamines), but at the end of the reaction (24 hours) the yields for the main products **10c** and **11c** is better than in toluene. Thus, *p*-Cymene, anisole and ethanol were better solvents than toluene, which opens the possibility of performing

hydroaminomethylation reactions not only in more efficient solvents, but also in environmentally friend solvents (PRAT *et al.*, 2016)

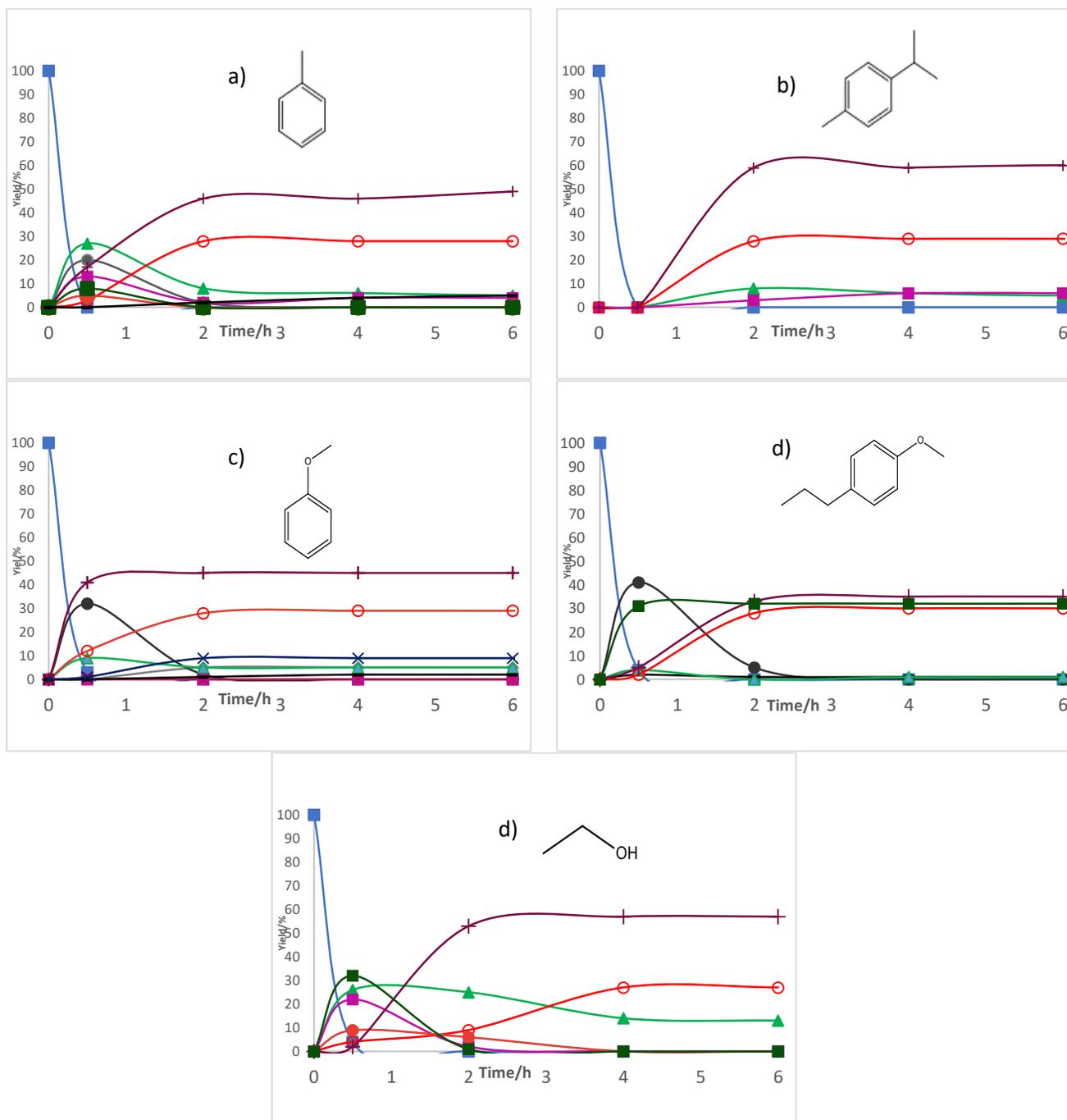


Figure 20. Kinetic curves for the HAM of estragole with morpholine a) Toluene, b) p-cymene, c) Anisole, d) Propyl-anisole, e) Ethanol

■ Estragole(z) ● Anethole(s) ■ Aldehyde γ(4) ▲ Aldehyde β(5) + Amine γ(10a) ○ Amine β(11a) ■ Enamine γ(7a) ● Enamine β(8a) — Alcohols X- Amine α(12c)

#### 4.5. Hydroaminomethylation of estragole with 2,6-dimethylmorpholine

The 2,6-dimethylmorpholine was purchased with 97% purity, but when carrying out the reactions, it was observed through gas chromatography (GC) the formation of 4 main products, two linear amines (see Figure 18 (c)) and two branched amines (see Figure 19 (d)) indicating that this came as a mixture of diastereomers, (see Figure 19, (a) and (b)). In this sense, to simplify the treatment of the data, the yields of the diastereomeric branched and linear amines were added together. An analogous procedure was made for the intermediate aldehydes and enamines.

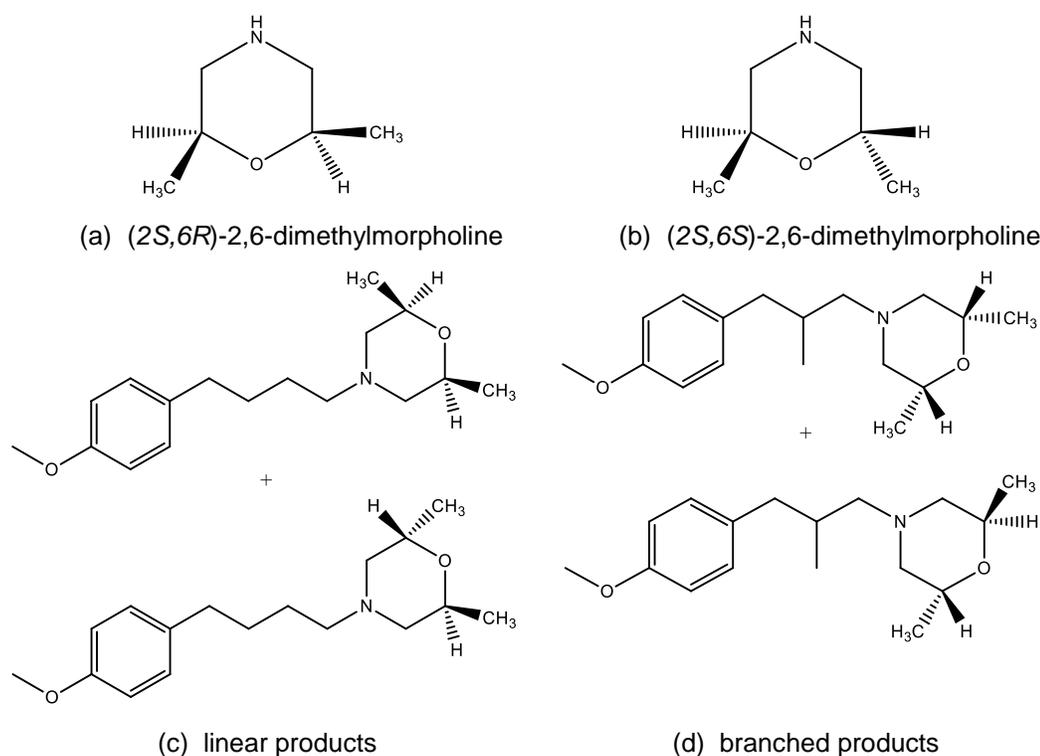


Figure 21. (a) and (b) starting reagents, (c) and (d) linear and branched products.

The results are presented in Table 7, runs 1-5. Both ethanol 91% and anisole 91% shown better yield for the amines **10d** and **11d** than toluene 88%, while the anisole 85% was similar to toluene. In the case of propyl anisole, the hydrogenation step of the enamine intermediate was not favored, leaving 34% of it. Also, in all cases, the branched aldehyde remained unreacted.

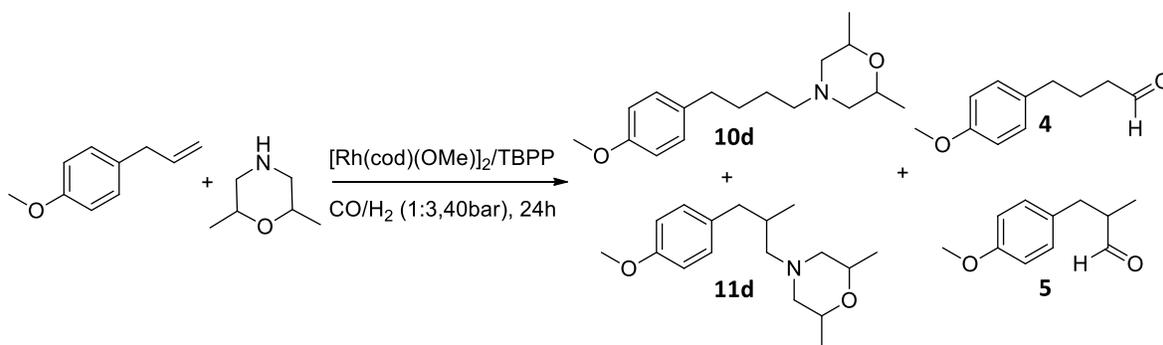


Table 7. Solvent influence in the hydroaminomethylation of estragole **2** with 2,6-dimethylmorpholine

Run	Solvent	Aldehyde (%)		Enamine (%)		Amines (%)	
		<b>5</b>	<b>9</b>	<b>10d</b>	<b>11d</b>	<b>total</b>	
<b>1</b>	Toluene	10	0	61	27	88	
<b>2</b>	<i>p</i> -Cymene	11	0	63	22	85	
<b>3</b>	Anisole	9	0	63	28	91	
<b>4</b>	Propyl anisole	5	34	50	11	61	
<b>5</b>	Ethanol	7	0	65	26	91	

Conditions: **2** ( $10 \cdot 10^{-3}$  mol); 2,6-dimethylmorpholine ( $11 \cdot 10^{-3}$  mol);  $[\text{Rh}(\text{cod})(\text{OMe})_2]$  ( $5 \cdot 10^{-6}$  mol); TPPB ( $5 \cdot 10^{-5}$  mol); solvent (20 mL); 40 bar ( $\text{CO}/\text{H}_2$  1:3); 120 °C, 24h. Conversion: >99%

The kinetics of the reactions were also studied with 2,6-dimethylmorpholine, see Figure 22. Comparing the reactions in *p*-Cymene and toluene, the behavior was similar. In the first 2 hours, in both solvents, the intermediates aldehydes **4d**, **5d**, and enamine the **7d** were observed. The intermediate **7d** was completely consumed after 2 hours of reaction, both in *p*-Cymene and toluene. The consumption of the branched aldehyde was slow in both solvents, remaining 10% in toluene and 11% in *p*-cymene. It was also determined that the maximum yield for the products of interest was reached in 2 hours of reaction.

The reaction in anisole had a similar behavior to that described above. Unlike the propyl anisole, this favored the formation of the isomer anethole in the first 30 min of reaction, which was consumed entirely after 2 hours. On the other hand, the hydrogenation of the branched enamine **8d** was not favored in this solvent, remaining 34% of it. As a consequence, a low yield for the branched amine 11% was

observed. So, in this solvent, the last stage (hydrogenation) is not favored, and furthermore, it can be assumed that the catalyst is deactivated after 4 hours since the product distribution does not change after this time.

The reaction in ethanol was slower than in toluene, as in the previous cases. All intermediates were observed in greater proportion than in toluene, which indicates that in ethanol the rate of the reaction is lower. In 6 hours, the maximum yield for the amines **10d** and **11d** was reached that was better than in toluene.

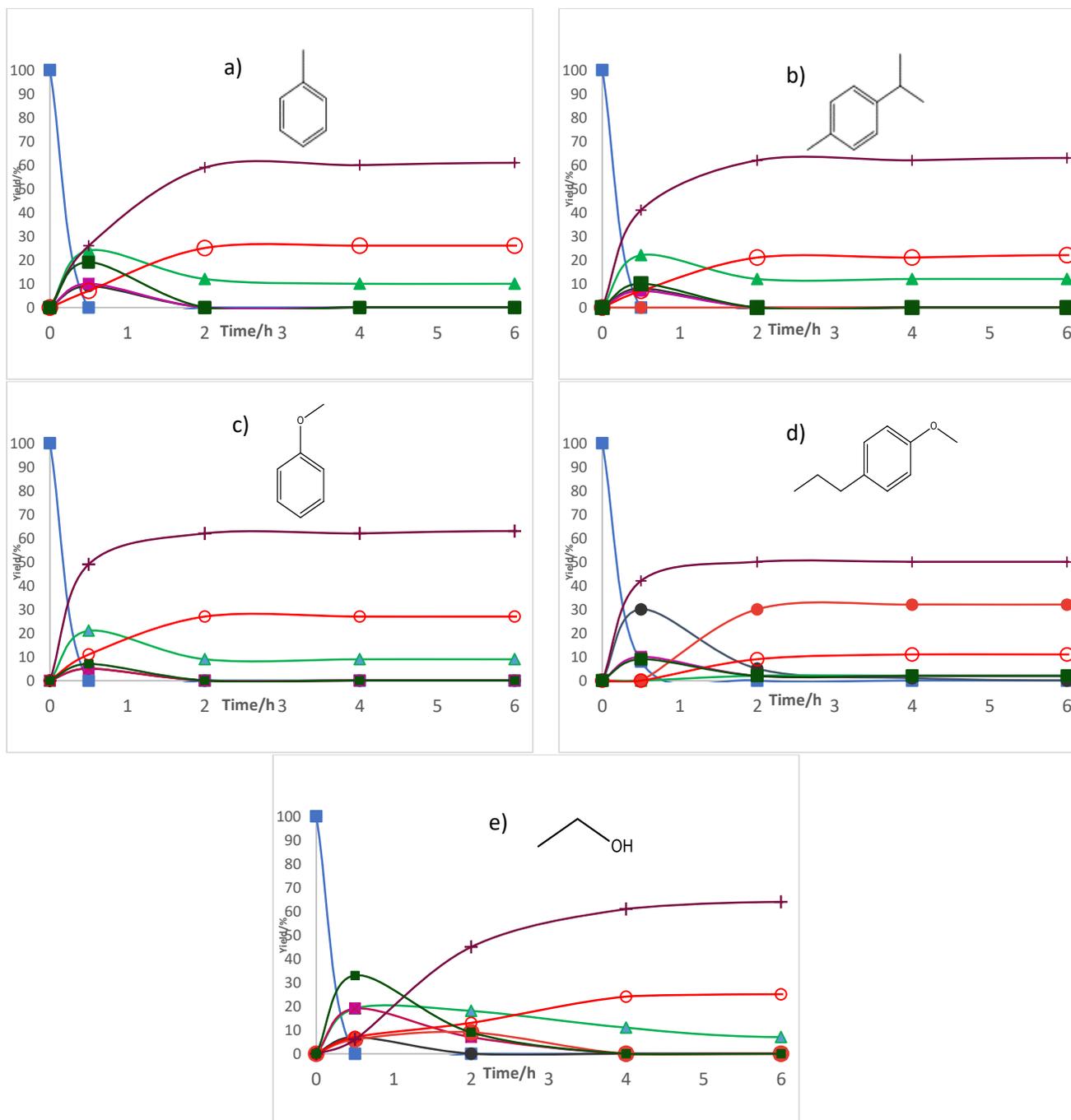


Figure 22. Kinetic curves for the HAM of estragole with 2,6-dimethylmorpholine a) Toluene, b) p-cymene, c) Anisole, d) Propyl-anisole, e) Ethanol

■ Estragole(2) ● Anethole(3) ■ Aldehyde  $\gamma$ (4) ▲ Aldehyde  $\beta$ (5) + Amine  $\gamma$ (10d) ○ Amine  $\beta$ (11d) ■ Enamine  $\gamma$ (7d) ● Enamine  $\beta$ (8d) — Alcohols

#### **4.6. Temperature influence in the hydroaminomethylation of estragole with different amines**

The temperature is an important variable in catalytic reactions, since it can influence both the performance of the reaction, and the selectivity of the products. In the case of di-butylamine at 120 °C, the regioselectivity for the branched amine **11a** was favored, the yield increased from 19% to 27%. But, at this temperature, 6% of aldehydes remained, while at 80 °C it not remained. With 4-methylpiperidine, no change was observed as the temperature changed. With morpholine as a counterpart, the selectivity for the products of interest was much better at 120 °C. At 120 °C, there were no aldehydes, while at 80 °C the condensation stage of the amine with the aldehyde was not favored remaining 43% of **4** and **5**. This can be attributed to the fact that in this system the activation energy necessary to form the products is greater in stage 2 of the HAM reaction. In this sense, it is necessary to apply greater energy (temperature) to overcome this barrier, which was observed with success at 120 °C. In the case of 2,6-dimethylmorpholine, it was only performed at 120 °C since with morpholine at 80 °C the reaction did not have good selectivity for the products of interest.

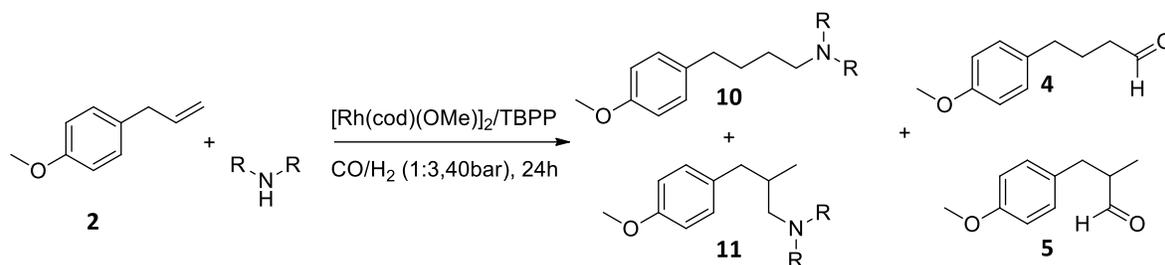


Table 8. Temperature influence in the hydroaminomethylation of estragole with different amines

Run	Amine (reagent)	Temperature °C	Aldehyde (%)		
			(4+5)	10	11
1	di-n-butylamine	80	0	65	19
		120	6	61	27
2	4-methylpiperidine	80	0	44	47
		120	0	44	47
3	Morpholine	80	58	15	6
		120	12	58	28

Conditions: **2** ( $10 \cdot 10^{-3}$  mol) amine ( $11 \cdot 10^{-3}$  mol);  $[\text{Rh}(\text{cod})(\text{OMe})_2]_2$  ( $5 \cdot 10^{-6}$  mol); TPPB ( $5 \cdot 10^{-5}$  mol); toluene (20 mL); 40 bar (CO/H<sub>2</sub> 1:3); 24 h.

#### 4.7. Solvent influence in the hydroaminomethylation of estragole with different amines

With the purpose of improving the reaction medium and increasing the range in the synthesis of new amines with potential biological activity, the hydroaminomethylation of estragole with four different amines, in toluene and ethanol was tested. The results are presented in Table 9, runs 1-4, below.

In the case of dibutylamine, (Table 9, run 1) in both solvents aldehydes remained in similar amounts. It was observed that the selectivity for the amines **10a** and **11a** was as better in ethanol, because the formation of side products (alcohols) was not observed. The concomitant hydrogenation of the aldehydes was completely suppressed in the presence of 4-methylpiperidine in all the solvents, which is another important difference between these two HAM systems. Moreover, the regioselectivity was different in two systems (not strongly but consistently): the  $\beta/\gamma$

ratio was of ca. 40/60 in the reactions with di-n-butylamine vs. 50/50 in those with 4-methylpiperidine.

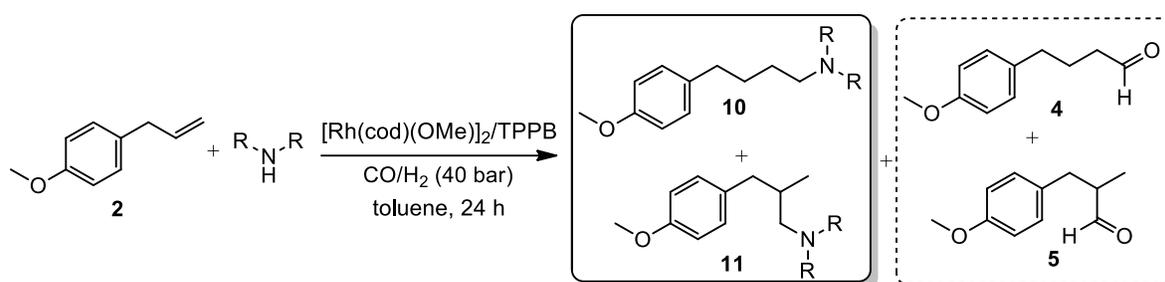


Table 9. Solvent influence in the hydroaminomethylation of estragole with different amines

Run	Amine	pKa	Solvent	Aldehydes (%) (4+5)	Alcohols (%)	Amines (%) 10	11
1	NH(Bu) <sub>2</sub>	11,39	Toluene	6	4	61	27
			Ethanol	5	0	63	28
2		11,27	Toluene	0	0	47	44
			Ethanol	0	0	51	45
3		8,49	Toluene	0	7	61	30
			Ethanol	8	0	61	32
4		11,12	Toluene	10	0	61	27
			Ethanol	7	0	65	26

Conditions: **2** ( $10 \cdot 10^{-3}$  mol) amine ( $11 \cdot 10^{-3}$  mol);  $[\text{Rh}(\text{cod})(\text{OMe})_2]_2$  ( $5 \cdot 10^{-6}$  mol); TPPB ( $5 \cdot 10^{-5}$  mol); temperature 120 °C solvent (20 mL); 40 bar (CO/H<sub>2</sub> 1:3); 24h.

Analyzing the value of pK<sub>a</sub> of all the amines, the most basic is the dibutylamine. This could favor coordination to the metal center, and influence the regioselectivity of the system. However, basicity cannot be considered as an isolated factor. It is also important to consider the structure, which takes into consideration the steric constraint. Thus, it is possible to suggest that 4-methylpiperidine, despite not being

the most basic amine, has less steric hindrance than dibutylamine and thus coordinate in the metal center during the hydroformylation stage.

In this sense, the nature of the original amine seems to affect the reactivity of rhodium species operating in the hydroformylation and hydrogenation steps of the HAM process, as well as in the undesirable hydrogenation of the aldehydes. Probably, the potential ability of the amines to coordinate on rhodium is responsible for the effects observed in these reactions. Nowadays, it is generally accepted that in HAM reactions the presence of large quantities of amines can modify significantly the coordination environment of the metal catalyst (RAOUFMOGHADDAM, 2014)

Finally, for morpholine and 2,6 dimethylmorpholine, the yield for the products of interest were as good in ethanol as in toluene.

#### 4.8. Influence of the amine/substrate ratio in the hydroaminomethylation of estragole with morpholine

The reaction of hydroaminomethylation of estragole with morpholine, all the amine is consumed in the first hours as described in Table 9, runs 1-4. The aldehyde remained at the end of the reaction due to lack morpholine to carry out stage 2 (amine condensation) of hydroaminomethylation. Thus, the ratio estragole: amine (1:1.1) was not enough to transform all aldehydes into the main products and the proportion amine/estragole was increased to 1.3. Results presented in Table 10, runs 1-2 shown that in toluene the yield for the amines of interest increased from 81% to 86%, but still there were aldehydes (4%). In the case of ethanol, the reaction was most favored, transforming all the aldehydes to the products of interest with a yield of 99%.

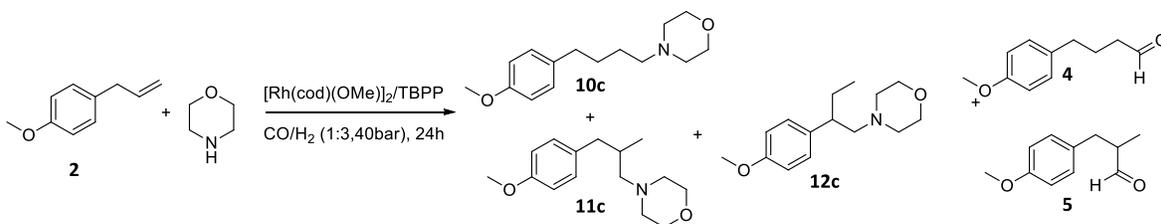


Table 10. Influence of the amine substrate ratio in the hydroaminomethylation of estragole with morpholine in toluene and ethanol

Run	Solvent	Substrate: Amine	Yield (%)	
			Aldehyde (4+5+6)	Amine (10+11+12)c
1	Toluene	1:1,1	9	81
		1:1,3	4	86
2	Ethanol	1:1,1	13	87
		1:1,3	0	99

Conditions: **2** ( $10 \cdot 10^{-3}$  mol) morpholine ( $13 \cdot 10^{-3}$  mol)  $[\text{Rh}(\text{cod})(\text{OMe})_2]_2$  ( $5 \cdot 10^{-6}$  mol); TPPB ( $5 \cdot 10^{-5}$  mol); solvent (20 mL); 40 bar (CO/H<sub>2</sub> 1:3); 120 °C, 24h.

In Table 11, runs 1-2 are present the results with *p*-Cymene and anisole in a ratio substrate: amine 1:1.4. Both in *p*-Cymene and anisole it was possible to transform the aldehydes in the corresponding amines, improving the yields for the products of interest in *p*-Cymene from 89% to 96% and anisole from 82% to 97%.

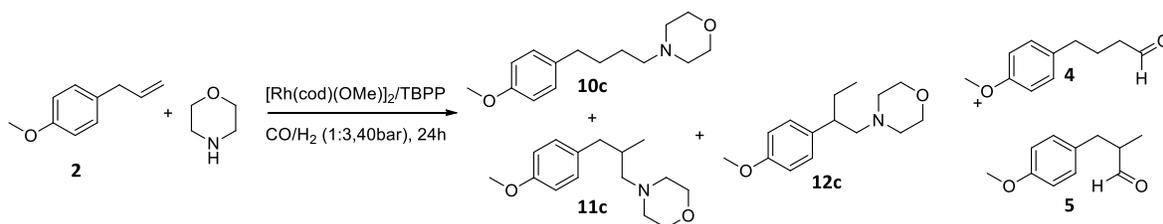


Table 11. Influence of the amine substrate ratio in the hydroaminomethylation of estragole with morpholine in *p*-Cymene and anisole

Run	Solvent	Substrate: Amine	Yield (%)	
			Aldehyde (4+5+6)	Amine (10+11+12)c
1	<i>p</i> -Cymene	1:1,1	5	89
		1:1,4	0	96
2	Anisole	1:1,1	8	82
		1:1,4	0	97

Conditions: **2** (10.10<sup>-3</sup>mol) morpholine (14.10<sup>-3</sup>mol) [Rh(cod)(OMe)<sub>2</sub>] (5.10<sup>-6</sup> mol); TPPB (5.10<sup>-5</sup> mol); solvent (20mL); 40 bar (CO/H<sub>2</sub> 1:3); 120 °C, 24h.

## 5. Conclusions

The hydroaminomethylation of bio-renewable estragole using di-n-butylamine, 4-methylpiperidine, morpholine, and 2,6-dimethylmorpholine as counterparts resulted in a series of novel amines with potential bioactivity in excellent yields. Some eco-friendly solvents were employed for the first time in this reaction. *p*-Cymene, anisole and ethanol proved to be excellent greener alternatives for toluene, the solvent conventionally used for hydroaminomethylation. The performance of *p*-Cymene and anisole was similar to that of toluene in most reactions; whereas the reactions in ethanol solutions showed better yields and selectivity as compared to toluene. Propyl anisole was not as good as the others solvents; important amounts of enamine was not hydrogenated.

The study of the kinetics in all the reactions allowed knowing the behavior of the intermediaries in the HAM of estragole. In all experiments with ethanol, the kinetics was slow as compared to toluene. However, after 24 hours, the yield for the products of interest was as good or better than in toluene.

Other important contribution of this work were the findings: i) an excess of amine counterpart is beneficial to ensure that all the intermediate aldehydes formed in the first stage (hydroformylation) are condensed (second stage) allowing a better conversion into the corresponding amine products in the hydrogenation step; ii) the nature of the amine seems to affect the reactivity of rhodium species operating in the hydroformylation step of the hydroaminomethylation process, and in the undesirable hydrogenation of the intermediately formed aldehydes.

The results of this research work was published in the journal Applied Catalysis A: General(DIAS, A, et al. 2019)

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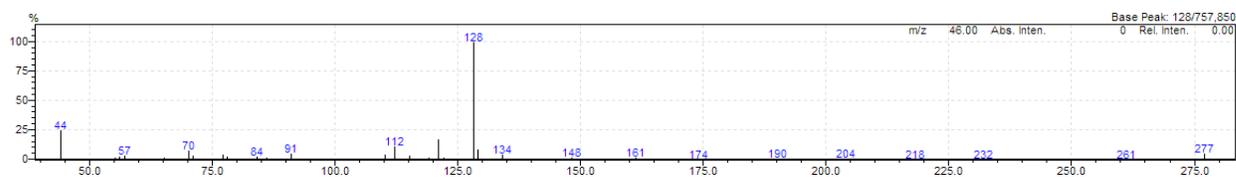
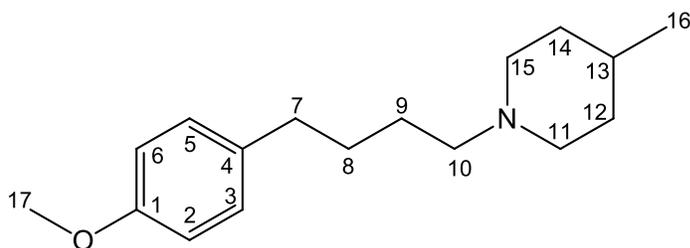
## 7. Appendix

### 7.1. Characterization of products

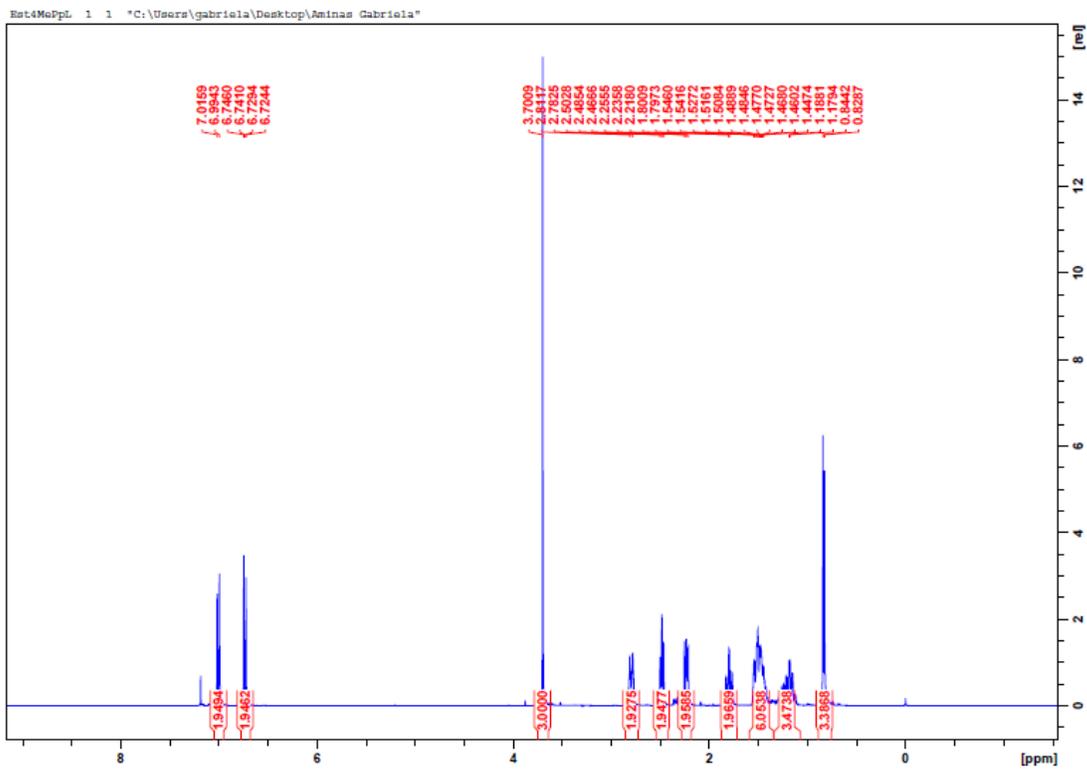
Compounds **3,4,5** were previously reported in (LÁSZLÓ, 1984).

Compounds **10a, 11a** and **12a** were previously reported in (OLIVEIRA *et al.*, 2015)

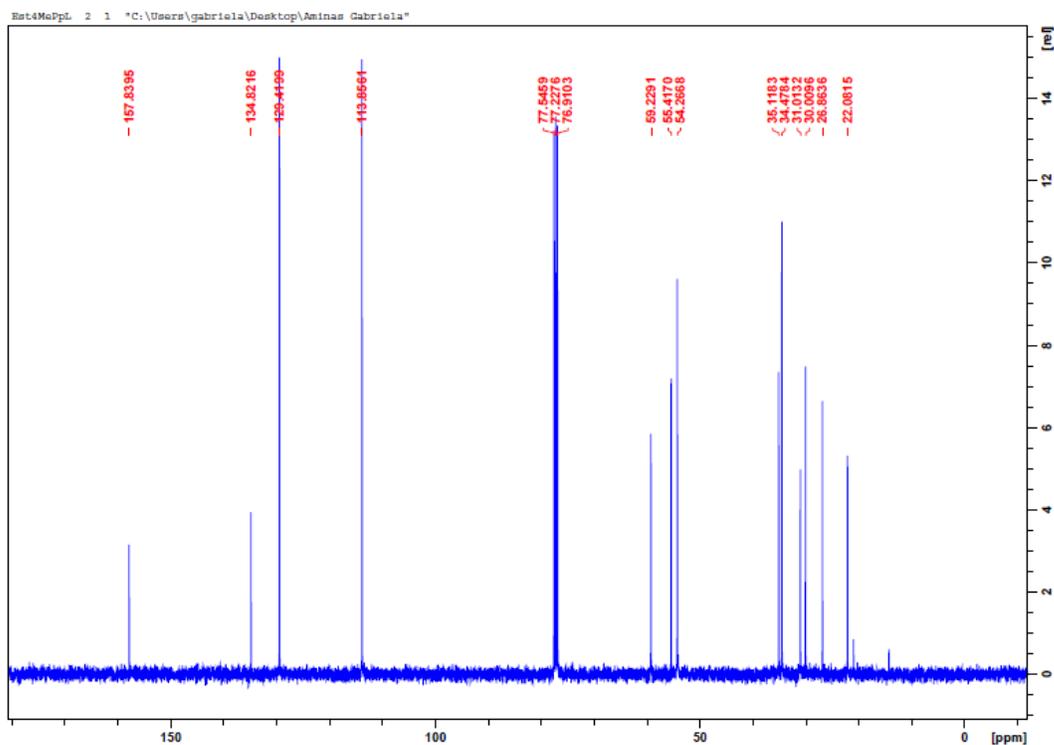
Compound **10b**: MS (70 eV, EI): *m/z* (%) 112 (100), 121 (10), 70 (10), 44 (10), 113 (8), 69 (4), 261 (4). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, Me<sub>4</sub>Si), δ= 0.84 (d, <sup>3</sup>J=6.2 Hz, 3H; C<sup>16</sup>H<sub>3</sub>), 1.18-1.19 (m, 4H; C<sup>12</sup>H<sub>2</sub>, C<sup>14</sup>H<sub>2</sub>), 1.45-1.55 (m, 5H; C<sup>8</sup>H<sub>2</sub>, C<sup>9</sup>H<sub>2</sub>, C<sup>13</sup>H), 1.80 (t, <sup>3</sup>J=11 Hz, 2H; C<sup>15</sup>H<sub>2</sub>), 2.24 (t, <sup>3</sup>J=7.5 Hz, 2H; C<sup>10</sup>H<sub>2</sub>), 2.48 (t, <sup>3</sup>J=7.2 Hz, 2H; C<sup>7</sup>H<sub>2</sub>) 2.78 (br.s, 1H; C<sup>11</sup>HH), 2.81 (br.s, 1H; C<sup>11</sup>HH), 3.70 (s, 3H; C<sup>17</sup>H<sub>3</sub>), 6.74 (d, <sup>3</sup>J=8.6 Hz, 4H; C<sup>2</sup>H<sub>2</sub>, C<sup>6</sup>H<sub>2</sub>), 7.01 (d, <sup>3</sup>J=8.6 Hz, 4H; C<sup>3</sup>H<sub>2</sub>, C<sup>5</sup>H<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> 25°C, Me<sub>4</sub>Si): δ =22.08 (C<sup>16</sup>), 26.86 (C<sup>9</sup>), 30.01 (C<sup>8</sup>), 31.01 (C<sup>13</sup>), 34.48 (C<sup>12</sup>, C<sup>14</sup>), 35.12 (C<sup>7</sup>), 54.26 (C<sup>11</sup>, C<sup>15</sup>), 55.42 (C<sup>17</sup>), 59.23 (C<sup>10</sup>), 113.85 (C<sup>2</sup>, C<sup>6</sup>), 129.42 (C<sup>3</sup>, C<sup>5</sup>), 134.82 (C<sup>4</sup>), 157.84 (C<sup>1</sup>).



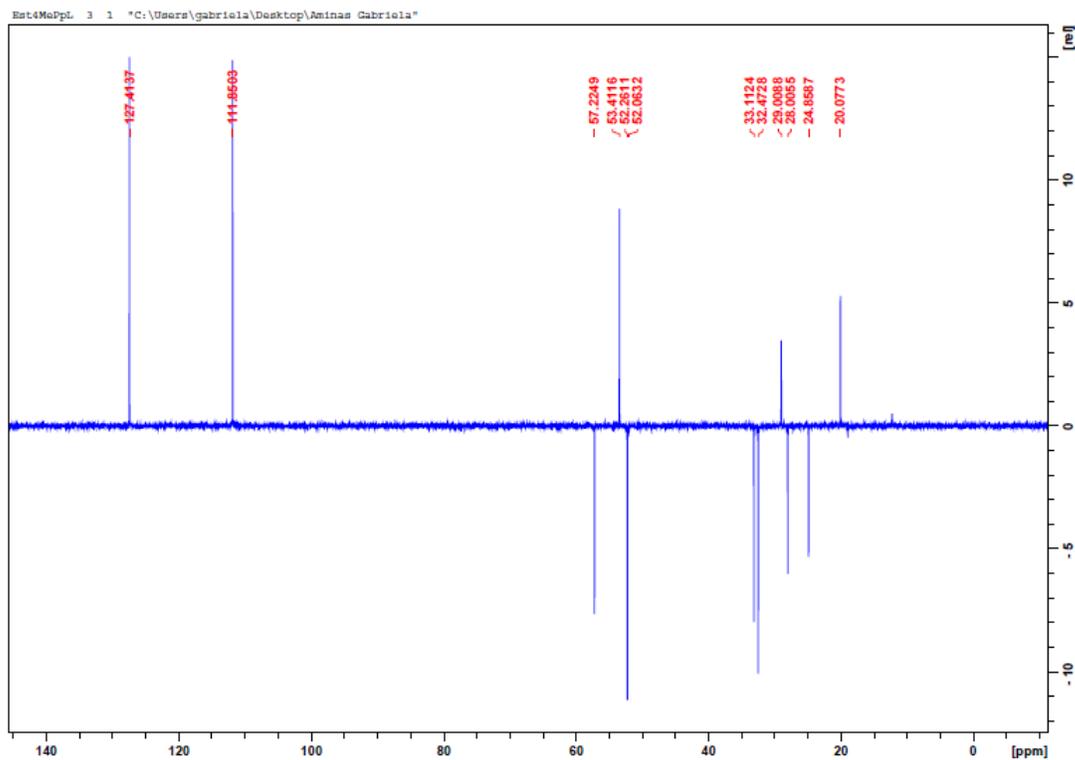
Mass spectrum 1-(4-(4-methoxyphenyl)butyl)-4-methylpiperidine



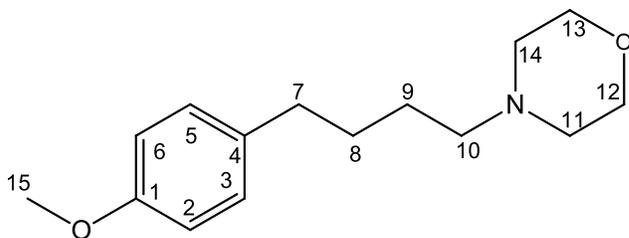
<sup>1</sup>H RMN spectrum 1-(4-(4-methoxyphenyl)butyl)-4-methylpiperidine

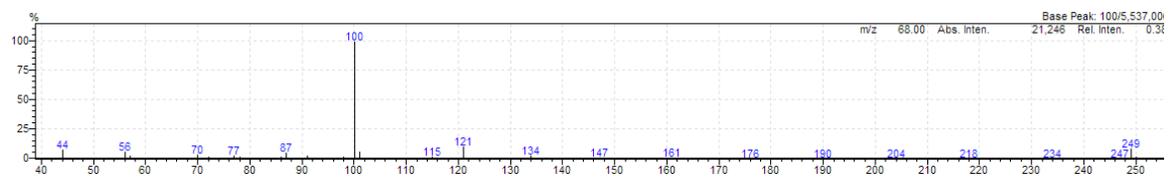


<sup>13</sup>C NMR spectrum 1-(4-(4-methoxyphenyl)butyl)-4-methylpiperidine

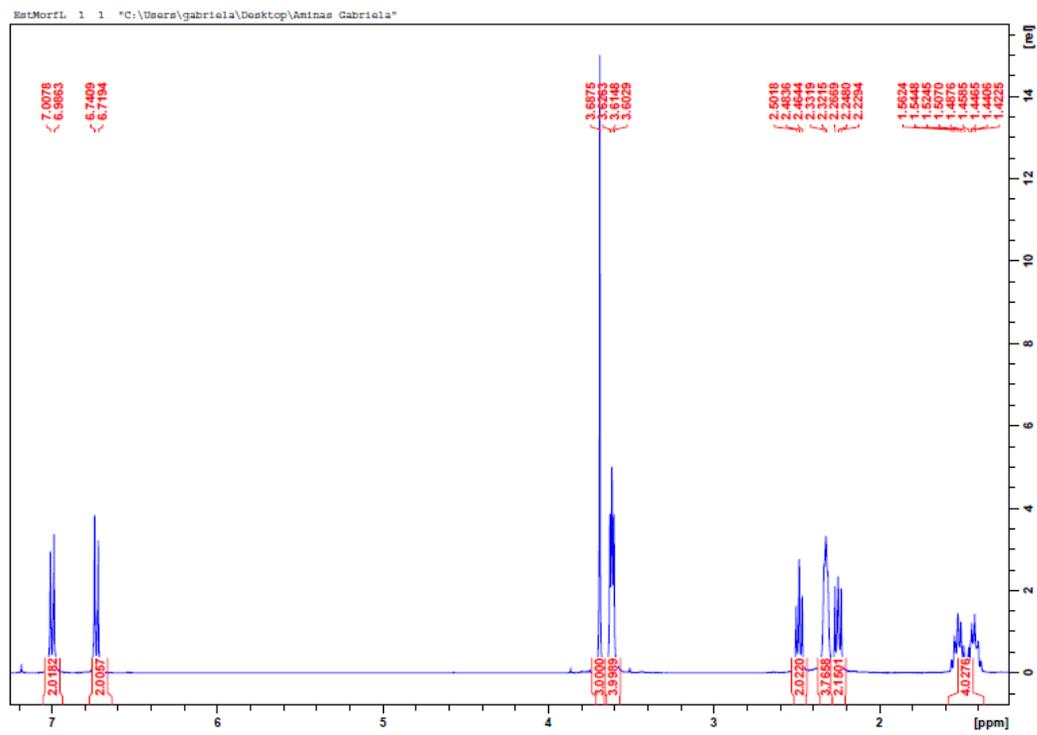


**Compound 10c:** MS (70 eV, EI):  $m/z$  (%) 100 (100), 121 (9), 249 (8), 44 (7), 101 (6), 56 (6),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C,  $\text{Me}_4\text{Si}$ ):  $\delta$  = 1.41-1.44 (m, 2H;  $\text{C}^9\text{H}_2$ ), 1.41-1.56 (m, 2H,  $\text{C}^8\text{H}_2$ ), 2.25 (t,  $^3J=7.5$  Hz, 2H;  $\text{C}^{10}\text{H}_2$ ), 2.33 (br.s, 4H;  $\text{C}^{11}\text{H}_2$ ,  $\text{C}^{14}\text{H}_2$ ), 2.48 (t,  $^3J=7.5$  Hz 2H;  $\text{C}^7\text{H}_2$ ), 3.61 (t,  $^3J=4.7$  Hz 4H;  $\text{C}^{12}\text{H}_2$ ,  $\text{C}^{13}\text{H}_2$ ), 3.69 (s, 3H;  $\text{C}^{15}\text{H}_3$ ), 6.73 (d,  $^3J=8.6$  Hz, 2H;  $\text{C}^2\text{H}$ ,  $\text{C}^6\text{H}$ ), 6.99 (d,  $^3J=8.6$  Hz, 2H;  $\text{C}^3\text{H}$ ,  $\text{C}^5\text{H}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , 25°C,  $\text{Me}_4\text{Si}$ ):  $\delta$  = 26.22 ( $\text{C}^9$ ), 29.62 ( $\text{C}^8$ ), 34.98 ( $\text{C}^7$ ), 53.90 ( $\text{C}^{11}$ ,  $\text{C}^{14}$ ), 55.33 ( $\text{C}^{15}$ ), 59.08 ( $\text{C}^{10}$ ), 67.10 ( $\text{C}^{12}$ ,  $\text{C}^{13}$ ), 113.81 ( $\text{C}^2$ ,  $\text{C}^6$ ), 129.34 ( $\text{C}^3$ ,  $\text{C}^5$ ), 134.58 ( $\text{C}^4$ ), 157.83 ( $\text{C}^1$ ).

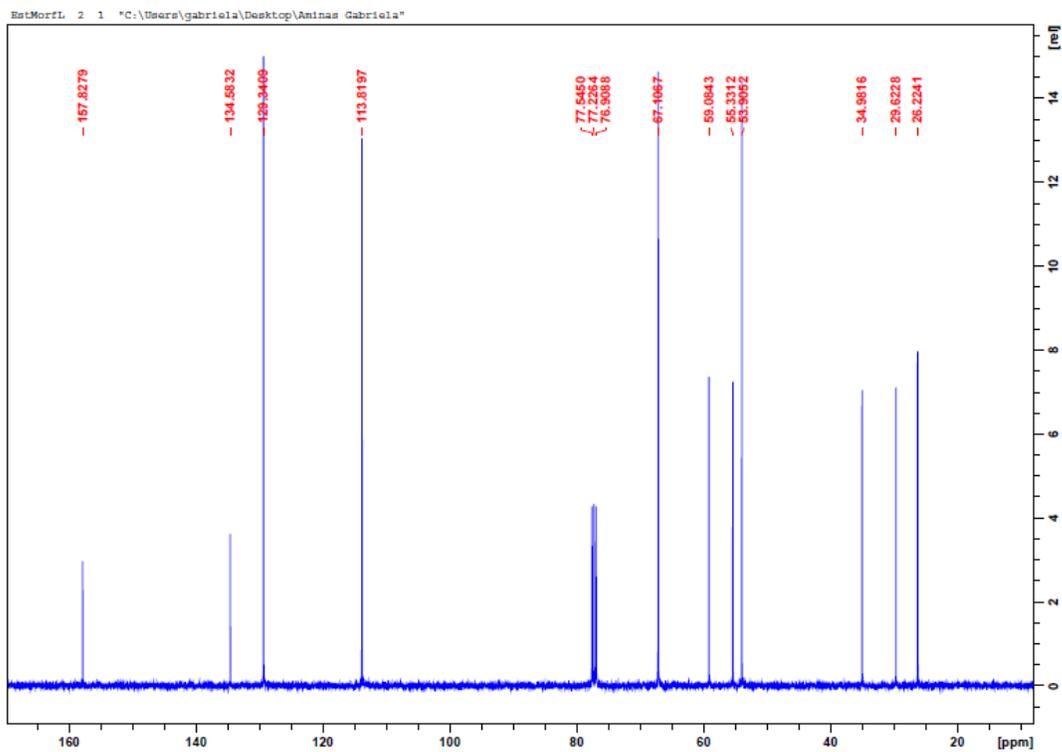




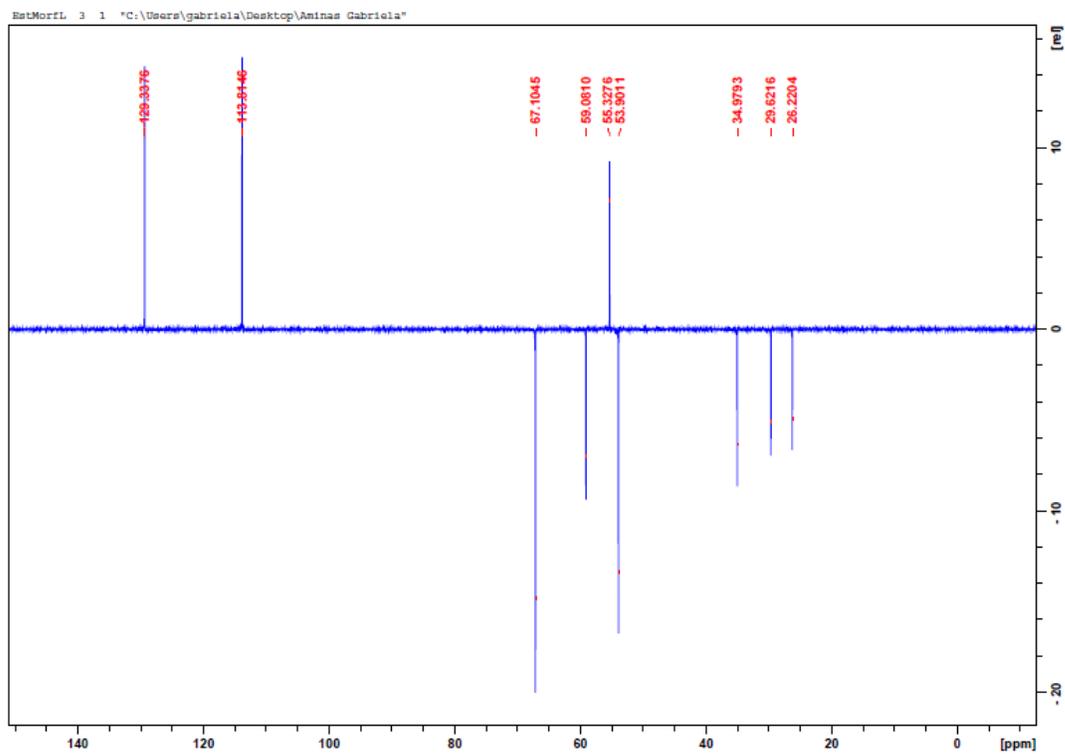
Mass spectrum of 4-(4-(4-methoxyphenyl)butyl)morpholine



<sup>1</sup>H RMN spectrum of 4-(4-(4-methoxyphenyl)butyl)morpholine

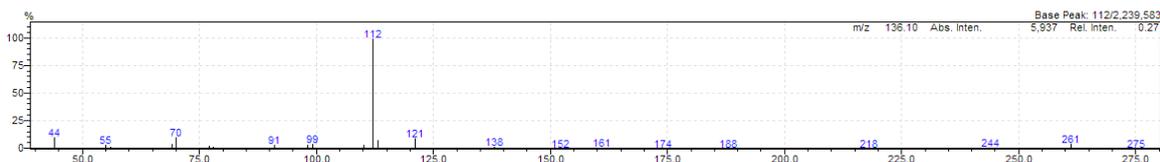
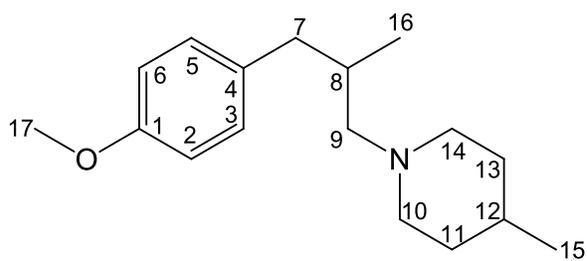


$^{13}\text{C}$  NMR spectrum of 4-(4-(4-methoxyphenyl)butyl)morpholine

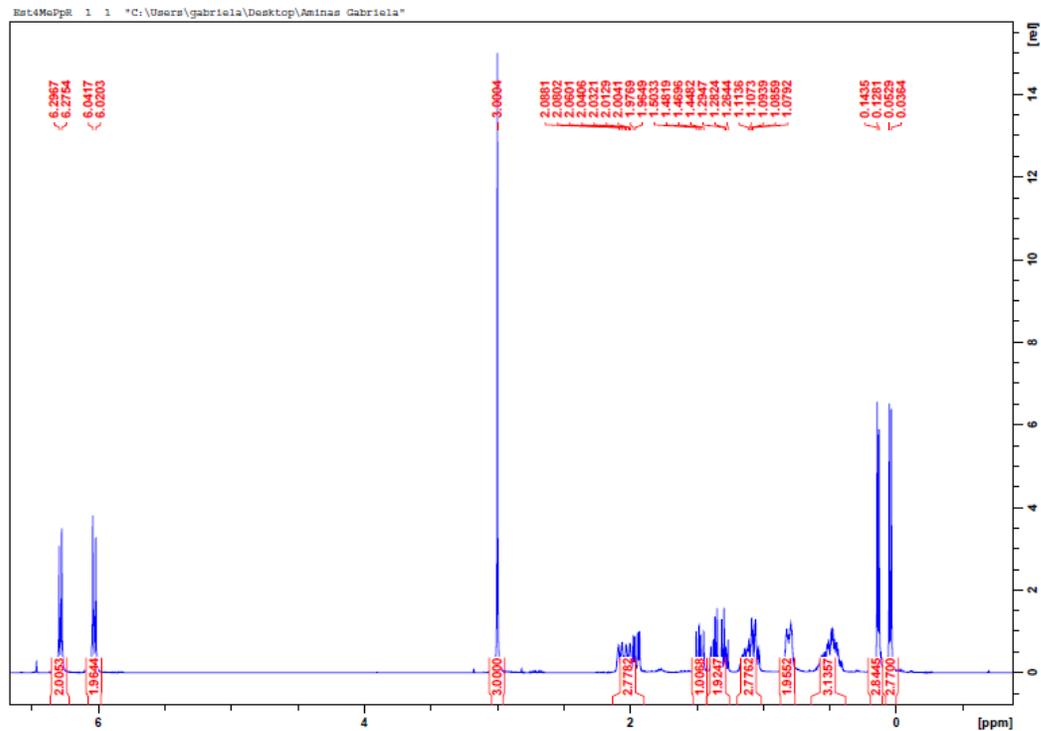


DEPT spectrum of 4-(4-(4-methoxyphenyl)butyl)morpholine

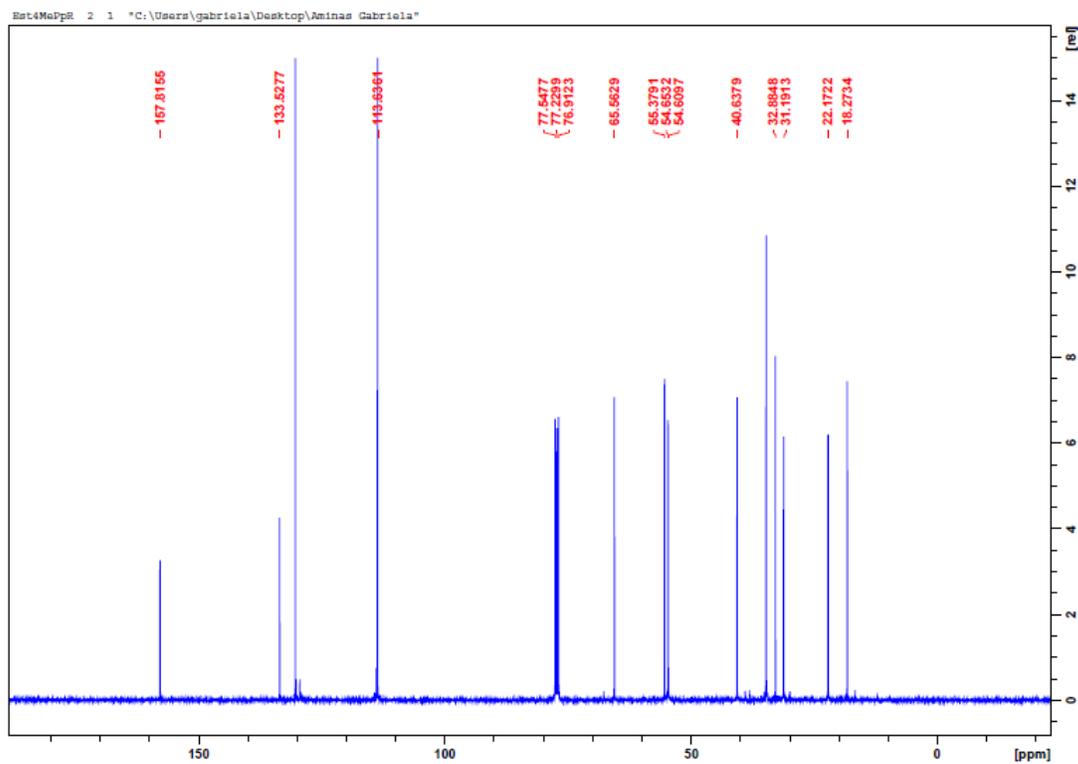
**Compound 11b:** MS (70 eV, EI):  $m/z$  (%) 112 (100), 70 (11), 44 (9), 121 (10), 113 (9), 121 (8), 69 (4), 261 (3).  $^1\text{H}$  RMN (400 MHz,  $\text{CDCl}_3$ , 25 °C,  $\text{Me}_4\text{Si}$ ),  $\delta$ = 0.75 (d,  $^3J$ = 6.6 Hz, 3H;  $\text{C}^{16}\text{H}_3$ ), 0.85 (d,  $^3J$ = 6.2 Hz, 3H;  $\text{C}^{15}\text{H}_3$ ), 1.15-1.25 (m, 4H;  $\text{C}^{11}\text{H}_2$ ,  $\text{C}^{12}\text{H}_2$ ), 1.50 (br.s, 1H;  $\text{C}^{13}\text{HH}$ ), 1.53 (br.s, 1H;  $\text{C}^{13}\text{HH}$ ), 1.74-1.85 (m, 3H;  $\text{C}^8\text{H}$ ,  $\text{C}^{10}\text{H}_2$ ), 2.04 (dd,  $^3J$ = 7.45 Hz, 2H;  $\text{C}^7\text{H}_2$ ), 2.18 (dd,  $^3J$ = 8.6 Hz, 2H;  $\text{C}^9\text{H}_2$ ), 2.67 (dd,  $^3J$ = 4.8 Hz, 2H;  $\text{C}^{14}\text{H}_2$ ), 3.71 (s, 3H;  $\text{C}^{17}\text{H}_3$ ), 6.74 (d,  $^3J$ = 8.6 Hz, 2H;  $\text{C}^2\text{H}$ ,  $\text{C}^6\text{H}$ ), 6.99 (d,  $^3J$ = 8.5 Hz, 2H;  $\text{C}^3\text{H}$ ,  $\text{C}^5\text{H}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$  25°C,  $\text{Me}_4\text{Si}$ ):  $\delta$  =18.27 ( $\text{C}^{16}$ ), 22.17 ( $\text{C}^{15}$ ), 31.18 ( $\text{C}^{12}$ ), 32.88 ( $\text{C}^8$ ), 34.71 ( $\text{C}^{11}$ ,  $\text{C}^{13}$ ), 40.63 ( $\text{C}^7$ ), 54.61 ( $\text{C}^{10}$ ,  $\text{C}^{14}$ ), 54.65 ( $\text{C}^{17}$ ), 65.56 ( $\text{C}^9$ ), 113.63 ( $\text{C}^2$ ,  $\text{C}^6$ ), 130.32 ( $\text{C}^3$ ,  $\text{C}^5$ ), 133.53 ( $\text{C}^4$ ), 157.81 ( $\text{C}^1$ ).



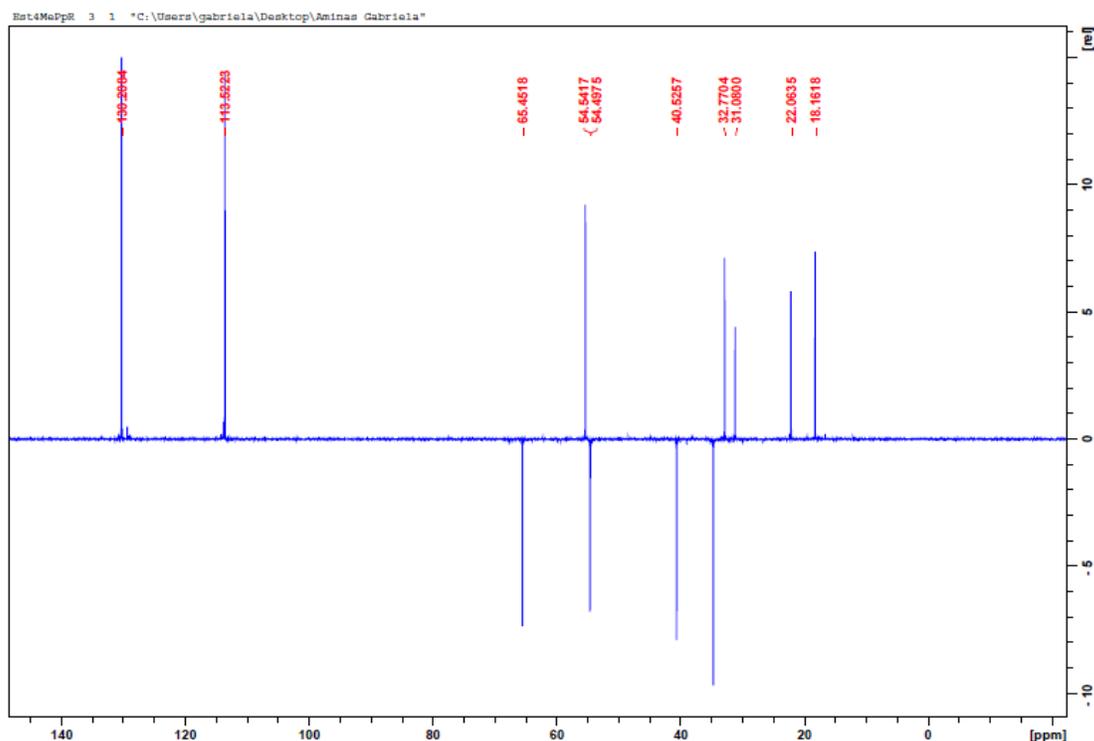
Mass spectrum of 1-(3-(4-methoxyphenyl)-2-methylpiperidine)



<sup>1</sup>H RMN spectrum 1-(3-(4-methoxyphenyl)-2-methylpiperidine

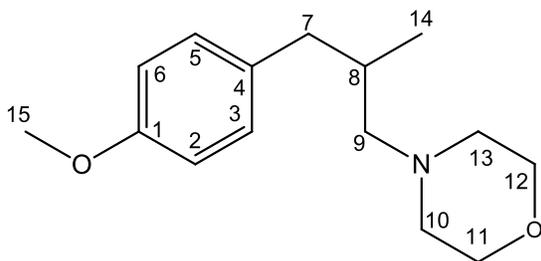


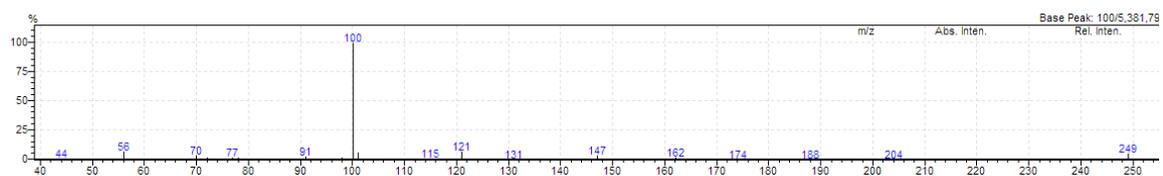
<sup>13</sup>C NMR spectrum 1-(3-(4-methoxyphenyl)-2-methylpiperidine



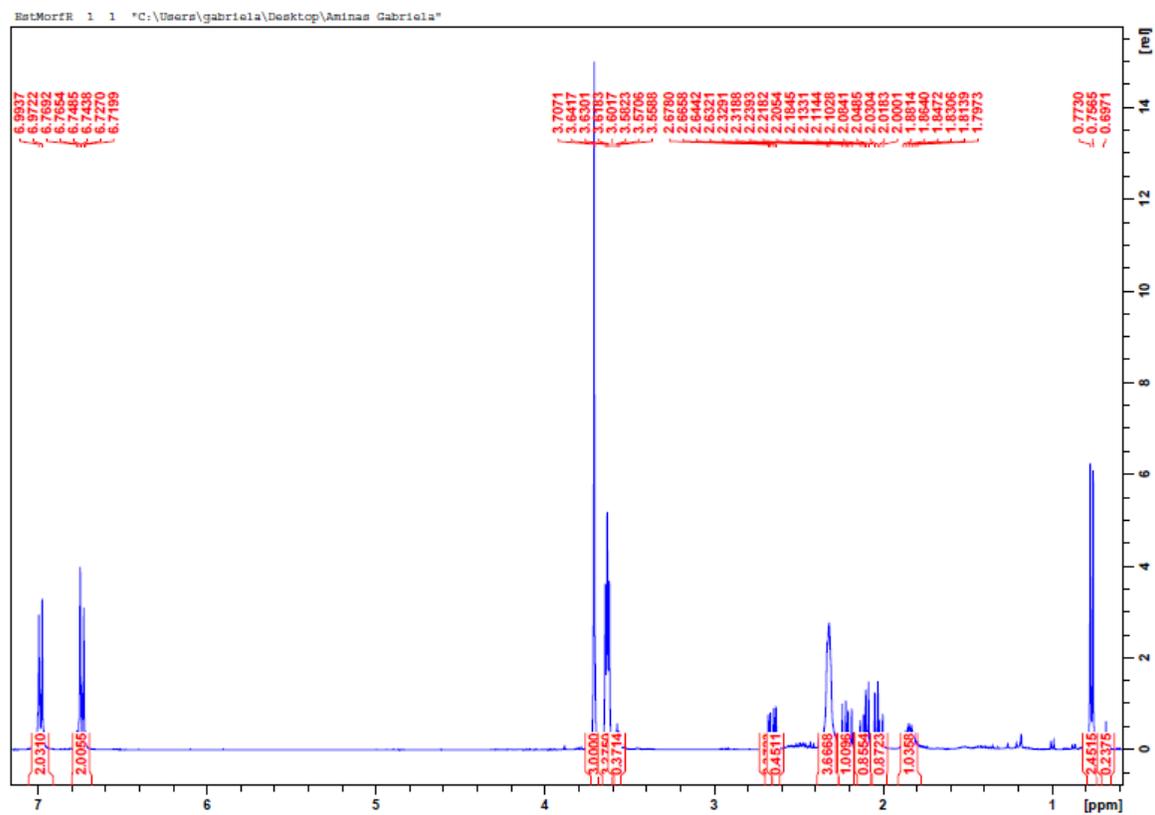
DEPT spectrum 1-(3-(4-methoxyphenyl)-2-methylpiperidine

**Compound 11c:** MS (70 eV, EI):  $m/z$  (%) 100 (100), 121 (6), 101 (6), 56 (6), 249 (5), 70 (3). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, Me<sub>4</sub>Si):  $\delta$  = 0.76 (d, <sup>3</sup>J = 6.6 Hz, 3H; C<sup>14</sup>H<sub>3</sub>), 1.75-1.85 (m, 1H; C<sup>8</sup>H), 2.07 (dd, <sup>3</sup>J = 7.3 Hz, 2H; C<sup>9</sup>H<sub>2</sub>), 2.21 (dd, <sup>3</sup>J = 8.4 Hz, 1H; C<sup>7</sup>HH), 2.32 (br.s, 4H; C<sup>10</sup>H<sub>2</sub>, C<sup>13</sup>H<sub>2</sub>), 2.65 (dd, <sup>3</sup>J = 4.85 Hz, 1H; C<sup>7</sup>HH), 3.63 (t, <sup>3</sup>J = 4.7 Hz, 4H; C<sup>11</sup>H<sub>2</sub>, C<sup>12</sup>H<sub>2</sub>), 3.71 (s, 3H; C<sup>15</sup>H<sub>3</sub>), 6.74 (d, <sup>3</sup>J = 8.6 Hz, 2H; C<sup>2</sup>H, C<sup>6</sup>H), 6.98 (d, <sup>3</sup>J = 8.6 Hz, 2H; C<sup>3</sup>H, C<sup>5</sup>H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> 25°C, Me<sub>4</sub>Si):  $\delta$  = 18.08 (C<sup>14</sup>), 32.29 (C<sup>8</sup>), 40.41 (C<sup>7</sup>), 54.23 (C<sup>10</sup>, C<sup>13</sup>), 55.39 (C<sup>15</sup>), 65.41 (C<sup>9</sup>), 67.29 (C<sup>11</sup>, C<sup>12</sup>), 113.69 (C<sup>2</sup>, C<sup>6</sup>), 129.41 (C<sup>3</sup>, C<sup>5</sup>), 133.14 (C<sup>4</sup>), 157.90 (C<sup>1</sup>).

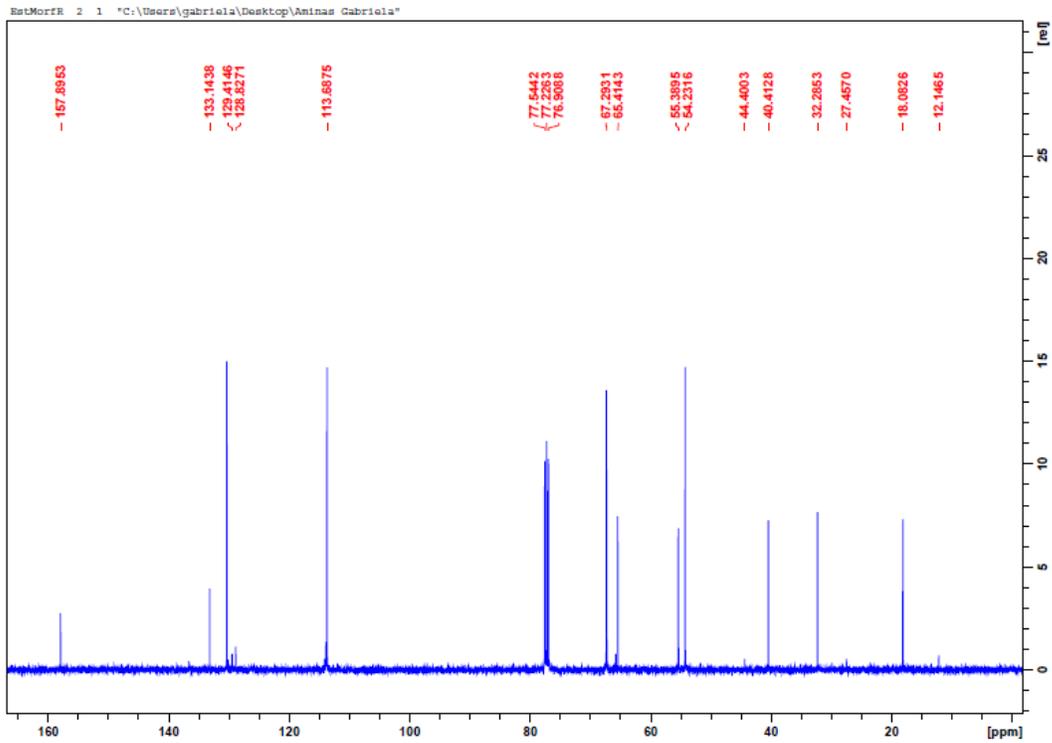




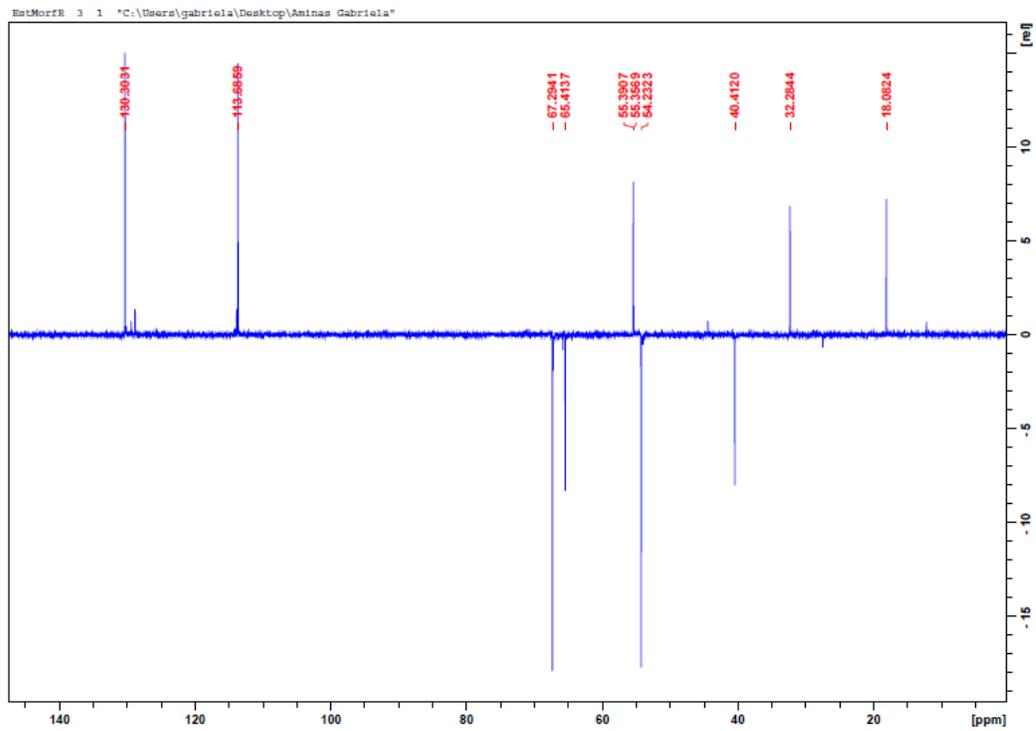
Mass spectrum of 4-(3-(4-methoxyphenyl)2-methylpropyl)morpholine



<sup>1</sup>H RMN spectrum of 4-(3-(4-methoxyphenyl)2-methylpropyl)morpholine

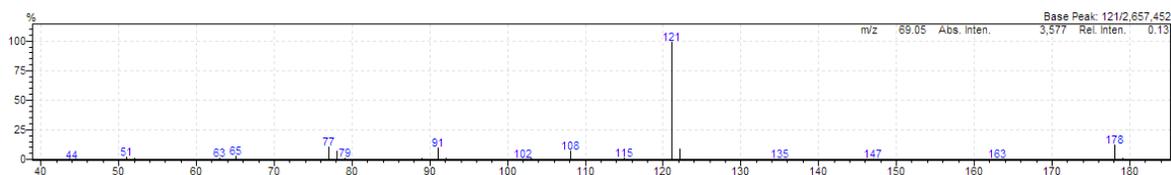
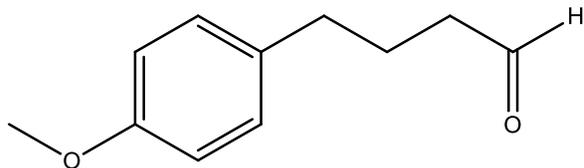


<sup>13</sup>C NMR spectrum of 4-(3-(4-methoxyphenyl)2-methylpropyl)morpholine



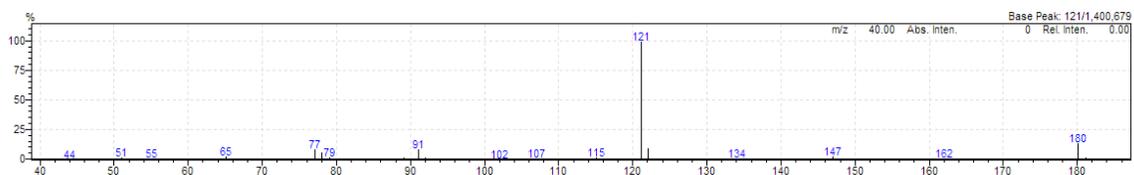
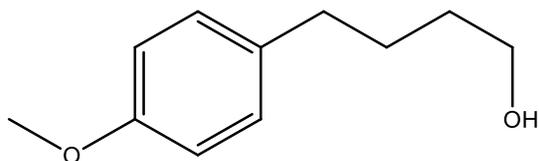
DEPT spectrum of 4-(3-(4-methoxyphenyl)2-methylpropyl)morpholine

**Compound 4:** MS (EI, 70 Ev): m/z 121 (100%), 178 (13%), 77 (11%), 91 (10%), 122 (9%), 78 (8%)



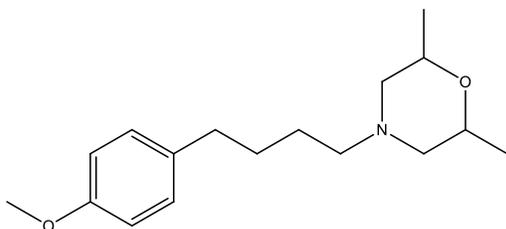
Mass spectrum of 4-(4-methoxyphenyl)butanal

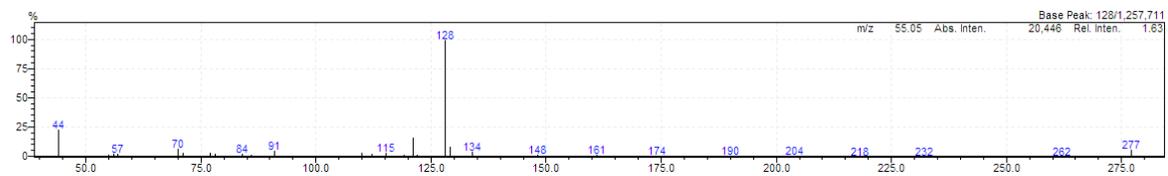
**Alcohol of compound:** 4-(4-methoxyphenyl)butan-1-ol: MS (EI, 70 Ev): m/z 121 (100%), 180 (14%), 122 (10%), 91 (9%), 162 (1%). The signal 162 refers to the loss of a water molecule



Mass spectrum of 4-(4-methoxyphenyl)butan-1-ol

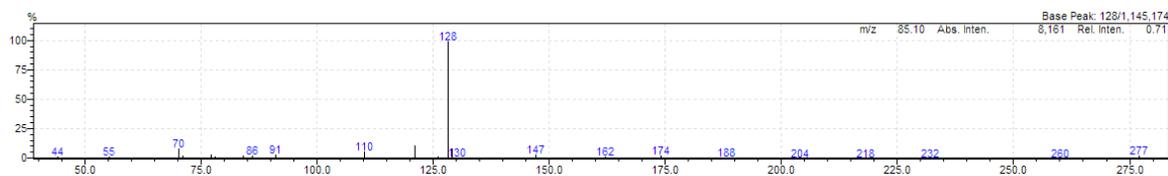
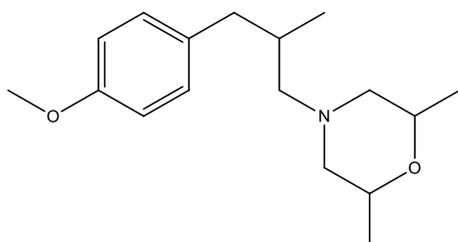
**Compound 10d:** MS (EI, 70 Ev): m/z 128 (100%), 44 (26%), 121 (17%), 129 (8%), 70 (7%), 277 (5%).





Mass spectrum of 4-(4-(4-methoxyphenyl)butyl)-2,6-dimethylmorpholine

**Compound 11d:** MS (EI, 70 Ev): m/z 128 (100%), 121 (11%), 129 (8%), 70 (8%), 110 (6%), 277 (1%).



Mass spectrum of 4-(3-(4-methoxyphenyl)2-methylpropyl)-2,6-dimethylmorpholine