Università
Ca'Foscari
Venezia

Scuola Dottorale di Ateneo
Graduate School

Dottorato di ricerca
in Scienze Chimiche
Ciclo XXVIII
Anno di discussione 2016

Synthesis of fine chemicals, such as pharmaceuticals, agrochemicals, fragrances by using catalytic reactions under homogeneous, heterogeneous and biphasic reaction conditions

(Sintesi di prodotti della chimica fine, quali farmaci, fitofarmaci e fragranze, mediante reazioni catalitiche in condizioni omogenee, eterogenee e bifasiche)

SETTORE SCIENTIFICO DISCIPLINARE DI AFFERENZA: CHIM/04
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DEDICATED TO MY PARENTS

ACKNOWLEGEMENT

This dissertation is the result of my Ph.D. project carried out at the Department of Molecular Sciences and Nanosystems, Ca'Foscari university of Venice, Italy. The project was financed in Italian Ph.D. fellowship by MIUR the ministry of Italian government.

I would like to express my sincere gratitude to my advisor Prof. Stefano Paganelli and Prof. Oreste Piccolo for giving me the opportunity of working on this interesting topic. Their group and experience the dynamic research environment supported by their enthusiasm for science and research. I have always appreciated their great support and valuable guidance during my tenure. It was a great pleasure working with Riccardo Tassini and Barbara Vicentini in lab. I would like to thank Dr. Laura Sperni for her assistance in the GC-MS analysis.

I would like to extend my gratitude to Prof. Marijan Kocevar and Dr. Marko Krivec, for accepting me to do the work at, Faculty of chemistry and chemical technology, university of Ljubljana, Slovenia. And special thanks for their support and guidance during my abroad stage.

I would also like to thank Dr. Omvir Singh, Dr. Sandip Bondage, Dr. Bapu Chaudhari and Dr. Suryakant Sapkal for his encouragement and constant guidance during the initial stage of my career as chemist and scientist-1 at Evotec India Pvt. Ltd. Thane, India and other colleagues from Arch pharma labs, ltd, Taloja. And I would like to thank my all friends for their support and fun moments shared together.

I would like to extend my thank to my father Damu (Pappa), my mother Bharatbai (Mummy), my brother Sachin and my sister Anjali have given me a lifetime of love and support. They have sacrificed so much for me and for their example of diligent hard work that permeated the fibers of our family and has had a profound impact on my life. Most importantly I must acknowledge the role of my wife Geeta in this work. While her primary contribution was to encourage me go abroad after my selection. Geeta and her Gulbarga family have supported and encouraged me. The time I have spent on this thesis research was filled with joy and happiness because of my family love & support. Last but not least, I thank the generous gift at the end of my Ph.D a new addition in our life, my little daughter Vikita.

Vikas D. Rathod.

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Chapter 1: Introduction

1.1 The pharmaceutical industry

The pharmaceutical industry develops, produces, and markets drugs for use as medications[1]. Pharmaceutical companies may deal with generic or brand medicines or medical devices. These products have to comply the number of laws and regulations that regularize the patenting, testing, safety, efficacy and finally marketing of drugs.

The pharmaceutical products goes in different phases; first one is drug discovery, i.e. the process by which potential drugs are discovered or designed. In the past decade's most drugs were discovered either by isolating the active ingredient from natural resources or by unexpected discovery or by me-too of known active ingredients. The modern approach generally focuses on understanding the metabolic route related to a disease situation or pathogen and tries to manipulate these pathways using molecular biology or biochemistry, often using *in-silico* modeling. Early-stage drug discovery has traditionally been carried out by universities, research institutions and research and development departments in industries.

The second phase (drug development) refers to activities undertaken after a compound is identified as a potential drug in order to establish its suitability as a medication treatment. Objectives of drug development are to determine appropriate pharmaceutical formulation and dosing, as well as to establish the drug safety and efficacy. Research in these areas generally includes a combination of *in vitro* and *in vivo* studies on animals and healthy volunteers. The cost of later stage development is usually done by bigger pharmaceutical companies[2]. Often, big multinational organizations exhibit vertical integration, participating in a broad range of drug discovery and development, manufacturing and quality control, marketing, sales, and distribution. Smaller organizations, on the other hand, generally focus on a specific aspect such as discovering drug candidates or developing formulations. Often, collaborative agreements between research organizations and major pharmaceutical companies are made to explore the potential of new drug substances. More recently, multi-national players are increasingly relying on contract research organizations to manage drug development[3].

The third phase is based on clinical trials and this stage is very expensive; only a small fraction of all compounds that are investigated for use in humans is eventually approved in most countries by government, appointed medical institutions or committee, who have to approve new drugs before

they can be marketed in those countries. A study by the consulting firm Bain & Company reported that the cost for discovering, developing and launching a new drug in market (which factored in marketing and other business expenses) (along with the prospective drugs that fail) increases over a five-year period to nearly $1.7 billion in 2003[4]. According to Forbes, in 2010, development costs were between $ 4 billion to $11 billion per drug[5]. It is also to underline that there is always the risk that a drug during its life before being launched (and sometimes also after the marketing) fails and is abandoned.

In the United States, the biggest pharmaceutical market, new pharmaceutical products must be approved by the Food and Drug administration (FDA) as a being both safe and effective. This process generally involves submission of an investigational new drug filing with adequate pre-clinical data to support proceeding with human clinical trials. Following Investigational New Drug (IND) approval, the three phases of increasingly larger human clinical trials may be conducted. During the Phase I generally studies of drug toxicity using healthy volunteers as patients are performed. In Phase II tests of pharmacokinetics and dosing on patients are included *versus* placebo treatment and in Phase III a suitable, usually very large, study of efficacy in the intended patient population is carried out. Following the successful completion of Phase III trials, a New Drug Application (NDA) is submitted to the FDA. Then the FDA reviews all data and if the product is seen as having a positive benefit-risk assessment, FDA will approve to market it in the United States[6].

A fourth phase of post-approval surveillance is also often required due to the fact that even the largest clinical trials cannot effectively predict the presence of rare side-effects. Post marketing surveillance ensures that safety of a drug is monitored very closely also after marketing. In certain cases, if severe side effects are found, its prescription may need to be limited to particular patient groups or pathologies , while for other patients the substance may be not authorized or the drug is withdrawn from the market. The FDA provides information about approved drugs in the Orange Book site[7].

Depending on a number of considerations, a company or a research institute may apply for a patent for a new drug, for a formulation, for a new therapeutical application or for the process of producing the drug, etc. If granted, exclusivity rights typically for about 20 years are allowed. However, only after rigorous studies and testing, which may take 10 to 15 years on average, governmental authorities will grant permission to the company to market and sell the drug[8]. Patent protection enables the owner of the patent to recover the costs of research and development through

high profit margins for the branded drug. In some cases an extension of patent life over the 20 years may be granted. When the patent protection for the drug expires, a generic version of the drug is usually developed and sold by a competing company. The development and approval of generics is less expensive, allowing them to be sold at a lower price. Often the owner of the branded drug will introduce a generic version or a better controlled release formulation or an improved new analogue of the active ingredient, before the patent expires, in order to get a head start in the generic market or to try to avoid competitors[9]. The patent expiration of products launched during the industry's "golden era" in the 1990s and the companies' failure to develop sufficient new blockbuster products to replace lost revenues has often resulted in corporate restructuring and/or industrial acquisitions.

In the U.S., the value of prescriptions increased over the period of 1995 to 2005 by 3.4 billion annually, a 61% increase. Retail sales of prescription drugs jumped 250% from $72 billion to $250 billion, while the average price of prescriptions more than doubled from $30 to $68[10]. For this high amount of demand cheaper generic version of drugs are necessary.

1.2. Active Pharmaceutical Ingredients

The Active Pharmaceutical Ingredients (APIs), the main ingredient of any drug are manufactured from raw materials either by chemical, physical or biochemical methods. Depending on the complexity of the molecule, synthesis of APIs may need multi-step complex chemistry utilizing a variety of processing technologies.

The quality of an API need to be the best possible; usually any unknown impurity must be lower than 0.1%, known impurity, if not toxic, may be 0.5% and the sum of total impurity is usually <1%. It requires validated analytical methods for impurity profile and for determining the stability of the product. Pharmacopoeias report often the characteristics of an API to be accepted for the market; when an API is not yet classified the producers utilize tentative specifications but each manufacture may use own standards.

In addition, the documentation, regulatory compliance, storage of APIs as well as packaging, labeling, repackaging, release and production should all be as per the standards set by the FDA or other National Health Organization. Client confidentiality is critical and suppliers need to maintain complete confidentiality while dealing with their clients. The supplier should have a suitable system to accept or reject all intermediate materials, raw materials, labeling or packaging materials as per

their discretion. All the manufacturing records must be thoroughly evaluated to ascertain all the important process steps have been followed. Only then an API may be released.

The dosage form for a finished pharmaceutical product (FPP) contains not only the active pharmaceutical ingredient but also excipients, which are the substances of the tablet, or the liquid where the API is suspended, or other pharmaceutically inert materials, which permit to protect or release selectively the drug in our body.

Patients often have difficulty to identify the active ingredients in their medication and are often unaware of the notion of an active ingredient. When patients are on multiple medications, active ingredients can interfere with each other, often resulting in severe or life-threatening complications. Now online services exist which can identify the active ingredient of most medications, such as the medicines database providing information on medications available in some countries, giving information on side effects and interactions among different drugs.

1.2.1 Definition of originator and generic drugs

Originator drug: The definition indicates the product, normally as a patented product, that was first authorized for marketing on the basis of the documentation of its efficacy, safety and quality, according to requirements at the time of authorization. The originator product has always one or more brand (trade) names.

Generic drug: Generic drugs are those where the original patent has expired and may now be produced by manufacturers other than the original innovator (patent-holding) company. The term "generic drug" or "generic medicine" can have varying definitions in different markets, however the term is commonly understood, as defined by the World Health Organization (WHO), to mean a pharmaceutical product which is usually intended to be interchangeable with the corresponding innovator product, is manufactured without a licence from the innovator company, and is marketed after the expiry date of the patent or other exclusive rights[11]. There are different legal requirements in different jurisdictions that define the specifics of what a generic medicine is. However, one of the main principles underpinning the safe and effective use of generic medicines is the concept of *bioequivalence.*

Bioequivalence has been defined as follows**:** two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to

both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards[12]. The purpose of establishing bioequivalence is to demonstrate equivalence between the generic medicine and the originator medicine in order to allow bridging of the pre-clinical and clinical testing performed on the originator drug[13].

As indicated before, a generic drug must result more economic then the brand one. Therefore its synthesis has to be more sustainable and possibly more environmental friendly. Many of the classical synthetic methodologies have broad scope but generate copious amounts of wastes, and the chemical industry, including the one that produces APIs, has been subjected to increasing pressure to minimize or, preferably, eliminate wastes in particular in western countries. Therefore it has become mandatory to pay attention to more efficient and sustainable productive processes, in agreement with the green chemistry principles[14] (Table1.1).

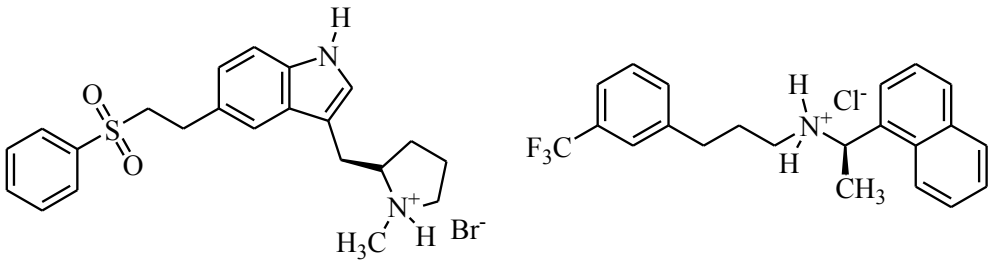
Table 1.1 The twelve green chemistry principles

1. It is better to prevent waste than to treat or clean up waste after is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separations agents etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirement should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be performed at ambient temperature and pressure.
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/de-protection, temporary modification of physical/chemical process) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in process monitoring and control prior to the formation of hazardous substances.
12. Substances and the forum of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

Although the concept of green chemistry is noble, it is mandatory to study the chemical processes from an industrial and economic point of view, so, the concept of “sustainable chemistry” was

introduced. The term “sustainable chemistry” includes the philosophy of green chemistry, the economic issues and the effects of certain choices for present and future[15]. By considering green chemistry approach nowadays in the research field, generic researcher concentrate focus on the synthesis of pharmaceutical drug with more sustainable way by controlling the formation of hazardous waste compared to originator synthesis and/or to reduce the total costs .

During the present research work, the choice of solvent, the use of efficient catalysts, the comparison of reactions carried out under batch traditional conditions and under microwaves (MW) conditions and other preparative parameters were studied inspired by these principles, to try to obtain greener and more sustainable syntheses of two APIs, that are going to become generic: Eletriptanhydrobromide and Cinacalcet hydrochloride (Figure 1.1). For the former API an attempt to improve some part of originator synthesis was made, for the latter drug a complete synthesis, different from the originator process, was carried out with some innovative modifications. The choice of these two molecules was driven also by the fact that both target molecules might involve similar reaction steps, i.e. a Heck cross-coupling reaction followed by a hydrogenation reaction. Furthermore in the case of Cinacalcet hydrochloride other steps, involving selective reductions, were interesting to study.



Eletriptan hydrobromide Cinacalcet hydrochloride

Figure 1.1 Structure of the two investigated APIs

1.3 General information on Eletriptan hydrobromide and Cinacalcet hydrochloride

Eletriptan hydrobromide: trade name Relpax®, Cas No [177834-92-3]; the originator patent is going to expire on 12th February 2016 in Europe, based on the expiry date of the product patent EP0592438, that received a supplementary protection certificate (SPC) of 5 years and 4 months, and on 26th December 2016 in USA, based on the expiry date of the product patent US5545644 that received an extension of the patent life of about 6 years[16].

This is a second generation triptan drug intended for treatment of migraine headaches. It is used as an abortive medication, blocking a migraine attack which is already in progress. Its mechanism of action is believed to reduce swelling of the blood vessels surrounding the brain. This swelling is associated with the head pain of a migraine attack. This API blocks the release of substances from nerve endings that cause more pain and other symptoms like nausea, and sensitivity to light and sound. It is thought that these actions contribute to relief of symptoms[17-18]. Common side effects include hypertension, tachycardia, headache, dizziness, and symptoms similar to angina pectoris. The drug has a relatively low potential for interactions. Notably, it is unlikely to interact to a relevant extent with beta blockers, tricyclic antidepressants and serotonin-specific reuptake inhibitors (SSRI) type antidepressants. Strong inhibitors of the liver enzyme Cytochrome P450 3A4 (CYP3A4), such as erythromycin and ketoconazole, significantly increase blood plasma concentrations and half life of this drug. Ergot alkaloids add to the drug's hypertensive effect[19]. Below (Table 1.2) worldwide sales figure and consumption of eletriptanhydrobromide are shown.

Table 1.2 Worldwide consumption of eletriptan hydrobromide

	Sales in $ (USD) Million			Consumption in Kg (Kilogram)		
Country	**Dec 2014**	**Dec 2013**	**Change in [%]**	**Dec 2014**	**Dec 2013**	**Change in [%]**
USA	307.8	282.9	8.8	461.4	483.6	-4.6
EU top 5	52.2	50.2	4	592.8	563.9	5.1
Rest of Europe	26.9	27	-0.4	263.5	254.3	3.6
Latin America	4.5	4.7	-4.3	28.9	29.1	-0.7
Rest of world	58.1	60.2	-3.5	390.5	365.6	6.8
Worldwide	449.5	424.8	5.8	1737.1	1696.6	2.4

Cinacalcet hydrochloride: trade name Sensipar ®in North America and Australia and Mimpara®, in Europe, Cas No [364782-34-3]; the originator patent is going to expire on 22th October 2019 in Europe/Italy, based on the expiry date of the product patent EP1203761, that received a supplementary protection certificate (SPC) of 5 years, and on 8th March 2018 in USA, based on the expiry date of the product patentUS6011068 that received an extension of the patent life of about 7 years[20].

Cinacalcethydrochloride is a drug that acts as a calcimimetic. i.e. it mimics the action of calcium on tissues by allosteric activation of the calcium-sensing receptor that is expressed in various human organ tissues. It is used to treat secondary hyperparathyroidism (elevated parathyroid hormone levels), a consequence of end-stage renal disease[21]. It is also indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma[22] and for the treatment of secondary hyperparathyroidism in people with chronic kidney disease on dialysis[23]. Cinacalcet can also be used to treat severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy[24].

Hypocalcemia(decreased calcium levels) is a contraindication of this API. Patients who have serum calcium levels less than 7.5 mg/dL should not be treated with Cinacalcet. Hypocalcemia symptoms include parathesias, myalgias, muscle cramping, tetany, and convulsions. Cinacalcet should not be administered until serum calcium levels are above 8.0 mg/dL and/or hypocalcemia symptoms are resolved.

Common side effects include stomach upset, vomiting, diarrhea, dizziness, nausea, weakness, chest pain etc. Clinical trials conducted in the United States by Amgen to determine whether the drug is safe for children were halted by the FDA in February 2013, following the death of a 14 year old patient[25]. Cinacalcet should be taken with food or after a meal for increased absorption of the medication and its dosing is patient dependent and needs to be individualized.

Regarding to the mechanism of action, Cinacalcet acts on the calcium-sensing receptors on the surface of the chief cell of the parathyroid gland that is the principal regulator of parathyroid hormone secretion (PTH)[26]. Cinacalcet increases the sensitivity of calcium receptors on parathyroid cells to reduce parathyroid hormone (PTH) levels and thus decrease serum calcium levels. As receptors are already activated by the calcimimetic (Cinacalcet), the native rise and fall of Calcium levels now interact with the remaining receptors, effectively lowering the threshold for activation of feedback on the parathyroid chief cells. Below (Table 1.3) worldwide sales figure and consumption of Cinacalcet hydrochloride are shown.

Table 1.3 Worldwide consumption of Cinacalcet hydrochloride

	Sales in $ (USD) Million			Consumption in Kg (Kilogram)		
Country	**Dec 2014**	**Dec 2013**	**Change in [%]**	**Dec 2014**	**Dec 2013**	**Change in [%]**
USA	899	767.4	17.1	1880.6	1826.4	3
EU top 5	207.7	191.4	8.5	864.5	800.2	8
Rest of Europe	73.5	72.8	1	307.6	293.6	4.8
Latin America	2.2	1.8	22.2	10.4	7.8	33.3
Rest of world	180.7	175.4	3	1207.8	1080.9	11.7
Worldwide	1363.2	1208.9	12.8	4271	4008.8	6.5

As explained above, the two targets (Eletriptan hydrobromide and Cinacalcet hydrochloride) involve some common transition metal catalyzed reactions, in particular Heck cross coupling followed by carbon-carbon double bond hydrogenation, and also other transformations that require catalysts; the main elements of the utilized transition metal catalysts for these reaction are palladium and rhodium. Catalysts play a very important role in modern technological society, in particular in the synthesis or production of pharmaceuticals, fine chemicals, agrochemicals, fuels, etc[27-28].

Generally, the main three important properties of catalysts are: activity, selectivity and stability. The stability of catalyst is most important property out of these three, because the catalysts that lose activity during a reaction process can be sometimes regenerated but they have to be replaced after many regenerations. The entire lifetime of a catalyst is important for the economics of the process[27] and also for the economic impact on the society[28].

1.4. Metal supported poly perfluorinated Lewis acid catalysts for acylation of heterocyclic compounds. Introduction

The acid catalyzed reactions play a very important role not only in the pharmaceuticals, petrochemical and bulk industry but also in the manufacture of a wide variety of fine and specialty chemicals, including agrochemicals, flavours and fragrances. The use of classic Brønsted acids (H_2SO_4, HF, HCl, p-toluenesulfonic acid etc.) or Lewis acids, such as $AlCl_3$, $ZnCl_2$, BF_3, is involved in many different transformations especially for their cheapness[29] but, the main problems of their use are the low selectivity and stability at higher temperature and the generation of inorganic salts during the work-up due to the neutralization of crude reaction mixtures. This fact leads to the production of large amounts of aqueous and inorganic wastes. A solution to this problem could be the replacement of classic acid catalysts with recyclable solids acids. Many different heterogeneous acid catalysts have been developed; for example, zeolites, heteropolyacids, supported metal oxides, clays and sulfonated perfluorocopolymers are widely used as Brønsted and Lewis acid in different types of reactions[30]. This choice has many advantages; separation and recycling is accessible, generally solid acids are safer and easier to handle than their classic analog, (e.g. HCl, H_2SO_4, HF); some classic acids systems are highly corrosive and require expensive reactors and equipment, product contamination by traces of (neutralized) catalyst this could be normally avoided when the catalyst would be solid.

In the cases of acid catalysis it is also important to underline the use of some metal triflates as Lewis acids in several different kinds of reaction instead of classical catalysts[31]. They are able to work in commercial organic solvents or also in water and often their use is in catalytic amount rather than in stoichiometric amount. However, it is also important to note that some disadvantages exist also here; for example, their preparation may require the use of expensive rare earths or precious metals. Furthermore, the recycling of these kind catalysts is not always possible and depends on nature and stability of the catalyst.

By considering all above advantages and disadvantages, during the study of this thesis work it was decided to investigate preparation, characterization and application of some metal supported poly-perfluorinated acid catalysts as new Lewis acid catalysts and to compare their properties with commercial metal triflates. As matter of fact the synthesis of Eletriptan hydrobromide molecule by originator root involves the acylation of 5-bromoindole by using a Grignard reagent and a complex acylchloride; this process requires very dry and inert conditions to perform the reaction and also needs an excess amount of the Grignard reagent. Therefore it was decided to explore a model acylation reaction catalyzed by metal triflates and metal supported poly-perfluorinated solid acid catalysts on 5-bromoindole using acetic anhydride as a acylating agent. In the case of successful results in the future it would be possible to investigate this reaction with the specific acyl chloride.

1.5. Polyester-based homogeneous Pd catalyst for the hydrogenation of α,β- unsaturated carbonyl compounds

During this thesis work, the application of a polyester-based homogeneous Pd catalyst[32] prepared in University of Florence was also studied. We investigated its catalytic activity in the hydrogenation of carbon-carbon double bond of some α,β- unsaturated carbonyl compounds, as we know these hydrogenated compounds are important for manufacturing useful fine chemicals as intermediates for the synthesis of pharmaceuticals, additives, food flavours and valuable building blocks for fragrances, etc.

1.6. Water-soluble [Rh]-thioligand species for selective hydrogenation of aromatic halo nitro compounds

During this thesis work, our research was also addressed to investigate rhodium species modified with a new cheap, water soluble thioligand, i.e. the dihydrothioctic acid sodium salt (DHTANa), a molecule which presents two -SH groups capable to work as a bidentate ligand for the rhodium atom. The use of water as co-solvent for biphasic reactions and of easily recyclable water-soluble catalysts are highly desirable for the realization of greener and more sustainable processes[33-35].The pre-catalyst was easily prepared by mixing $[Rh(COD)Cl]_2$ and the thioligand in water; this mixture, under inert atmosphere, remains stable for months and it is possible to see by NMR spectrum that there is an interaction of Rh with sulphur atoms.

To perform the reaction in biphasic system, different kinds of solvents as ionic liquid, per-fluorinated compounds, supercritical fluids and water may be considered[33] but without any doubt, water is the most sustainable solvent as it presents the following properties:

1. It is non toxic;
2. It is not flammable;
3. It is polar and simple to separate from many organic solvents;
4. It is inexpensive and available in large quantity;
5. Its density is different from many organic solvents;
6. Gases dissolve well in it;
7. It has amphoteric behavior;
8. Contaminations are easily recognizable.

To use water as a solvent, it is necessary to design a hydrophilic catalyst or a catalyst having hydrophilic ligands such as, for e.g. sulphonated phosphines. The application of this type of catalysts in industrial hydroformylation processes represents one of the most striking example of this catalytic methodology[36].Other ligands with hydrophilic groups (SO_3^-; COO^-; NMe_3^+; OH^-;etc.) may be also used[34].

Results obtained in the hydrogenation reaction of different α,β-unsaturated carbonyl substrates with this new water soluble Rh[(DHTA)Na] species were very promising, observing good catalytic activities and possibility for recycling. Now here we studied the application of this catalyst to the hydrogenation of some halo-nitro compounds to verify selectivity and applicability to the preparation of halo-anilines, that are valuable intermediates in the production of some agrochemicals, azo-dyes and pigments, bactericides and pharmaceuticals, etc.

1.7. Microwave assisted studies of Heck cross coupling, hydrogenation and reductive amination reaction. Introduction

Our further research was also addressed to investigate the total synthesis of Cinacalcet hydrochloride under Microwave irradiation. The microwave irradiation was firstly reported on the use in organic chemistry in the mid-1980s[37-39]. After that dedicated commercial microwave reactors for chemical synthesis became available, a wider spread of microwave energy in academic and industry for various chemical transformations was promoted. Nowadays, this enabling technology has been considerably exploited in organic synthesis and drug discovery[40]. Microwave

technology triggers heating into the reacting system by either dipolar polarization or ionic conduction. When irradiated at microwave frequencies, electromagnetic waves pass through the dipoles or ions of the sample and cause the molecules to oscillate. In this process, energy is lost in the form of heat through molecular friction and dielectric loss. Because microwave radiation is introduced into the reaction system remotely without direct physical contact with reaction materials, this can lead to a rapid temperature increase throughout the sample causing less by-products or decomposition of products. In contrast, conventional heating of organic reactions such as oil baths, sand baths or heating mantles are rather slow and create an internal temperature gradient, which may result in localized overheating and reagent decomposition when heated for longer periods. The most prominent advantage of controlled microwave dielectric heating for chemical synthesis is the dramatic reduction in reaction time from days and hours to minutes. Moreover, microwave heating is able to reduce side reactions, increase yields, improve reproducibility, allow to control of temperature and pressure, and even realize "impossible" reactions by conventional heating. In early days, microwave heating was often used as an optional protocol when a particular reaction has failed to proceed under other conditions or requires exceedingly long reaction time or high temperature. A large number of articles have been published in the area of microwave synthesis, including a number of general and specific review, articles[41-45] and several books[46-52].

In particular, transition metal-catalyzed reactions are of enormous significance to form carbon-carbon and carbon-heteroatom bonds in organic synthesis. These reactions typically need hours or days to reach completion under conventional heating conditions and often require an inert atmosphere. Microwave heating has been demonstrated over the past few years to significantly expedite these transformations, in most cases without an inert atmosphere. Furthermore, the inverted temperature gradients under microwave conditions may lead to an increased lifetime of the catalyst by elimination of wall effects[53]. For this reason we decided to study the transition metal catalyzed Heck cross coupling followed by hydrogenation of carbon-carbon double bond and direct metal catalyzed reductive amination reaction.

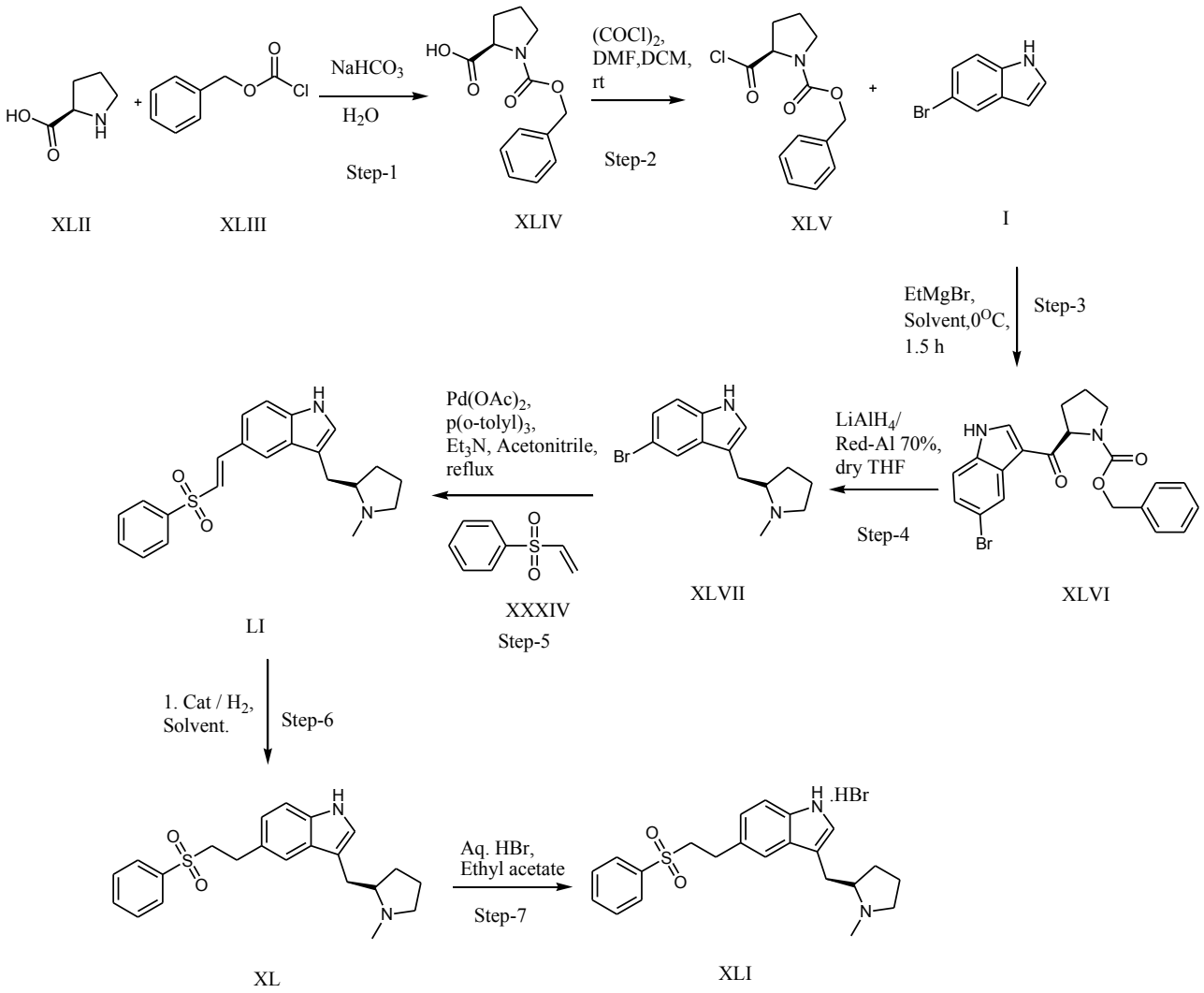
Chapter 2: Aim of thesis

The main aim of this thesis work was to try to develop greener and more sustainable processes. It requires not only to prepare and apply new catalytic systems or compare them with the best commercially available catalysts, but also to study different reaction parameters as type of solvent, preferring greener ones, productivity, selectivity, etc. and try to find the best compromise also by a preliminary raw material cost evaluation.

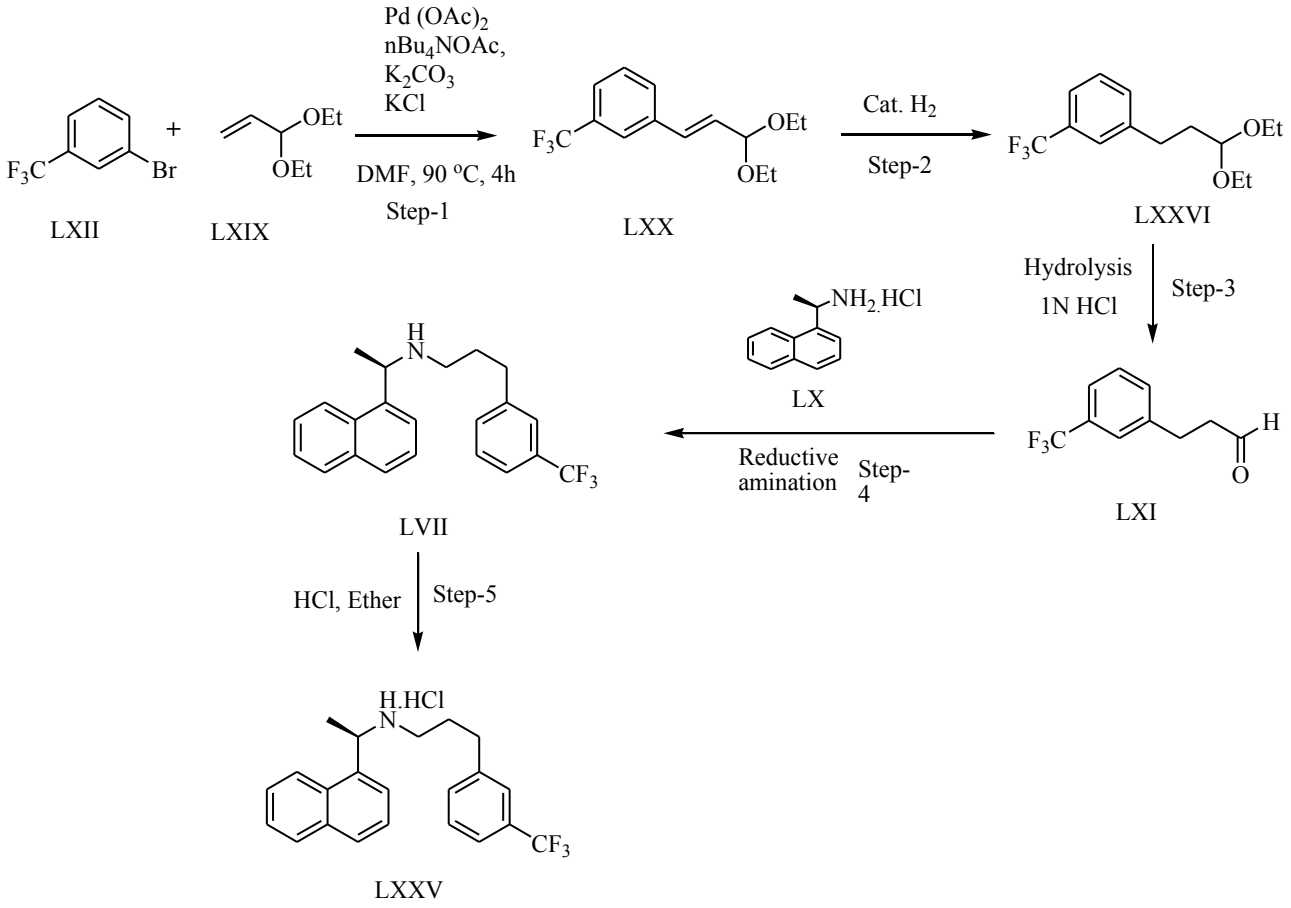
In this research activity new heterogeneous, homogeneous and water soluble catalysts suitable for hydrogenation, reduction, C-C bond formation reactions, as part of the current research work in the laboratory where this thesis was carried out, will be prepared and applied in different reactions of potential industrial interest. These activities, during this Ph.D. tenure, would have permitted to me either to deep my knowledge in the production of catalysts and fine chemicals or to open new improved routes for greener synthesis.

As detailed application, key steps or total synthesis, of two active pharmaceutical ingredients (APIs), Eletriptan hydrobromide and Cinacalcet hydrochloride, will be studied working under conventional heating mode as well as under microwave-assisted irradiation.

In scheme 2.1 and scheme 2.2, the synthetic path of both target compounds are shown.



Scheme 2.1 Synthetic scheme of Eletriptan hydrobromide according to the originator[54]



Scheme 2.2 Alternative synthetic scheme of Cinacalcet hydrochloride compared with the originator route

In both synthetic schemes, Heck cross coupling reaction and hydrogenation of carbon-carbon double bonds are involved, so we will focus our attention on the optimization of these two reactions in order to increase both yield and selectivity but, at the same time, lowering the amount of catalyst and reaction time.

Heck reactions will be carried out in the presence of some homogeneous palladium based catalysts at different reaction conditions (temperature, time and greener solvent) and in the presence or absence of different phosphino ligands and bases.

Hydrogenations will be performed in the presence of known homogeneous and/or heterogeneous catalysts, working in different reaction conditions. In particular, our main goal will be to test in particular the activity of new homemade heterogeneous catalysts at very low metal content as 0.28 % Pd/Al_2O_3 and 0.18 % Rh/Al_2O_3 and to compare their activities with those of commercially available catalysts. Furthermore, very interestingly, a new a polyester-based homogeneous Pd

catalyst will be employed in the hydrogenation process. This homogeneous macrocomplex can be easily separated from the reaction mixture by methanol induced precipitation and thus it can be easily recycled. This system therefore combines the activity and selectivity of a homogeneous catalyst with the easy recovery and recyclability of a heterogeneous one. The activity of the new catalysts will be first tested on model substrates and then applied to the target molecules.

In order to decrease reaction time and to increase product selectivity, some of these catalytic reactions will be carried out under microwave irradiation and the results compared to those obtained under conventional reaction conditions. The majority of the microwave-promoted reactions reported so far depend on homogeneous catalysis and are catalyzed by palladium[55].

In the synthesis of Eletriptan we will address our attention also to the synthesis of the important intermediate (**XLV**) this is not commercially available and represents a key intermediate to be acylated to the corresponding ketone (**XLVI**) (Scheme 2.1). Friedel-Craft acylations catalyzed by conventional catalysts present many drawbacks as the stoichiometric amount of catalyst and the formation of wastes. In order to reduce wastes, also heterogeneous acid catalysts have been developed including the use of acid groups functionalized polymers. Among these polymers, one thoroughly investigated and used as Brønsted and Lewis acid catalyst in organic synthesis is Nafion® and its metal salts. However, this polymer presents a very low surface area so that the activity of this material in non-swelling solvents may be very low. In the last years Solvay Specialty Polymers S.p.A. produced a new perfluorinated polymers so we will prepare the corresponding new iron and gallium salts to be used in the Friedel-Craft acylation. Preliminary experiments will be carried out acylation on 5-bromo-1H-indole **(I)** chosen as model substrate and then the catalysts in future could be applied to the target molecule. A comparison with known catalysts will be done.

Chapter 3: Novel catalysts and applied research for the synthesis of fine chemicals. Results and discussion

3.1. Brønsted and Lewis acid catalysis: Introduction

Acid catalysts play a key role in petrochemical and bulk industry but also in manufacturing a wide variety of fine and specialty chemicals including pharmaceuticals, agrochemicals, flavours and fragrances. The use of traditional Brønsted and Lewis acids is generally characterized by the high amount of unwanted wastes generated during the work-up and in certain cases also when low reaction conversion and selectivity are obtained. As earlier reported in 1991, the use of water-compatible lanthanide metal triflates, as Lewis Acid catalysts, was described[56]. After this review literature, many triflates have been developed and applied in organic synthesis. An interesting advantage is that these catalysts can be used in true catalytic amount, unlike many other traditional Lewis acid catalysts, in some reactions such as Friedel-Craft acylation reaction and, furthermore, they can also work in mixture of organic/water solvents. Another advantage is that sometimes there is the possibility to recover them from the crude reaction mixture and to reuse for next reaction. However, rare earth metals are expensive and precious; for this reason other triflates have been investigated such as Zn, Fe, Ga and In triflates[57], being these metals more available in nature and much cheaper in comparison to other rare earth metals.

In order to reduce wastes and maintain the sustabinility, also heterogeneous acid catalysts have been developed including the use of polymers functionalized with acid groups . Among these polymers, one thoroughly investigated and used as Brønsted and Lewis acid catalyst in organic synthesis, is Nafion® which was developed by W. Grot at DuPont in 1960s. It is synthesized by the free radical copolymerization reaction between tetrafluoroethylene and perfluorinated vinyl ether monomers (Figure 3.1.1).

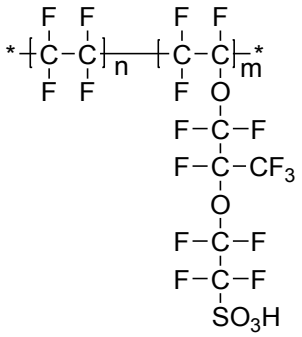


Figure 3.1.1. Structure of Nafion®

Nafion® polymer was the first polymer belonging to the ionomers class. The use of Nafion®, as Brønsted acid, and its salts (such as Cr, Ce, Hg) as catalysts for acylation, alkylation, nitration, polymerization, sulfonation, oxidation, hydration and other reactions is deeply described in literature[58-59]. However this polymer presents some disadvantages, the major being the very low surface area so that the activity of this material in non-swelling solvents may be very low. This in turn has limited the application in Brønsted acid catalyzed reactions. In order to increase the acid site accessibility of Nafion® resin-based catalysts, a class of solid acid catalysts based on a high surface area Nafion® resin silica nanocomposite, has been then developed, where nanometer sized Nafion® resin particles are entrapped within a highly porous silica network[60-61]. The property of other Nafion® salts as Lewis acids have been less studied; only recently Nafion®-Fe[62] and Nafion®-Ga[63-64] were prepared by cation exchange reaction procedure starting from Nafion®-K salt and $FeBr_3$ or $GaBr_3$ in halogenated solvents at reflux temperature and then used as catalysts. Even if they are claimed as green Lewis acid catalysts the protocol for their preparation produces a lot of wastes.

During this thesis work and a contemporary research investigation in the group where this thesis was performed, the preparation, characterization and application of metal salts of another polyfluorinated polymer were carried out. This polyfluorinated polymer is known as Aquivion® PFSA (PerFluoroSulfonic Acid, and from here afterwards called as Aquivion®) and it is produced by Solvay Specialty Polymers S.p.A. by emulsion free radicals co-polymerization reaction between tetra-fluoroethylene and a suitable sulfonyl vinil ether. The structure of Aquivion® is shown below (Figure 3.1.2).

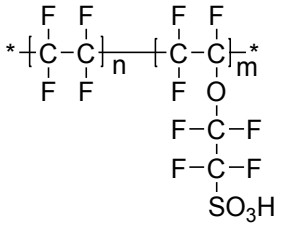
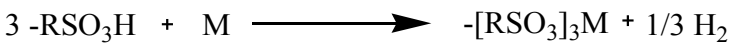


Figure 3.1.2. Structure of Aquivion®

In particular Aquivion®-Fe, -Ga or –In, never investigated before in literature, were synthesized using a simple and more sustainable approach, according to the following Scheme 3.1.1:



Scheme 3.1.1. Reaction between metal and sulfonic groups of Aquivion®

It was thought that one mole of metal could react with three sulfonic groups so that three moles of Aquivion®, where the load of sulfonic groups is equal to 1 eq. per 870 g of polymer were necessary. The procedure to obtain Aquivion®-M is described in detail in the experimental part (paragraph 6.5.3.1). The preparation was carried out at reflux temperature in acetonitrile for many hours.

During the preparation of Aquivion®-In, it was observed that the reaction between metal and polymer was very slow: after 48 h, the presence of unreacted Indium was observed and the polymer remained partially white into the reactor. After two weeks the polymer became grey but some Indium particles were still observed. Better results were obtained when we prepared Aquivion®-Fe and Aquivion®-Ga. The reaction time was 48 h, after that it was found that the polymer was yellow when iron was used and grey in the case of Aquivion®-Ga shown in (figure 3.1.3).

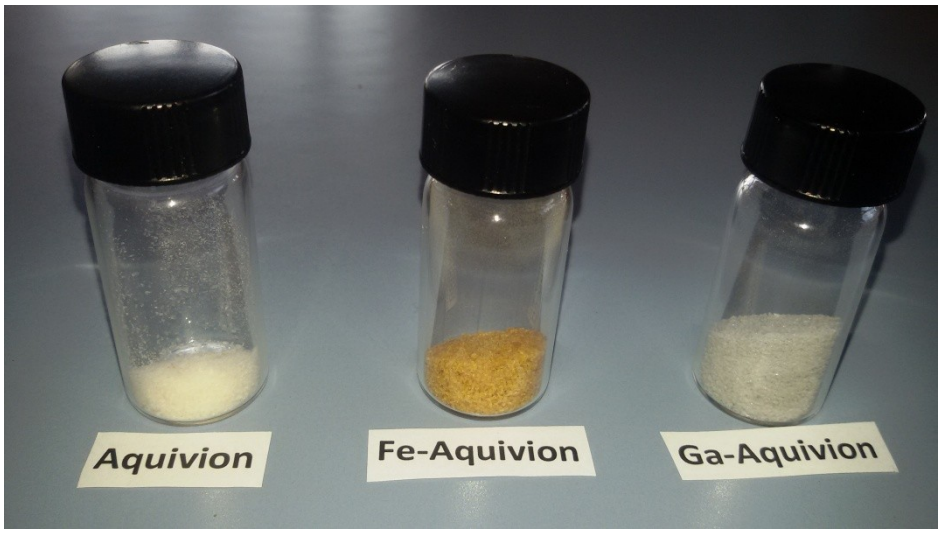


Figure 3.1.3 Colour difference between Aquivion® and Aquivion®-M

During the preparation of these two species, relevant residual pieces of metals were not detected. After analysis, kindly made by Solvay Specialty Polymer S.p.A staff adopting the method reported in the experimental part (paragraph 6.5.3.2), the following results were obtained (Table 3.1.1)

Table 3.1.1 Determination of metal loading in Aquivion®-Fe and Aquivion®-Ga

Sample	Theoretical metal loading (w/w %)	Determined metal loading (w/w %)	Theoretical metal loading (mol/mol %)	Determined metal loading (mol/mol %)	$-SO_3H$ exchanged (%)
Aquivion®-Fe	2.140	2.053	33.33	32.01	96.03
Aquivion®-Ga	2.670	3.033	33.33	37.85	113.57

At the light of the obtained analytical data, it is possible to say that the preparation protocol developed seems to be effective in quantitatively exchange the sulfonic acid functions available in Aquivion®; the slight differences from the 100 % theoretical amount are probably due to light weighing errors of both reagents during the preparation of the catalysts. The present procedure permits to obtain in a simple way these Aquivion® salts, the reaction solvent may be easily recovered and the metalized polymer, after a rapid drying under vacuum, is ready for use as Lewis catalyst[65]. Further analysis were made by using advanced techniques are explained below.

The technique ATR-FTIR allows to collect useful information without any manipulation of the sample[66]; for this reason it was used for registering spectra of Aquivion® and its salts (Figure 3.1.4). The more interesting and diagnostic zone seemed to be that between 1800 cm^{-1} and 1400 cm^{1} where the spectrum of Aquivion® (**a**) presents a broad band centred at 1735 cm^{-1} and both Aquivion-Fe and -Ga spectra (**b** and **c**, respectively) have three peaks between 1660 and 1450 cm^{-1}. However, a sample of Aquivion® powder, after treatment with acetonitrile at reflux temperature for 8h, was filtered with some difficulty (a film was formed instead of the starting powder): the sample was dried under vacuum and reanalyzed by ATR-FTIR; (Figure 3.1.4 (**d**)). In the obtained spectrum three peaks, instead of the previous broad band, are observed between 1800cm^{-1} and 1400 cm^{-1}.

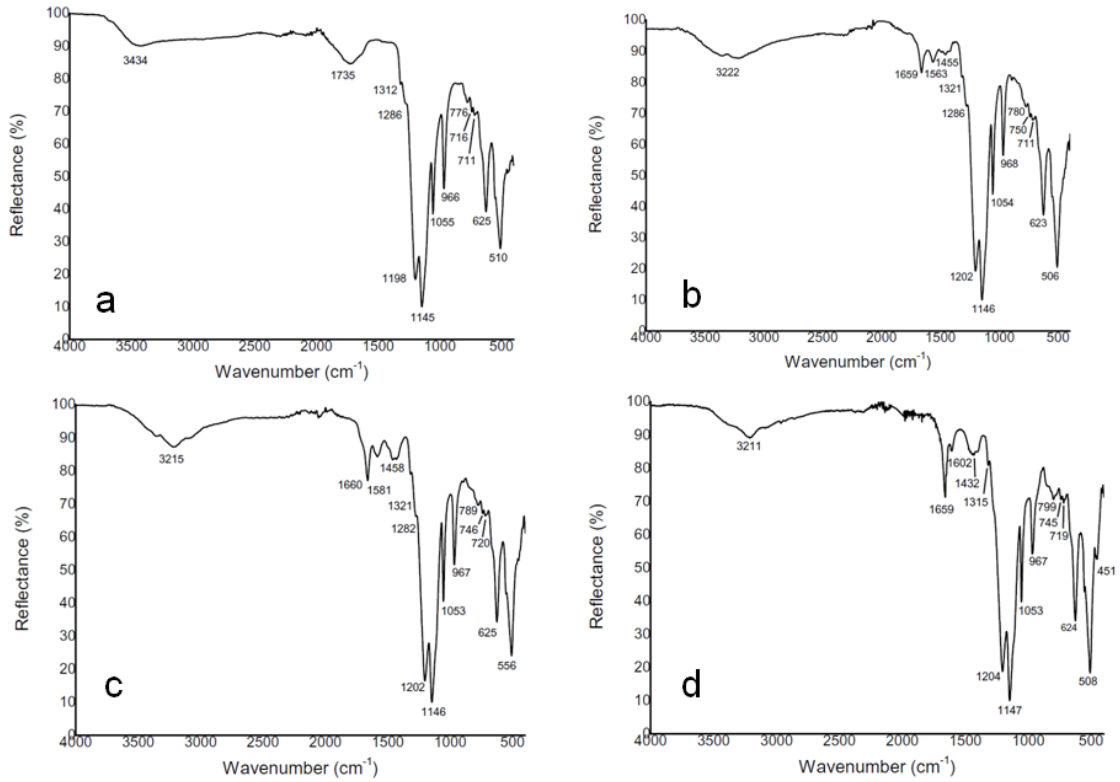


Figure 3.1.4: ATR-FTIR spectra obtained for respectively: Aquivion® (a); Aquivion®-Fe (b); Aquivion®-Ga (c); Aquivion® treated with acetonitrile (d)

A possible interpretation of this different result is that in spectrum a) in this region were present also bands due to a small amount of water originally present in Aquivion® powder (signals could be attributed to the bending of –OH bond) that was removed by treatment with acetonitrile. Therefore no substantial difference was found between Aquivion® and its salts by using this analytical technique.

The TG-DSC curves of the Aquivion® and its salts, obtained from 30 to 650 °C under N_2 flow rate, are reported in (Figure 3.1.5). All thermograms show three mass losses and a behavior similar to that of Nafion® comparing to literature results[67]. As expected, Aquivion® is a little bit more stable than Nafion®. Interesting is the mass loss observed in the temperature range 180-300 °C that can be related to the decomposition of $–SO_3$ groups, in agreements with other studies**.** This mass loss is clearly present in the TG-DSC Aquivion® curve (Figure 3.1.5, a), but it is less evident and defined for the Aquivion®-Fe and Aquivion®-Ga (Figure 3.1.5, b and c respectively). Both the Aquivion® salts seem to have a more stable temperature profile also in the range 300-400 °C with a minimum mass loss. This enhancement would permit to use both Aquivion® salts also in Lewis acid catalyzed gas phase reactions.

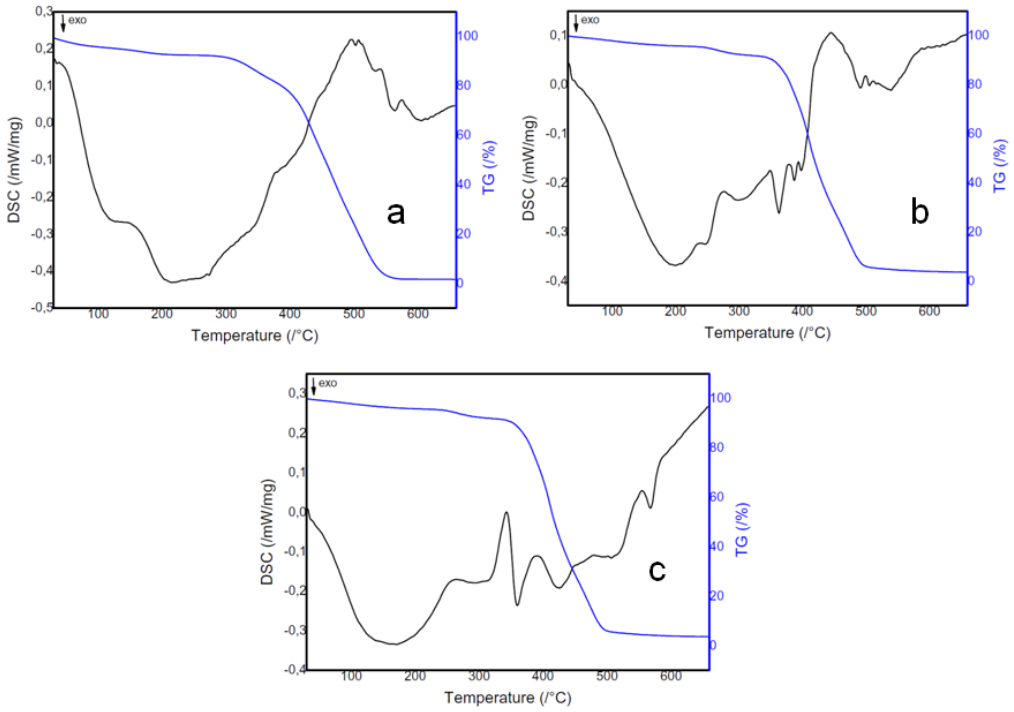


Figure 3.1.5: TG-DSC thermograms of Aquivion® (a), Aquivion®-Fe (b) and Aquivion®-Ga (c)

Finally, samples of Aquivion®-Fe and -Ga, analyzed by optical microscopy, compared to Aquivion® show a nearly homogeneous distribution of metallic cationic species in the polymer even if the presence of small amount of unreacted metallic particles cannot be excluded (Figures 3.1.6; a, b, c).

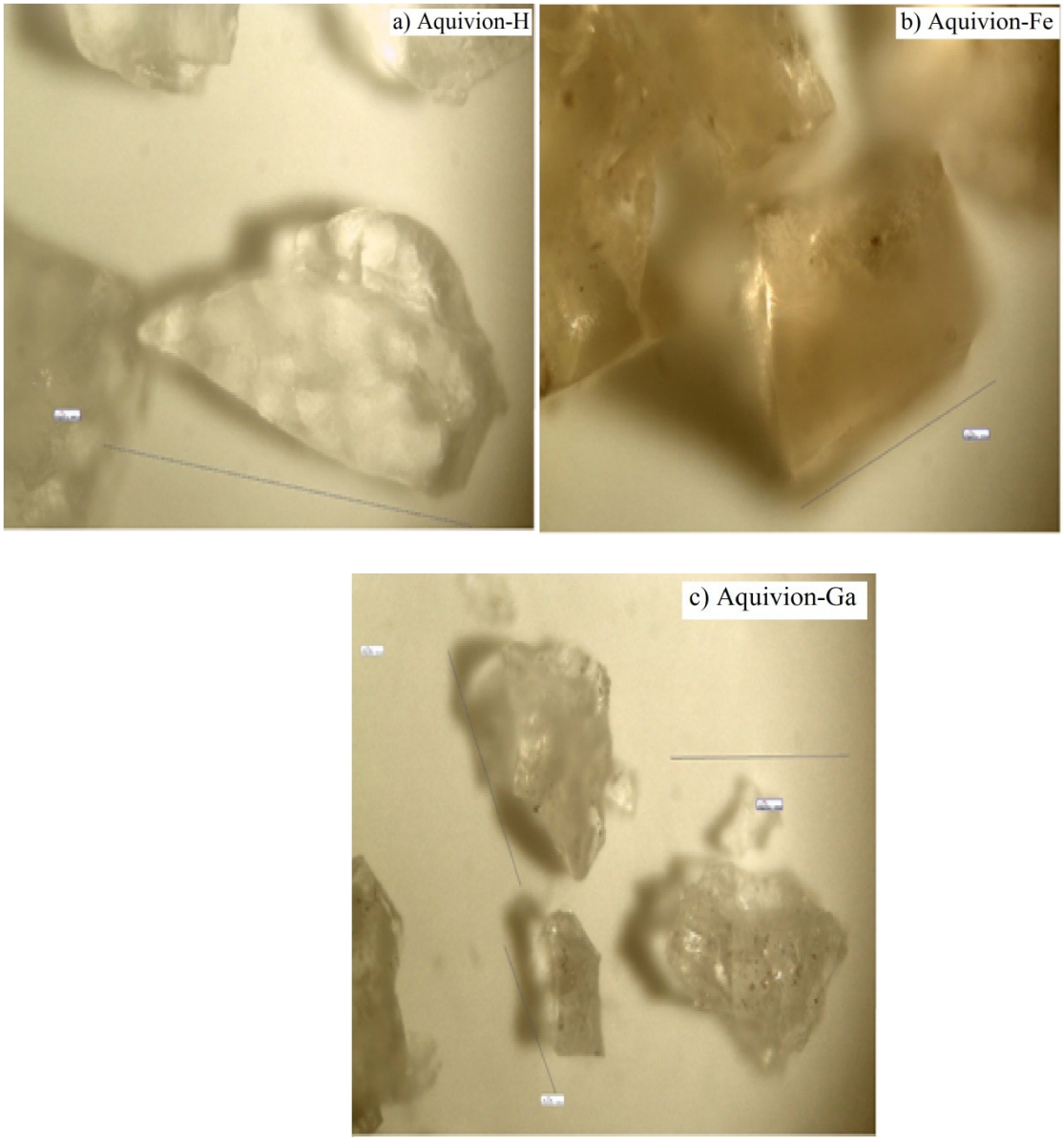


Figure 3.1.6: Optical microscopic images of a) Aquivion®, b) Aquivion®-Fe, c) Aquivion®-Ga

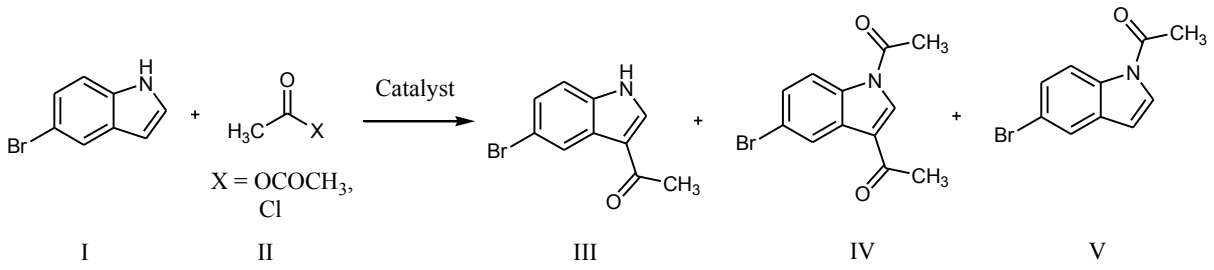
Probably the preparative protocol here adopted could be conveniently applied also for preparing the corresponding metalized Nafion® and is surely more sustainable than the previously described procedure[68]. The application of these new Lewis acids in Friedel-Crafts acylation of some heterocyclic compounds was studied (Scheme 3.1.2).

3.1.1 Applications of Aquivion®-M and Aquivion®

In this work of thesis, the catalytic applications of Aquivion®-M species in the Friedel-Craft acylation of 5-bromo-1H-indole **(I)** was studied because it could be a useful alternative for the synthesis of intermediates for the antimigrane Eletriptan hydrochloride (in the originator synthetic root the acylation of indole derivative requires the use of a Grignard reagent).

Another application which will be described later in Chapter-4 regards the use of Aquivion®-Fe as catalyst in the $NaBH_4$ reductive amination step of the synthesis of the pharmaceutical Cinacalcet.

3.1.1.1 Acetylation of 5-bromo-1H-indole (I) catalyzed by Aquivion®-M, Aquivion® or commercial metal triflates



I II III IV V

Scheme 3.1.2 Acetylation of 5-bromo-1H-indole (I) catalyzed by Aquivion®-M, Aquivion® or metal triflates

The acetylation of **(I)** was initially carried out by using acetic anhydride as acylating agent, different commercial metal triflates[69] as catalysts and in presence or absence of another solvent. In the first reaction by using 5 mol % of $In(OTf)_3$ as catalyst (run 1) it was observed that after 24 h reaction time the conversion was only 40 %; this is probably due to the low reaction temperature (25 °C). In fact, in a further experiment (run 2) carried out under the same conditions of (run 1) but increasing the reaction temperature at 90 °C, after 12 h, 95 % conversion was obtained; after work-up and purification 3-acyl-5-bromo-1H-indole product **(III)** gave 92 % isolated yield. When the reaction was carried out using acetonitrile as a solvent and only equimolar amount of acetic anhydride only 18 % of conversion was observed (run 3), while using acetyl chloride as acylating agent, 56 % conversion was found but the reaction mixture contained 32 % of 3-acyl-5-bromo-1H-indole **(III)** and 24 % of 1,3 di-acyl-5-bromo-indole **(V)** (run 4). Then experiments were carried out also using 5 mol % of $Ga(OTf)_3$ as catalyst; the obtained results are shown in Table 3.1.2 (runs 5 and 6); in neat

acetic anhydride 96 % conversion and excellent selectivity toward 3-acyl-5-bromo-1H-indole **(III)** was obtained; at the same reaction conditions but using acetonitrile as solvent a lower conversion was found.

Table 3.1.2 Acylation of 5-bromo-1H-indole (I) catalyzed by $In(OTf)_3$ and $Ga(OTf)_3$

Run	Catalysts	T (°C) / t (h)	Solvent	Conv. [%]	III [%]	IV [%]	V [%]
1[a]	$In(OTf)_3$	25/24	Acetic anhydride	40	40	-	-
2	$In(OTf)_3$	90/12	Acetic anhydride	95	95	-	-
3[c]	$In(OTf)_3$	90/12	Acetonitrile	18	18	-	-
4[d]	$In(OTf)_3$	90/12	Acetonitrile	56	32	-	24
5[e]	$Ga(OTf)_3$	90/12	Acetic anhydride	96	95	-	1
6[f]	$Ga(OTf)_3$	90/12	Acetonitrile	53	52.3	-	0.7

Reaction conditions: [a] Substrate **(I)** (0.5 g, 2.5 mmol), acetic anhydride (1.03 gm, 10.09 mmol), **$In(OTf)_3$** (71 mg, 5 mol%). [b] Same conditions of run 1 but T = 90 °C, t = 12 h. [c] Same conditions of run 2 but acetic anhydride (0.259 gm, 2.5 mmol) and solvent acetonitrile were used. [d] Same conditions of run 2 but acetyl chloride (0.199 gm, 2.5 mmol) was used. [e] Substrate **(I)** (0.5 g, 2.5 mmol), acetic anhydride (1.03 gm, 10.09 mmol), **$Ga(OTf)_3$** (65.7 mg, 5 mol %), T = 90 °C, t = 12 h. [f] same conditions of run 5 but solvent acetonitrile was used.

The acetylation of 5-bromo-1H-indole **(I)** was studied also using Aquivion®-Ga: very promising results, shown in (Table 3.1.3), were obtained. The acetylation carried out with acetic anhydride and with a molar ratio substrate (**I**)/-$R(SO_3)_3Ga$ 320/1 at 90 °C for 2 h, in absence of solvent, afforded 100 % conversion giving 96% of 3-acyl-5-bromo-1H-indole **(III)** and 4 % of 1,3 di-acyl-5-bromo-indole **(V)** (run 1). By using this procedure the work up was very simple. After completion of the reaction, the catalyst was filtered off and the solution was concentrated under vacuum. The isolated yield of the crude 3-acyl-5-bromo-1H-indole **(III)** was about 95 %. Then the recovered catalyst was reused for three successive recycling experiments (Table 3.1.3, runs 2-4), maintaining a very good activity and selectivity towards the desired product 3-acyl-5-bromo-1H-indole **(III)**. Then reaction was carried out with acetic anhydride at 90 °C for 2 h in the presence of acetonitrile as solvent, giving 74 % conversion and complete selectivity to the desired product 3-acyl-5-bromo-1H-indole **(III).** The acylation of **(I)** was also carried out in the presence of Aquivion®. The reaction was performed at 90 °C for 2 h with a substrate **(I)**/-$R(SO_3H)$ molar ratio 320/1, in absence of any solvent, and using acetic anhydride as acylating agent (Table 3.1.3, run 6). After 2 h of reaction

time, the conversion of starting material was 90 % but the isolated yield of the desired product, after filtration of the catalyst and concentration under vacuum, was only 50 %. In absence of any catalyst no reaction was found (run 7).

Table 3.1.3 Acylation of 5-bromo-1H-indole (I) catalyzed by Aquivion®-Ga or Aquivion®

Run	Catalyst	T (°C) / t (h)	Solvent	Conv. [%]	III [%]	IV [%]	V [%]
1[a]	Aquivion-Ga	90/2	Acetic anhydride	100	96	-	4
2[b]	Aquivion-Ga	90/2	Acetic anhydride	100	95	-	5
3[b]	Aquivion-Ga	90/2	Acetic anhydride	100	94	-	6
4[b]	Aquivion-Ga	90/2	Acetic anhydride	100	96	-	4
5[c]	Aquivion-Ga	90/2	Acetonitrile	74	74	-	-
6[d]	Aquivion	90/2	Acetic anhydride	90	60	5	25
7[e]	-	90/2	Acetic anhydride	-	-	-	-

Reaction conditions: [a] Substrate **(I)** (2.22 g, 11.29 mmol) Acetic anhydride (4.61 gm, 45.19 mmol) Aquivion®-Ga (98 mg, **I**/-R$(SO_3)_3$-Ga 320/1 molar ratio). [b] Reaction carried out by using the catalyst recovered from the previous run. [c] Same conditions of run 1 but acetyl chloride (0.886 g, 11.29 mmol) and acetonitrile 10 mL were used. [d] Same conditions of run 1 but by using only Aquivion® [(**I** / -R$(SO_3)_3$), 320/1]. [e] same conditions of run 1 but without catalyst.

Similar good results were obtained also using Aquivion®-Fe as catalyst (Table 3.1.4). For comparison the same reaction was studied also in the presence of cheap SiO_2/ZrO_2as catalyst, using the conditions reported in footnotes of Table 3.1.4 (runs 6 and 7), but the results were modest, obtaining at the best 20 % conversion.

Table 3.1.4 Acylation of 5-bromo-1H-indole (I) catalyzed by Aquivion®-Fe and SiO_2/ZrO_2

Run	Catalyst	T (°C) / t (h)	Solvent	Conv. [%]	III [%]	IV [%]	V [%]
1[a]	Aquivion-Fe	90/2	Acetic anhydride	100	92	-	8
2[b]	Aquivion-Fe	90/2	Acetic anhydride	100	95	-	5
3[b]	Aquivion-Fe	90/2	Acetic anhydride	98	94	-	4
4[b]	Aquivion-Fe	90/2	Acetic anhydride	90	86	-	4
5[c]	Aquivion-Fe	90/2	Acetonitrile	55	54	-	1
6[d]	SiO_2/ZrO_2	90/2	Acetic anhydride	No	-	-	-
7[e]	SiO_2/ZrO_2	90/22	Acetonitrile	20	20	-	-

Reaction conditions: [a] Substrate **(I)** (2.22 g, 11.29 mmol) Acetic anhydride (4.61 gm, 45.19 mmol) Aquivion®-Fe (98 mg, **I**/-$R(SO_3)_3$-Fe 320/1 molar ratio), T = 90 °C, t = 2 h. [b] Reaction carried out by using the catalyst recovered from the previous run. [c] Same conditions of run 1 but acetonitrile 10 mL where used. [d] Same conditions of run 1 but by using catalyst SiO_2/ZrO_2 10 % (w/w). [e]Same conditions of run 6 but acetonitrile solvent where used.

In order to get information on the selectivity of this reaction, a kinetic study of the reaction catalyzed by Aquivion®-Ga in acetic anhydride, used either as reagent or as solvent, was carried out. The results are reported in Table 3.1.5. Also at very low conversion, small amounts of 1-acetyl-5-bromo-indole **(V)** and 1,3-diacetyl-5-bromo-indole **(IV)** are present in the reaction mixture; noteworthy, the amounts of these products remain very low also at complete substrate conversion and even if in the presence of an excess of acylating reagent. In any case the regioselectivity is good and this can be due to the steric hindrance of the catalyst structure. Furthermore, it is to underline that on the contrary to what usually observed in the presence of other Lewis acids[70-73] with Aquivion®-Ga or Aquivion®-Fe no detectable amount of by-products, due to self-polymerization of the indole moiety, was observed. After purification by column chromatography, an isolated yield of about 85 % of **(III)** was obtained.

Table 3.1.5 Kinetic study result of acylation of 5-brom-1H-indole (I) by using Aquivion®-Ga

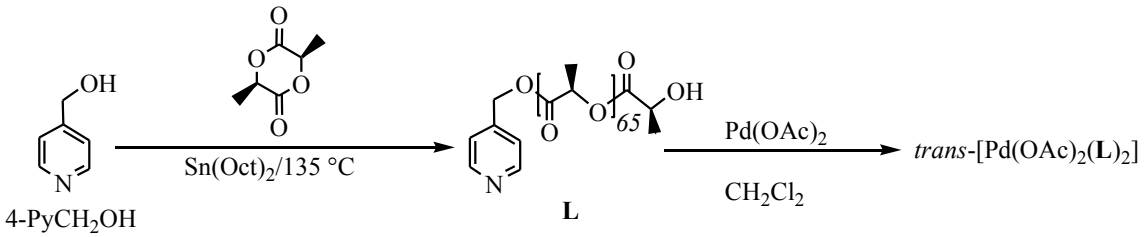
Sample analysis time (min)	Conv. [%]	III [%]	IV [%]	V [%]
30	35.3	33	1	1.3
60	85.3	81	1.8	2.4
90	94.5	87.6	4.4	2.5
120	100	92	5	3

Reaction conditions: Substrate **I**(2.22 g, 11.29 mmol) Acetic anhydride (4.61 gm, 45.19 mmol) Aquivion®-Ga (98 mg, **I**/-R$(SO_3)_3$-Ga 320/1 molar ratio), T = 90 °C, t = 2 h.

On the basis of these results we can assert that the performances of these new catalysts in Friedel-Craft acylation of indole, as well as of other electron rich heterocycles[65], working under solvent-free conditions or using acylating reagent also as solvent, are promising and permit to obtain products of high purity in good yield by a simple work-up and with less wastes.

3.2 Hydrogenation applications and characterization of a new Pd-pyridine poly(l-lactide) macrocomplex

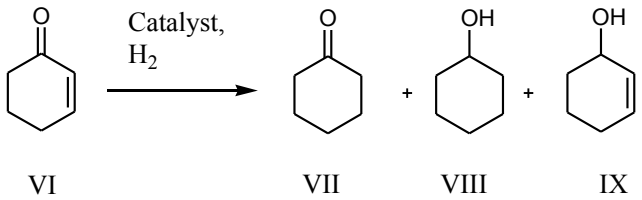
Recently, an innovative Pd-pyridine poly(l-lactide) macrocomplex, *trans*-[$Pd(OAc)_2(L)_2$], was prepared at the University of Florence by reaction of $Pd(OAc)_2$ with 4-pyridinemethylene-end-capped poly(l-lactide) (macroligand **L**)[74], as shown in Scheme 3.2.1[75], and it was applied to catalyze the aerobic oxidation of selected primary and secondary alcohols[76].



Scheme 3.2.1 Synthetic scheme for to prepare Pd-pyridine poly(l-lactide) macrocomplex

During an exploratory research carried out in the present thesis work it was investigated the capability of *trans*-[$Pd(OAc)_2(L)_2$] to catalyze also the hydrogenation of selected bifunctionalized fine chemical substrates, precisely 2-cyclohexen-1-one (**VI**), (E)-4-phenylbut-3-en-2-one **(X)**, (E)-4-(6-methoxy-2-naphthyl)but-3-en-2-one (**XIII**), (E)-3-phenylprop-2-enal **(XVI)** and (2E)-3-(1,3-benzodioxol-5-yil)-2-methyl-prop-2-enal (**XIX**). An experiment on the unsaturated intermediate of Eletriptan was also performed and it will be reported in the dedicated paragraph (**4.1**). The macrocomplex resulted soluble under the applied catalytic conditions but, upon addition of a hydrocarbon solvent or preferably methanol, the polymer-anchored Pd catalyst precipitated allowing the separation from the reaction solution. Therefore it could be interesting to verify its recyclability and to have information on its structural characteristics before and after use. A first set of reaction was carried out on 2-cyclohexen-1-one (**VI**).

3.2.1 Hydrogenation of 2-cyclohexen-1-one (VI) catalyzed by trans-*[Pd(OAc)$_2$(L)$_2$]*



VI VII VIII IX

Scheme 3.2.2 Hydrogenation of 2-cyclohexen-1-one (VI)

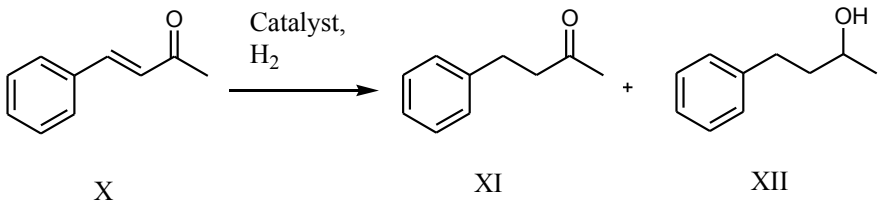
After optimization of the reaction conditions, 100 % of both conversion and selectivity to **(VII)** was achieved (run 8, table 3.2.1). After each experiment, the catalytic system was precipitated by simply adding methanol to the solution. The catalyst was then filtered, dried under vacuum and reused in a consecutive experiment: noteworthy, the catalytic activity and selectivity to cyclohexanone **(VII)** remained unchanged even after three recycling experiments (run 9-11, table 3.2.1). As *trans*-[Pd(OAc)$_2$(**L**)$_2$] was synthesized from Pd(OAc)$_2$ and the polylactide ligand **(L)**, a reaction was carried out in the presence of Pd(OAc)$_2$ alone without any external ligand and in the same experimental conditions, in order to make a comparison of the two systems: cyclohexanone **(VII)** was obtained with a 95 % yield already after 1h, but the catalyst decomposed with formation of an unsoluble and catalytically inactive Pd black, not suitable for any recycle (run 1, table 3.2.1). Also carrying out the reaction at the same reaction conditions but in the presence of pyridine (Py) as external ligand (Pd/Py = 1/2 molar ratio), 65 % of cyclohexanone **(VII)** was formed but again Pd black was observed in the mixture (run 2, table 3.2.1). Furthermore, in an experiment carried out in the presence of Pd(OAc)$_2$ and tetrabutylammonium bromide as the ligand[77], the conversion was only 20 % (run 3, table 3.2.1) after 3h, so evidencing the good performance of the polyester-based Pd catalyst.

Table 3.2.1 Hydrogenation of 2-cyclohexen-1-one (VI) catalyzed by Pd (II) catalysts

Run	Pre-Catalyst/ Catalyst	t [h]	Conversion [%][a]	VII yield [%]	VIII yield [%]
1[b]	$Pd(OAc)_2$	1	95	95	nd
2[b]	$Pd(OAc)_2$/Py (1/2)	3	65	65	nd
3	$Pd(OAc)_2$/TBAB	3	20	20	nd
4	*trans*-$[Pd(OAc)_2(L)_2]$	1	30	30	nd
5[c]	$[Pd](L)_2$	1	37	37	nd
6[c]	$[Pd](L)_2$	1	35	35	nd
7	*trans*-$[Pd(OAc)_2(L)_2]$	2	70	70	nd
8	*trans*-$[Pd(OAc)_2(L)_2]$	3	>99	>99	nd
9[c]	$[Pd](L)_2$	3	>99	>99	nd
10[c]	$[Pd](L)_2$	3	>99	>99	nd
11[c]	$[Pd](L)_2$	3	>99	>99	nd

Reaction conditions: substrate = 10.5 mmol; substrate (**VI**)/Pd (molar ratio) = 1000/1; toluene = 10 mL; $p(H_2)$ = 0.1 MPa; T = 30 °C; TBAB = tetrabutylammonium bromide; Py = pyridine. [a]: Determined by GC (n-dodecane as internal standard)[b]: Pd black was formed. [c]: Reaction carried out by using the catalytic palladium species *trans*-$[Pd(OAc)_2(L)_2]$, indicated as $[Pd](L)_2$,recovered from the previous run. nd = not detected in the reaction mixture.

3.2.2 Hydrogenation of (E)-4-phenylbut-3-en-2-one (X) catalyzed by trans-*[Pd(OAc)$_2$(L)$_2$]*



X XI XII

Scheme 3.2.3 Hydrogenation of (E)-4-phenylbut-3-en-2-one (X)

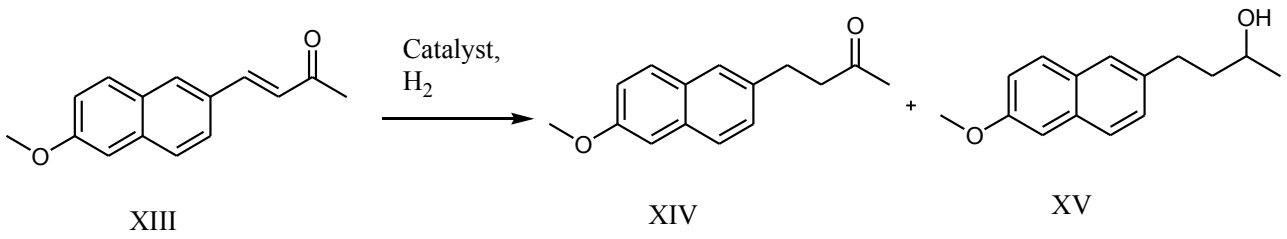
The polyester-based Pd catalyst showed good activity also in the hydrogenation of unsaturated ketone (E)-4-phenylbut-3-en-2-one **(X)** (Scheme 3.2.3, Table 3.2.2). In this case ketone **(XI)** was quantitatively obtained, as the sole reaction product, after 3 h at 30 °C, under 0.1 MPa of H_2 and by using a 1000/1 substrate/Pd molar ratio. The catalyst, recovered by adding methanol to the reaction mixture, was used in three successive experiments in which it showed unchanged activity and selectivity (run 2-5, Table 3.2.2).

Table 3.2.2. Hydrogenation of (X) catalyzed by *trans*-[Pd(OAc)$_2$(L)$_2$]

Run	t (h)	Conversion [%][a]	XI yield [%]	XII yield [%]
1	1	20	20	nd
2	3	>99	>99	nd
3[b]	3	>99	>99	nd
4[b]	3	>99	>99	nd
5[b]	3	>99	>99	nd
6[c]	3	39	39	nd

Reaction conditions: substrate = 5.6 mmol; substrate(**X**)/Pd (molar ratio) = 1000/1; toluene = 10 mL; p(H_2) = 0.1 MPa; T = 30 °C. [a]: Determined by GC (n-dodecane as internal standard). b[a] : Reaction carried out by using the catalyst recovered from the previous run. [c]: Experiment carried out by using 25 ml of toluene instead of 10 ml. nd = not detected in the reaction mixture.

3.2.3 Hydrogenation of (E)-4-(2-methoxynaphthalen-6-yl)but-3-en-2-one (XIII) catalyzed by **trans-*[Pd(OAc)$_2$(L)$_2$]***



XIII XIV XV

Scheme 3.2.4 Hydrogenation of (E)-4-(2-methoxynaphthalen-6-yl)but-3-en-2-one (XIII)

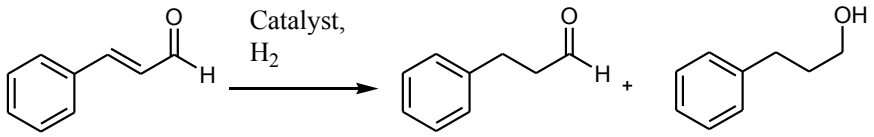
Once aware of the capability of the catalyst to hydrogenate selectively the C=C double bond, some hydrogenation experiments on the α,β-unsaturated ketone **(XIII)**, a valuable precursor of Nabumetone **(XIV)**, a nonsteroidal anti-inflammatory, analgesic and antipyretic drug (Scheme 3.2.4, Table 3.2.3) were carried out. Many synthetic procedures to prepare Nabumetone are described in the literature and all of them involve the selective hydrogenation of the carbonyl conjugated C=C double bond[78]. Usually, heterogeneous catalysts as Pd/C, Ni Raney[79], Rh/Al_2O_3[80] and Cu/SiO_2[81] are employed, and in some cases, when the catalyst is Pd, its pre-activation or the use of a base is necessary to obtain a good selectivity. The hydrogenation of **(XIII)** was studied at different H_2 pressures and reaction times, while keeping constant at 30 °C the temperature and with a substrate to catalyst molar ratio of 1000/1. A first experiment carried out at 0.1 MPa of H_2 for 3 h gave a very low conversion to **(XIV)**. However, on increasing both pressure and reaction time (2 Mpa, 5 h) a 56 % conversion was obtained; in this case also 2 % of alcohol **(XV)** was formed (run 5, table 3.2.3). By comparing these results with those obtained with the structurally related **(X)**, a sharp decrease of the reaction rate can be observed. The lower activity of the catalyst with respect to the reaction on **(X)** should be ascribed to the high dilution of the reaction, due to the low solubility of the substrate in the solvent employed. As a matter of fact, when the reaction was carried out on ketone **(X)** by using 25 mL of toluene instead of 10 mL, conversion, after 3 h, was only 39 % instead of 100 % (run 6, table 3.2.3). The catalyst, recovered as above described, was reused in three consecutive recycling experiments and its activity remained practically unchanged. Noteworthy the selectivity to **(XIV)** was always very high, ranging from 96 to 100 %.

Table 3.2.3. Hydrogenation of (E)-4-(2-methoxynaphthalen-6-yl)but-3-en-2-one (XIII) catalyzed by *trans*-[Pd(OAc)$_2$(L)$_2$]

Run	P(H_2) MPa	t (h)	Conversion [%][a]	XIV yield [%]	XV yield [%]
1	0.1	3	2	2	nd
2	0.1	24	57	57	nd
3	1	3	15	15	nd
4	2	3	44	44	nd
5	2	5	56	54	2
6[b]	2	5	52	51	1
7[b]	2	5	55	54	1
8[b]	2	5	52	52	nd

Reaction conditions: substrate = 5.5 mmol; substrate(**XIII**)/Pd (molar ratio) = 1000/1; T = 30 °C; toluene = 25 mL.[a]: Determined by GC (n-dodecane as internal standard). [b]: Reaction carried out by using the catalyst recovered from the previous run. nd = not detected in the reaction mixture.

3.2.4 Hydrogenation of (2E)-3-phenylprop-2-enal (XVI) catalyzed by trans-*[Pd(OAc)$_2$(L)$_2$]*



XVI XVII XVIII

Scheme 3.2.5 Hydrogenation of (2E)-3-phenylprop-2-enal (XVI)

Interesting results were obtained also in the hydrogenation of (2E)-3-phenylprop-2-enal (*trans*-cinnamaldehyde) **(XVI)** (Scheme 3.2.5, Table 3.2.4). Indeed, the hydrogenation of unsaturated aldehydes, in particular *trans*-cinnamaldehyde, is an important process for the production of some useful fine chemicals as intermediates for the synthesis of pharmaceuticals, additives for food flavours and valuable building blocks for fragrances. Initially **(XVI)** was hydrogenated in the presence of the polyester-based Pd catalyst by using a 1000/1 substrate to Pd molar ratio, at 30 °C and 0.1 MPa of H_2 for 6 h, obtaining a very low conversion to 3-phenylpropanal **(XVII)** (9 %) (run

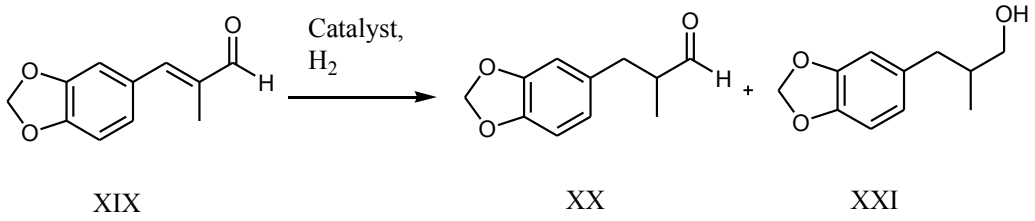
1, table 3.2.4). When the reaction time was prolonged to 24 h, a 96 % conversion was achieved but also a small amount (6 %) of alcohol **(XVIII)** was recovered (run 2, Table 3.2.4). When the reaction temperature was increased to 60 °C the conversion rose to 70 % in 6 h but in detriment of selectivity, since **(XVII)** and **(XVIII)** were also produced in equal amount (run 3, table 3.2.4); moreover, in these conditions, the catalyst was not stable and Pd black was formed. A very good conversion (96 %) was obtained at 30 °C and 2 MPa of H_2 for 6 h, maintaining a substrate to Pd molar ratio 1000/1: **(XVII)** was the prevailing product being the alcohol **(XVIII)** formed in small amount (5 %) (run 4, table 3.2.4). The recovered catalyst maintained a very good activity also in three recycling experiments affording complete conversions and 95 % selectivity to the saturated aldehyde **(XVII)** (run 5-7, table 3.2.4).

Table 3.2.4. Hydrogenation of (2E)-3-phenylprop-2-enal (XVI) catalyzed by *trans*-$[Pd(OAc)_2(L)_2]$

Run	T (°C)	P(H_2) MPa	t (h)	Conversion [%][a]	XVII yield [%]	XVIII yield [%]
1	30	0.1	6	9	9	nd
2	30	0.1	24	96	90	6
3[b]	60	0.1	6	70	35	35
4	30	2	6	96	91	5
5[c]	30	2	6	>99	95	5
6[c]	30	2	6	>99	95	5
7[c]	30	2	6	>99	95	5

Reaction conditions: substrate = 3 mmol; substrate(**XVI**)/Pd (molar ratio) = 1000/1; toluene = 10 mL.[a]: Determined by GC (n-dodecane as internal standard). [b]: Pd black was formed. [c]: Reaction carried out by using the catalyst recovered from the previous run. nd = not detected in the reaction mixture.

3.2.5 Hydrogenation of 3-(1,3-benzodioxol-5-yil)-2-methyl-propenal (XIX) catalyzed by trans-[Pd(OAc)$_2$(L)$_2$]



XIX XX XXI

Scheme 3.2.6 Hydrogenation of 3-(1,3-benzodioxol-5-yil)-2-methyl-propenal (XIX)

As an application of the described catalytic system, the hydrogenation of 3-(1,3-benzodioxol-5-yil)-2-methyl-propenal **(XIX)**, an α,β-unsaturated aldehyde precursor of Helional® **(XX)**, a valuable fragrance used in both feminine and masculine perfumes[82-92] was studied (Scheme 3.2.6, table 3.2.5). A first experiment carried out at 30 °C and 0.2 MPa of H_2 for 3 h and using a 1000/1 substrate to Pd molar ratio gave a very disappointing result (conversion 5 %) (run 1, table 3.2.5). Increasing the substrate/Pd ratio to 100/1, conversion raise up to 28 % after 2 h, but despite the improvement in conversion the selectivity was still very unsatisfactory as both (**XX**) and the corresponding alcohol **(XXI)** were formed (run 2, table 3.2.5). A complete conversion was obtained at 30 °C and 0.5 MPa of H_2 for 7 h: **(XX)** was formed but the major product was **(XXI)** (67 %) (run 3, table 3.2.5). The catalyst was recycled in three consecutive experiments but even if conversions were always very high a certain deactivation of the catalyst occurred, so showing a decreased ability to hydrogenate the carbonyl group (run 4-6, table 3.2.5). Noteworthy, the catalyst showed a lower activity with respect to **(XVI)**: surely, the presence of the methyl group in α-position to the carbonyl group makes more difficult the coordination of Pd to the sterically hindered trisubstituted C=C double bond. Moreover, the high dilution could strongly influence the reaction rate analogously to that hypothesized for the hydrogenation of ketone **(XIII)**.

Table 3.2.5. Hydrogenation of 3-(1,3-benzodioxol-5-yil)-2-methyl-propenal (XIX) catalyzed by *trans*-[Pd(OAc)$_2$(L)$_2$]

Run	p(H_2) MPa	t (h)	Conversion [%][a]	XX yield [%]	XXI yield [%]
1[b]	0.2	3	5	5	nd
2	0.2	2	28	13	15
3	0.5	7	>99	33	67
4[c]	0.5	7	>99	27	73
5[c]	0.5	7	96	36	60
6[c]	0.5	7	91	41	50

Reaction conditions: substrate = 1.05 mmol; substrate(**XIX**)/Pd (molar ratio) = 100/1; toluene = 10 mL; T=30 °C. [a]: Determined by GC (n-dodecane as internal standard). [b]: Reaction carried out by using a (**XIX**)/Pd (molar ratio) = 1000/1. [c]: Reaction carried out by using the catalyst recovered from the previous run. nd = not detected in the reaction mixture.

3.2.6 Homogeneity test of trans-[Pd(OAc)$_2$(L)$_2$]

When transition-metal complexes are used as precatalysts in hydrogenation processes it is important to establish the nature of the active species. The true catalyst may be a homogeneous metal complex or active metal particles present in solutions as colloids or metal nanoclusters, formed under reaction conditions. As Hg(0) is able to poison heterogeneous (colloidal or nanoparticulate) metal catalysts while it does not deactivate true homogeneous metal complexes, the hydrogenation of 2-cyclohexen-1-one **(VI)** at 0.1 MPa of H_2 and 30 °C for 3 h was carried out in the presence of Hg(0), according to a procedure described in the literature[93]. The catalytic activity remained unchanged, so indicating that it is due most likely to an homogeneous metal complex.

3.2.7 ^{1}H-NMR analysis and stability of trans-[Pd(OAc)$_2$(L)$_2$]

The behavior of the complex *trans*-[Pd(OAc)$_2$(L)$_2$] has been studied by ^{1}HNMR spectroscopy, ICP and XRD analysis in collaboration with the University of Florence and Padova, respectively. ^{1}HNMR was an useful technique to study this system (Figure 3.2.1). The formation of *trans*-[Pd(OAc)$_2$(**L**)$_2$] was confirmed by changing in chemical shift (δ) of aromatic hydrogen signals of

(L) (8.68 *ortho*-H and 7.46 *meta*-H ppm, trace **A**) to different δ (8.79 *ortho*-H, 8.67 *meta*-H ppm, trace **B**). After three catalytic runs no evidence of palladium nanoparticles (signals at 8.82 *ortho*-H, 8.62 *meta*-H ppm, **trace D**) were detected. The pattern of signals of *trans*-[$Pd(OAc)_2$(**L**)$_2$] was changed (8.82 *ortho*-H, 7.58 *meta*-H ppm, trace **C**). Probably this was due to the formation, after work up, of palladium(II) species, like palladium oxides, still bound to **(L)**. Moreover, ICP analysis showed only a 0.36 % loss of palladium (mol/mol) after the first catalytic run (2-cyclohexen-1-one (**VI**) hydrogenation, 3 h, 30 °C and P(H_2) = 0.1 MPa).

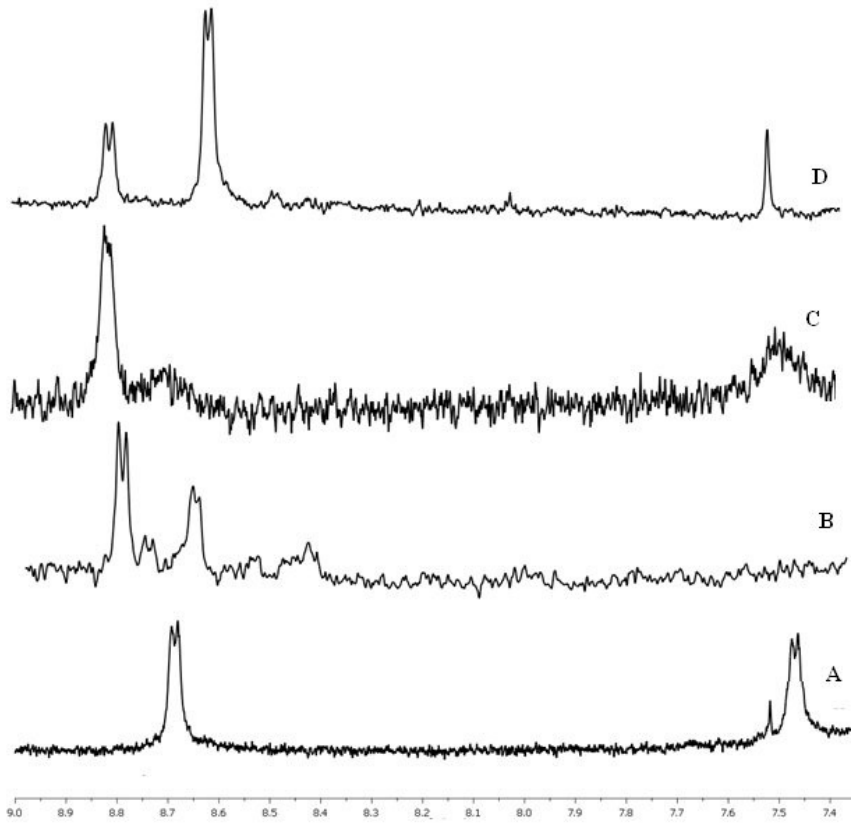


Figure 3.2.1 ^{1}H-NMR analysis and catalyst stability of complex *trans*-[$Pd(OAc)_2(L)_2$]

XPS investigation was performed on the fresh catalyst and after the first catalytic run (2-cyclohexen-1-one **(VI)** hydrogenation, 3 h, 30 °C and P(H_2) = 0,1 MPa) in order to evaluate its chemical composition before and after the hydrogenation reaction. In both cases, the expected elements, i.e. palladium, nitrogen, carbon, and oxygen were found. (Figure 3.2.2, A) shows the XPS spectra related to the Pd3d regions before (continuous line) and after (dotted line) the hydrogenation process and work-up. Similar features for the peaks were observed, suggesting an alike electronic

environment around palladium in the fresh catalyst and after the reaction and recovery. In particular, both spectra are composed of a doublet corresponding to the emission from the spin-orbit split $3d_{5/2}$ and $3d_{3/2}$ core levels. The corresponding binding energy peaks positions at 337.1 and 342.2 eV are assigned to divalent Pd^{2+} ions in palladium compounds[94]. Therefore, the interpretation of the Pd3d spectra indicates that palladium, which is reduced under the catalytic conditions, is however reoxidized, during the work-up and recovery, probably for the action of air[95-96]. Regarding the C1s line, a complex shape profile is found with the presence of at least three different carbon-related contributions, as shown in (Figure 3.2.2, B). Peak fitting revealed three components centred at binding energies (BE) 284.8 eV (C_I), 286.8 eV (C_{II}) and 288.7 eV (C_{III}). According to the chemical structure of the palladium macrocycle, the dominant lower energy component (C_I) can be ascribed to aliphatic carbon; a second component (C_{II}) at higher BE can be associated to oxygen-bound carbon; a third component (C_{III}) at even higher BE that can be coherently assigned to the electron-depleted carboxylic carbon.

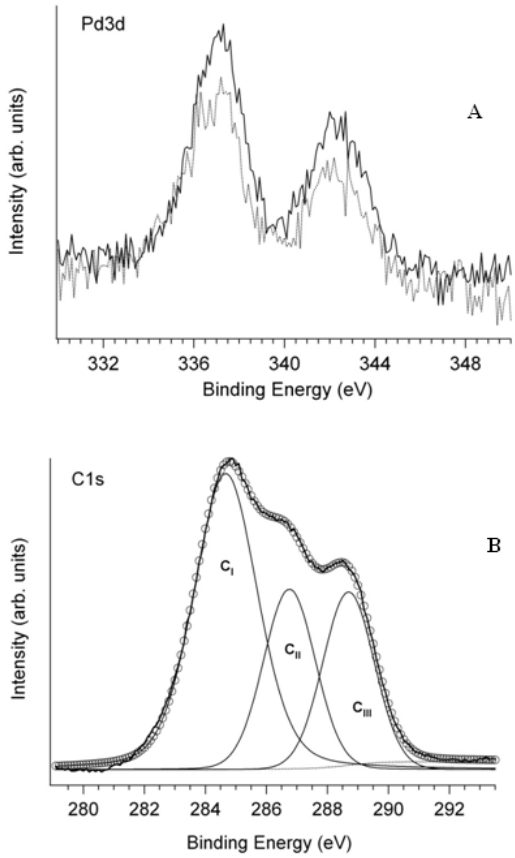


Figure 3.2.2 XPS analysis of *trans*-$[Pd(OAc)_2(L)_2]$

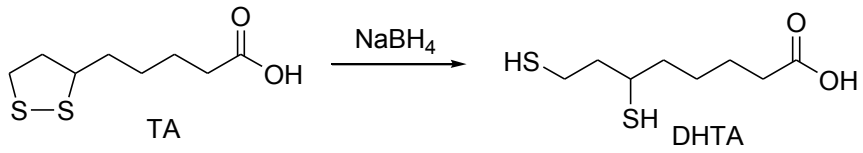
On the basis of the reported results *trans*-[$Pd(OAc)_2(L)_2$] has showed an interesting activity and good recyclability in the hydrogenation of some α,β-unsatured carbonyl compounds. It is to point out that this homogeneous catalyst is easily separated from the reaction mixture by simple addition of methanol to the reaction mixture and the recovered catalytic system maintains a good activity and selectivity also in recycling experiments. Considering both the data collected and the easy recyclability, this homogeneous catalytic species is a promising and peculiar catalyst for the hydrogenation of α,β-carbonyl compounds, even if the selectivity may be strongly affected by the substrate shape.

3.3 Catalytic applications of new water-soluble Rh-based catalysts

Water, as environmentally friendly solvent, indicates the use of intrinsically soluble metal complexes such as hydroxides and aqueous-complex or the utilization of hydrophilic ligands.

During this thesis work and a contemporary research investigation in the group where this thesis was performed[97], it was decided to re-prepared dihydrothioctic acid (DHTA) and to investigate the possibility to use it as simple, easily available and low cost ligand for rhodium species. This compound has two thiolic groups in position 6 and 8 of the chain, potentially able to complex rhodium. In addition, the carboxylic group, once salified, could strongly promote the solubility of the complex in water and behave as further co-ordination site. Ideally, it would be possible to obtain a soluble complex in water, potentially suitable in aqueous biphasic catalysis.

DHTA is easily obtained by reduction of thioctic acid (TA) with $NaBH_4$[98] (scheme 3.3.1).



Scheme 3.3.1. Reduction of thioctic acid (TA) into dihydro thioctic acid (DHTA)

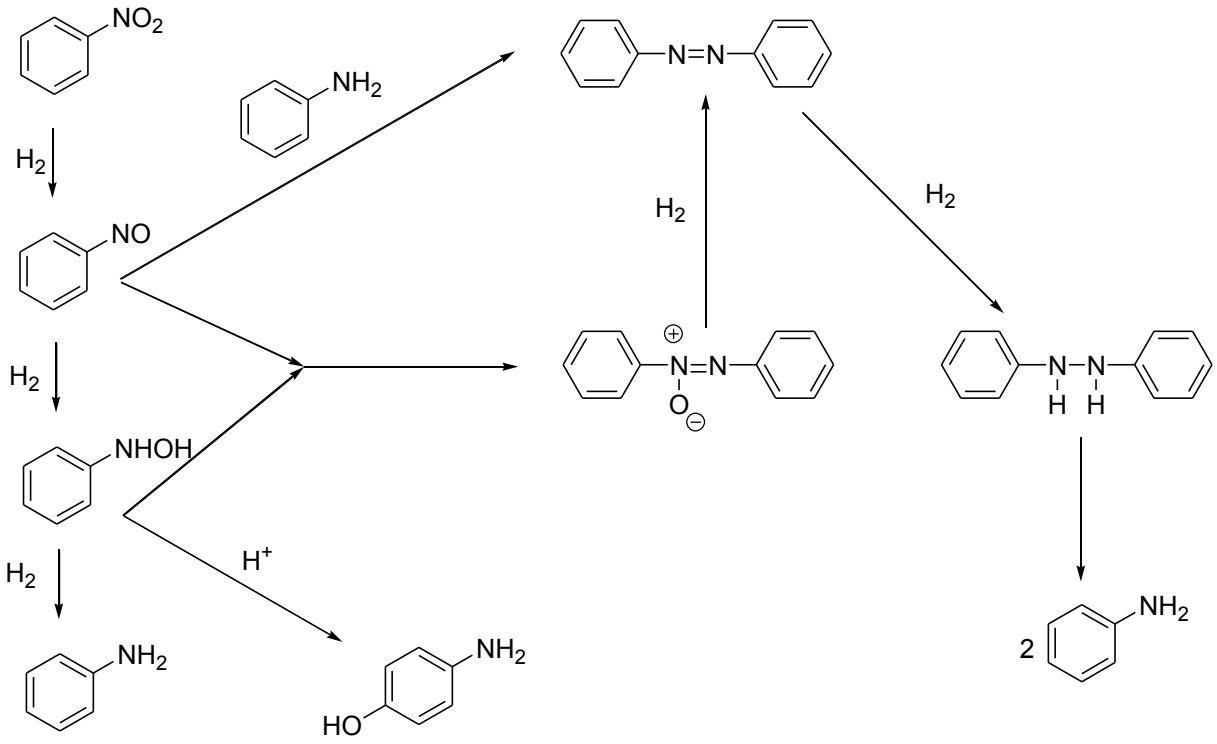
Thioctic acid, also known as α-lipoic acid, is the oxidized form of DHTA and is widely available on the market at low price. It is a natural molecule present in low concentration in the human body with essential functions in aerobic metabolism. It is produced industrially and sold as dietary supplement and antioxidant. DHTA is not very soluble in water, but after salification with Na_2CO_3, the salt form (DHTANa) is obtained. This form is soluble in water and for this reason, DHTANa can be used as bidentate ligand for rhodium species. In this way, it would be possible to obtain a catalytic species working in aqueous medium or in aqueous biphasic system.

The catalytic species was prepared by introducing the $[Rh(COD)Cl]_2$ (COD = 1,5-cyclooctadiene) in a deaerated aqueous solution containing the sodium salt of DHTA, by using a molar ratio ligand/metal 1:1. The solution obtained was stocked under nitrogen at 4 °C and showed good stability for medium-long time, maintaining its catalytic activity.

This obtained system was analyzed by ^{1}H-NMR and IR spectroscopy. Comparing the proton spectra of the free ligand with the spectra of the complex, a chemical shift of the signal attributed to the proton near to thiolic groups was observed. The proton on C_6 shifted from 2.92 to 3.61 ppm while the signals of the protons on C_8 shifted from 2.60 to 3.12 ppm. This would indicate a possible chelation of the sulfur atoms to the metal center. The infrared spectrum of the complex, recorded between 4400 and 400 cm^{-1}, showed the disappearance of the band at 2560 cm^{-1} due to SH stretching, present in the spectrum of the free ligand[99].

3.3.1 Reduction of aromatic nitro compounds. Introduction

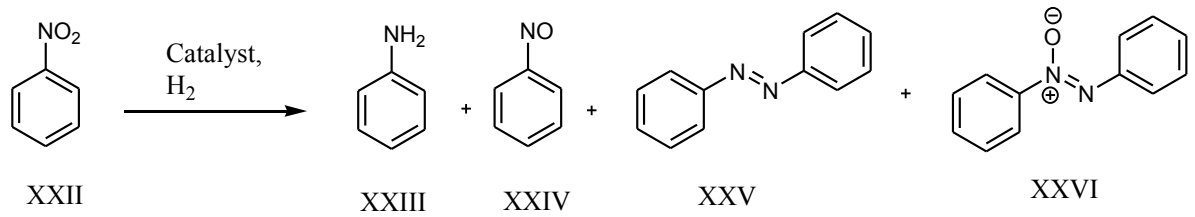
Aromatic nitro compounds are reduced to the corresponding amines which are utilized as important industrial intermediates for the synthesis of pigments, azo dyes, rubbers, amino-resins, herbicides and other fine chemicals. Over the years, many different methods to reduce nitro group have been developed such as reduction by using Fe in hydrochloric or acetic acid, by using sulphides, tin or stannous chloride in hydrochloric acid; however these methods are not sustainable due to the formation of waste sludge[100]. For these reasons, to-day nitroaromatic compounds are reduced to aromatic amines mainly by catalytic hydrogenation[101]. In this reaction, the oxygen atoms of the nitro group are progressively replaced by hydrogen; the reduction proceeds by formation of different intermediates. The currently most accepted reaction mechanism was proposed by Haber in 1898 (scheme 3.3.2).



Scheme 3.3.2 Haber reduction mechanism for nitrobenzene

Therefore, at the light of the complexity of the reaction, it is possible to obtain many by-products if the reduction is performed by using inefficient catalysts. For these reason it was decided to study the activity and selectivity of novel water soluble Rh-thioligand catalyst [Rh(DHTANa)] in the selective hydrogenation of industrially valuable aromatic halo-nitro compounds to obtain the corresponding halo-anilines. A comparison study with homemade, low metal content, heterogeneous 0.18 % Rh/Al_2O_3 is also described.

3.3.2 Reduction of nitrobenzene (XXII) catalysed by [Rh(DHTANa)]



XXII XXIII XXIV XXV XXVI

Scheme 3.3.3 Reduction of Nitrobenzene (XXII)

Aniline (**XXIII**) is obtained by reduction of nitrobenzene (**XXII**), and is a very important industrial compound in different fields, especially for polymers, rubbers, agrochemicals, dyes and drugs industries. It is mainly obtained by reduction of **(XXII)** although it can be produced by ammonolysis of chlorobenzene or phenol. During this work of thesis, the reduction of **(XXII)** was investigated by using two different homemade Rh-based catalysts as new water soluble [Rh(DHTANa)] and 0.18 % Rh/Al_2O_3 (Table 3.3.1).

The first catalytic system applied in the hydrogenation of nitrobenzene was Rh[(DHTA)Na]. The reaction, carried out in the biphasic aqueous system H_2O/THF at 80 °C and 5 MPa of H_2 for 24 h, by using a substrate to palladium molar ratio 1000/1, gave 100 % aniline **(XXIII)**. After that reaction performed by lowering the H_2 Pressure at 80 °C and 2 MPa of H_2 for 24 h afforded exclusively aniline **(XXIII)** with 99 % yield. After extraction of the organic products with diethyl ether, the catalyst was easily recovered by separation of the aqueous phase from the organic one and used in three consecutive recycling experiments without loss of activity (runs 2-5, table 3.3.1). The reduction was also carried out lowering pressure but a low conversion was observed (run 6).

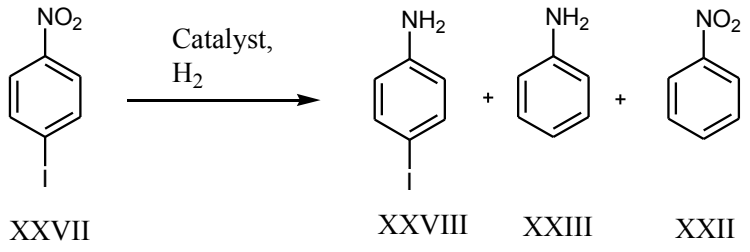
We studied two catalytic system for the reduction of **(XXII)** to compare the obtained results. Reaction carried out in the presence of new water soluble [Rh(DHTANa)] and homemade 0.18 % Rh/Al_2O_3 utilizing the condition reported in (table 3.3.1, run 7) afforded exclusively aniline **(XXIII)** with 99 % yield. Furthermore, it is also important to note that it was possible to recover and re-use also heterogeneous catalyst (run 8, Table 3.3.1) and both activity and selectivity remained almost unchanged.

Table 3.3.1 Reduction of nitrobenzene (XXII) catalyzed by [Rh(DHTANa)] or 0.18 % Rh/Al_2O_3

Run	Catalyst	$p(H_2)$ MPa	T (°C) / t (h)	Conv [%]	XXIII Yield [%]	XXIV [%]	XXV [%]	XXVI [%]
1[a]	[Rh(DHTANa)]	5	80/24	100	100	-	-	-
2[b]	[Rh(DHTANa)]	2	80/24	100	99	-	-	-
3[c]	1° recycling	2	80/24	100	98	-	-	-
4[c]	2° recycling	2	80/24	100	99	-	-	-
5[c]	3° recycling	2	80/24	100	97	-	-	-
6[d]	[Rh(DHTANa)]	1	80/24	55	55	-	-	-
7[e]	0.18%Rh/Al_2O_3	2	80/24	100	99	-	-	-
8[f]	1° recycling	2	80/24	100	99	-	-	-

Reaction conditions: [a] substrate **(XXII)** = (0.620 g, 5 mmol); Rh[(DHTA)Na] 0.005M solution (1 mL), (substrate **XXII**/ Rh[(DHTA)Na] molar ratio 1000/1); THF = 2 mL, H_2O = 2 mL; [b] Same conditions of run 1 but $p(H_2)$ was 2 Mpa.[c] Reaction carried out by using the catalyst recovered from the previous run 2. [d]Same conditions of run 1 but $p(H_2)$ was 1 Mpa. [e] substrate **(XXII)** = (0.620 g, 5 mmol); Rh/Al_2O_3 0.18 % (0.288 gm) substrate **XXII** / Rh/Al_2O_3 molar ratio = 1000/1; THF = 2 mL, H_2O = 2 mL; [f] Experiment carried out by using the catalyst recovered from the previous run 7.

3.3.3 Reduction of 1-Iodo-4-nitrobenzene (XXVII) catalysed by [Rh(DHTANa)]



XXVII XXVIII XXIII XXII

Scheme 3.3.4 Reduction of 1-Iodo-4-Nitrobenzene (XXVII)

When aromatic halo-nitro compounds are hydrogenated, some dehalogenation is observed. The extent of dehalogenation depends on many factors: on the kind of halogen (I > Br > Cl > F) and its position on the molecule (ortho > para >meta), on the activity and amount of catalyst, on the kind of metal and support, on the kind of solvent, on pressure and temperature. To improve the

chemoselectivity of the reaction, during the past twenty years many different catalysts have been developed involving noble metals such as Pd, Pt, Ru and Rh and non-noble metals such as Fe, Co, Ni, Cu and Zn[102]. However, it is generally accepted that some commercially available Ni, Pd and Pt catalysts lack the necessary selectivity when substituted nitrobenzene are treated by H_2[103]. For these reasons, the search for new catalysts did not stop and for example Ru[104] or Co nanoparticles as catalysts have been recently developed. At the light of these considerations, it was decided to test the selectivity of the new water soluble catalyst and homemade catalytic systems in the hydrogenation of a substrate containing both a nitro- and a halo-group: for this purpose we studied hydrogenation of 1-iodo-4-nitrobenzene (**XXVII**) (Scheme 3.3.4, Table 3.3.2).

Table 3.3.2 Reduction of 1-Iodo-4-Nitrobenzene (XXVII) catalyzed by [Rh(DHTANa)] or 0.18 % Rh/Al_2O_3

Run	Catalyst	p(H_2) MPa	T (°C) / t (h)	Conv [%]	XXVIII yield [%]	XXIII [%]	XXII [%]
1[a]	[Rh(DHTANa)]	4	60/24	85	85	-	-
2[b]	[Rh(DHTANa)]	4	80/24	100	97	2	1
3[c]	1° recycle	4	80/24	85	80	3	2
4[c]	2° recycle	4	80/24	30	30	-	-
5[d]	0.18%Rh/Al_2O_3	4	80/24	97	38	60	-
6[e]	1° recycle	4	80/24	97	40	57	-

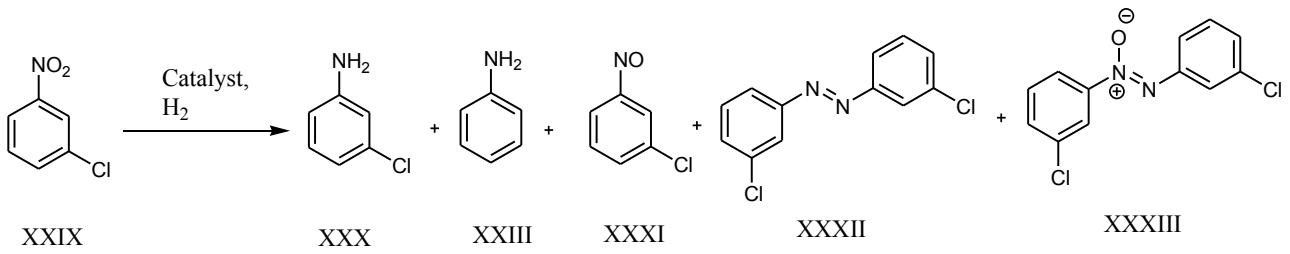
Reaction conditions: [a] substrate **(XXVII)** = (0.312 g, 1.25 mmol); Rh[(DHTA)Na] 0.005M solution (1 mL), (substrate **XXVII**/ Rh[(DHTA)Na] molar ratio 500/1); Toluene = 2 mL, H_2O = 2 mL; [b] Same conditions of run 1 but T = 80 °C.[c] Reaction carried out by using the catalyst recovered from the previous run 2. [d] substrate **(XXVII)** = (0.312 g, 1.25 mmol); 0.18 % Rh/Al_2O_3 (0.286 gm) substrate **XXVII** / Rh molar ratio = 500/1; Toluene = 4 mL; [e] Experiment carried out by using the catalyst recovered from the previous run 5.

The first reaction was carried by using [Rh(DHTANa)] in H_2O/THF at 60 °C and 4 Mpa H_2 for 24 h, gave a 85 % conversion to **(XXVIII)** and dehalogenation is observed. To get complete conversion we increased the reaction temperature at 80 °C and 4Mpa H_2 for 24 h, gave 100 % conversion (run 2, table 3.3.2). Then all the experiment was carried out by utilizing above condtion with **(XXVII)**/ catalyst ratio 500/1. Run 3 and 4 were carried out by using recovered catalytic phase from previous run. In the presence of fresh catalyst experiment a good activity and selectivity was observed towards formation of desired product (run 2 and in the first recycle, Table 3.3.2) and in second

recycle a decrease in catalyst activity was detected. Noteworthey, the formation of small amounts of **(XXIII)** and **(XXII)** was detected (runs 2 and 3, Table 3.3.2) either in presence of fresh catalyst or in first recycling experiment.

Also the homemade 0.18 % Rh/Al_2O_3 was investigated and analogously to the [Rh(DHTANa)] catalysts it's activity was also tested in one recycling experiment by utilizing the condition reported in Table 3.3.2 (run 5 and 6) with **(XXVII)**/catalyst molar ratio 500/1: at 97 % conversion, the reaction mixture contained 38-40 % desired product **(XXVIII)** and 57-60 % dehalogenation product **(XXIII)**. In general, surprisingly, only the reduction of the nitro group was observed by using new water soluble [Rh(DHTANa)] with **(XXVII)**/catalyst molar ratio 500/1 and only small amounts of dehalogenation were detected under the adopted conditions (Table 3.3.2). On the contrary using 0.18 % $Rh/Al2O_3$ more dehalogenation product was obtained compared to desired product. For selective reduction of only nitro group in presence of a halo group the [Rh(DHTANa)] catalyst system is the best choice.

3.3.4 Reduction of 1-Chloro-3-nitrobenzene (XXIX) catalysed by [Rh(DHTANa)]



XXIX XXX XXIII XXXI XXXII XXXIII

Scheme 3.3.5 Reduction of 1-Chloro-3-nitrobenzene (XXIX)

Another substrate investigated during this work of thesis was 1-chloro-3-nitrobenzene **(XXIX)**. By reduction of **(XXIX)** is possible to obtain 3-chlorobenzenamine **(XXX)**, better known as m-chloroaniline or 3-chloroaniline. This compound is an intermediate for dyes, drugs, and pesticides[105]. An important application **(XXX)** is also in the manufacture of antimalarial drugs such as chloroquine and amodiquin[106].

In the hydrogenation of **(XXIX)** is desirable to obtain the selective hydrogenation of the nitro-group, without dehalogenation. This selectivity depends on the kind of catalyst used and on the reaction conditions. In order to reduce the by-side reactions (particularly dehalogenation) often

poisoned catalysts were adopted[107]. Recently good results in selective hydrogenation of **(XXIX)** with hydrazine have been reported by using a Co catalyst modified with Mo-carbide or with isopropanol by using Ru nanoparticles stabilized on modified Montmorillonite clay.

Since new water soluble [Rh(DHTANa)] catalyst and homemade 0.18 % Rh/Al_2O_3 are simple to prepare and showed a good activity towards both the reduction of nitro group and in the hydrodechlorination reaction, it was decided to study the activity and selectivity of these catalytic systems in the reduction of **(XXIX)** (Table 3.3.3).

Table 3.3.3 Reduction of 1-Chloro-3-nitrobenzene (XXIX) catalyzed by [Rh(DHTANa)] or 0.18 % Rh/Al_2O_3

Run	Catalyst	p(H_2) MPa	T (°C) / t (h)	Conv [%]	XXX yield [%]	XXIII [%]	XXXI [%]
1[a]	[Rh(DHTANa)]	4	80/24	100	100	-	-
2[b]	[Rh(DHTANa)]	4	80/24	100	100	-	-
3[b]	[Rh(DHTANa)]	4	80/24	98	98	-	-
4[b]	[Rh(DHTANa)]	4	80/24	99	99	-	-
5[c]	0.18%Rh/Al_2O_3	4	80/24	98	81	17	-
6[d]	0.18% Rh/Al_2O_3	4	80/24	90	75	15	-

Reaction conditions: [a] substrate **(XXIX)** = (0.395 g, 2.5 mmol); Rh[(DHTA)Na] 0.005M solution (1 mL), (substrate **XXIX**/ Rh[(DHTA)Na] molar ratio 500/1); Toluene = 2 mL, H_2O = 2 mL; [b] Reaction carried out by using the catalyst recovered from the previous run 1. [c] substrate **(XXIX)** = (0.395 g, 2.5 mmol); 0.18 % Rh/Al_2O_3 (0.286 gm) substrate **XXIX** / Rh molar ratio = 500/1; Toluene = 4 mL; [d] Experiment carried out by using the catalyst recovered from the previous run 5.

Performing the reaction using water soluble [Rh(DHTANa)] catalyst, complete conversion and 100 % selectivity were obtained under drastic condition at 80 °C and 4 Mpa of H_2 for 24 h : 100 % formation of desired product **(XXX)** and no dehalogenation occurs (Table 3.3.3, run 1). Furthermore this catalyst showed good recyclability after three successive recycled experiment and also good selectivity (Table 3.3.3, run 2-4).

Then we investigated the reaction using homemade 0.18 % Rh/Al_2O_3 for comparative results of two catalytic systems. Performing the reaction by using 0.18 % Rh/Al_2O_3 catalyst at 80 °C and 4 Mpa of H_2 for 24 h almost complete conversion was observed but lower selectivity (Table 3.3.3, run 5): the

reaction mixture contained 81 % of desired product **(XXX)** and 17 % **(XXIII)**. The catalyst was recycled and used for next reaction (Table 3.3.3, run 6): at 90 % conversion it gave 75 % of desired product **(XXX)** and 15 % **(XXIII)**. At the light of this results, this catalyst does not show 100 % selectivity compared to [Rh(DHTANa)].

In conclusion, new water soluble [Rh]-thioligand species, i.e. [Rh(DHTANa)] catalyst, showed a good activity and selectivity in the hydrogenation of aromatic nitro group and aromatic halo nitro compounds without formation of dehalogenation products. Homemade 0.18 % Rh/Al_2O_3 showed a good activity and selectivity in the hydrogenation of aromatic nitro group; however when a halo atom is present on the aromatic ring, relevant amounts of dehalogenated product were observed (Table 3.3.3).

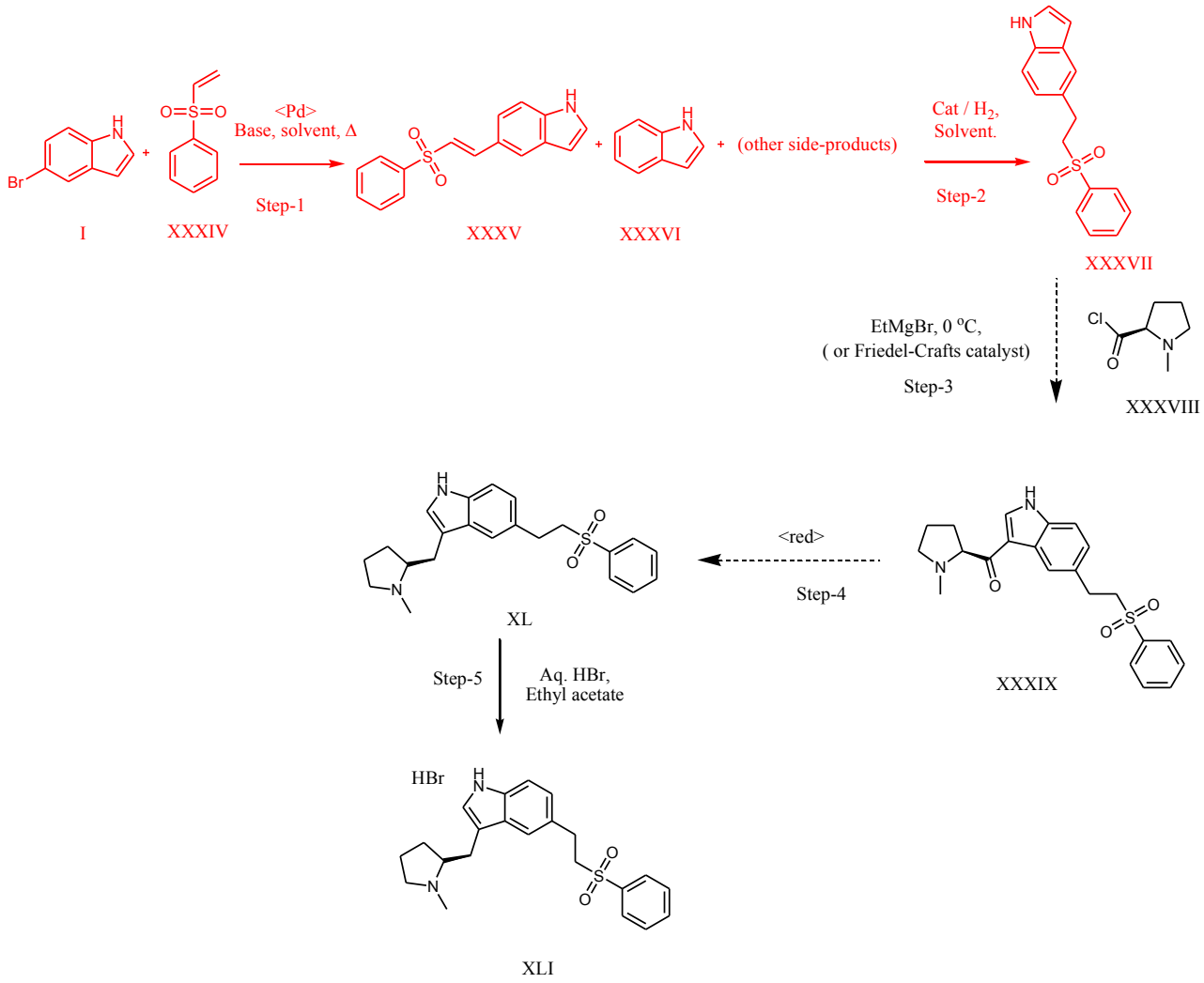
Table 3.3.4. Comparison between [Rh(DHTANa)] and homemade 0.18 % Rh/Al_2O_3 catalysts.

Reactions	Catalysts	Observation
Reduction of nitrobenzene **(XXII)**	[Rh(DHTANa)]	High activity and selectivity, no formation of intermediate, recycling is possible
	0.18 % Rh/Al_2O_3	High activity and selectivity, no formation of intermediate, recycling is possible
Reduction of 1-Iodo-4-Nitrobenzene **(XXVII)**	[Rh(DHTANa)]	High activity and selectivity, small amounts of dehalogenation were detected, recycling is possible but slightly decrease of activity is observed.
	0.18 % Rh/Al_2O_3	Good activity, selectivity was not so high, large amount of dehalogenation was detected, recycling is possible.
Reduction 1-Chloro-3-nitrobenzene **(XXIX)**	[Rh(DHTANa)]	High activity and selectivity, no formation of dehalogenation product was observed, recycling is possible
	0.18 % Rh/Al_2O_3	Good activity, selectivity was not so high, 20% of dehalogenation was detected, recycling is possible.

Chapter 4: Investigation on the synthesis of two APIs; Eletriptan hydrobromide and Cinacalcet hydrochloride. Results and discussion

4.1. Study of Heck and hydrogenation reactions on 5-bromo-1H-indole (I)

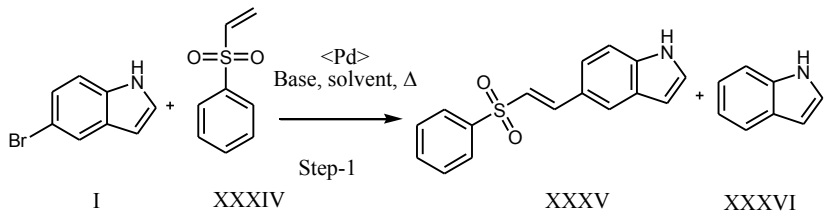
One of the main objects of this thesis work was to develop more sustainable processes for the synthesis of the APIs Eletriptan and Cinacalcet. Both reaction schemes involve Heck cross coupling reaction followed by an hydrogenation. As reported in Scheme 4.1.1, 5-bromo-1H-indole **(I)**, a suitable model substrate for Eletriptan, was coupled with phenyl vinyl sulfone **(XXXIV**) under Heck reaction conditions and then the resulting mixture was hydrogenated in the presence of a suitable catalyst to obtain product **(XXXVI)**. Both reactions require modulated conditions and selective catalysts because of possible side reactions. It is to note that intermediate **(XXXVII)** could be also an intermediate of an alternative route to Eletriptan, depicted in the same Scheme 4.1.1, but not yet tested. First of all, the Heck cross coupling reaction was investigated using some commercially available homogeneous catalysts such as: Palladium (II) acetate alone or in combination with phosphine ligands; bis(dibenzylideneacetone)palladium(0) and suitable phosphines; bis(tri-o-tolylphosphine) palladium(0); bis(tri-tert-butylphosphine)palladium(0); bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II). In the patent literature of the originator route to Eletriptan (see, chapter 2, scheme 2.1) the catalytic precursor employed is $Pd(OAc)_2$ in the presence of tri-o-tolylphosphine.



Scheme 4.1.1 Heck and hydrogenation reaction starting from 5-bromo-1H-indole (I) (in red) and a potential alternative approach to Eletriptan hydrobromide

4.1.1 Synthesis of 5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (XXXV) by Heck cross coupling reaction

The results obtained in the Heck reaction using different reaction parameters are shown in (Tables 4.1.1 and 4.1.2).



Scheme 4.1.2 Heck cross coupling on 5-bromo-1H-indole (I)

Starting from literature conditions[108] $Pd(OAc)_2$ (8 mol%) was used, at 105 °C for 9 h, in DMF and in the presence of triethylamine (Table 4.1.1, run 1) but the reaction gave unsatisfactory results: besides 9 % of indole **(XXXVI)**, due to the dehalogenation of 5-bromo-1H-indole, also ~6 % of a byproduct, N,N-diethyl-2-(phenylsulfonyl)ethan-1-amine, was formed, probably by reaction between sulfone and triethylamine to give the corresponding tetralkylammonium salt and following elimination of ethylene at high temperature. Better results were observed simply changing the base; N,N-dicyclohexylmethylamine, under the same experimental conditions (run 2), permitted to obtain good conversion (95 %) and quite satisfactory yield (85 %) of the desired product **(XXXV)** together to 10 % of indole. As expected no other byproduct was observed. A more efficient and more selective catalyst was Bis(dibenzylideneacetone)palladium(0) (run 3); it was then possible to reduce the amount of catalyst (run 7) obtaining 100 % conversion and 97 % analytical yield of the desired product **(XXXV)**. It should be probably possible to reduce further to 1 % the quantity of the catalyst, on the basis of encouraging result of run 10, simply prolonging the reaction. Less satisfactory was the attempt to use greener solvents than DMF, such as acetonitrile, 2-methyltetrahydrofuran and cyclopentyl-methyl-ether (runs 4-6); a deactivation of catalyst was observed with precipitation of inactive Pd black. At the light of all above results Heck reaction with 3 mol % of bis(dibenzylideneacetone)palladium(0) and tri-o-tolylphosphine as a ligand and N,N-dicyclohexylmethylamine as a base gave promising results towards the formation of the desired product **(XXXV)** with good selectivity (run 7, Table 4.1.1). Then we studied the reaction with 3 mol % of catalyst by using D-glucose as a co-catalyst[109] by adopting the condition reported in run 8: 77

% conversion was obtained but the reaction mixture contained only 39 % of **(XXXV)** and 42 % of **(XXXVI)**. Finally, the reaction was carried out by using tetrabutylammonium bromide as a co-ligand, already employed in other Heck reactions to stabilize colloidal Pd[110] (run 9), but, quite surprisingly, no reaction occurred.

Table 4.1.1 Heck reaction experiments using some homogeneous palladium species in the presence of tri-o-tolylphosphine

Run	[Pd] / (cat/subst. mol%)	Solvent	T (°C) / t(h)	Conv. [%]	XXXV [%]	XXXVI [%]
1[a,b]	Pd $(OAc)_2$/(8)	DMF	105/9	85	70	9
2[c]	Pd $(OAc)_2$/(8)	DMF	105/9	95	85	10
3[d]	$Pd(dba)_2$/(8)	DMF	105/7	100	95	5
4[e]	$Pd(dba)_2$/(8)	ACN	85/7	56	50	6
5[f]	$Pd(dba)_2$/(8)	2Me-THF	85/7	55	49	6
6[g]	$Pd(dba)_2$/(8)	CPME	85/7	60	52	8
7[h]	$Pd(dba)_2$/(3)	DMF	105/7	100	97	3
8[i]	$Pd(dba)_2$/(3)	DMF	105/7	77	39	42
9[j]	$Pd(dba)_2$/(3)	DMF	105/15	-	-	-
10[k]	$Pd(dba)_2$/(1)	DMF	105/7	90	88	2

Reaction conditions : [a] Substrate **(I)** = (0.1 g, 0.51 mmol), Substrate **(XXXIV)** = (0.102 g, 0.61 mmol), $Pd(OAc)_2$ (9.1 mg, 0.040 mmol), tri-o-tolylphosphine (31 mg, 0.102 mmol), triethylamine (0.103 g, 0.102 mmol), N,N-dimethylformamide (DMF) (5 mL); [b] 6% of N,N-diethyl-2-(phenylsulfonyl)ethan-1-amine as side product; [c] Same condition of run 1, but N,N-dicyclohexylmethylamine (0.198 g, 0.102 mmol) was used as base; [d] Same condition of run 2, but Bis(dibenzylideneacetone)palladium(0) (23.4 mg) was used instead of $Pd(OAc)_2$; [e] Same condition of run 3, but Acetonitrile (ACN) (5 mL) was used as solvent; [f] same condition of run 3 but 2-methyltetrahydrofuran (2Me-THF) (5 mL) was used as solvent; [g] same condition of run 3 but cyclopentylmethylether (CPME) (5 mL) was used as solvent; [h] same condition of run 3, but Bis(dibenzylideneacetone)palladium(0) (8.8 mg) was used. [i] same condition of run 7, but glucose 10 % (10 mg) was added; [j] same condition of run 7, but tetrabutylammonium bromide (0.328 g) was added; [k] same condition of run 3, but Bis(dibenzylideneacetone)palladium(0) (2.9 mg,) was used.

Then a new set of conditions was tested verifying the effect of changing the phosphine ligand as well as the use of preformed catalyst containing tri-o-tolylphosphine. The results are reported in (Table 4.1.2).

The Heck reaction using the commercially available homogeneous catalyst bis(tri-o-tolylphosphine)palladium(0) gave poor results in comparison with those obtained in the presence of the *in situ* prepared catalyst (Table 4.1.1 vs. Table 4.1.2). On the contrary, better results were observed using another commercially available homogeneous catalyst, bis(tri-tert-butylphosphine)palladium(0). This is in agreement with recent literature data[111] where Heck cross coupling reaction of vinyl sulfoxides, sulfides and sulfone with different aryl iodides or bromides are carried out in the presence of this bulky phosphine complex $Pd[P(t\text{-}Bu)_3]_2$ in combination with triethylamine as the base: an active catalyst is formed, able to couple an aryl halide with a sulphur bearing substrate. By adopting the condition reported in Table 4.1.2 (run 4) with 10 mol % of bis(tri-tert-butylphosphine)palladium(0) catalyst loading, 100 % conversion was obtained with 95 % yield of the desired product **(XXXV)** and 5 % of dehalogenation byproduct **(XXXVI)**. Then, optimizing the reaction conditions (temperature, time, solvent, amount of catalyst) it was possible to achieve satisfactory results. In particular it is interesting to underline that it was possible to work with a greener solvent as CPME at 70 °C for 2.5 h obtaining a 97 % conversion and no dehalogenated by-product obtained. On the basis of the fact that this catalyst is very sensible to oxygen, it is possible to suppose that working under more controlled conditions and with a higher amount of reagents a reduced amount of catalyst could be used.

Table 4.1.2 Heck reaction using other homogeneous palladium (0) catalysts

Run	[Pd] / (cat/subst. mol%)	Solvent	T (°C) / t(h)	Conv. [%]	XXXV [%]	XXXVI [%]
1[a]	Pd $[P(o\text{-}tolyl)_3]_2$/(8)	DMF	105/7	90	78	12
2[b]	Pd $[P(o\text{-}tolyl)_3]_2$/(3)	DMF	105/7	50	37	13
3[c]	Pd $[P(o\text{-}tolyl)_3]_2$/(1)	DMF	105/7	30	30	-
4[d]	Pd $[P(t\text{-}Bu)_3]_2$/(10)	DMF	105/7	100	95	5
5[d]	Pd $[P(t\text{-}Bu)_3]_2$/(10)	DMF	105/2.5	95	95	-
6[e]	Pd $[P(t\text{-}Bu)_3]_2$/(10)	DMF	70/2.5	96	96	-
7[f]	Pd $[P(t\text{-}Bu)_3]_2$/(10)	CPME	70/2.5	97	97	-
8[g]	Pd $[P(t\text{-}Bu)_3]_2$/(10)	DMF	70/2.5	95	95	-
9[h]	Pd $[P(t\text{-}Bu)_3]_2$/(8)	DMF	70/2.5	75	75	-
10[i]	Pd $[P(t\text{-}Bu)_3]_2$/(8)	DMF	100/2.5	96	96	-
11[j]	Pd $[P(t\text{-}Bu)_3]_2$/(5)	DMF	100/2.5	80	80	-

Reaction conditions : [a] Substrate **(I)** = (0.1 g, 0.51 mmol), Substrate **(XXXIV)** = (0.102 g, 0.61 mmol), Bis(tri-o-tolylphosphine)palladium(0) (29.1 mg,), triethylamine (0.103 g, 0.102 mmol), N,N-dimethylformamide (DMF) (5 mL); [b] Same condition of run 1, but Bis(tri-o-tolylphosphine)palladium(0) (10.9 mg,) was used; [c] Same condition of run 1, but Bis(tri-o-tolylphosphine)palladium(0) (3.6 mg) was used; [d] Reaction conditions : Substrate **(I)** = (0.1 g, 0.51 mmol), Substrate **(XXXIV)** = (0.102 g, 0.61 mmol), Bis(tri-tert-butylphosphine) palladium(0) (26 mg), triethylamine (0.103 g, 0.102 mmol), N,N-dimethylformamide (DMF) (5 mL); [e] Same condition of run 4, but at lower temperature; [f] Same condition of run 6, but cyclopentylmethylether (CPME) (5 mL) was used as solvent; [g] Same condition of run 6, but N,N-dicyclohexylmethylamine (0.198 g, 0.102 mmol) was used as base; [h] Same condition of run 6, but Bis(tri-tert-butylphosphine) palladium(0) (20.8 mg) was used; [i] Same condition of run 9, but at higher temperature. [j] Same condition of run 10, but Bis(tri-tert-butylphosphine) palladium(0) (13 mg) was used.

In summary, under the best reaction experiments so far:

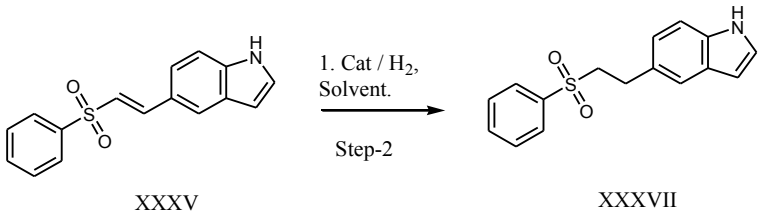
- Using bis(dibenzylideneacetone)palladium(0) and tri-o-tolylphosphine only 3 mol% of catalyst loading for completion of reaction was necessary in DMF; 97% of product **(XXXV)** was formed and only 3% dehalogenation of **(I)** was observed (Table 4.1.1, run7).

- Using bis(tri-tert-butylphosphine)palladium(0), 10 mol% of catalyst was necessary by using CPME as solvent, but this catalyst is more selective and no dehalogenation by-product was found (Table 4.1.2, run 7).

Both conditions represent an improvement if compared to literature[112] conditions and they are promising for a scaling-up.

4.1.2 Synthesis of 5-(2-(phenylsulfonyl)ethyl)-1H-indole (XXXVII) by using different low metal content heterogeneous catalyst

During this work of thesis one of the object was to develop a more sustainable process for the hydrogenation of pure Heck product **(XXXV)** as well as of crude reaction mixture containing **(XXXV)** and by-products (Scheme 4.1.1, Step 2). A comparison of the activity of a commercial 10 % Pd/C with home-made Pd or Rh on alumina catalysts, i.e. 0.28 % Pd/Al_2O_3 and 0.18 Rh/Al_2O_3[113], was made and the obtained results are summarized in Table 4.1.3.



XXXV XXXVII

Scheme 4.1.3 Hydrogenation of Heck product (XXXV) catalyzed by heterogeneous catalyst

At first, the hydrogenation of the isolated pure Heck product **(XXXV)** was studied. The reaction was carried out in toluene at 50 °C with 0.3 MPa of H_2 for 18 h, by using a commercial available 10 % Pd/C, but the result was very poor with a very low conversion of the starting material (table 4.1.3, run 1). On the contrary, the home-made 0.18 % Rh/Al_2O_3 resulted a very active catalyst and it was possible to work under milder conditions to obtain a full conversion into **(XXXVII)**; the best compromise was obtained according to (table 4.1.3, run 7), even if it will be possible to repeat the result with a lower reaction time. It was also possible to hydrogenate directly the crude Heck reaction mixture but a greater amount of this catalyst was necessary (table 4.1.3, run 10). On the contrary 0.28 % Pd/Al_2O_3 catalyst was not so reactive for the hydrogenation of the carbon-carbon double bond (table 4.1.3, run 11); perhaps impurities such as the phosphine ligand, or more

probably the corresponding phosphine oxide, present in the crude reaction mixture, could poison palladium catalyst. Last but not least reaction was performed in presence of other catalysts; polyester based *Trans*-[$Pd(OAc)_2(L)_2$] and new water soluble [Rh(DHTANa)] catalyst gave less satisfactory results (table 4.1.3, run 12, 13).

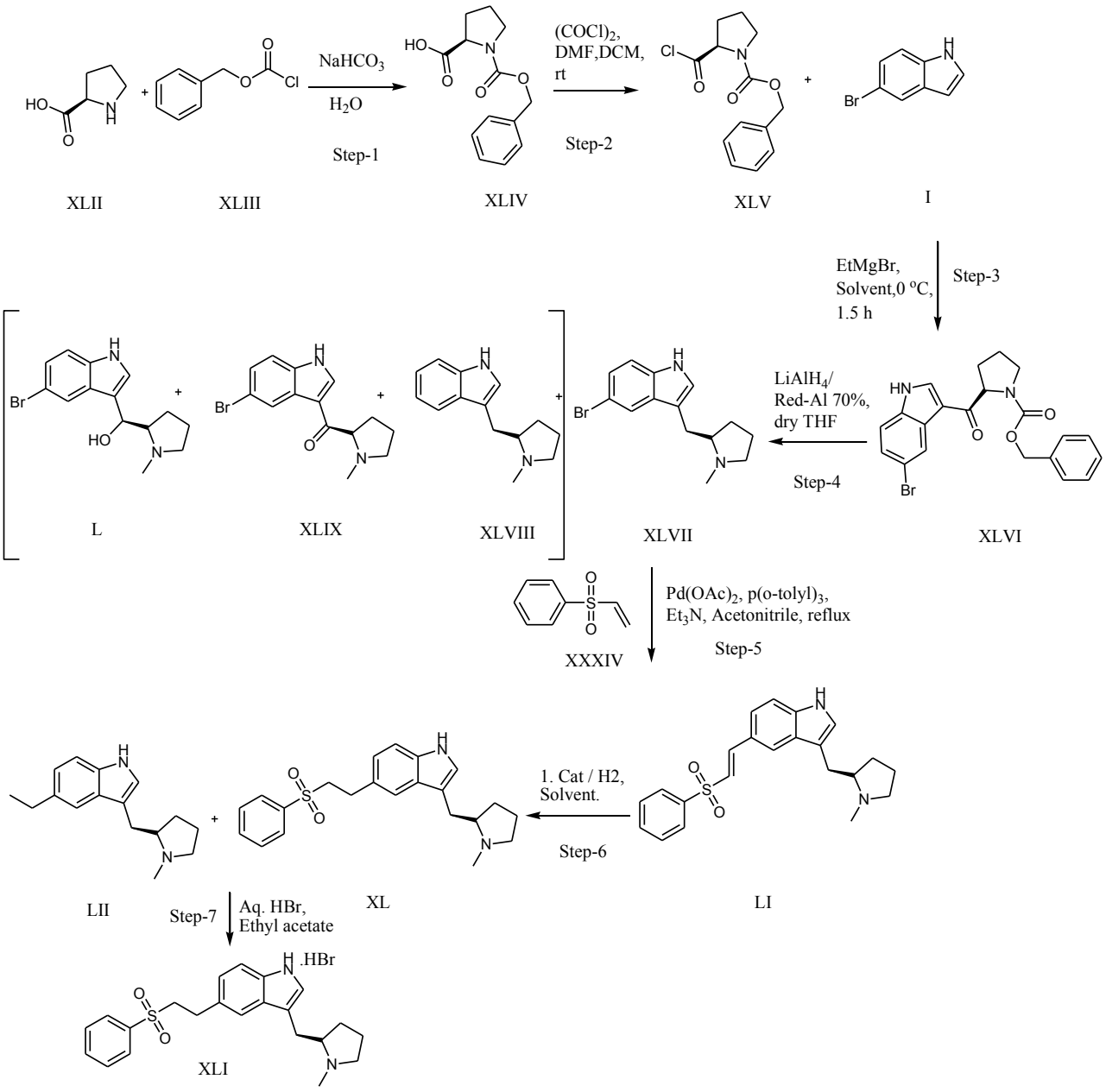
Table 4.1.3 Hydrogenation of Heck product (XXXV) to (XXXVII) by heterogeneous catalyst

Run	Catalyst	Sub/cat molar ratio	$P(H_2)$ MPa	T (°C) / t (h)	XXXVII [%]
1[a]	Pd/C 10%	18/1	0.3	50/18	12.5
2[b]	Rh/Al_2O_3 0.18%	18/1	0.3	50/18	100
3[c]	Rh/Al_2O_3 0.18%	100/1	0.3	50/18	100
4[c]	Rh/Al_2O_3 0.18%	100/1	0.2	50/18	100
5[d]	Rh/Al_2O_3 0.18%	500/1	0.2	50/18	100
6[e]	Rh/Al_2O_3 0.18%	1000/1	0.2	50/18	80
7[e]	Rh/Al_2O_3 0.18%	1000/1	0.2	80/18	100
8[e]	Rh/Al_2O_3 0.18%	1000/1	0.2	80/6.5	96
9[f]	Rh/Al_2O_3 0.18%	1000/1	0.2	80/6.5	17
10[g]	Rh/Al_2O_3 0.18%	100/1	0.2	80/8	98
11[h]	Pd/Al_2O_3 0.28%	100/1	0.2	80/8	50
12[i]	*Trans*-[$Pd(OAc)_2(L)_2$]	100/1	5	80/18	90
13[j]	Rh[DHTANa]	50/1	0.2	40/16	50

Reaction conditions: [a] pure substrate **(XXXV)** = (0.1 g, 0.353 mmol), 10 % Pd/C = 20.8 mg , Toluene = 4 mL;. [b] same condition of run 1 but 0.18 % Rh/Al_2O_3 = 1.12 g was used; [c] same condition of run 1 but 0.18 % Rh/Al_2O_3 = 0.20 g was used; [d] same condition of run 1 but 0.18 % Rh/Al_2O_3 = 40.1mg was used; [e] same condition of run 1 but 0.18 % Rh/Al_2O_3 = 20.2mg was used; [f] same condition of run 8 but **(XXXV)** crude Heck reaction mixture = (0.1 g, 0.353 mmol); [g] same condition of run 9 but 0.18 % Rh/Al_2O_3 = 0.20 g was used; [h] Same condition of run 10 but, 0.28 % Pd/Al_2O_3 = 0.179 mg, was used; [i] Same condition of run 10 but, *Trans*-[$Pd(OAc)_2(L)_2$], was used; [j] Sub-**XXXV** (0.1 g, 0.353 mmol), Rh[DHTANa], Toluene = (2 mL), water (2 ml).

In summary, home-made 0.18 % Rh/Al_2O_3 catalyst showed excellent activity and selectivity for the hydrogenation of carbon-carbon double bond on pure as well as crude **(XXXV)**.

4.2 Complete synthesis of Eletriptan hydrobromide *via* originator route



Scheme 4.2.1 Eletriptan hydrobromide reaction route according to originator synthesis

4.2.1 Synthesis of 5-bromo-3-[(R)-1-methyl-pyrrolidin-2-ylmethyl]-1H-indole (XLVII)

In the literature patent[114-118] a process for preparation of **(XLVII)** intermediate is described, starting from L-proline: by reaction with benzyloxycarbonyl chloride in the presence of $NaHCO_3$ in water overnight N-benzyloxycarbonyl-D-proline **(XLIV)** is obtained; this intermediate is then treated with 1.1 equivalent of oxalyl chloride in dry dichloromethane for 2 h to afford N-benzyloxy-prolinoyl chloride **(XLV)**. Subsequently, the acylation of **(I)**[119] is obtained by adding simultaneously N-benzyloxy-prolinoyl chloride and ethyl magnesium bromide by two dropping funnels to a solution of 5-bromo-1H-indole in dry dichloromethane to give 2-(5-bromo-1H-indole-3-carbonyl)-pyrrolidine-1-carboxylic acid benzyl ester **(XLVI),** which is finally reduced by lithium aluminium hydride (LAH) in dry tetrahydrofuran to afford 5-bromo-3-[(R)-1-methyl-pyrrolidin-2-ylmethyl]-1H-indole **(XLVII)**.

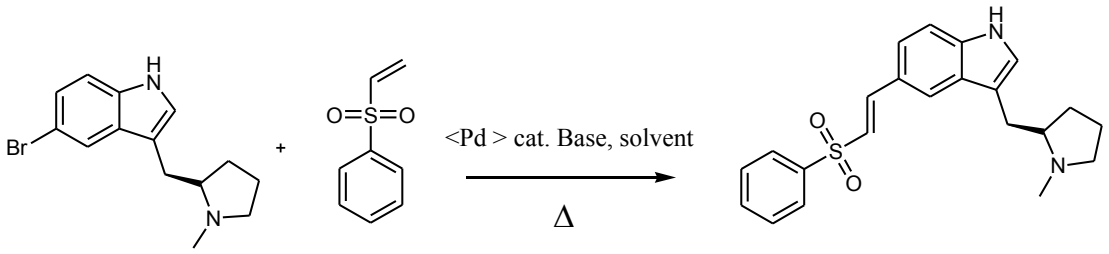
This procedure[120-121] was repeated with some modifications pure N-benzyloxycarbonyl-D-proline **(XLIV)** was obtained as a white solid in 99 % yield and quantitative transformation into crude N-benzyloxy-prolinoyl chloride **(XLV)**, a pale yellow oil, was carried out. After work-up and purification, 90 % yield of 2-(5-bromo-1H-indole-3-carbonyl)-pyrrolidine-1-carboxylic acid benzyl ester (**XLVI**) was obtained as a white solid. It is to underline that a fine tuning of the literature reaction protocol[119] was necessary: change of solvent, slow addition (about 3 h) and in a synchronous way of solutions of the N-benzyloxy-prolinoyl chloride **(XLV**) in THF and 1M ethylmagnesium bromide in THF to a cooled solution of **(I)** in THF at 0 °C, maintaining the temperature of the resulting mixture at 10-15 °C. Using the literature procedure and dichloromethane as solvent only 50 % yield was obtained in this step.

Finally the LAH reduction of **(XLVI)** in THF at reflux temperature, under nitrogen atmosphere, required a large amount of reducing agent (3.9 eq.) and long reaction time (up to 39 h) to afford, after work-up and purification by column chromatography, the target intermediate 5-bromo-3-[(R)-1-methyl-pyrrolidin-2-ylmethyl]-1H-indole **(XLVII)** in 56 % yield[122]. This reaction was carried out using as starting conditions the literature protocol but surely it would have required a deep optimization and a more sustainable procedure. In fact the crude **(XLVII)** contained as by-products **(XLVIII)** (1.03 %), **(XLIX)** (0.14 %) and **(L)** (10.75 %)[123] that were difficult to remove from the reaction mixture and could contaminate the desired product.

By adopting another procedure described in literature[117] compound **(XLVII)** was synthesized in high yield, reacting a solution of **(XLVI)** in anhydrous THF with 2 eq of 70 % solution of sodium

dihydro-bis(2-methoxyethoxy) aluminate in toluene at a temperature below 48 °C. The reaction was over in 3 h and then, after work-up, crude **(XLVII)** was recovered in 90 % yield; after crystallization the purity of **(XLVII)**, determined by HPLC and by ^{1}H-NMR, resulted to be 95 %, with impurities **(XLVIII)** (~2.2 %), **(XLIX)** (~2.1 %), **(L)** (~0.5) present in very low amount.

4.2.2 Study of Heck reaction on intermediate 5-Bromo-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole (XLVII)



XLVII XXXIV LI

Scheme 4.2.2 Synthesis of 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (LI) by using different homogeneous catalysts

The Heck reaction protocol described in literature[124] was at first replicated utilizing the conditions reported in run 1; after evaporation under reduced pressure the residue was purified by column chromatography using silica gel by elution with dichloromethane / methanol / ammonia(98/1.9/0.1) to afford the title compound (R)5-trans-(2-Ethylsulfonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole **(LI)** as a white solid in 70 % yield.

Then the reaction was carried out in presence of 3 mol % of $Pd(OAc)_2$ and the more hindered organic base N,N-dicyclohexylmethylamine to study the effect of base towards the formation of the desired product (run 2) but the same result was obtained.

In order to improve the conversion and yield towards the desired product **(LI)**, the reaction was performed in presence of another commercially available homogeneous catalyst (bis(dibenzylideneacetone)palladium(0)) with 3 mol % of loading and a more hindered organic base in acetonitrile or in cyclopentylmethylether as reaction medium at reflux temperature for 7 h: conversion was ≥90 % (runs 3 and 4) and **(LI)**, after work-up and purification, was recovered in 85-

90 % yield. Using CPME (data not reported in the Table) and 8 mol % of catalyst loading a complete conversion and a higher yield were obtained.

Working in presence of another commercially available homogeneous catalyst bis(tri-o-tolylphosphine)palladium(0), the best results were obtained using the same conditions of run 7 but using 8 mol % of catalyst loading in the presence of the cheaper tri-ethylamine as base and in the greener solvent CPME (table 4.2.1, run 7): 95 % conversion and 92 %isolated yield of **(LI)** were achieved.

With bis(tri-tert-butylphosphine)palladium(0) the best results were obtained in acetonitrile in the presence of triethylamine (runs 9 and 11) and with 8 mol % and 5 mol % of catalyst loading respectively. With a lower catalyst loading a longer reaction time was required (12 h vs. 5 h)[125-126].

Finally using the new bulky palladium phosphine complex i.e. (Pd(amphos)Cl_2) [Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)], the results were less satisfactory (run 13) also using 8 mol % of catalyst and increasing the reaction time to 16 h. This catalyst was recently prepared at the University of Florence and used during this thesis work with success in some hydrogenation reactions (Chapter 3, pages 33-43). No attempt, for the moment, to recover and reuse this catalyst was made. This point needs to be investigated in the future.

Table 4.2.1 Heck reaction using different homogeneous palladium catalysts

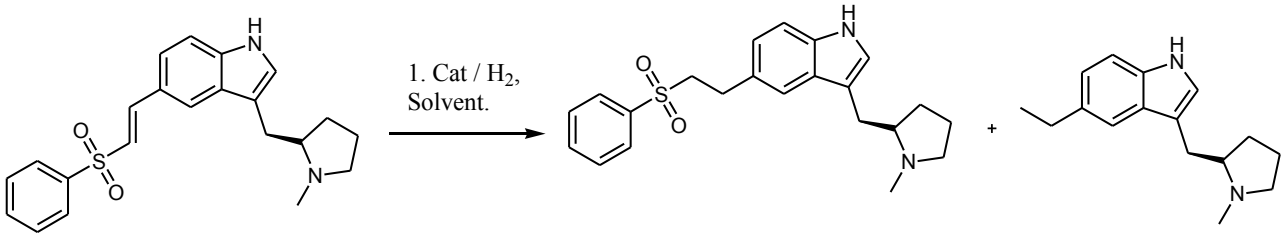
Run	[Pd] / (cat/subst. mol%)	T (°C) / t(h)	Base	Solvent	Conv. [%]	LI Isolated yield [%]
1[a]	$Pd(OAc)_2/P(o\text{-}tolyl)_3/(8)$	85/16	Et_3N	ACN	76	70
2[b]	$Pd(OAc)_2/P(o\text{-}tolyl)_3/(3)$	85/16	DCHMA	ACN	75	70
3[c]	$Pd(dba)_2/P(o\text{-}tolyl)_3/(3)$	85/7	DCHMA	ACN	95	90
4[d]	$Pd(dba)_2/P(o\text{-}tolyl)_3/(3)$	85/7	DCHMA	CPME	90	85
5[e]	$Pd[P(o\text{-}tolyl)_3]_2/(3)$	85/7	DCHMA	ACN	55	45
6[f]	$Pd[P(o\text{-}tolyl)_3]_2/(8)$	85/7	DCHMA	ACN	92	87
7[g]	$Pd[P(o\text{-}tolyl)_3]_2/(8)$	85/7	Et_3N	CPME	95	92
8[h]	$Pd[P(t\text{-}Bu)_3]_2/(3)$	85/5	Et_3N	ACN	50	45
9[i]	$Pd[P(t\text{-}Bu)_3]_2/(8)$	85/5	Et_3N	ACN	95	92
10[j]	$Pd[P(t\text{-}Bu)_3]_2/(8)$	100/5	Et_3N	CPME	45	41
11[k]	$Pd[P(t\text{-}Bu)_3]_2/(5)$	85/12	Et_3N	ACN	94	90
12[l]	$Pd(Amphos)Cl_2/(8)$	85/7	Et_3N	ACN	50	n.d.
13[m]	$Pd(Amphos)Cl_2/(8)$	85/16	Et_3N	ACN	85	80
14[n]	$Pd(Amphos)Cl_2/(8)$	85/16	Et_3N	CPME	65	n.d.

Reaction condition: [a] Substrate **(XLVII)** = (1 g, 3.41 mmol), Substrate **(XXXIV)** = (0.688 g, 4.09 mmol), $Pd(OAc)_2$ (61.2 mg), tri-o-tolylphosphine (14.5 mg, 0.477 mmol); triethylamine (0.689 g, 6.82 mmol); Acetonitrile (10 mL); [b] Same conditions of run 1 but $Pd(OAc)_2$ (22.9 mg) and DCHMA (1.33 g, 6.82 mmol) were used; [c] same condition of run 2 but, $Pd(dba)_2$ (58.8 mg), tri-o-tolylphosphine (14.5 mg, 0.477 mmol) were used; [d] same condition of run 3 but, CPME (10 mL) solvent were used; [e] same condition of run 3 but, $Pd[P(o\text{-}tolyl)_3]_2$ (73.2 mg) were used; [f] same condition of run 5 but, $Pd[P(o\text{-}tolyl)_3]_2$ (195 mg, 8 mol%) catalyst were used; [g] same condition of run 6 but, triethylamine (0.689 g, 6.82 mmol), CPME (10 mL) were used; [h] same condition of run 1 but, $Pd[P(t\text{-}Bu)_3]_2$ (52.3 mg) and t = 5h where used; [i] same condition of run 8 but, $Pd[P(t\text{-}Bu)_3]_2$ (139.6 mg, 8 mol %) catalyst were used; [j] same condition of run 9 but, T = 100 °C, t = 5h, CPME (10 mL) solvent were used; [k] same condition of run 9 but $Pd[P(t\text{-}Bu)_3]_2$ (87.2 mg, 5 mol %), T = 85 °C, t = 12h were used. [l] same condition of run 1 but, $Pd(Amphos)Cl_2$ (193.3 mg), T = 85 °C, t = 7h were used; [m] same condition of run 12 but, t = 16h were used; [n] same condition of run 13 but, CPME (10 mL) solvent were used.

In conclusion, after this investigation, it is possible to say that better conditions compared to the originator protocol were surely obtained. Probably, on the basis of cost of reagents, the best compromise was found using conditions of run 3 that are promising for further investigation and optimization in scaling-up.

4.2.3 Hydrogenation of 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (LI) in presence of different homemade heterogeneous catalysts

The hydrogenation of the carbon-carbon double bond of substrate **(LI)** (scheme 4.2.3) catalyzed by homemade 0.28 % Pd/Al_2O_3 and 0.18 % Rh/Al_2O_3 catalyst was studied and for comparison, results obtained by using some commercial catalysts are also reported.



LI XL LII

Scheme 4.2.3 Hydrogenation of 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (LI)

4.2.3.1 Hydrogenation of 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (LI) catalyzed by 0.18% Rh/Al_2O_3

As showed in (Table 4.2.2) and adopting the condition reported in run 1, a complete conversion was found; the reaction mixture was analyzed by HPLC, as described in the experimental part (paragraph 6.4.4), to give **(XL)** in 84 area % and by-product **(LII)** in16 area %. Trying to optimize reaction parameters to obtain high yield and better selectivity, many experiments were carried out using lower amount of catalyst and lower temperature (runs 2-6) but the results were unsatisfactory. Also lowering the H_2 pressure high amount of hydrogenolysis by-product was observed (run 7). To verify if the by-product formation was dependent on the reaction time, it was carried out an experiment using reaction conditions adopted for run 1 but reducing the time only to 30 min instead of 17 h. Surprisingly, also in this case a full conversion was observed but without any improvement of selectivity (run 8 vs. run 1). The catalyst used in this experiments was recycled (run 9), observing practically the same activity but worst selectivity. Finally the reaction was carried out adding 1 equivalent of oxalic acid (run 10) or sodium acetate (run 11) with respect to the starting material but

also in these experiments no improvement of selectivity was found and a higher amount of by-product was observed working in the presence of the oxalic acid. Also this result was surprising because the hydrogenation of this substrate with palladium catalyst, according to literature protocols[127-128], is always carried out in the presence of a strong acid such as methanesulfonic acid and also the alumina used in Rh catalyst as support presents acidic characteristics. By lowering the hydrogen pressure no improvement was observed for what selectivity and conversion are concerned. It was realized that using the reaction conditions adopted for run 8 as well as run 1 a full conversion is obtained but no change in selectivity occurs by changing reaction time; this fact was confirmed by other two experiments where the reaction time was 1 h and 1.5 h, respectively. It is to note that, on this substrate, Rh catalyst is active but less selective, if compared to previous results obtained in the hydrogenation of the model substrate **(XXXV)**.

Table 4.2.2 Hydrogenation of (LI) catalyzed by 0.18 % Rh/Al_2O_3

Run	Sub/cat molar ratio	$p(H_2)$ Mpa	T (°C) / t (h)	Conv [%]	XL [%]	LII [%]
1[a]	10/1	0.5	80/17	100	84	16
2[b]	50/1	0.5	80/17	97	55	42
3[c]	50/1	0.5	60/17	97	60	37
4[d]	50/1	0.5	50/17	77	57	20
5[e]	50/1	0.5	40/17	78	60	18
6[f]	50/1	0.5	30/17	64	53	11
7[g]	50/1	0.2	80/17	82	46	36
8[h]	10/1	0.5	80/0.5	100	84	16
9[i]	1° recycle	0.5	80/0.5	96	52	44
10[j]	10/1	0.5	80/0.5	88	55	33
11[k]	10/1	0.5	80/0.5	100	74	26

Reaction conditions: [a] Substrate **(LI)** = (0.1g, 0.263 mmol), 0.18 % Rh/Al_2O_3 (1.50 g), Toluene: Methanol (4:1) = 4 mL. [b] Same conditions of run 1 but 0.18 % Rh/Al_2O_3 (0.3 g). [c] Same conditions of run 2 but T = 60 °C., [d] Same conditions of run 2 but T = 50 °C. [e] Same conditions of run 2 but T = 40 °C. [f] Same conditions of run 2 but T = 30 °C., [g] Same conditions of run 2 but $p(H_2)$ was 0.2 Mpa. [h] Same conditions of run 1 but t = 30 min. [i] Using the catalyst recovered from run 8. [j] Same conditions of run 8 but 1eq of Oxalic acid was added. . [k] Same conditions of run 8 but 1eq of sodium acetate was added.

4.2.3.2 Hydrogenation of 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (LI) catalyzed by 0.28% Pd/Al_2O_3 or commercial 5% Pd(Fe)/C

Unlike the catalyst based on Rh, on this substrate, excellent results were obtained by using the catalyst based on Pd (0.28 % Pd/Al_2O_3). Different reaction parameters were studied and, after a fine tuning, conditions adopted (table 4.2.3) for run 9 permitted to obtain full conversion of unsaturated reagent and quite satisfactory selectivity (94-95 %) into the target product **(XL)**. It is to underline that it was possible to recycle two times the catalyst without any loss of activity and selectivity (runs 10 and 11). Furthermore, the presence of a base such as sodium acetate gave a slight improvement in selectivity (run 12); on the contrary the effect of an inorganic base such as K_2CO_3 was negative either on the conversion or on the selectivity (run 13). The reaction was carried out also in the presence of the commercial catalyst 5 % Pd(Fe)/C but it was less efficient respect to the homemade catalyst : it was necessary to use much more precious metal to obtain similar results (run 15). Last but not least reaction was performed in presence of other catalysts; polyester based *Trans*-$[Pd(OAc)_2(L)_2]$ and new water soluble [Rh(DHTANa)] catalyst gave less satisfactory results (table 4.2.3, run 16, 17).

Table 4.2.3 Hydrogenation of (LI) by 0.28 % Pd/Al_2O_3 and 5 % Pd(Fe)/C

Run	Catalyst	Sub/cat molar ratio	$p(H_2)$ Mpa	T (°C) / t (h)	Conv. [%]	XL [%]	LII [%]
1[a]	0.28% Pd/Al_2O_3	10/1	0.5	80/1	100	91	9
2[b]	0.28% Pd/Al_2O_3	10/1	0.5	50/1	100	91	9
3[c]	0.28% Pd/Al_2O_3	50/1	0.5	50/1	100	90	10
4[d]	0.28% Pd/Al_2O_3	50/1	0.1	50/1	14	13.5	0.5
5[e]	0.28% Pd/Al_2O_3	50/1	0.1	30/24	100	92	8
6[f]	0.28% Pd/Al_2O_3	50/1	0.1	40/20	100	91	9
7[g]	0.28% Pd/Al_2O_3	100/1	0.1	40/20	100	91	9
8[h]	0.28% Pd/Al_2O_3	150/1	0.1	40/16	100	93	7
9[i]	0.28% Pd/Al_2O_3	200/1	0.1	40/16	100	94	6
10[j]	0.28% Pd/Al_2O_3	200/1	0.1	40/16	100	94	6
11[j]	0.28% Pd/Al_2O_3	200/1	0.1	40/16	100	94	6
12[k]	0.28% Pd/Al_2O_3	200/1	0.1	40/16	100	95	5
13[l]	0.28% Pd/Al_2O_3	200/1	0.1	40/16	42	38	4
14[m]	5% Pd(Fe)/C	200/1	0.1	40/16	21	21	-
15[n]	5% Pd(Fe)/C	50/1	0.1	40/16	99	92	7
16[o]	*Trans*-$[Pd(OAc)_2(L)_2$	100/1	5	80/18	90	85	5
17[p]	Rh[DHTANa]	50/1	0.2	40/16	50	20	30

Reaction conditions: [a] Substrate **(LI)** = (0.1g, 0.263 mmol), 0.28 % Pd/Al_2O_3 (1 g), Toluene: Methanol (4:1) = 4 mL, $p(H_2)$ = 0.5 Mpa, , T = 80 °C, t = 1 h. [b] Same conditions of run 1 but, T = 50 °C. [c] Same conditions of run 2 but, 0.28 % Pd/Al_2O_3 (0.2 g). [d] Same conditions of run 3 but, $p(H_2)$ was 0.1 Mpa . [e] Same conditions of run 4 but, T = 30 °C and t= 24 h, [f] Same conditions of run 5 but, T = 40 °C and t = 20 h. [g] Same conditions of run 6 but, 0.28 % Pd/Al_2O_3 (0.1 g). [h] Same conditions of run 6 but, 0.28% Pd/Al_2O_3 (0.075 g). and t = 16 h. [i] Same conditions of run 8 but, 0.28 % Pd/Al_2O_3 (0.05 g). [j] Reaction carried out by using the catalyst recovered from the previous run. [k] Same conditions of run 9 but, 0.5eq of NaOAc (10.7 mg) was added. [l] Same conditions of run 9 but, 10 % of K_2CO_3 (10 mg) was added. [m] Same conditions of run 9 but, commercial catalyst 5% Pd(Fe)/C (4.2 mg) was used.; [n] Same conditions of run 14 but 5% Pd(Fe)/C (17 mg) was used; [o] Substrate **(LI)** = (0.1g, 0.263 mmol), *Trans*-$[Pd(OAc)_2(L)_2]$ sub/cat ratio 100/1, Toluene: = 4 mL, $p(H_2)$ = 5 Mpa, , T = 80 °C, t = 18 h; [p] Substrate **(LI)** = (0.1g, 0.263 mmol), Rh[DHTANa] sub/cat ratio 50/1, $p(H_2)$ = 5 Mpa, , T = 40 °C, t = 16 h), Toluene = (2 mL), water (2 ml).

Also in this case, making a kinetic study experiment, utilizing the best reaction conditions, it was possible to confirm that the formation of impurity **(LII)** is generated simultaneously during the hydrogenation of substrate **(LI)** (Table 4.2.4)

Table 4.2.4 Hydrogenation of (LI) Kinetic study by 0.28 % Pd/Al_2O_3

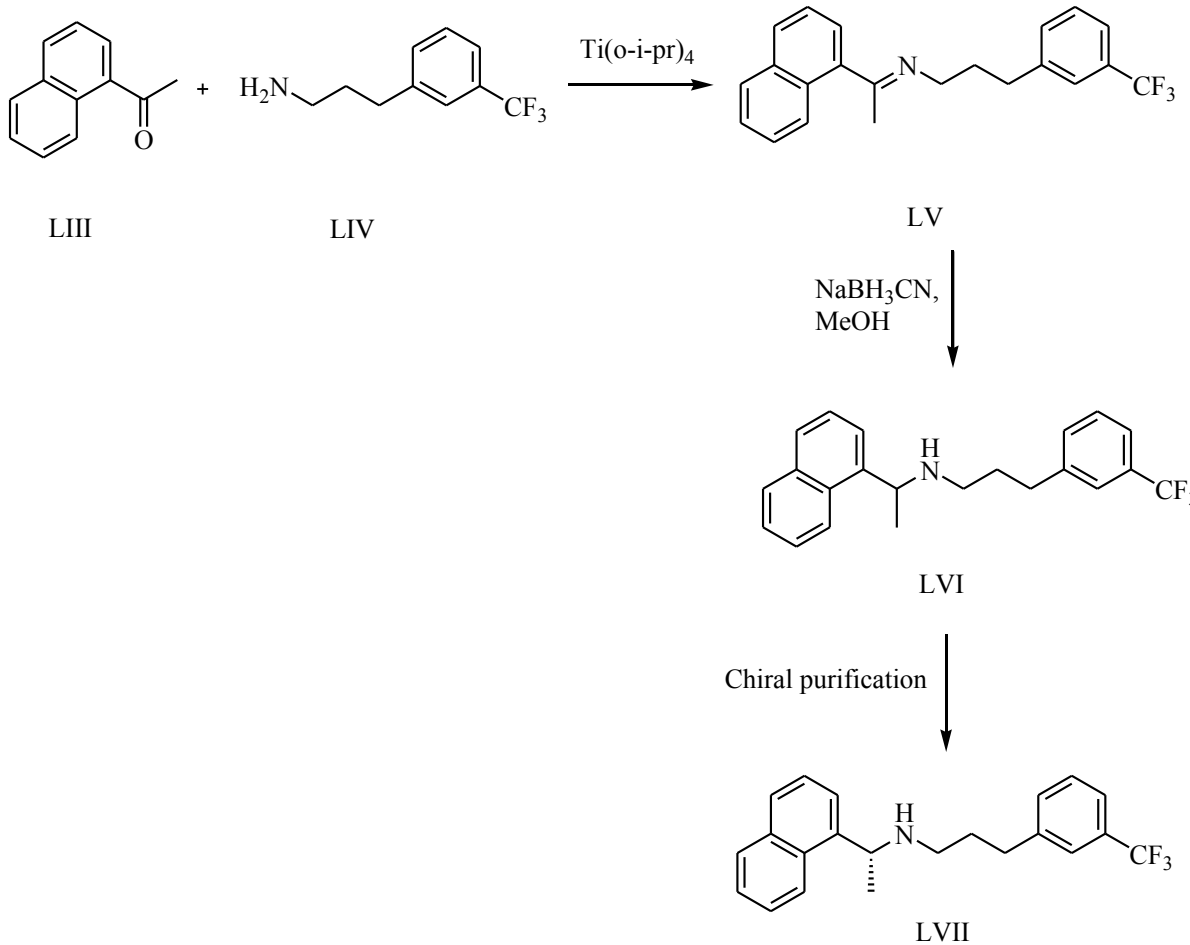
Sample analysis time (min)	Conv [%]	XL [%]	LII [%]
1	14.0	13.2	0.8
6	62.5	57.7	4.8
20	97.3	89.1	8.2
24	100	91.6	8.4

Reaction condition: [a] Substrate **(LI)** = (0.1g, 0.263 mmol), 0.28 % Pd/Al_2O_3 (0.050 g), Toluene: Methanol (4:1) = 4 mL, $p(H_2)$ = 0.1 Mpa, 40 °C.

In conclusion, the homemade 0.28 % Pd/Al_2O_3 showed to be very active also using reaction conditions different and simpler than those reported in the literature[129] and it seems a promising catalyst for the synthesis of Eletriptan, even if a further investigation to identify a catalyst with a superior selectivity could be still appropriate.

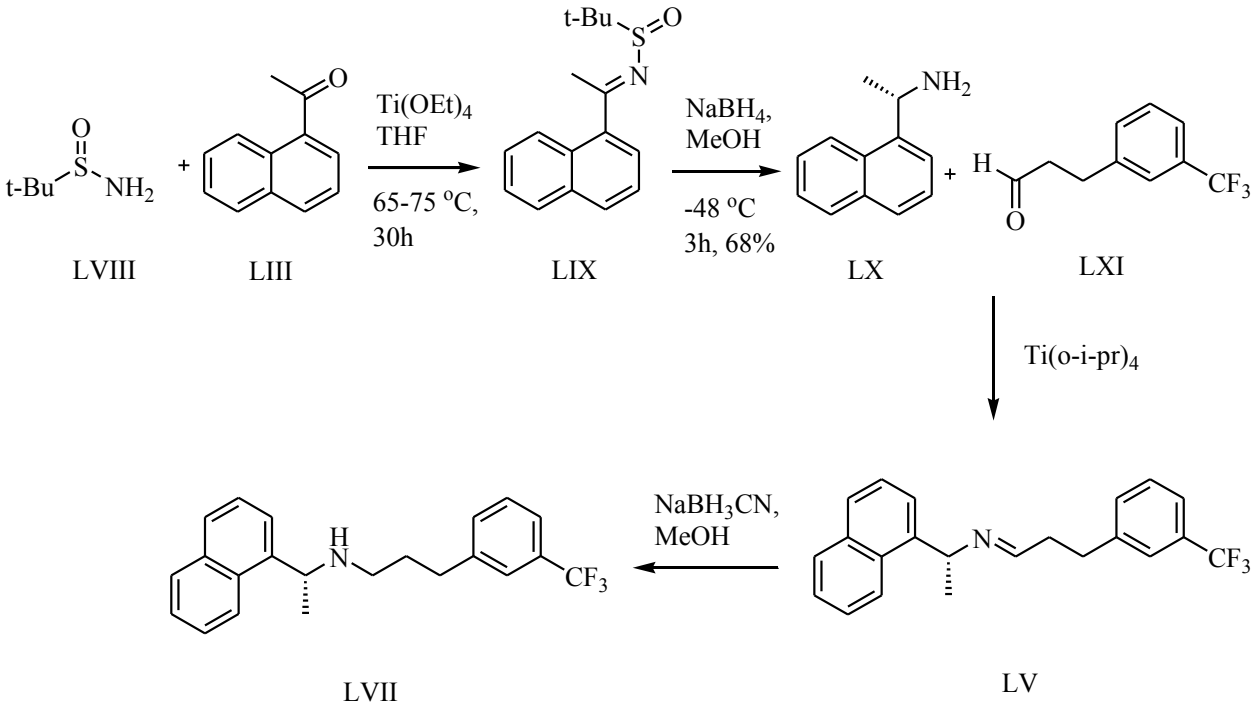
4.3 Synthesis of Cinacalcet hydrochloride: state of art

Several methods have been reported in the literature[130-146] for the synthesis of (R-N-[1-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]propan-1-amine Cinacalcet hydrochloride **(LXXV)**. Here a selection of these synthetic methods is depicted . In one of the first synthesis[147] the product was prepared by condensation of 1-acetyl naphthalene and 3-[3 (trifluoromethyl)phenyl]propylamine **(LIV)** in the presence of titanium (IV) isopropoxide and subsequent reduction of the resulting imine with sodium cyanoborohydride (Scheme 4.3.1) The obtained racemic Cinacalcet was then resolved by chiral column chromatography[148-150]. However, from the point of view of green and sustainable chemistry, this procedure is not suitable because it utilizes reagents such as titanium isopropoxide which is highly hygroscopic and expensive, as well as toxic, and ethanolic or methanolic sodium cyanoborohydride solutions, which is highly toxic and flammable, and not environmentally friendly. Furthermore the final resolution produces, as waste, the wrong enantiomer.



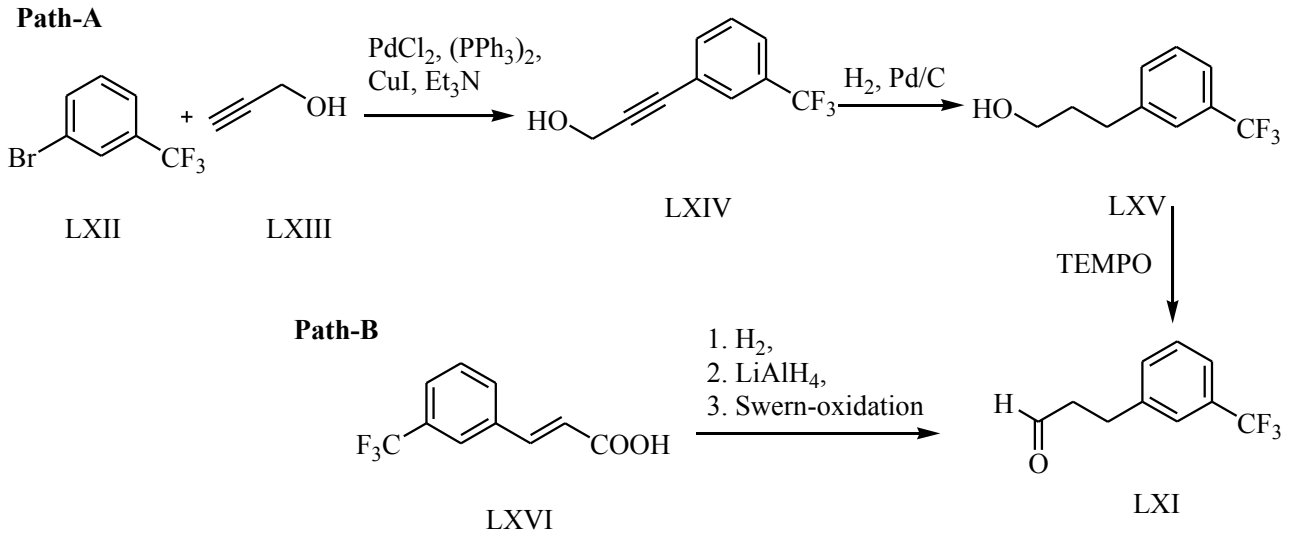
Scheme 4.3.1. First reaction scheme of Cinacalcet according to the originator

In a next approach[151] (scheme 4.3.2) chiral tert-butanesulfinamides **(LVIII)** was reacted with 1-acetylnaphthalene **(LIII)** to produce, after work-up, (R)-1-(naphthalen-1-yl)ethanamine hydrochloride **(LX)**, which was subsequently treated with 3-(3-trifluoromethylphenyl)propanal **(LXI)** in the presence of titanium (IV) isopropoxide and then reduced to the resulting imine with sodium cyanoborohydride to afford directly enantiopure Cinacalcet **(LVII)**, so avoiding the final chromatographic resolution.



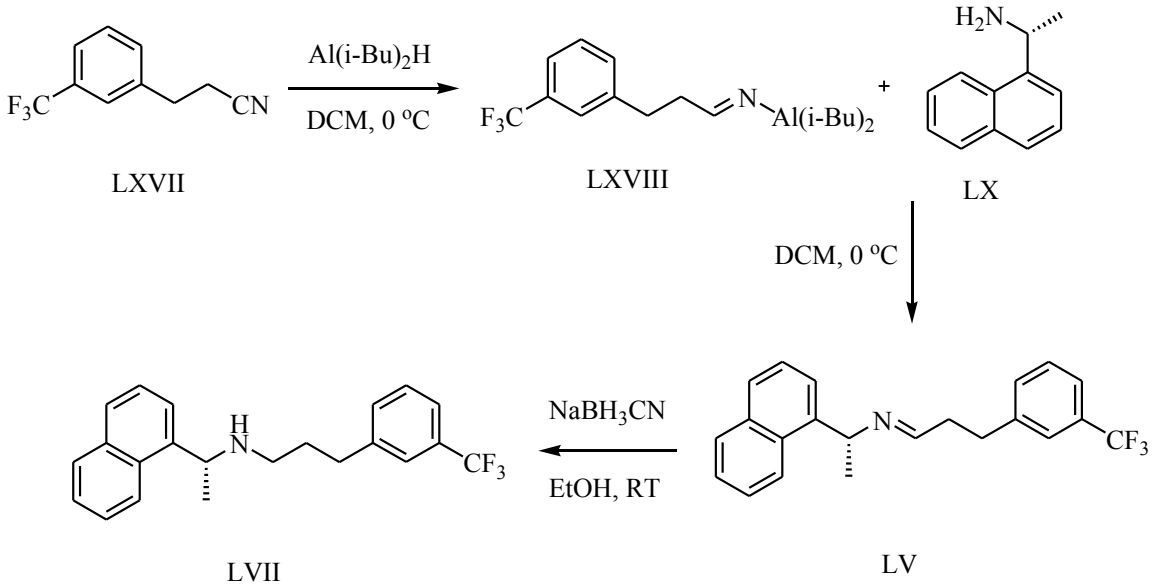
Scheme 4.3.2 Second reaction scheme of Cinacalcet according to the originator

The synthesis of **(LXI)**, key intermediate of this process, is disclosed in a footnote[152] and was made starting from commercially available 3-trifluoromethylcinnamic acid **(LXVI)** (Scheme 4.3.3, path-B). This process involves the hydrogenation of the double bond of **(LXVI)** followed by $LiAlH_4$ reduction of the carboxylic moiety to the corresponding alcohol, which is then oxidized to aldehyde **(LXI)** by Swern oxidation. The Swern oxidation reaction involves reagents such as oxalyl chloride and dimethyl sulfoxide which are not environmentally friendly and does not give high yield. In another patent literature[153] it is described a method to synthesize the same aldehyde **(LXI)** by oxidation of 3-(3-trifluoromethylphenyl)propan-1-ol **(LXV)** with an oxidizing agent (sodium hypochlorite) using a nitroxyl compound as catalyst (TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxi free radical). The corresponding alcohol intermediate is prepared by a Sonogashira coupling between 3-bromobenzotrifluoride **(LXII)** and propargyl alcohol **(LXIII)**, using a palladium compound and cuprous salt as catalysts, followed by a triple-bond reduction (Scheme 4.3.3, path-A).



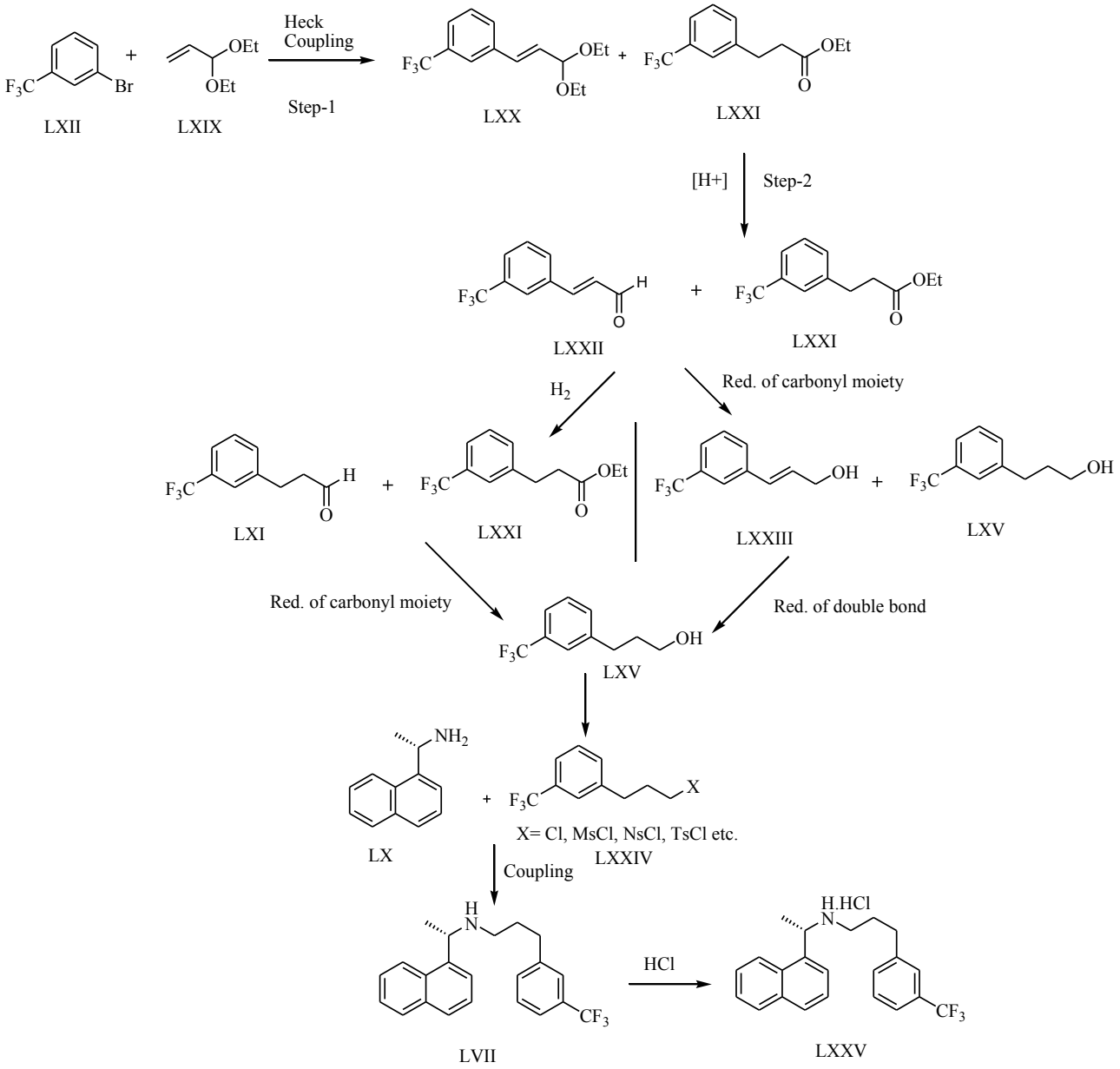
Scheme 4.3.3 Possible syntheses of key intermediate 3-(3-(Trifluoromethyl)phenyl)propanal (LXI)

In another approach[154] depicted in (Scheme 4.3.4) 3-(3-(trifluoromethyl)phenyl)propanenitrile **(LXVII)** is treated with Al(i-Bu)$_2$H in dichloromethane at 0 °C to get the intermediate **(LXVIII)** which *in situ* reacts with (R)-1-(naphthalen-1-yl)ethanamine **(LX)** under nitrogen atmosphere in dichloromethane at 0 °C to get the intermediate **(LV)**. The last part of the synthesis is the same of the previous schemes. From a green chemistry point of view this process however is not sustainable because it requires stoichiometric amount of Al(i-Bu)$_2$H which is highly hygroscopic, pyrophoric and expensive, as well as toxic, and again, ethanolic sodium cyanoborohydride, which is highly toxic and flammable, and not environmentally friendly.



Scheme 4.3.4 Another approach to obtain Cinacalcet

Furthermore a different strategy, more similar to our approach, is here described[155]. Using Heck coupling reaction[156-157] in the first step, 3-bromobenzotrifluoride **(LXII)** was reacted with acrolein diethyl acetal **(LXIX)** in presence of 2 % Pd/C as catalyst and inorganic base, in N-methyl-2-pyrrolidone at 140 °C for 2.5 h; at the end of the reaction and after work-up, a mixture of 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene **(LXX)** and ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)** in a ratio 1:1.2 (Scheme 4.3.5) was obtained. Then, hydrolysis of the resulting mixture with 1M HCl at room temperature for 3 h afforded the (E)-3-(3-(trifluoromethyl)phenyl)acryladehyde **(LXXII)** and ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)**. The resulting mixture was then reduced by using one of the metal hydride reducing agents such as sodium borohydride ($NaBH_4$)[158-159] lithium borohydride ($LiBH_4$), calcium borohydride [$Ca(BH_4)_2$], lithium aluminium hydride ($LiAlH_4$) or complexes of B_2H_6 with THF, Et_3N or Me_2S. For example when $LiAlH_4$ was used in THF at -5 °C for 40 min (E)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol **(LXXIII)** and 3-(3-(trifluoromethyl)phenyl)propan-1-ol **(LXV)** were recovered. Then obtained mixture was hydrogenated in the presence of 5 % Pd/C to get 3-(3-(trifluoromethyl)phenyl)propan-1-ol **(LXV)** as shown in Scheme 4.3.5 Then in the patent[155] the OH group was converted into a good leaving group in the presence of the inorganic base K_2CO_3 at 10 °C for 5 h and the obtained compound **(LXXIV)** was reacted with (R)-1-(naphthalen-1-yl)ethanamine hydrochloride **(LX)** in acetonitrile and in the presence of base at 100-120 °C for 24 h to afford Cinacalcet.

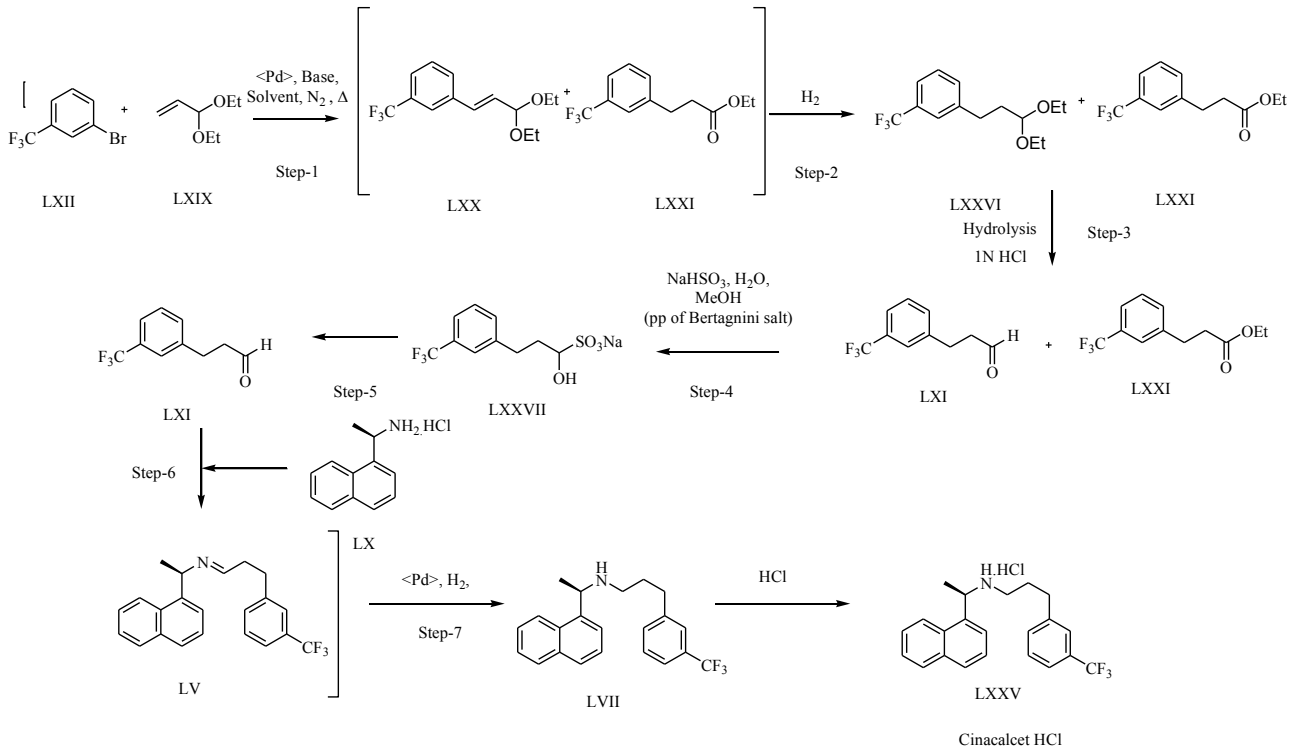


Scheme 4.3.5 A further reaction scheme of Cinacalcet hydrochloride

Also this Scheme presents some advantages and disadvantages in comparison to previous methods. Therefore, during this research work, it was decided to modify this last synthetic route studying either the optimization of Heck coupling, especially for improving the selectivity, or changing the other steps to realize an original, greener and more sustainable process.

4.4 Complete synthesis of Cinacalcet hydrochloride by an original improved synthetic strategy

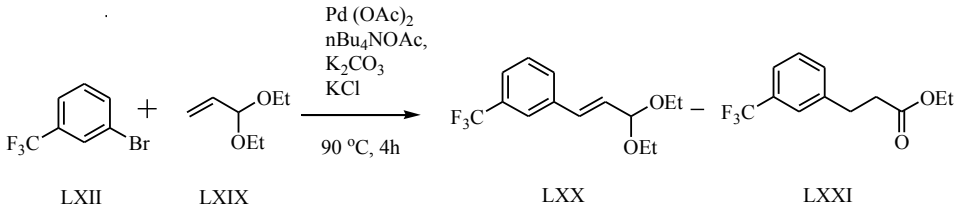
The initial idea of the present research project is depicted in Scheme 4.4.1.



Scheme 4.4.1 Synthesis of Cinacalcet hydrochloride through purification of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) *via* Bertagnini salt.

4.4.1 Heck reaction of 1-Bromo-3-(trifluoromethyl)benzene (LXII) and acrolein diethyl acetal (LXIX)

In the first step Heck cross coupling reaction was initially studied by utilizing the conditions reported in literature by Cacchi et.al[160] for the synthesis of analogous cinnamaldehyde derivatives in the presence of palladium (II) acetate, nBu_4NOAc, K_2CO_3, KCl in N,N-dimethylformamide at 90 °C for 3-4 h, obtaining the mixture of compound 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene **(LXX)** and ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)** in the ratio of 85:15 [161] (scheme 4.4.2).



LXII LXIX LXX LXXI

Scheme 4.4.2 Heck reaction of 1-Bromo-3-(trifluoromethyl)benzene (LXII) and acrolein diethyl acetal (LXIX)

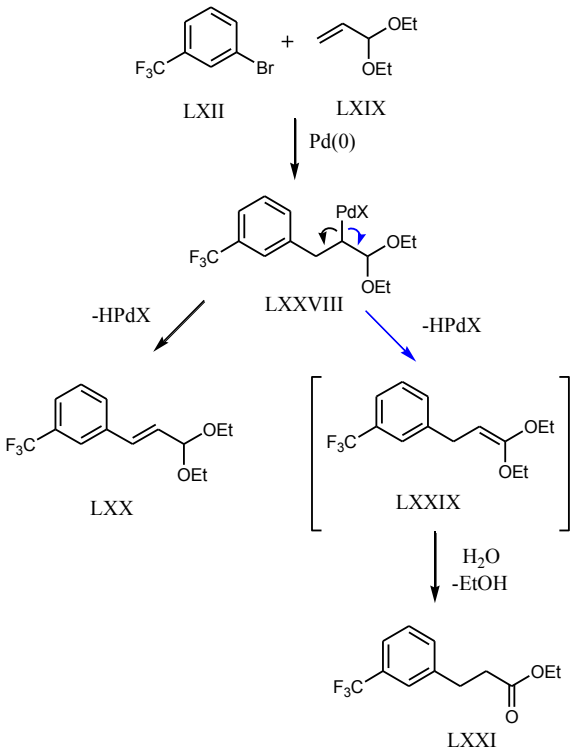
This encouraging result presented however a critical problem, i.e. the use of DMF as solvent. It is not a green solvent, it has been linked to cancer in humans, according to INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC), and is thought to cause birth defects[162]. Most manufacturers of DMF lists 'life' or 'chronic' as a health hazard in their MSDS since DMF is not readily disposed by the body. There is also a concrete risk that in the next future its use is banned in Europe. For this reason a detailed study of this reaction was carried out exploring greener solvents but also different reaction parameters to try to understand if it was possible to improve the selectivity. In all experiments palladium acetate was the catalyst. The results are reported in Table 4.4.1

Table 4.4.1 Obtained results of Heck reaction in different conditions.

Run	Ligand	Solvent	Base	Additive	Conv. [%]	LXX yield [%]	LXXI yield [%]
1[a]	nBu_4NOAc	DMF	K_2CO_3	KCl	100	85	15
2[b]	nBu_4NOAc	DMF	K_2CO_3	-	100	80	20
3[c]	nBu_4NOAc	γ-valerolactone	K_2CO_3	KCl	100	95	5
4[d]	nBu_4NOAc	2-Me-THF	K_2CO_3	KCl	100	93	7
5[e]	nBu_4NOAc	CPME	K_2CO_3	KCl	100	80	20
6[f]	nBu_4NBr	DMF	K_2CO_3	KCl	100	40	60
7[g]	nBu_4NBr	DMF	$LiOH.H_2O$	KCl	100	60	40
8[h]	nBu_4NBr	DMF	DBU	-	58	58	-
9[i]	nBu_4NBr	DMF	NaOMe	-	1	-	1
10[j]	nBu_4NBr	DMF	Cs_2CO_3	-	29	7	22
11[k]	nBu_4NBr	DMF	Et_3N	-	66	1	65
12[l]	nBu_4NBr	DMF	DCHMA	-	95	50	45
13[m]	nBu_4NOAc	DMF	K_2CO_3	KCl	100	99	1

Reaction conditions: [a] Substrate **(LXII)** (1g, 4.44mmol), Substrate **(LXIX)** (0.867g, 6.66mmol), $Pd(OAc)_2$ (29 mg, 0.133mmol), nBu_4NOAc 90 % (1.33g, 8.88mmol), KCl (0.33g, 4.44mmol), K_2CO_3 (0.919g, 6.66mmol), 90 °C, solvent = 10 mL, t = 4h. [b] Same conditions of run 1 but without KCl. [c] Same conditions of run 1 but γ-valerolactone was used. [d] Same conditions of run 1 but 2-methyltetrahydrofuran was used. [e] Same conditions of run 1 but cyclopentylmethylether was used. [f] Same conditions of run 1 but *n*Bu_4NBr was used. [g] Same conditions of run 6 but $LiOH.H_2O$ (0.279 g, 6.66 mmol) was used. [h] Same conditions of run 6 but DBU (1.014 g, 6.66 mmol) was used and without KCl. [i] Same conditions of run 8 but NaOMe (0.360 g, 6.66 mmol) was used. [j] Same conditions of run 8 but Cs_2CO_3(2.17 g, 6.66 mmol) was used. [k] Same conditions of run 8 but Et_3N (0.673 g, 6.66 mmol) was used. [l] Same conditions of run 8 but N,N-dicyclohexylmethylamine (1.29 g, 6.66 mmol) was used. [m] Same conditions of run 1 but nBu_4NOAc 97 % (2.67 g, 8.88 mmol) was used.

A possible mechanism to explain the formation of the two products, 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene **(LXX)** and ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)**, is presented in Scheme 4.4.3.



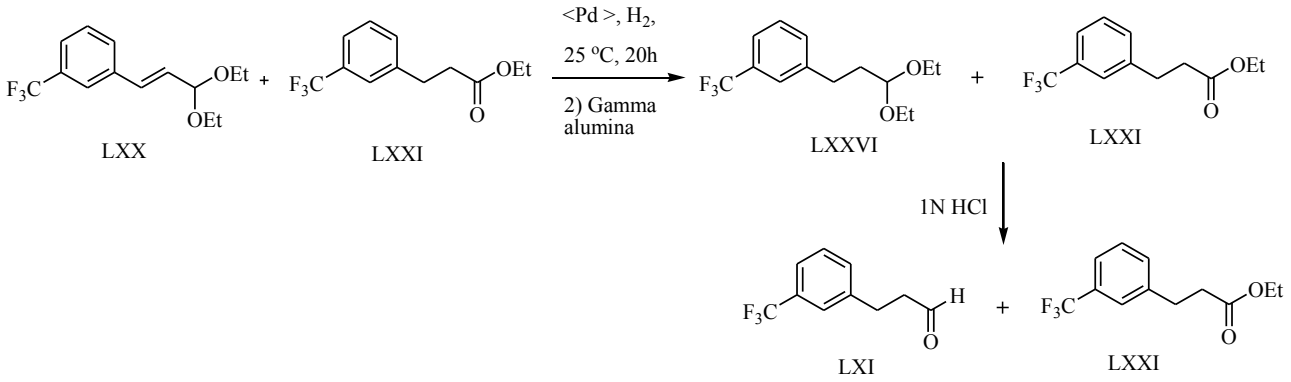
Scheme 4.4.3 Plausible mechanism of formation of products 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene (LXX) and Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate (LXXI)

It is reasonable that the nature of the base may affect the fate of decomposition of the alkyl palladium intermediate **(LXXVIII)**. As a matter of fact, a big effect on the selectivity was found working with different organic and inorganic bases but, at the present, it is difficult to give a clear explanation of this result. If we compare runs 8, 11 and 12, we can suppose that the steric hindrance plays an important role favoring the decomposition of **(LXXVIII)** to product **(LXX)**. Also the nature of X group (halide or acetate) bonded to palladium in **(LXXVIII)** could be important; it is to underline the strong effect on selectivity using, as ligand, nBu_4NOAc or nBu_4NBr (run 1 *vs* run 6 where the selectivity ratio is 85/15 and 40/60, respectively). Finally, as concerning solvent, it was possible to find two greener solvents that, at the same reaction conditions, gave better selectivity than DMF: gamma-valerolactone (run 3; 95/5) and 2-Me-THF (run 4; 93/7). On the contrary,

CPME afforded a less satisfactory result (run 5; 80/20). Last but not least, the best selectivity (99/1, run 13) was obtained using nBu_4NOAc 97 % instead of nBu_4NOAc 90 %; unfortunately, nBu_4NOAc 97 % is very expensive and is difficult to find on large scale; for this reason we studied the reaction using nBu_4NOAc 90 % which is less expensive and easily available in industrial amount.

4.4.2 Hydrogenation of 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene (LXX) by utilizing the same Heck catalyst followed by hydrolysis of 1-(3,3-Diethoxypropyl)-3-(trifluoromethyl)benzene (LXXVI)

As shown in (Scheme 4.4.4) it is possible to realize a one-pot process, combining the Heck cross coupling step with the subsequent carbon-carbon double bond hydrogenation[163], using the same catalyst simply changing the reaction atmosphere from nitrogen to hydrogen. At standard optimized conditions, (0.1 Mpa of H_2, 25 °C, 20 h), hydrogenation of **(LXX)** to **(LXXVI)** resulted 100 % conversion yield as compound **(LXXI)** present in the range 5-20 % (Table 4.4.1), only considering best Heck reactions), remained unchanged in the reaction mixture. During this synthesis the innovative idea was to recover Palladium catalyst at the end of the reaction by absorption on γ-alumina. To the crude hydrogenation reaction mixture alumina was added and then the suspension was filtered on sintered glass, washed with organic solvent to recover the adsorbed product and finally with water to remove soluble inorganic material. After drying the alumina under vacuum, the material was analyzed showing 0.18 % of palladium content. This recovered catalyst (Pd/Al_2O_3) was later used for reductive amination reaction (step 7, Scheme 4.4.1) and the results will be presented in paragraph 4.4.5.

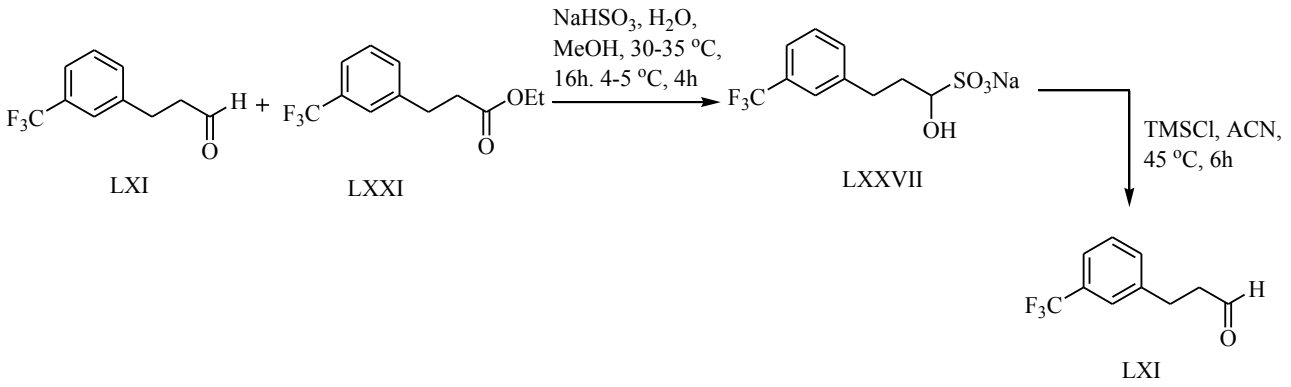


Scheme 4.4.4 Synthesis of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI)

The organic phase was treated with aqueous HCl to cleavage the acetal **(LXXVI)** to get compound (**LXI**) in excellent yield, >90 %, (Scheme 4.4.4); the standard reaction conditions were 30 °C for 1-6 h; longer reaction times were necessary when ethereal solvents, such as Me-THF and CPME were present, due to the initial inhomogeneity of reaction mixture. If the reaction mixture contained polar solvents such as DMF, γ-valerolactone etc., the acetal deprotection was very fast. After work-up and evaporation of the solvent, **(LXI)** and unchanged by-product **(LXXI)** were recovered.

4.4.3 Purification of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) by bisulfite adduct and regeneration of the aldehyde

Purification of crude carbonyl compounds by crystallization as their bisulfite adducts and subsequent regeneration of pure carbonyl derivatives is a known technique[164]. However, it is necessary to tune the reaction conditions to achieve good results, in particular with aldehydes. The crude mixture containing **(LXI)** and **(LXXI)** (ratio 80-95 %/20-5 %) gave quickly a precipitate when treated with sodium bisulfite in ethanol: water (2:1); the resulting suspension was stirred at 35 °C for 16 h and subsequently at 5 °C for 4 h, then the solid was filtered and washed with methyl tert-butyl ether to remove the impurity **(LXXI).** The adduct **(LXXVII)** was recovered with nearly quantitative yield in agreement with literature[165] (scheme 4.4.5).

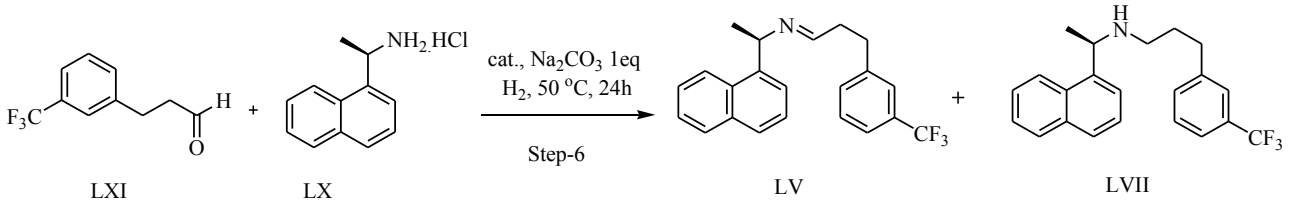


Scheme 4.4.5 Purification of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) by bisulfite adduct and regeneration of the aldehyde

The regeneration of aldehyde **(LXI)** was carried out adapting a literature protocol[166]. Sodium 1-hydroxy-3-(3-trifluoromethylphenyl)propane-1-sulfonate **(LXXVII)** was treated with TMS-Cl at 45 °C, using acetonitrile or toluene as preferred solvents, monitoring the conversion by ^{1}H-NMR analysis of filtered samples, until the quantitative transformation of **(LXI)** was obtained in about 6 h. Then the reaction mixture was cooled to room temperature, diluted with toluene and the organic phase was extracted with water and brine, then dried over sodium sulphate, filtered and concentrated under vacuum to afford pure **(LXI)** in 95 % yield.

4.4.4 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) catalyzed by homemade 0.28 % Pd/Al_2O_3 and 0.18 % Rh/Al_2O_3

Reductive amination of aldehydes, without isolation of the corresponding imine derivative, is an important transformation in organic synthesis from a process efficiency point of view. There are two types of reducing agents used for reductive amination of aldehydes with amines: metal catalyzed hydrogenation and hydride reducing agents. Both approaches, presenting advantages and disadvantages and being critical as concerning selectivity, were investigated during this thesis work. Here the results obtained in metal catalyzed hydrogenation, by using the homemade low metal content catalysts 0.28 % Pd/ and 0.18 % Rh/Al_2O_3, are reported.



Scheme 4.4.6 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) catalyzed by homemade 0.28 % Pd/Al_2O_3 and 0.18 % Rh/Al_2O_3

Initially the reaction was performed in the presence of 0.28 % Pd/Al_2O_3 with **(LXI)**/catalyst molar ratio 1000/1 at 50 °C and 0.2 Mpa H_2 for 24 h in toluene (run 1, Table 4.4.2). A 100 % conversion was achieved but 20 % of imine intermediate **(LV)** was found. When the hydrogen pressure was increased to 0.5 Mpa the conversion was 100 % and selectivity to **(LVII)** was 98 %, obtaining 92 % as isolated yield (run 2). The recovered catalyst showed a very good activity also in three recycling experiments affording complete conversion (run 3-5), high selectivity towards the desired product **(LVII)** and only small amount of intermediate imine **(LV)** (1-2 %).

The reaction was performed in the presence of another homemade catalyst, 0.18 % Rh/Al_2O_3, at the same experimental conditions, but the results were less efficient (run 6): at 100 % conversion of the starting aldehyde, still 38 % of the imine intermediate **(LV)** was recovered. Maybe working under more drastic conditions also 0.18 % Rh/Al_2O_3 could be a suitable catalyst to obtain a complete formation of desired product **(LVII)**, but this point was judged not interesting to explore. It is interesting to note that with both catalysts it was not observed the formation of alcohol **(LXV)** (Scheme 4.3.5) or the partial hydrogenation of naphthalene ring, possible by-products of this reaction.

Table 4.4.2 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) catalyzed by 0.28 % Pd/Al_2O_3 and 0.18 % Rh/Al_2O_3

Run	Catalyst	Conv.[%]	LV[%]	LVII[%]
1[a]	0.28 % Pd/Al_2O_3	100	20	80
2[b]	0.28 % Pd/Al_2O_3	100	2	98
3[c]	0.28 % Pd/Al_2O_3	100	1	99
4[c]	0.28 % Pd/Al_2O_3	100	1	99
5[c]	0.28 % Pd/Al_2O_3	100	3	97
6[d]	0.18 % Rh/Al_2O_3	100	38	68

Reaction conditions: [a] Substrate-(**LXI**) = (1 g, 4.95 mmol), Substrate-(**LX**) = (1.02 g, 4.95 mmol), Na_2CO_3 (0.524 g, 4.95 mmol), 0.28 % Pd/Al_2O_3 (0.188 g, (**LXI**)/cat ratio 1000/1), p(H_2) = 0.2 Mpa, T = 50 °C, t = 24 h Toluene = 5mL.[b] Same conditions of run 1, but p(H_2) was 0.5 Mpa. [c] Reaction carried out by using the catalyst recovered from the previous run. [d] Same conditions of run 2, but 0.18% Rh/Al_2O_3 (0.283 g, (**LXI**)/cat ratio 1000/1) were used.

4.4.5 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) catalyzed by recovered 0.18 % Pd/Al_2O_3

Interesting results were obtained also using, as catalyst, 0.18 % Pd/Al_2O_3 recovered from Heck cross coupling and hydrogenation reaction described above.

Utilizing the conditions reported in Table 4.4.3, (run 1) with (**LXI**)/catalyst molar ratio 200/1, a 100 % conversion was achieved and only 3 % of the imine intermediate **(LV)** was observed. The same result was obtained decreasing the hydrogen pressure to 0.2 Mpa (run 2). The recovered catalyst showed a very good activity also in three recycling experiments (run 3-5) affording the desired product **(LVII)** with 90 % isolated yield. When the reaction was performed with a (**LXI**)/catalyst molar ratio = 500/1, at the same experimental conditions, 40 % of the imine intermediate **(LV)** was obtained; probably it should be possible to obtain complete formation of the desired product simply by using a longer reaction time or increasing H_2 pressure.

Table 4.4.3 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) catalyzed by recovered 0.18 % Pd/Al_2O_3

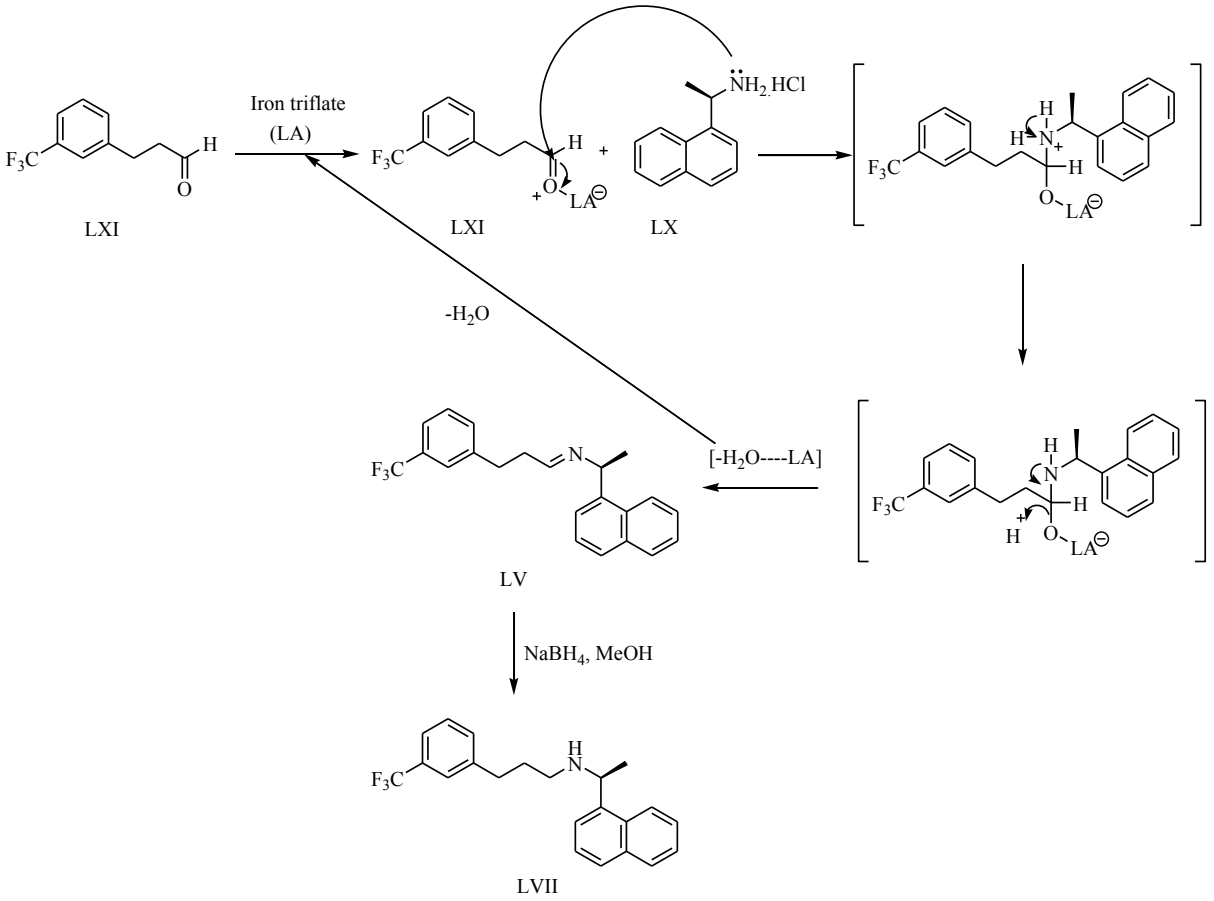
Run	Conv.[%]	LV[%]	LVII[%]
1[a]	100	3	97
2[b]	100	3	97
3[c]	100	3	97
4[c]	100	4	96
5[c]	100	4	96
6[d]	100	40	60

Reaction conditions: [a] Substrate **(LXI)** = (1 g, 4.95 mmol), Substrate **(LX)** = (1.02 g, 4.95 mmol), Na_2CO_3 (0.524 g, 4.95 mmol), 0.18 % Pd/Al_2O_3 (1.46 g, (**LXI**)/cat ratio 200/1), $p(H_2)$ = 0.5 Mpa, T = 50 °C, t = 6 h Toluene = 5 mL. [b] Same conditions of run 1 but $p(H_2)$ was 0.2 Mpa. [c] Reaction carried out by using the catalyst recovered from the previous run. [d] Same conditions of run 2 but (**LXI**/cat molar ratio 500/1) was used.

4.4.6 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) by hydrides in the presence of Aquivion®-Fe as catalyst

In literature, the reductive amination reaction may be performed using sodium cyanoborohydride ($NaBH_3CN$) as a reducing agent (Borch reaction)[167] and this protocol has wide applicability. $NaBH_3CN$ is a comparatively weak reducing agent which works under mild acidic conditions. The control of the reaction pH is important for smooth and selective reductive amination reactions. Usually the pH range required for reduction of ketones and aldehydes to the corresponding alcohols is in range between 3-4, whereas for iminium cation required pH is between 6-7. $NaBH_3CN$ works fine within above mentioned pH ranges without causing unusable side reactions. Nevertheless this method suffers for the formation of highly toxic by-products such as HCN and NaCN. $NaBH(OAc)_3$ and 2-picolineborane may be used as safer alternatives[168], because they present low toxicity and can be used in the presence of water, but their use is quite expensive. A cheaper hydride is $NaBH_4$ but usually is less selective and may give high quantity of alcohols, as side-product, if the reaction conditions are not well controlled and/or imine is not pre-formed. Selective reductive amination reaction with $NaBH_4$, in the presence of Fe-triflates [$Fe(OTf)_3$] catalyst was recently reported[169]. It is important to note that, in contrast with other metals, iron products are

usually non-toxic for the environment. With regard to the reaction mechanism, $Fe(OTf)_3$, as a Lewis Acid (LA) catalyst, may activate the carbonyl functionality and generate a very reactive electrophilic source. Amine, used as substrate, reacts with this activated species to form the hemiaminol equivalent. Afterwards, dehydration happening regenerates the catalyst. *In situ* generated imine intermediate is then reduced with sodium borohydride affording the desired product.(Scheme 4.4.7).



Scheme 4.4.7 Possible mechanism for reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) by $NaBH_4$ catalyzed by iron species as Lewis acid

However, even if the use of Fe-triflate in this reaction may appear a good alternative to traditional methods, it should be noted that such kind of catalyst is not recoverable and recyclable. For this reason, in the present research, Aquivion®-Fe was investigated as a catalyst in reductive amination reaction. Aquivion®-Fe may be considered a heterogeneous "iron triflate equivalent" which is readily removable from the reaction mixture and is potentially recyclable.

In the first reaction aldehyde **(LXI)** and catalyst Aquivion®-Fe were added into the flask at the same time and this mixture was stirred for 10 minutes; then (R)-1-(naphthalen-1-yl)ethanamine hydrochloride **(LX)** and $NaBH_4$ were added. It was observed that when the catalyst was used, the formation of the imine intermediate **(LV)** is practically simultaneous but practically no reduction to **(LXV)** occurs. As soon as the methanol is added, the amine **(LVII)** is quickly formed and after 1h the reaction is complete (table 4.4.4, run 1). The work-up of the crude mixture was simple : water was added and the catalyst was filtered off. The organic phase was separated from the aqueous phase and the latter phase was extracted with dichloromethane. The organic phase was collected, the solvent was removed and after distillation under vacuum the desired product **(LVII)** was obtained in pure form with 95 % isolated yield. The recovered catalyst maintained a very good activity also in two recycling experiments affording complete conversion (table 4.4.4, run 2 and 3), with high selectivity to the desired product **(LVII)**.

Carrying out the reaction in absence of catalyst (table 4.4.4, run 4), but adopting the above described procedure, it was observed that the formation of the imine intermediate **(LV)** is much lower than when Aquivion®-Fe is used. After 1 hour, 60 % of unreacted **(LXI)** was detected and, when methanol was added, the immediate formation of 50 % of by-product **(LXV)** occurred.

Table 4.4.4 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) by $NaBH_4$ catalyzed by Aquivion®-Fe

Run	Conv [%]	LV [%]	LVII [%]	LXV [%]
1[a]	100	-	100	-
2[b]	100	1	99	-
3[b]	100	1	99	-
4[c]	60	-	10	50

Reaction conditions: [a] Substrate **(LXI)** = (1 g, 9.90 mmol), Substrate **(LX)** = (2.05 g, 9.90 mmol), Na_2CO_3 (1.48 g, 9.90 mmol), $NaBH_4$ (0.37 g, 9.90 mmol), Aquivion®-Fe (28 mg, 0.032 mmol, (**LXI**/catalyst molar ratio 300/1), in dichloromethane = 10 mL, T = 25 °C, t = 1 h, 2 mL methanol were added after 1 h. [b] Reaction carried out by using the catalyst recovered from the previous run. [c] in absence of catalyst.

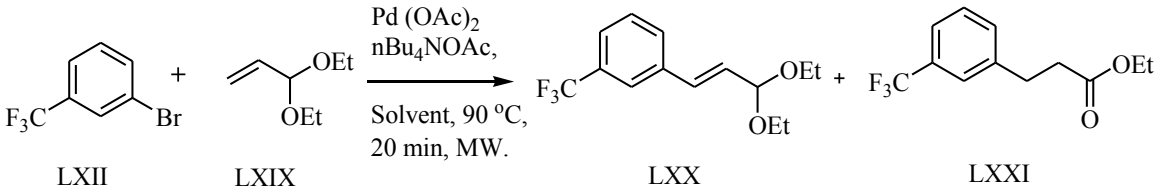
From the obtained results, catalyst Aquivion®-Fe is necessary to obtain the desired product with excellent selectivity and >95 % isolated yield. This iron triflate equivalent is a recyclable green Lewis acid.

4.5 Complete synthesis of Cinacalcet hydrochloride under microwave conditions. Introduction

The advantage and application of microwaves, as an efficient heating source for organic transformation[170-172] , was recognized in the mid of 1980s. Since after, many successful reactions with dramatically enhanced reaction rates have been disclosed. Very good yields and clean reactions have been obtained using only small amounts of energy and short reaction time[173]. The possibility of employing milder and less toxic reagents and solvents offers a further advantage of using this heating technology. The non inert-atmosphere conditions and the simple experimental procedure of many microwave reactions offer additional convenience in chemical synthesis, especially for high-throughput applications. Till 1995, almost 200 articles had been published on the beneficial effect of microwave irradiation in organic transformations. Today's date this number is above 1100. The majority of the microwave-promoted reactions reported so far, that depend on homogeneous catalysts, are catalyzed by palladium[174]. In this thesis homogeneous palladium catalyzed Heck cross coupling, hydrogenation reactions and heterogeneous metal catalyzed reductive amination reaction for the synthesis of Cinacalcet were investigated to verify the possibility to improve conventional batch results.

4.5.1 Heck cross coupling reaction of 3-bromobenzotrifluoride (LXII) and acrolein diethyl acetal (LXIX) under microwave irradiation.

The Heck cross coupling reaction of 3-bromobenzotrifluoride **(LXII)** and acrolein diethyl acetal **(LXIX)** (scheme 4.5.1), catalyzed by homogeneous $Pd(OAc)_2$, in different solvents, was investigated under microwave irradiation, in CEM Discover microwave processor equipped with a 300 W power source and the results are reported in (Table 4.5.1).



LXII LXIX LXX LXXI

Scheme 4.5.1 Heck cross coupling reaction of 3-bromobenzotrifluoride (LXII) and acrolein diethyl acetal (LXIX) under microwave

The first microwave experiment was carried out by using a CEM Discover system with a 10 mL CEM microwave vial setup adopting the conditions above reported (run 1). Before starting the reaction it was necessary to deoxygenate the solvent by bubbling argon for 10 min, then the reaction was run with 3 mol % of $Pd(OAc)_2$ as catalyst, at 90 °C for 10 min in DMF. By applying the following microwave parameters, the given input microwave power was 5W, ramp time 5 min, reaction hold time 10 min, with maximum pressure limit 300 psi: a 75 % conversion was observed and the mixture contained 70 % of the desired product **(LXX)** and 5 % of the by-product **(LXXI)**. In the next reaction (run 2) the reaction hold time was increased up to 20 min and 100 % conversion was found to afford 90 % of the desired product **(LXX)** and 10 % of the by-product **(LXXI)**. The reaction in runs 1 and 2 worked in presence of 2 mmol of nBu$_4$NOAc, 1 mmol of KCl and 1.5 mmol of K_2CO_3; since nBu$_4$NOAc is also a base the reaction was performed in absence of KCl and K_2CO_3 with very interesting and encouraging results (run 3) : 100 % conversion with a 91/9 ratio **(LXX)/(LXXI)**. Even if DMF is an excellent solvent for MW applications, for the reasons previously reported about this solvent, it was necessary to study the reaction in an alternative greener solvent, such as THF, 2-MeTHF, CPME, γ–valerolactone, EtOH or under solvent less conditions. Excellent results, comparable with those obtained in DMF, were observed in 2-MeTHF, γ-valerolactone and THF (runs 4-6). On the contrary, poor results were found in ethanol, as expected, and in cyclopentylmethylether (CPME) (runs 7 and 8, respectively). Finally, the reaction was carried out under neat conditions: in this case a complete conversion was obtained but only the by-product **(LXXI) (**40 % yield) was identified together with a large amount of unidentified tarry material (run 9).

Table 4.5.1 $Pd(OAc)_2$ catalyzed Heck cross coupling reaction under microwave irradiation

Run	Solvent	Conv. [%][j]	LXX [%]	LXXI [%]
1[a]	DMF	75	70	5
2[b]	DMF	100	80	20
3[c]	DMF	100	91	9
4[d]	2-Me-THF	100	92	8
5[e]	γ - Valerolactone	100	91	9
6[f]	THF	100	90	10
7[g]	EtOH	7	5.5	1.5
8[h]	CPME	13	12	1
9[i]	No solvent	100	-	40

Reaction condition: [a] Substrate **(LXII)** : (0.240 g, 1 mmol), substrate **(LXIX)** : (0.208 g, 1.59 mmol), $Pd(OAc)_2$ (7.1 mg, 3 mol %), n-Bu_4NOAc (90 %) (0.714 g, 2 mmol), K_2CO_3 (0.220 g, 1.5 mmol), KCl (81.5 mg, 1 mmol), T = 90 °C, t = 10 min, Solvent = 2 mL, Microwave condition: power-5 W, Ramp time-5 min, Hold time- 20 min, Temperature- 90 °C, Pressure limit- 300 psi. Amounts % of products were determined by GC (using n-dodecane as internal standard). [b] Same conditions of run 1, but t = 20 min was used. [c] Substrate **(LXII)** : (0.240 g, 1 mmol), substrate **(LXIX)** : (0.208 g, 1.59 mmol), $Pd(OAc)_2$ (7.1 mg, 3 mol %), n-Bu_4NOAc (90 %) (0.714 g, 2.1 mmol), T = 90 °C, t = 20 min, Solvent = 2 mL. [d] Same conditions of run 3, but 2-methyltetrahydrofuran was used as solvent. [e] Same conditions of run 3, but γ-valerolactone was used as solvent. [f] Same conditions of run 3 but tetrahydrofuran was used as solvent. [g] Same conditions of run 3 but ethanol was used as solvent. [h] Same conditions of run 3 but cyclopentylmethylether was used as solvent. [i] Same conditions of run 3 but reaction was carried out without added solvent.

A further series of experiments was then carried out to try to reduce the amount of used catalyst to 1%. The results are reported in (Table 4.5.2).

Using γ-valerolactone as a reaction medium and a lower amount of catalyst (run 2), a similar result to that previously obtained (run 5, Table 4.5.1) was achieved; quite surprisingly in 2-methyltetrahydrofuran, at the same reaction conditions, only 76 % conversion was obtained (run3) but the selectivity was always good (**LXX**/**LXXI**;73/3). At the moment a clear explanation is not possible, but probably the latter solvent contains any impurity which may partially poison the catalyst and this effect is more evident when a lower amount of $Pd(OAc)_2$is used.

Table 4.5.2 Further $Pd(OAc)_2$ catalyzed Heck cross coupling reaction experiments under microwave irradiation

Run	Solvent	Conv.[%]	LXX[%]	LXXI[%]
1[a]	DMF	100	85	15
2[b]	γ-valerolactone	100	90	10
3[c]	2-MeTHF	76	73	3

Reaction condition :[a] Substrate **(LXII)** (0.240 g, 1 mmol), substrate **(LXIX)** (0.208 g, 1.59 mmol), $Pd(OAc)_2$ (2.37 mg, 1mol%), n-Bu4NOAc (90 %) (0.714 g, 2.1 mmol), T = 90 °C, t = 20 min, Solvent = 2 mL. Microwave condition: power-5 W, Ramp time- 5 min, Hold time- 20 min, Temperature- 90 °C, Pressure limit- 300 psi. Amounts % of products were determined by GC (using n-dodecane as internal standard). [b] Same conditions of run 1, but γ-valerolactone was used as solvent. [c] Same conditions of run 1, but 2-methyltetrahydrofuran was used as solvent

Summarizing, Heck cross coupling reaction (step 1 of Cinacalcet synthesis) was carried out with success, under microwave irradiation, in short time by using greener conditions and less amount of reagents, to afford high yield of the mixture **(LXX)** and **(LXXI)** with satisfactory selectivity (90-92 %)/(10-8 %).

4.5.2 Hydrogenation of carbon-carbon double bond under microwave irradiation. Introduction

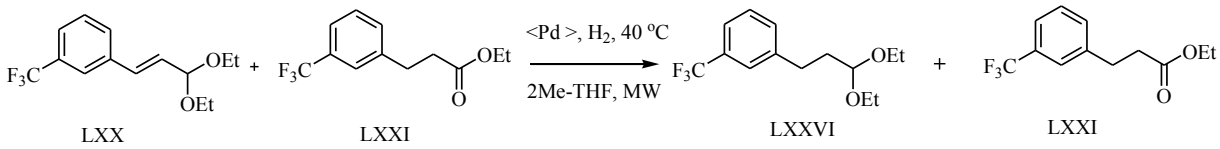
As several other types of metal-catalyzed reactions, hydrogenation reactions also benefit from the use of microwave irradiation to accelerate the reaction, improve the yields and shorter the reaction time[175]. Unlike conventional hydrogenation methods in which usually gaseous hydrogen is used, hydrogenation reactions performed in a microwave equipment typically require the addition of a reagent that may generate hydrogen gas in situ or will transfer hydrogen directly to the substrate. Ammonium formate is the most common hydrogen donor used for microwave-assisted hydrogenation reactions[176], but the drawbacks of using ammonium formate in a sealed microwave reaction vessel are either the development of high pressures, due to the generation of carbon dioxide, or the sublimation of the ammonium formate at high temperatures. Moreover, an excess of the ammonium formate is typically necessary to run the reaction to completion so requiring additional purification. Other hydrogen donors that have been reported in microwave assisted hydrogenations include sodium formate[177], isopropanol for ketone reductions[178], solid-supported

formate[179], and sodium borohydride for imine reductions[180]. While these microwave assisted hydrogenation reactions give good yields of the reduced product, the additional hydrogen donor reagent typically increases the problem of purification at the end of the reaction. Gaseous hydrogen will be a more suitable reagent as it requires no additional purification step for its removal, but the introduction of hydrogen gas into the MW reaction vessel can be challenging.

A further problem to carry out hydrogenations under MW conditions is due to the use of a heterogeneous precious-metal catalyst or of colloidal catalytic metal particles, because the rate-determining step may occur on the surface of the microwave absorbing catalyst. Therefore, hydrogenation reactions are considered as almost ideal model transformations to study the role of specific microwave effects resulting from selective catalyst heating[181]. As reported in literature[182] microwaves may indeed accelerate the hydrogenation reaction and have an influence on the outcome of the reaction. For these reasons it seemed worthy to study the hydrogenation of the crude mixture of the Heck reaction containing palladium species using molecular hydrogen under microwave irradiation (Cinacalcet step 2).

4.5.3.1 Hydrogenation under microwave irradiation of Heck reaction crude mixtures 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene (LXX) and ethyl3-(3-(trifluoromethyl)phenyl)propanoate (LXXI)

All microwave-assisted hydrogenations of Heck cross coupling crude mixtures, containing palladium species derived from 3 % $Pd(OAc)_2$, were performed on 1 mmol scale, in 2-methyltetrahydrofuran (2 mL) as solvent, in 10 mL CEM Discover vials.



LXX LXXI LXXVI LXXI

Scheme 4.5.2. Hydrogenation of 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene (LXX) under microwave irradiation

CEM Discover single mode microwave reactor equipped with a 300 W power source and 300 psi pressure source was used. A 10 mL fiber optic accessory was equipped with a gas inlet to allow introduction of hydrogen gas into the reaction vessel. The vial containing Heck reaction crude mixture (containing compound **(LXX)**, **(LXXI)** and palladium species) from runs 1 of (Table 4.5.3) was hydrogenated with 0.2 Mpa of H_2, at 40 °C for 1 h to afford 78 % conversion (reaction conversion on the basis of compound **(LXX)** to **(LXXVI)**, while compound **(LXXI)** remained unchanged) which was determined by GC-fid and GC-MS using n-dodecane as internal standard. This microwave method was used: power 1-5 W, ramp time 5 min, pressure limit 300 psi. To try to obtain a complete conversion in next reaction the reaction time was extended to 2 h (Table 4.5.3, run 2) observing 91 % conversion. Finally the hydrogenation of mixture of **(LXX)** and **(LXXI)** was carried out for 4h in pre-pressurized single-mode microwave reactor setup fitted with an internal fiber-optic temperature probe. The progress of the hydrogenation could be nicely followed online by monitoring the hydrogen pressure decrease in the sealed vessel. Indeed in the third trial (Table 4.5.3, run 3), a 100 % conversion from **(LXX)** to **(LXXVI)** was observed with a quantitative transformation. The obtained hydrogenated reaction mixture was filtered on diatomaceous earth to remove the spent catalyst and other insoluble material, then the organic solution was concentrated under reduced pressure to afford a mixture of **(LXXVI)** (92 %) and **(LXXI)** (8 %).

Table 4.5.3 Hydrogenation of 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene (LXX) under microwave irradiation

Run	Conv. of LXX [%]	LXXVI [%]	LXXI [%]
1[a]	78	78	8
2[b]	91	91	8
3[c]	100	92	8

Reaction Condition: [a] Reactin mixture [Substrate **(LXX)** (92 %) and **(LXXI)** (8 %)] (1 mmol scale), $p(H_2)$ = 0.2 Mpa, T = 40 °C, t = 1 h, 2-MeTHF = 2 mL., [b]Same conditions of run 1, but t = 2h. [c] Same conditions of run 1, but t = 4h.

An experiment on 2 mmol scale was also attempted at the same experimental conditions using 4mL of 2Me-THF t in 10 mL CEM Discover vial but this reaction mixture was difficult to hydrogenate

under microwave conditions. According to the literature[183] the stirring speed and dilution of reaction mixture may play a critical role on the outcome of the MW hydrogenation processes. Here we also made the same observation obtaining only 40 % conversion of compound **(LXX)** to **(LXXVI)** in this experiment. This is probably due to the fact that hydrogen contained in the top part of the reaction vial (headspace) needs to diffuse to the liquid phase up to the bottom part in which the catalytic process occurs and hydrogen is consumed[184]. Increased stirring influences the gas-liquid interfacial area and thus effects the hydrogenation rate, which is a known phenomenon in hydrogenation chemistry. From a chemical engineering standpoint it is clear, that the 10 mL cylindrical tube used for most microwave experiments in single-mode reactors today, in particular, in combination with a comparatively ineffective magnetic stirring system, is not an ideal reactor for gaseous transformations of this type of reactions.

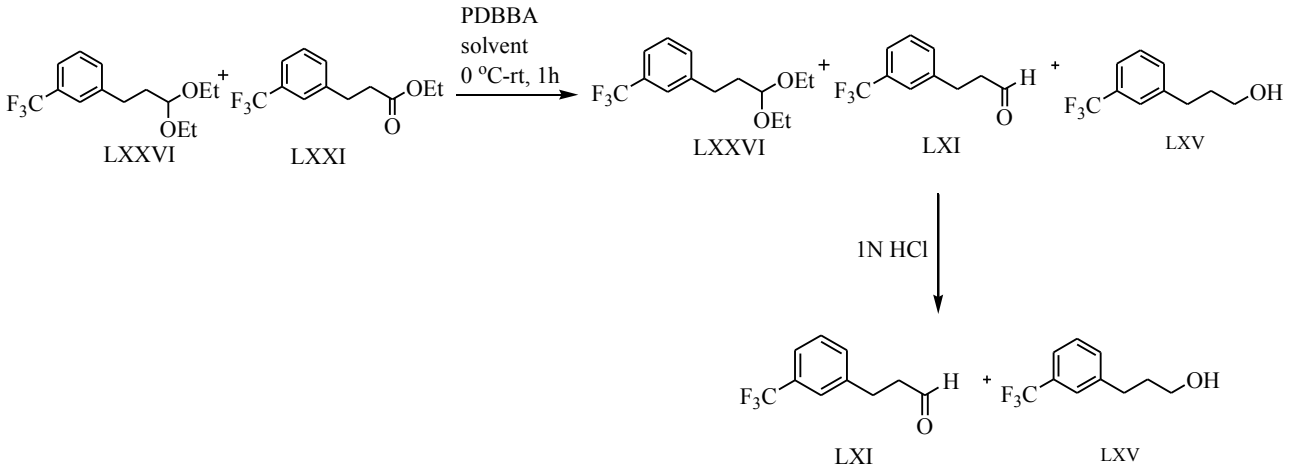
Summarizing MW hydrogenation for step 3 of Cinacalcet reaction scheme is possible and doesn't change the outcome composition. With laboratory MW equipment in batch mode there are not big advantages if compared with conventional reaction protocol even if it is possible to reduce reaction time.

4.6 Selective reduction of an ester group to aldehyde

The reduction of esters to aldehydes is one of the most important synthetic reaction in organic synthesis and a number of reducing agents are reported[185-191]. One of the most popular reducing agents for this transformation is diisobutylaluminum hydride (DIBAL-H)[192], which is commercially sold pure or preferably diluted in an inert solvent; although this reagent provides reasonable yields (48-88 %), it is expensive and requires a very low reaction temperature (-78 °C) to increase the selectivity. Very recently it was reported in literature that simple modifications of commercial DIBAL-H permit to reduce various esters to aldehydes at milder conditions and the selectivity may be good even if depends on the substrate to reduce. Lithium diisobutyl-t-butoxyaluminum hydride (LDBBA)[193], sodium diisobutyl-t-butoxyaluminum hydride (SDBBA)[194] and potassium diisobutyl-t-butoxyaluminum hydride (PDBBA)[195] , obtained by reaction of DIBAL-H with alkaline metals t-butylate, are these new selective reducing agents.

4.6.1 Reduction of Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate by-product (LXXI) to 3-(3-(Trifluoromethyl)phenyl)propanal (LXI)

During the present research work it was decided to explore the reduction of the mixture **(LXXVI)** and **(LXXI)**, previously recovered after the hydrogenation step in the Cinacalcet synthetic scheme, by PDBBA (Scheme 4.6.1) as well as by SDBBA and DIBAL-H. From the point of view of the optimization process to obtain a better yield of the desired product, it would be necessary to reduce selectively the by-product **(LXXI)** to the desired compound **(LXI)**. The results are reported in (Table 4.6.1).



Scheme 4.6.1 Reduction of Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate (LXXI) to 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) by PDBBA complex

A first experiment was carried out using the PDBBA complex prepared according to the protocol reported in literature[195] and adopting the reaction conditions reported in Table 4.6.1, (run 1). To the solution containing mixture of **(LXXVI)** and **(LXXI)** in dry toluene cooled to 0 °C, 1.3 equivalent of PDBBA solution was added dropwise, and then the mixture was allowed to heat to room temperature and maintained for 4 h under stirring until complete disappearance of **(LXXI)**. After acidic work-up and concentration of the solvent the residue contained 96 % of **(LXI)** and 4 % of by-product **(LXV)**; after following purification 3-(3-(trifluoromethyl)phenyl)propanal **(LXV)** was recovered in >90 % isolate yield. Then the selectivity of the reaction was explored changing the solvent (runs 2 and 3), the amount of PDBBA necessary to complete the reaction and the reaction time. The best result was obtained using toluene as a solvent with 1.25 equivalent of PDBBA complex in 1h (run 4) : 100 % conversion, 97 % of desired product **(LXI)** and only 3 % of by-product **(LXV)**. By comparison a lower selectivity was found using SDBBA prepared according to the conditions reported in literature[194], working either in toluene or in DCM (runs 5 and 6). Finally this reaction was studied using 1.1 equivalent of DIBAL-H: the selectivity was very poor despite working at very low reaction temperature (-75 °C) (run 7) that is not suitable for industrial scale.

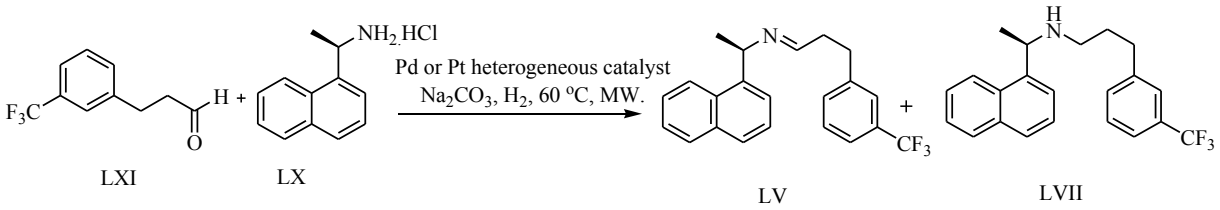
Table 4.6.1 Reduction of Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate (LXXI) to 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) by PDBBA complex

Run	Complex	Complex equivalent	T (°C) / t (h)	Solvent	Conv. of LXXI[%]	LXI [%]	LXV [%]
1[a]	PDBBA	1.3	0-25/4	Toluene	100	96	4
2[b]	PDBBA	1.3	0-25/4	DCM	100	92	8
3[c]	PDBBA	1.3	0-25/4	THF	100	90	10
4[d]	PDBBA	1.25	0-25/1	Toluene	100	97	3
5[e]	SDBBA	1.3	0-25/4	Toluene	100	90	10
6[f]	SDBBA	1.3	0-25/4	DCM	100	85	15
7[g]	DIBALH	1.1	-75/1	THF	100	60	40

Reaction Condition: [a] Mixture of Substrate **(LXXVI)** and **(LXXI)** [0.5 g (87.5 mg of **(LXXI)** present, 0.355 mmol], PDBBA complex solution (0.910 mL, 1.3equiv referred to **(LXXI)**, 0.5M solution in THF-heptane), T = 0-25 °C, t = 1 h, Solvent = 5 mL. [b] Same conditions of run 1, but Dichloromethane was used as solvent. [c] Same conditions of run 1, but tetrahydrofuran was used as solvent. [d] Same conditions of run 1 but 1.25 equiv. of PDBBA was used. [e] Same conditions of run 1, but 1.3equiv. of SDBBA was used. [f] Same conditions of run 5, but Dichloromethane was used as solvent. [g] Same conditions of run 1, but 1.1 equiv. of DIBALH was used at -75 °C.

4.7 Preparation of Cinacalcet by reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) catalyzed by homemade 0.28 % Pd/Al_2O_3 and 0.27 % Pt/Al_2O_3 under microwave irradiation

As previously reported, the use of microwave irradiation to perform chemical transformations involving heterogeneous transition-metal catalysts is becoming more and more popular in the scientific area[196-198]. For these transformations, the use of microwave heating appears to be particularly attractive, but also problematic, since heterogeneous supported metal catalysts are generally strongly microwave absorbing[199]. Here the use of homemade heterogeneous catalysts, 0.28 % Pd/Al_2O_3 and 0.27 % Pt/Al_2O_3, and by comparison commercial 1 % Pt/C, in the reductive amination reaction (step 6 of Cinacalcet reaction scheme) is reported (Scheme 4.7.1; Table 4.7.1).



LXI LX LV LVII

Scheme 4.7.1 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) catalyzed by homemade 0.28 % Pd/Al_2O_3 and 0.27 % Pt/Al_2O_3 under microwave irradiation.

A first experiment, carried out in the presence of homemade 0.28 % Pd/Al_2O_3 under the conditions reported in (Table 4.7.1, run 1) with 0.5 Mpa of H_2, at 50 °C, for 4 h, only 64 % of the desired product **(LVII)** and 36 % of the intermediate imine were obtained. It was speculated that the low conversion could be due to a deactivation effect of generated water on the catalyst. For this reason in next experiment (run 2) the reaction was performed in the presence of anhydrous $MgSO_4$ to remove water but the result was poor. To drive the reaction towards completion it was decided to increase the reaction temperature and time. Working at the conditions reported in Table 4.7.1 (run 3) a 99 % yield of the desired product **(LVII)** was achieved and a similar result was also obtained reducing the amount of catalyst (run 4). Incomplete reaction with high amount of intermediate imine was surprisingly found using 2-methyltetrahydrofuran as a solvent under microwave irradiation (run 5). A very positive result was achieved by using another home catalyst, 0.27 % Pt/Al_2O_3 (run 6), with 98 % of the desired product **(LVII)**. On the contrary, 1 % Pt/C commercial catalyst, at the same experimental conditions, was not efficient (run 7).

Table 4.7.1 Reductive amination of 3-(3-(Trifluoromethyl)phenyl)propanal (LXI) and (R)-1-(naphthalen-1-yl)ethanamine hydrochloride (LX) under microwave irradiation

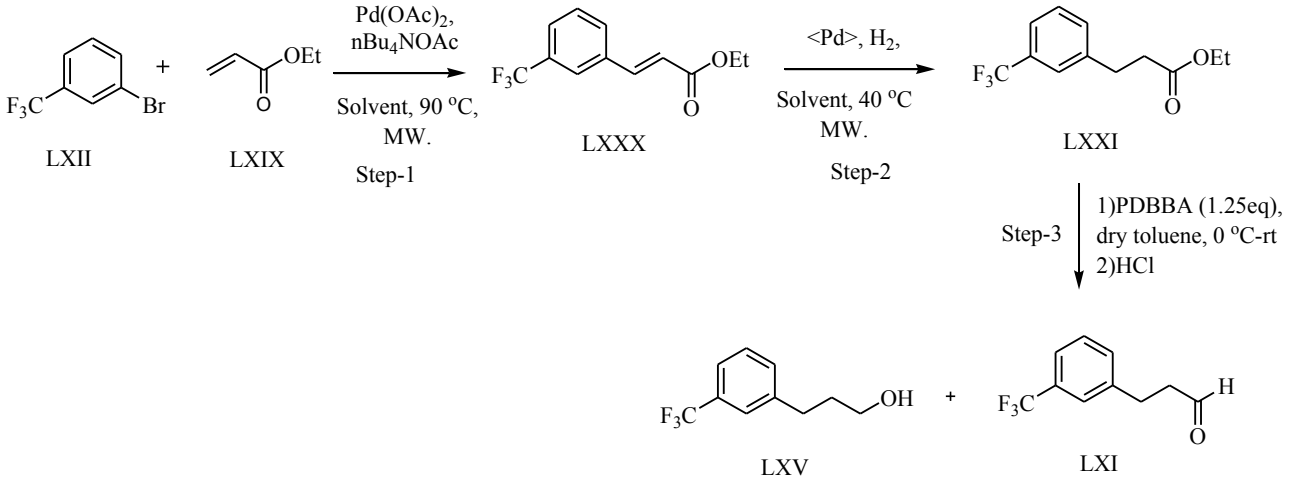
Run	T (°C) / t (h)	Conv.[%]	LV[%]	LVII[%]
1[a]	50/4	100	36	64
2[b]	50/4	100	49	51
3[c]	60/8	100	-	100
4[d]	60/8	100	1	99
5[e]	60/8	100	48	42
6[f]	60/8	100	2	98
7[g]	60/8	100	52	48

Reaction condition :[a] Substrate **(LXI)** (100 mg, 0.5 mmol), Substrate **(LX)** (102 mg, 0.5 mmol), Na_2CO_3 (52 mg, 0.5 mmol), Pd/Al_2O_3 (35.12 mg, **(LXI)** / catalyst molar ratio 500/1), $p(H_2)$ = 0.5 Mpa, T = 50 °C, t = 4 h, Toluene = 2 mL. Microwave condition: power 20 W to reach the temp , then 2W, Ramp time 5 min, Hold time until the end of reaction, Pressure 300 psi. [b]Same conditions of run 1, but $MgSO_4$ (59.5 mg, 0.5 mmol) was also added. [c] Same conditions of run 1, but T = 60 °C, t = 8 h, were used. [d] Same conditions of run 3, but 0.28 % Pd/Al_2O_3 (18.8 mg, **(LXI)**/catalyst molar ratio 1000/1) were used. [e] Same conditions of run 3, but 2-methyltetrahydrofuran was used as solvent. [f] Same conditions of run 3, but 0.27 % Pt/Al_2O_3 (35.7 mg, **(LXI)**/catalyst molar ratio 1000/1) were used. [g] Same conditions of run 3, but1 % Pt/C (9.6 mg, **(LXI)**/catalyst molar ratio 1000/1) were used.

In conclusion, both homemade heterogeneous catalyst 0.28 % Pd/Al_2O_3 and 0.27 % Pt/Al_2O_3 were used with success in this hydrogenation under microwave irradiation. This result is very encouraging for further applications. In future it will be also necessary to verify the activity and selectivity of recycled catalysts after microwave irradiation in order to improve product economy and sustainability.

4.8. Alternative synthesis of 3-(3-(trifluoromethyl)phenyl)propanal (LXI).

During the present research activity, a possible alternative synthetic protocol to prepare **(LXI)** was explored, too. It requires the same type of reactions previously studied and the main difference is the use of ethyl acrylate instead of the diethyl acetal of acrolein in Heck coupling reaction . This implies therefore that it was possible to obtain a pure ester **(LXIX)** to be subjected to reduction with PDBBA. (Scheme 4.8.1)



Scheme 4.8.1 Alternative synthesis of 3-(3-(trifluoromethyl)phenyl)propanal (LXI)

4.8.1 Heck reaction using 1-Bromo-3-(trifluoromethyl)benzene (LXII) and ethyl acrylate (LXIX) under microwave conditions

In Table 4.8.1 are reported the obtained results.

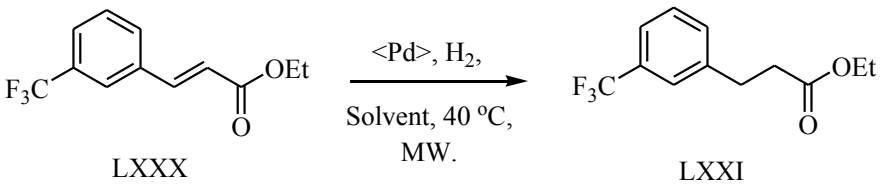
Table 4.8.1 Heck cross coupling under microwave irradiation using ethyl acrylate (LXIX)

Run	Solvent	Conv.[%][e]	LXXX[%]
1[a]	DMF	100	100
2[b]	2-MeTHF	100	100
3[c]	γ - Valerolactone	100	100
4[d]	THF	100	100

Reaction condition: [a] Substrate **(LXII)** (0.240 g, 1 mmol), Substrate **(LXIX)** (0.128 g, 1.27 mmol), $Pd(OAc)_2$ (6.28 mg, 3 mol%), n-Bu_4NOAc (90 %) (0.714 g, 2 mmol), T = 90 °C, t = 20 min, Solvent = 2 mL.CEM Discover system with a 10 mL CEM microwave vial setup, input microwave power was 5 W, ramp time 5 min, reaction hold time 20 min, with maximum pressure limit 300 psi; conversion and yield were determined by GC (using n-dodecane as internal standard).[b] Same conditions of run 1, but 2-methyltetrahydrofuran was used as solvent. [c] Same conditions of run 1, but γ-valerolactone was used as solvent. [d] Same conditions of run 1, but tetrahydrofuran was used as solvent.

All microwave experiments afforded, in 20 min at 90 °C, 100 % conversion and quantitative yield of the unsaturated ester **(LXXX)**. It was possible to use green solvents for this reaction. Probably a lower amount of catalyst could be used in the future.

4.8.2 Hydrogenation of crude (E)-ethyl 3-(3-(trifluoromethyl)phenyl)acrylate (LXXX) under microwave irradiation.

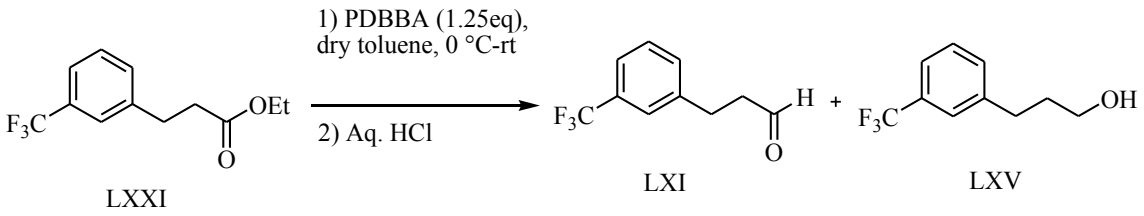


LXXX LXXI

Scheme 4.8.2 Hydrogenation of (E)-ethyl 3-(3-(trifluoromethyl)phenyl)acrylate (LXXX) under microwave irradiation

The reaction was carried on the crude product of the previous step in CEM Discover pre-pressurized single-mode microwave reactor setup fitted with an internal fiber-optic temperature probe equipped with a 300 W power source and 300 psi pressure limit. A 10 mL fiber optic accessory was equipped with a gas inlet to allow introduction of hydrogen gas to the reaction vessel, The vial containing crude compound **(XXXII)** was subjected to hydrogenation using 0.2 Mpa of H_2, at 40 °C for 4 h affording 100 % conversion and quantitative yield of saturated ester. The following microwave parameters were used: power 1-5 W, ramp time 5 min, pressure limit 300 psi. The progress of the hydrogenation was followed online by monitoring the hydrogen pressure decrease in the sealed-vessel experiments. The obtained hydrogenated reaction mixture was filtered as usual to remove insoluble materials and catalyst, then the organic solution was concentrated under reduced pressure to afford **(LXXI)** in quantitative yield.

4.8.3 Selective reduction of Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate (LXXI) to 3-(3-(Trifluoromethyl)phenyl)propanal (LXI)



LXXI LXI LXV

Scheme 4.8.3 Selective reduction of ester LXXI to aldehyde LXI by PDBBA.

In Table 4.8.3 are reported the obtained results.

Excellent results were obtained in toluene using the best conditions previously investigated obtaining >90 % of isolated yield of the target aldehyde (run 5). It was also verified the behavior of another reducing agent, LDBBA (Lithium diisobutyl-t-butoxyaluminum hydride) prepared according to the protocol reported in literature[193] but the selectivity was not so promising with this complex (runs 6,7). Finally, the performances of SDBBA and of DIBAL-H confirmed the results previously obtained.

In conclusion, also this synthetic approach to obtain aldehyde **(LXI)** under MW conditions is simply and very efficient and suitable for scaling-up. From a preliminary total cost evaluation it is

little bit more expensive than the approach using acrolein diethyl acetal, because it requires a larger amount of PDBBA.

Table 4.8.3 Selective reduction of Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate (LXXI) to 3-(3-(Trifluoromethyl)phenyl)propanal (LXI)

Run	Complex (equiv.)	T (°C) /t (h)	Solvent	Conv. [%]	LXI [%]	LXV [%]
1[a]	PDBBA (1.3)	0-25/4	DCM	100	95	5
2[b]	PDBBA (1.3)	0-25/4	THF	100	85	15
3[c]	PDBBA (1.3)	0-25/4	Hexane	100	90	10
4[d]	PDBBA (1.3)	0-25/4	Toluene	100	95	5
5[e]	PDBBA (1.25)	0-25/1	Toluene	100	97	3
6[f]	LDBBA (1.3)	-12/1	DCM	96	66	30
7[g]	LDBBA (1.3)	-12/1	Toluene	100	45	55
8[h]	SDBBA (1.3)	0-25/4	DCM	100	88	12
9[i]	SDBBA (1.3)	0-25/4	Toluene	100	90	10
10[j]	DIBALH (1.1)	-70/1	THF	100	30	70

Reaction condition: [a] Substrate **(LXXI)** (0.250 g, 1 mmol), PDBBA Complex solution (2.6 mL, 1.3 equiv referred to **(LXXI)**, 0.5M solution in THF-Hexane), T = 0-25 °C, t = 4 h, Solvent = 5 mL. [b] Same conditions of run 1, but tetrahydrofuran was used as solvent. [c] Same conditions of run 1, but Hexane was used as solvent. [d] Same conditions of run 1, but Toluene was used as solvent. [e] Same conditions of run 1 but PDBBA Complex solution (1.25 equiv, 0.5M solution in THF-heptane) was used. [f] Substrate **(LXXI)** (0.250 g, 1 mmol), LDBBA Complex solution (2.6 mL, 1.3 equiv, 0.5M solution in THF-Hexane), T = -12 °C, t = 1 h, Solvent = 5 mL. [g]Same conditions of run 6, but Toluene was used as solvent. [h]Same conditions of run 1, but SDBBA Complex solution (1.25 equiv, 0.5M solution in THF-heptane) was used. [i] Same conditions of run 1, but Toluene was used as solvent. [j] Same conditions of run 1 but 1.1 equiv. of DIBALH was used at -70 °C for 1h.

Chapter 5: Conclusion

During this research activity some targets has been achieved. Below the more relevant obtained results are reported.

- The preparation of some Aquivion®-M salts (Fe, Ga, In) by direct reaction of the ionomer with these metals to obtain new potential solid Lewis acids is an innovative result of the present research. This protocol is surely more sustainable than the exchange of cations used until now with other perfluorinated sulfonic polymers. The use of Aquivion®-H and Aquivion®-M as potential catalysts was investigated in different reactions. The salt forms of Aquivion® may be considered a polymeric metallic triflate equivalent and are recyclable green Lewis acids. They show a good catalytic system for the acylation of electron rich heterocyclic compounds, and surely of an indole derivative, here studied, and are a more sustainable alternative to the classical acylation catalysts, such as $SnCl_4$ or $AlCl_3$, and also to some commercial heterogeneous solid acids. Also the obtained results in Lewis acid catalyzed reductive amination with sodium borohydride are very promising. These results are a good basis for the development and use of this ionomer, especially as iron and gallium salts, for other reactions requiring the use of Lewis Acid catalysts. The simple preparation, the possibility of recycling and of working, if reagents and products are liquid, under solvent-free mode, are the major strengths of these new Lewis acids species. However, further studies must still be done to test their versatility and selectivity.

- Characterization and applications of a new Pd-pyridine poly(l-lactide) macrocomplex to test its potential activity in hydrogenation of α,β–unsaturated carbonyl compounds; in particular, investigation of its versatility, activity, selectivity and recyclability for the synthesis of fine chemicals. It was investigated the capability of *trans*-$[Pd(OAc)_2(L)_2]$ to catalyze the hydrogenation of selected bifunctionalized fine chemical substrates, precisely 2-cyclohexen-1-one (**VI**), (E)-4-phenylbut-3-en-2-one **(X)**, (E)-4-(6-methoxy-2-naphthyl)but-3-en-2-one (**XIII**), (E)-3-phenylprop-2-enal **(XVI)** and (2E)-3-(1,3-benzodioxol-5-yil)-2-methyl-prop-2-enal (**XIX**). On the basis of the obtained results *trans*-$[Pd(OAc)_2(L)_2]$ has showed an interesting activity and good recyclability in the hydrogenation of some α,β-unsatured carbonyl compounds. It is to point out that this homogeneous catalyst is easily separated from the reaction mixture by simple addition of methanol to the reaction mixture and the recovered

catalytic system maintains a good activity and selectivity also in recycling experiments. Considering both the data collected and the easy recyclability, this homogeneous catalytic species is a promising and peculiar catalyst for the hydrogenation of α,β-carbonyl compounds, even if the selectivity may be strongly affected by the substrate shape.

- The preparation of water soluble Rh-species, by using a cheap ligand such as dihydrothioctic acid salt, was performed and its potential activity as catalyst in selective reduction of different halo nitro benzene was verified. The reaction was performed at 80 °C, 4 MPa of H_2 for 24 h with a substrate/Rh molar ratio 500/1 and quantitative conversion of halo nitro benzene into the corresponding halo anilines was observed also in the third recycle of the catalyst. Furthermore, the good stability of [Rh(DHTANa)] in water, under inert atmosphere for almost 3 months, was verified.

- **Eletriptan hydrobromide:** Heck cross coupling reaction conditions, using commercially available different homogeneous palladium catalysts in presence of phosphine ligand and more hindered organic base, were investigated on the model substrate 5-bromo-1H-indole **(I)** obtaining results comparable or improved respect to literature data. Also in the subsequent hydrogenation reaction some home-made catalysts, in particular 0.18 % Rh/Al_2O_3 catalyst, showed excellent activity and selectivity. Then Heck cross coupling and the hydrogenation reaction were studied on key intermediates of Eletriptan, but it was necessary to tune again the experimental conditions to obtain results better than those of the state of art. The best compromise for the Heck reaction was achieved using the following conditions: $Pd(dba)_2$ and $P(o\text{-}tolyl)_3$ as catalyst with cat/sub. 3 mol%, in acetonitrile, using N,N-dicyclohexylmethylamine as base, with an early quantitative conversion and 90 % isolated yield. Different reaction parameters were studied in the hydrogenation reaction and, after a fine tuning, best result were obtained on substrate (**LI**) working under mild conditions ($p(H)_2$ = 0.1 MPa, T = 40 °C, t = 16 h, sub/cat molar ratio 200/1) with 0.28 % Pd/Al_2O_3. The obtained results are promising compared to commercial heterogeneous catalysts even if a further investigation to identify a catalyst with a superior selectivity could be still appropriate before scaling up the synthesis of Eletriptan.

- **Cinacalcet hydrochloride:** We optimized Heck cross coupling reaction followed by hydrogenation of carbon-carbon double bond in the presence of different greener solvents, in particular γ-valerolactone, cyclopentylmethylether and 2-methyl-tetrahydrofuran instead of N,N-dimethylformamide, and a selected base and ligand, so increasing the product selectivity and yield under conventional heating conditions. For hydrogenation of carbon-carbon double bond we utilized the same palladium catalyst employed for Heck cross coupling reaction and, at the end of hydrogenation reaction, recovery of palladium species by adsorption of metal on a γ-alumina was tested with success (this catalyst was then used in a following step for direct metal catalyzed reductive amination reaction, in the presence of molecular hydrogen). After recovery of the crude 3-(3-(Trifluoromethyl)phenyl)propanal **(LXI)**, impure for the presence of about 10 % of Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)**, by crystallization as the bisulfite adduct and following regeneration, a pure aldehyde was obtained, which was finally transformed into target Cinacalcet. For the last step, two different strategies were adopted: metal catalyzed hydrogenation or Lewis acid catalyzed reduction with $NaBH_4$. Both approaches, presenting advantages and disadvantages and being critical as concerning selectivity, were investigated, without isolation of the corresponding imine intermediate. Analysing the results of this thesis it is possible to say that an improved synthetic protocol of Cinacalcet, with some novelty respect of the state of art, was achieved. In particular: the use of greener solvents in Heck reaction; the cascade process, unifying two steps with the same catalyst, simply changing the reaction atmosphere from nitrogen to hydrogen; the optimization of crude aldehyde purification step via Bertagnini salt; the use of 0.28 % Pd/Al_2O_3 which showed a very good activity, recyclability and high selectivity towards the target product in the reductive amination step; the high total yield of the full process. Also the alternative Lewis acid catalyzed reductive amination with hydride, realized using the home-made new catalyst Aquivion®-Fe, is surely an improved strategy respect to the literature.

- The approach using MW condition instead of conventional heating was a success: Heck cross coupling reaction (step 1 of Cinacalcet synthesis) was carried out in short time, greener conditions, using lower amount of reagents, to afford high yield of the mixture 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene **(LXX)** and Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)** with satisfactory (90-92 %)/(10-8 %) selectivity. Subsequent hydrogenation of carbon-carbon double bond utilizing the same catalyst employed for Heck cross coupling was realized using CEM Discover single mode microwave reactor

equipped with a 10 mL fiber optic accessory with a gas inlet to allow introduction of hydrogen gas into the reaction vessel. Utilizing the condition 0.2 Mpa of H_2, at 40 °C for 4 h, 100 % conversion of reaction on the basis of compound **(LXX)** to **(LXXVI)** (92 %), while compound **(LXXI)** remained unchanged (8-10 %), was obtained. Then this mixture of 1-(3,3-Diethoxypropyl)-3-(trifluoromethyl)benzene **(LXXVI)** and Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)** was selectively treated with PDBBA (potassium diisobutyl-t-butoxyaluminum hydride) with the aim to reduce selectively only the by-product ester to aldehyde. Compound 3-(3-(Trifluoromethyl)phenyl)propanal **(LXI)** was obtained with >90 % yield and >99 % chemical purity. Study of direct metal catalyzed reductive amination reaction under MW irradiation, in the presence of low metal content homemade heterogeneous 0.28 % Pd/Al_2O_3 and 0.27 % Pt/Al_2O_3 catalyst, was also performed and both catalysts showed good applicability. This result is very encouraging for further applications. However, in the future it will be necessary to verify the activity and selectivity of recycled catalysts after microwave irradiation in order to improve product economy and sustainability.

- It was also studied a possible alternative synthetic protocol to prepare 3-(3-(Trifluoromethyl)phenyl)propanal **(LXI)**. The same type of reactions above described was investigated but using ethyl acrylate instead of the diethyl acetal of acrolein in Heck coupling reaction followed by hydrogenation. This implies therefore that it was possible to obtain a pure Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)** to be subjected to reduction with PDBBA. This synthetic approach to obtain 3-(3-(Trifluoromethyl)phenyl)propanal **(LXI)** under MW conditions is simple and very efficient and suitable for scaling-up. From a preliminary total cost evaluation it is little bit more expensive than the approach using acrolein acetal, because it requires a larger amount of PDBBA complex

Chapter 6: Experimental section

6.1 Commercial reagents, materials and solvents

1-Iodo-4-nitrobenzene (Sigma-Aldrich)

1-Chloro-3-nitrobenzene (Sigma-Aldrich)

1,4-Dioxane (Sigma-Aldrich)

2-Cyclohexen-1-one (Sigma-Aldrich)

2-Methyltetrahydrofuran (Sigma-Aldrich)

3-Bromobenzotrifluoride (Sigma-Aldrich)

5-Bromo-1H-indole (Sigma-Aldrich)

Acrolein diethyl acetal (Sigma-Aldrich)

Acetic anhydride (Sigma-Aldrich)

Acetyl chloride (Sigma-Aldrich)

Acetone (Sigma-Aldrich)

Acetonitrile (Sigma-Aldrich)

Absolute ethanol (VWR)

Benzyl chloroformate (Sigma-Aldrich)

n-Butyl lithium 3M solution in tetrahydrofuran (Sigma-Aldrich)

Cinnamaldehyde (Sigma-Aldrich)

Cyclopentylmethylether (Sigma-Aldrich)

Caesium carbonate (Sigma-Aldrich)

Di-isopropyl ethylamine (Sigma-Aldrich)

Di-isobutylaluminum hydride 1M solution in hexane (Sigma-Aldrich)

Dichloromethane (Sigma-Aldrich)

Dimethylitaconate (Sigma-Aldrich)

Dimethylacetamide (Sigma-Aldrich)

(E)-4-(2-Methoxynaphthalen-6-yl)but-3-en-2-one (Allichem LLC)

(E)-3-(Benzo[d][1,3]dioxol-6-yl)-2-methylacrylaldehyde ()

(E)-4-Phenyl-3-buten-2-one (Janseen Chimica)

Ethyl magnesium bromide 3M solution in methyl-tert-butyl ether (Sigma-Aldrich)

Ethylacrylate (Sigma-Aldrich)

Ethyl acetate (Sigma-Aldrich)

D-glucose (Sigma-Aldrich)

γ-valerolactone (Sigma-Aldrich)

γ-Alumina (Sigma-Aldrich)

Hydrochloric acid (Sigma-Aldrich)

Isopropanol (Sigma-Aldrich)

Lithium aluminum hydride (Sigma-Aldrich)

L-Proline (Sigma-Aldrich)

Methanol (Sigma-Aldrich)

Methyl-tert-butyl ether (Sigma-Aldrich)

Methanesulfonic acid (Sigma-Aldrich)

Nitrobenzene (Carlo Erba)

N,N-dicyclohexylmethylamine (Sigma-Aldrich)

N,N-dimethylformamide (Sigma-Aldrich)

n-Hexane (Sigma-Aldrich)

Oxalyl chloride (Sigma-Aldrich)

Phenyl vinyl sulfone (Sigma-Aldrich)

Potassium-tert-butoxide (Sigma-Aldrich)

Potassium carbonate (Sigma-Aldrich)

Potassium chloride (Sigma-Aldrich)

Petroleum ether (Sigma-Aldrich)

(R)-1-(naphthalen-1-yl)ethanamine hydrochloride (Sigma-Aldrich)

Sodium borohydride (Sigma-Aldrich)

Mixture of Sodium bisulfite and metabisulfite($NaHSO_3.Na_2S_2O_5$) (Sigma-Aldrich)

Sodium carbonate (Sigma-Aldrich)

Sodium hydrogen carbonate (Carlo Erba)

Sodium acetate (Sigma-Aldrich)

Sodium sulfate (Sigma-Aldrich)

Sodium-tert-butoxide (Sigma-Aldrich)

Sodium hydroxide (Carlo Erba)

Tri-ethylamine (Sigma-Aldrich)

Tri-methyl silylchloride (Sigma-Aldrich)

Tri-octylamine (Sigma-Aldrich)

Tetrabutylammoniumbromide (Sigma-Aldrich)

Tetrabutylammoniumacetate (Sigma-Aldrich)

Tetrabutylammoniumacetate 90% (Tokyo chemical industry)

Tetrahydrofuran (Sigma-Aldrich)

Toluene (Sigma-Aldrich)

Xylene (Sigma-Aldrich)

6.2 Commercial catalysts, ligands and polymers

Platinum on charcoal (1% Pt/C). (Johnson-Matthey)

Palladium-Iron on charcoal (5% Pd(Fe)/C). (Johnson-Matthey)

Palladium on charcoal 10% Pd/C (Chimet). (Johnson-Matthey)

Bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] (Sigma-Aldrich).

Bis[tri(o-tolyl)phosphine]palladium(II) [$Pd[P(o\text{-}Tol)_3]_2$] (Sigma-Aldrich).

Bis(tri-tert-butylphosphine)palladium(0) [$Pd(t\text{-}Bu_3P)_2$] (Sigma-Aldrich).

Bis(di-tert-butyl(4-dimethylaminophenyl)phosphines)dichloropalladium(II)[$Pd(amphos)Cl_2$] (Sigma-Aldrich).

Palladium (II) acetate [$Pd(OAc)_2$] (Sigma-Aldrich).

Tri(o-tolyl)phosphine (Sigma-Aldrich)

Aquivion® (Solvay Specialty Polymers)

Indium (Sigma Aldrich)

Gallium (Sigma Aldrich)

Iron (Sigma-Aldrich)

6.3 Purification of solvents

The purification of solvents was performed as reported in literature[200]

6.3.1 Diethyl ether

In a 1000 mL three neck bottom flask, were taken 500 mL of commercial diethyl ether, 30 g of benzophenone and small pieces of metallic sodium were added in to the flask under nitrogen atmosphere. The solvent was refluxed for 12 hours under nitrogen atmosphere. After this time, diethyl ether was transferred by distillation into a bottle containing activated 4Å molecular sieves for further use.

6.3.2 Dichloromethane

In a 1000 mL double neck bottom flask, were taken 500 mL of dichloromethane and 50 g of $CaCl_2$ were added under nitrogen. The resulting solution was stirred for 24 h, then it was filtered under nitrogen and transferred into a 1000 mL double neck round bottom flask, where 50 g of drierite were previously taken. Then dichloromethane was refluxed for 8 hours and subsequently recovered by distillation into a bottle containing activated 4Å molecular sieves for further use.

6.3.3 Tetrahydrofuran

In a 1000 mL three neck bottom flask, were taken 500 mL of commercial tetrahydrofuran, 30 g of benzophenone and small pieces of metallic sodium were introduced under nitrogen. The solvent was refluxed for 12 hours under nitrogen atmosphere. After this time, the solvent was collected in a receiver under nitrogen and then transferred into a 1000 mL three neck bottom flask containing $LiAlH_4$. Tetrahydrofuran was maintained at reflux for six hours. After this time, the solvent was transferred by distillation into a bottle containing activated 4Å molecular sieves for further use.

6.3.4 Toluene

In a 1000 mL three neck bottom flask, were taken 500 mL of commercial toluene, 30 g of benzophenone and small pieces of metallic sodium were added in to the flask under nitrogen atmosphere. The solvent was refluxed for 12 hours under nitrogen atmosphere. After this time, toluene was transferred by distillation into a bottle containing activated 4Å molecular sieves for further use.

6.4 Analytical Methods

6.4.1 Proton Nuclear Magnetic Resonance analysis

^{1}H NMR spectra of the all organic compounds were recorded by using a Bruker Avance 300 MHz. instrument and samples were dissolved in deuterated chloroform, or deuterated methanol or deuterated water.

6.4.2 Gas chromatographic analysis

GC analysis were performed on a Agilent Technologies 6850 series instrument equipped by an HP-5 (Agilent) capillary column (30m x 0.32mm x 0.25 μm film thickness) and a flame ionizator detector (FID). The gas chromatograph is interfaced with a computer. The GC parameters were as follows: initial temperature 50 °C; initial time 5 min; heating ramp 10 °C/min; final temperature 280 °C, final time 5 min; injector temperature 280°C; detector temperature 280 °C, gas carrier flow (N_2) 2 mL/min, injection volume 0.1 μL.

6.4.3 GC-MS analysis

GC-MS analysis were performed on a ThermoFinnigan (Trace CG 2000) instrument equipped with an HP-5 capillary column (30m x 0.32mm x 0.25 μm film thickness) and a quadrupole mass spectrometer (ThermoFinnigan Trace MS) interfaced with a computer. The GC parameters were as follows: initial temperature 60 °C; initial time 5 min; heating ramp 10 °C/min; final temperature 280 °C, final time 5 min; injector temperature 280 °C; detector temperature 280 °C, gas carrier flow (N_2) 0.8 mL/min, injection volume 0.1 μL.

6.4.4 HPLC analysis

HPLC analysis where performed on an Agilent 1100 series instrument, equipped with an YMC HPLC column, (150 X 4.6 mm) and a peristaltic pump. The flow of the eluent mixture Milli-Q ultrapure water/Acetonitrile/phosphoric acid (70/30/0.1 %) was set at 1 mL/min, 5 μL injection volume.

6.4.5 IR-Analysis

The IR spectra of [Rh(DHTANa)], Aquivion®, Aquivion®-Fe, Aquivion®-Ga and Aquivion®-In were record by using an FTIR Nicolet Magna 750 instrument. The samples were prepared on KBr pellets.

6.4.6 Thermogravimetry (TG) and differential scanning Calorimetry (DSC)

Thermogravimetry (TG) and differential scanning Calorimetry (DSC) were performed simultaneously using a Netzsch 409/C apparatus. Data were collected with STA Netzsch software and then processed with Origin 9 software. The temperature program used was set up experimentally from 30 °C, 10 °C/min to 650 °C (660°C). The instrument was purged with N_2 at a flow rate of 40 mL/min. The sample mass ranged around 16.21 ± 0.56 mg; samples were massed in an aluminium crucible by the TG internal balance. Alumina was used for the internal calibration The thermograms obtained of these new species, as well as of Aquivion-H.

6.5 Experimental part A) The Investigation of the activity of new catalysts able to improve greener process involved in the synthesis of two molecules of pharmaceutical interests

6.5.1 New low metal content catalysts and new water soluble species

0.18% Rh/Al_2O_3

0.28% Pd/Al_2O_3

0.27% Pt/Al_2O_3

[Rh(DHTANa)]

6.5.1.1 Preparation of homemade 0.18 % Rh/Al_2O_3, 0.28 % Pd/Al_2O_3 and 0.27 % Pt/Al_2O_3

All homemade catalysts were prepared by adopting the procedure below reported. For example the procedure to obtain 0.18 % Rh/Al_2O_3 catalyst is reported,

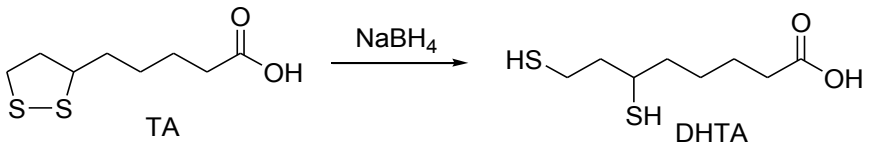
50 mg of $RhCl_3$ (0.00023 mol of Rh), 0.36 mL (0.0008 mol) of TOA (d = 0.809 g/mL) and 10 mL of dry THF were introduced in a 150 mL stainless steel autoclave under nitrogen. The autoclave was pressurized with 0.5 Mpa of hydrogen and warmed at 25 °C for 24 hours under stirring. After this time, the solution was introduced into a 250 mL double neck jacket round bottom flask containing 10 g of alumina and 30 mL of dry THF. The mixture was stirred for 24 h at 25 °C under hydrogen atmosphere. After this time, the solid was filtered by sintered glass filter and washed with 50 mL of dry THF. The recovered catalyst was dried under vacuum at 0.06 MPa. After atomic absorption the detected amount of Rh was 0.18%.

Adopting the same procedure a homemade Pd/Al_2O_3 and Pt/Al_2O_3 catalyst were prepared by using: 50 mg of $PdCl_2$ (0.00028 mol of Pd), 0.44 mL (0.00098 mol) of TOA (d = 0.809 g/mL) and 10 g of Al_2O_3. After atomic absorption, the detected amount of Pd content was 0.28 %.

41 mg of $PtCl_2$ (0.00015 mol of Pt),0.24 mL (0.00054 mol) of TOA and 10 g of Al_2O_3 respectively. After atomic absorption, the detected amount of Pt was 0.27 %.

6.5.2 Preparation of water soluble specie [Rh(DHTA)Na]

6.5.2.1 Synthesis of dihydro thioctic acid (DHTA) and DHTANa



The preparation of this compound was performed by adopting the procedure described in the literature with small modifications.

In a 25 mL round bottom flask equipped with magnetic stirrer, 0.21 g (0.0025 mol) of Na_2CO_3 dissolved in 12 mL of water and 0.510 mg of thioctic acid (**TA**) (0.0025 mol) were introduced. After complete dissolution of acid (**TA**), the solution was cooled in an ice bath and then 0.19 g (0.005 mol) of $NaBH_4$ were slowly added. The mixture was stirred for 2h at 4 °C. Subsequently, the mixture was acidified at pH = 1 by 2M solution of HCl and extracted with $CHCl_3$ (3x10 mL). The recovered organic phase was dried on Na_2SO_4, filtered and the solvent was removed by rotavapor. The desired product **DHTA** was obtained in 98 % yield as a transparent liquid. DHTA was stocked at -20 °C under nitrogen.

^{1}H-NMR ($CDCl_3$) δ (ppm): 10.1 (bs, 1H, OH), 2.89 (m, 1H, S-CH), 2.7 (m, 2H, S-CH_2), 2.4 (t, *J* = 7.1 Hz, 2H, CH_2-COOH,), 1.92-1.94 (m, 8H, $(CH_2)_4$), 1.36 (t, *J* = 7.9 Hz, 1H, SH,), 1.31 (d, *J* = 7.6 Hz, 1H, SH,); ^{13}C-NMR ($CDCl_3$) δ (ppm): 180.4 (COOH), 43.1 (SH-CH_2-CH_2-CH), 39.7 (CH_2-COOH), 39.1 (CH_2-CH-SH), 34.3 (CH-SH), 26.9 (CH-CH_2-CH_2), 24.7 (CH_2-CH_2-COOH), 22.7 (CH_2-SH)

The corresponding sodium salt was obtained by treating 0.507 g (0.0025 mol) of DHTA with 1 equivalent of Na_2CO_3 dissolved in 10 mL of distilled water.

^{1}H-NMR (H_2O/D_2O):δ (ppm): 2.92 (m, 1H, S-CH), 2.6 (m, 2H, S-CH_2), 2.08 (t, *J* = 7.2 Hz, 2H, CH_2-COONa), 1.85-1.78 (M, 2H, HS-CH_2-CH_2-CH-SH), 1.72-1.3 (m, 10H, $(CH2)_4$; 2SH).

6.5.2.2 Synthesis of [Rh(DHTANa)]

In a 25 mL round bottom flask, equipped with magnetic stirrer, 0.010 g (0.05 mmol) of **TA** was dissolved in 10 mL of deaerated distilled water containing 1 equivalent of Na_2CO_3 under nitrogen. The mixture was then stirred until the complete salification of acid **TA**. Subsequently 0.0124 g (0.025 mmol) of $[Rh(COD)Cl]_2$ was added and the mixture was stirred until complete dissolution. The obtained red-orange Rh solution ([Rh] = 0.005 M) seems to be stable on the air but it was stocked under nitrogen at 4 °C for safety. The complex was also isolated in a solid form: the water was removed under vacuum, and the obtained solid was re-dissolved in methanol, filtered and re-precipitated with small additions of diethyl ether. The obtained precipitate was filtered and finally dried. The obtained orange solid is stable on the air and it was characterized by NMR.

^{1}H-NMR (H_2O/D_2O):δ (ppm): 3.61 (m, 1H, S-CH), 3.12 (m, 2H, S-CH_2), 2.08 (t, J = 7.2 Hz, 2H, CH_2COONa), 1.85-1.78 (m, 2H, HS-CH_2-CH_2-CH-SH), 1.72-1.3 (m, 10H, $(CH_2)_4$; 2 SH).

6.5.3 New Aquivion®-M catalysts

Aquivion®-Fe

Aquivion®-Ga

Aquivion®-In

6.5.3.1 Preparation of salified form of Aquivion®-M

For example, the preparation of Aquivion®-Fe is here reported.

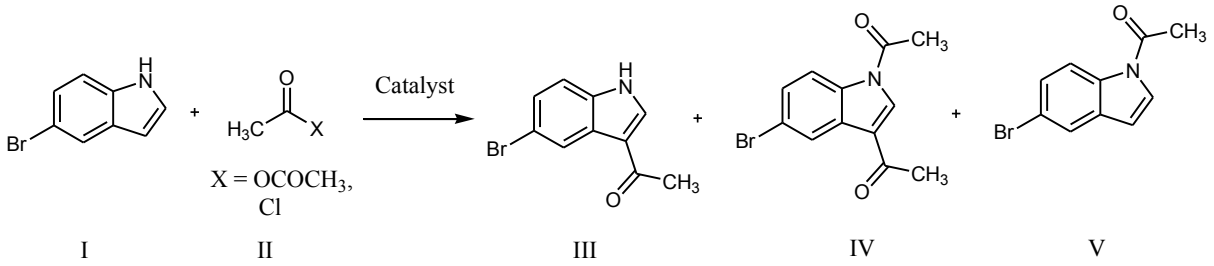
In 250 mL three necks round bottom flask equipped with mechanical stirrer and reflux condenser, 10 g (870g/eq. of –SO_3H) of Aquivion®, 0.214 g (0.0038 mol) of Iron metal and 50 mL of acetonitrile were introduced. The solution was heated at reflux for 48 h. After this time, acetonitrile was removed by rotavapor and subsequently the Aquivion®-Fe was dried under vacuum at 6 Pa. The recovered catalyst was grinded on agate mortar and stored into a bottle. The final determined Iron amount was 2.05 % w/w (theoretic: 2.14 % w/w)
Adopting the same procedure, Aquivion®-Ga and Aquivion®-In were prepared, by using 0.267 g of Ga and 0.440 g of In for 10 g of Aquivion® respectively.

6.5.3.2 Analysis of Aquivion®-Fe, Aquivion®-Ga and Aquivion®-In

In a closed vessel each sample (50 mg) was suspended in a mixture of concentrated HNO_3 (65 %, 6 mL) and concentrated HCl (37 %, 2 mL). The vessel was pressurized with N_2 till reaching a pressure of 40 Atm and then heated at 250 °C for 45 min. The clear and transparent liquid was recovered and then metal content determined through ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometry). The analysis was repeated twice.

6.5.4 Acylation of 5-bromo-1H-indole (I) catalyzed by metal triflates and by Aquivion®-M

6.5.4.1 General procedure for the acylation of 5-bromo-1H-indole (I) catalyzed by metal triflates



I II III IV V

For example, here the procedure adopted for experiments of table 3.1.2, paragraph 3.1.1, results and discussion

In a dry 10 mL two neck glass jacketed round bottom flask equipped with a reflux condenser and a magnetic stirring bar, (0.5 g, 2.5 mmol) of 5-bromo-1H-indole **(I),** acetic anhydride (1.03 g, 10.09 mmol), Metal triflates (71 mg, 5 mol %) were introduce and the mixture was stirred at 90 °C for 12 h. The reaction flask was then cooled to room temperature, the catalyst was filtered off by using a sintered glass filter and the organic solution was analyzed by GC and GC-MS: 95 % conversion of (**I**) to (**III**) was obtained. The filtrate was then distilled off under reduced pressure and the crude mixture was purified by flash-chromatography (eluent: n-hexane : ethyl acetate, 80/20): the title compound 3-Acyl-5-bromo-1H-indole (**III**) was obtained as a brownish solid (0.545 g, 90-95 % yield).

3-Acyl-5-bromo-1H-indole (**III**) : ^{1}H-NMR (300MHz, CD_3OD) δ (ppm): 8.39 (s, 1H), 8.19 (s, 1H), 7.40-7.33 (dd, *J* = 13.5 Hz, 2H), 2.52 (s, 3H); GC-MS m/z : 237 $[M]^+$; 222 $[M, -CH_3]^+$; 194 $[M, -CH_3CO]^+$; 169 $[M, -C_4H_4O]^+$.

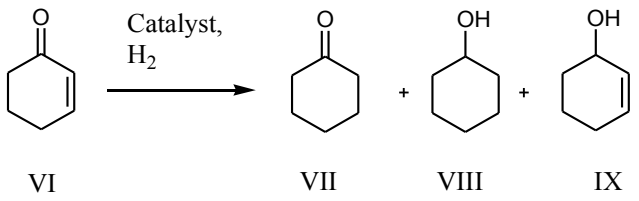
6.5.4.2 General procedure for acylation of 5-bromo-1H-indole (I) catalyzed by Aquivion®-Ga, Aquivion®-Fe, Aquivion®

For example, here the procedure adopted for experiments of table 3.1.3 and 3.1.4, paragraph 3.1.1, of results and discussion

In a dry 10 mL two neck glass jacketed round bottom flask equipped with reflux condenser and magnetic stirring bar, (2.22 g, 11.29 mmol) of 5-bromo-1H-indole **(I),** acetic anhydride (4.61 g, 45.19 mmol), and Aquivion®-Ga (98 mg, **I**/-R$(SO_3)_3$-Ga 310/1 molar ratio) were introduced; the mixture was then stirred at 90 °C for 2 h. The reaction flask was then cooled to room temperature, the catalyst was filtered off by using a sintered glass filter and the organic solution was analyzed by GC and GC-MS: 98 % conversion of **(I)** to (**III)** was detected. Then the filtrate was distilled under reduced pressure and the crude mixture was purified by flash-chromatography (eluent: n-hexane : ethyl acetate, 80/20) affording the title compound 3-Acyl-5-bromo-1H-indole (**III**) as a brownish solid (2.58 g, 90-97 % yield).

6.5.5 Hydrogenation of α,β-unsaturated carbonyl compounds catalyzed by Pd-pyridine poly(l-lactide) macrocomplex

6.5.5.1 Procedure for the Hydrogenation of cyclohexen-1-one (VI)



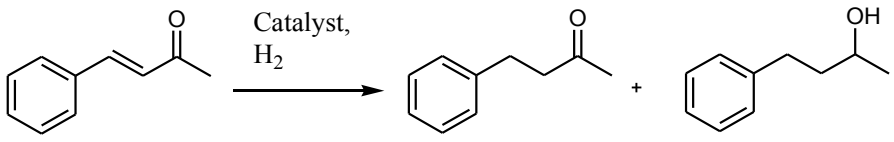
VI VII VIII IX

For example, here the procedure adopted for experiments of table 3.2.1, paragraph 3.2.1, of results and discussion

In a Schlenk tube, 0.100 g of polyester-based Pd catalyst (**VI**/catalyst molar ratio 1000/1), (1.08 g, 10.5 mmol) of cyclohexen-1-one **(VI)** and 10 mL of toluene were introduced. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen atmosphere, then the autoclave was pressurized with 0.1 Mpa of H_2 and stirred for 3 h at 30 °C. Then the reactor was cooled at room temperature and the residual gas was released. The mixture was analyzed by GC and GC-MS: 100 % conversion into cyclohexanone (**VII**) was detected. After completion of the experiment the catalytic system was precipitated by adding methanol to the solution. The catalyst was then filtered, dried under vacuum and reused in a consecutive experiments adopting the above described procedure.

GC-MS m/z **(VII)** : 98 $[M]^+$; 82 $[M-O]^+$; 55 $[M-C_2H_3O]^+$; 42 $[M-C_4H_8]^+$.

6.5.5.2 Procedure for the hydrogenation of (E)-4-phenylbut-3-en-2-one (X)



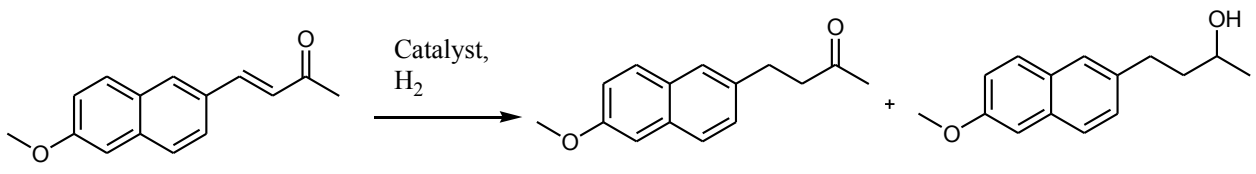
X XI XII

For example, here the procedure adopted for experiments of table 3.2.2, paragraph 3.2.2, of results and discussion

In a Schlenk tube, 0.050 g of polyester-based Pd catalyst (**X**/catalyst molar ratio 1000/1), (0.833 g, 5.6 mmol) of (E)-4-phenylbut-3-en-2-one (**X**) and 10 mL of toluene were introduced. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen atmosphere, then the autoclave was pressurized with 0.1 Mpa of H_2 and stirred for 3 h at 30 °C. Then the reactor was cooled at room temperature and the residual gas was released. The mixture was analyzed by GC and GC-MS: 100 % conversion into (E)-4-phenylbut-3-en-2-one **(XI)** was detected. After completion of the experiment the catalytic system was precipitated by adding methanol to the solution. The catalyst was then filtered, dried under vacuum and reused in a consecutive experiments adopting the above described procedure.

GC-MS m/z (**XI**) : 148 $[M]^+$; 133 $[M-O]^+$; 106 $[M-C_2H_3O]^+$; 91 $[M-C_4H_8O]^+$.

6.5.5.3 Procedure for the hydrogenation of (E)-4-(2-methoxynapthalen-6-yl)but-3-en-2-one (XIII)



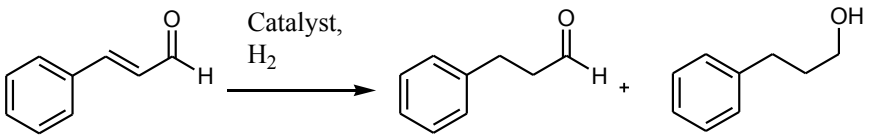
XIII XIV XV

For example, here the procedure adopted for experiments of table 3.2.3, paragraph 3.2.3, of results and discussion

In a Schlenk tube, 0.050 g of polyester-based Pd catalyst (**XIII**/catalyst molar ratio 1000/1), (1.25 g, 9.9 mmol) of (E)-4-(2-methoxynapthalen-6-yl)but-3-en-2-one **(XIII)** and 25 mL of toluene were introduced. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen atmosphere, then the autoclave was pressurized with 2 Mpa of H_2 and stirred for 5 h at 30 °C. Then the reactor was cooled at room temperature and the residual gas was released. The mixture was analyzed by GC and GC-MS: 52 % conversion in to **(XIV)** was detected. After completion of the experiment the catalytic system was precipitated by adding methanol to the solution. The catalyst was then filtered, dried under vacuum and reused in a consecutive experiments adopting the above described procedure.

GC-MS m/z **(XIV)** : 228 $[M]^+$;171 $[M - C_4H_7O]^+$; 128 $[M - C_5H_9O_2]^+$

6.5.5.4 Procedure for the hydrogenation of (2E)-3-phenylprop-2-enal (XVI)



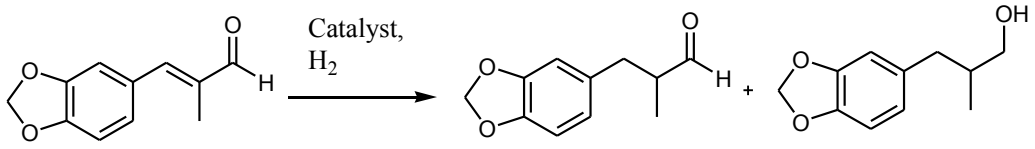
XVI XVII XVIII

For example, here the procedure adopted for experiments of table 3.2.4, paragraph 3.2.4, of results and discussion.

In a Schlenk tube, 0.041 g of polyester-based Pd catalyst (**XVI**/catalyst molar ratio 1000/1), 0.615 g, 4.65 mmol) of (2E)-3-phenylprop-2-enal **(XVI)** and 10 mL of toluene were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, then the autoclave was pressurized with 2 Mpa of H_2 and stirred for 6 h at 30 °C. Then the reactor was cooled at room temperature and the residual gas was released. The mixture was analyzed by GC and GC-MS: 100 % conversion [(2*E*)-3-phenylprop-2-enal] **(XVII)** 95 % and 5 % of 3-Phenylpropan-1-ol **(XVIII)** was detected. After completion of the experiment the catalytic system was precipitated by adding methanol to the solution. The catalyst was then filtered, dried under vacuum and reused in a consecutive experiments adopting the above described procedure.

GC-MS m/z **(XVII)** : 134 $[M]^+$;105 $[M –HCO]^+$; 91 $[M –C_2H_3O]^+$; 78 $[M –C_3H_6O]^+$.
GC-MS m/z **(XVIII)** : 136 $[M]^+$; 118 $[M –H_2O]^+$; 105$[M –CH_4O]^+$; 91 $[M –C_2H_5O]^+$; 77 $[M – C_3H_7O]^+$.

6.5.5.5 Procedure for the hydrogenation of (E)-3-(benzo[d][1,3]dioxol-6-yl)-2-methylacryaldehyde (XIX)



XIX XX XXI

For example, here the procedure adopted for experiments of table 3.2.5, paragraph 3.2.5, of results and discussion.

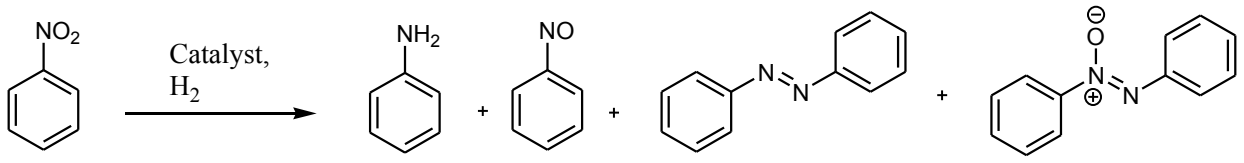
In a Schlenk tube, 0.050 g of polyester-based Pd catalyst (**XIX**/catalyst molar ratio 100/1), (0.108 g, 0.568 mmol) of (E)-3-(benzo[d][1,3]dioxol-6-yl)-2-methylacryaldehyde **(XIX)** and 5 mL of toluene were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen atmosphere, then the autoclave was pressurized with 0.5 Mpa of H_2 and stirred for 7 h at 30 °C. The reactor then was cooled at room temperature and the residual gas was released. The mixture was analyzed by GC: 100 % conversion was obtained it contains **(XX)** 33 % and **(XXI)** 67 % was detected. After completion of the experiment the catalytic system was precipitated by adding methanol to the solution. The catalyst was then filtered, dried under vacuum and reused in a consecutive experiments adopting the above described procedure.

GC-MS m/z (XX): 192 $[M]^+$; 164 $[M, -CHO]^+$; 135 $[M, -C_3H_6O]^+$; 122 $[M, -C_4H_6O]^+$.

GC-MS m/z (XXI): 194 $[M]^+$; 165 $[M, -CHO]^+$; 136 $[M, -C_3H_6O]^+$; 124 $[M, -C_4H_6O]^+$.

6.5.6 Reduction of aromatic halo nitro compounds

6.5.6.1 Reduction of nitrobenzene (XXII) catalyzed by [Rh(DHTA)Na]



XXII XXIII XXIV XXV XXVI

For example, here the procedure adopted for experiments of table 3.3.1, paragraph 3.3.2, of results and discussion

In a Schlenk tube, 1 mL of 0.005 M solution of [Rh(DHTANa)] in 2 mL of degassed distilled water, nitrobenzene **(XXII)** (0.620 g, 5 mmol) and 2 mL of tetrahydrofuran were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 2 Mpa of H_2 and stirred for 24 h at 80 °C. The reactor was then cooled to room temperature and the residual gases released. Diethyl ether was added and the organic phase was separated, dried on Na_2SO_4 and analyzed by GC and GC–MS: 100 % conversion of nitrobenzene **(XXII)** was detected (99 % of **XXIII**). The catalytic aqueous phase was recovered and reused for further experiments.

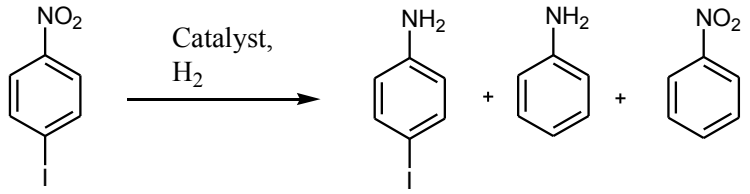
GC-MS m/z (XXIII) : 93 $[M]^+$; 76 $[M –NH_3]^+$; 66 $[M –HCN]^+$

6.5.6.2 Reduction of nitrobenzene (XXII) catalyzed by 0.18% Rh/Al_2O_3

For example, here the procedure adopted for experiments of table 3.3.1, paragraph 3.3.2, of results and discussion.

In a Schlenk tube, nitrobenzene **(XXII)** (0.620 g, 5 mmol), 0.288 g of 0.18 % Rh/Al_2O_3 (**XXII**/catalyst molar ratio 1000/1) and 5 mL of THF were introduced. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 2 Mpa of H_2 and stirred for 24 h at 80 °C. After this time, the residual gas was released, and the catalyst was filtered on a sintered glass filter, washed with 10 mL of diethyl ether and dried under vacuum. The recovered organic phase was analyzed by GC and GC-MS. Quantitative conversion of substrate nitrobenzene **(XXII)** in to aniline **(XXIII)** was detected. The catalyst was recycled for further experiments.

6.5.6.3 Reduction of 1-Iodo-4-Nitrobenzene (XXVII) catalyzed by [Rh(DHTA)Na]



XXVII XXVIII XXIII XXII

For example, here the procedure adopted for experiments of table 3.3.2, paragraph 3.3.3, of results and discussion.

In a Schlenk tube, 1 mL of 0.005 M solution of [Rh(DHTANa)] in 2 mL of degassed distilled water, 1-iodo-4-nitrobenzene **(XXVII)** (0.312 g, 1.25 mmol) and 2 mL of toluene were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 4 Mpa of H_2 and stirred for 24 h at 80 °C. The reactor was then cooled to room temperature and the residual gases released. Diethyl ether was added and the organic phase was separated, dried on Na_2SO_4 and analyzed by GC and GC–MS: 100 % conversion of **(XXVII)** was detected (97 % of 4-Iodobenzenamine **(XXVIII)**, 2% of Aniline **(XXIII)**, 1% of nitrobenzene **(XXII)**). The catalytic aqueous phase was recovered and reused for further experiments.

GC-MS m/z (XXVIII) : 93 $[M]^+$; 76 $[M –NH_3]^+$; 66 $[M –HCN]^+$

GC-MS m/z (XXIII) : 93 $[M]^+$; 76 $[M –NH_3]^+$; 66 $[M –HCN]^+$

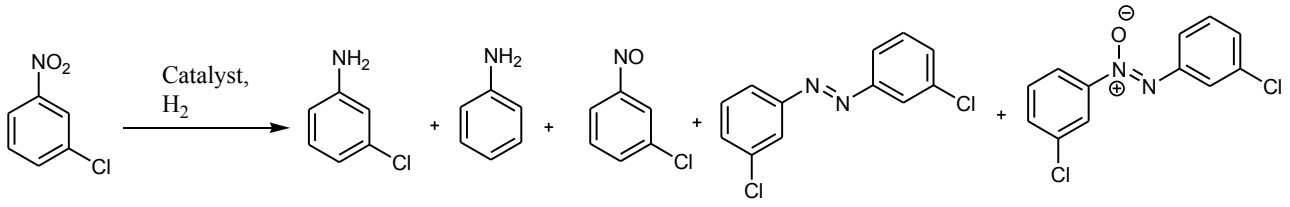
GC-MS m/z (XXII) :123 $[M]^+$; 93 $[M –NO]^+$;77 $[M –NO_2]^+$; 65 $[M –CONO]^+$; 51 $[M –C_2H_4NO_2]^+$

6.5.6.4 Reduction of 1-Iodo-4-Nitrobenzene (XXVII) catalyzed by 0.18% Rh/Al_2O_3

For example, here the procedure adopted for experiments of table 3.3.2, paragraph 3.3.3, of results and discussion.

In a Schlenk tube, 1-iodo-4-nitrobenzene **(XXVII)** (0.312 g, 1.25 mmol), 0.286 g of 0.18 % Rh/Al_2O_3 (**XXVII**/catalyst molar ratio 500/1) and 5 mL of toluene were introduced. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 4 Mpa of H_2 and stirred for 24 h at 80 °C. After this time, the residual gas was released, and the catalyst was filtered on a sintered glass filter, washed with 10 mL of diethyl ether and dried under vacuum. The recovered organic phase was analyzed by GC and GC-MS: 97 % conversion was detected (38 % of 4-Iodobenzenamine **(XXVIII)** and 60 % of Aniline **(XXIII)**). The catalyst was recycled for further experiments.

6.5.6.5 Reduction of 1-Chloro-3-nitrobenzene (XXIX) catalyzed by [Rh(DHTA)Na]



XXIX XXX XXIII XXXI XXXII XXXIII

For example, here the procedure adopted for experiments of table 3.3.3, paragraph 3.3.4, of results and discussion.

In a Schlenk tube, 1 mL of 0.005 M solution of [Rh(DHTANa)] in 2 mL of degassed distilled water, 1-chloro-3-nitrobenzene **(XXIX)** (0.395 g, 2.5 mmol) and 2 mL of toluene were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 4 Mpa of H_2 and stirred for 24 h at 80 °C. The reactor was then cooled to room temperature and the residual gases released. Diethyl ether was added and the organic phase was separated, dried on Na_2SO_4 and analyzed by GC and GC–MS: 100 % conversion of 1-Chloro-3-nitrobenzene **(XXIX)** to 3-Chlorobenzenamine **(XXX)** was detected. The catalytic aqueous phase was recovered and reused for further experiments.

GC-MS m/z (XXX) : 127 $[M]^+$; 100 $[M - HCN]^+$; 92 $[M - Cl]^+$; 65 $[M - Cl\text{-}HCN]^+$

6.5.6.6 Reduction of 1-Chloro-3-nitrobenzene (XXIX) catalyzed by 0.18% Rh/Al_2O_3

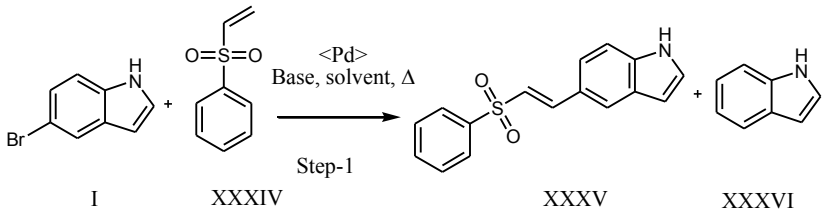
For example, here the procedure adopted for experiments of table 3.3.3, paragraph 3.3.4, of results and discussion.

In a Schlenk tube, 1-chloro-3-nitrobenzene **(XXIX)** (0.395 g, 2.5 mmol), 0.286 g of 0.18 % Rh/Al_2O_3 (**XXIX**/catalyst molar ratio 500/1) and 5 mL of toluene were introduced. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 4 Mpa of H_2 and stirred for 24 h at 80 °C. After this time, the residual gas was released, and the catalyst was filtered on a sintered glass filter, washed with 10 mL of diethyl ether and dried under vacuum. The recovered organic phase was analyzed by GC and GC-MS: 98% conversion (81 % of **(XXX)** and 17 % of **(XXIII)**) was detected. The catalyst was recycled for further experiments.

6.6 Experimental part B) The optimisation of the synthesis of Eletriptan hydrobromide and Cinacalcet hydrochloride

6.6.1 Synthesis of Eletriptan hydrobromide

6.6.1.1 General procedure for the synthesis of 5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (XXXV)



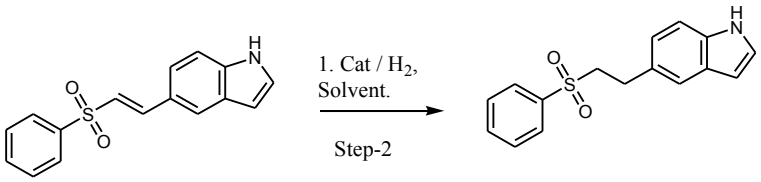
I XXXIV XXXV XXXVI

For example, here the procedure adopted for experiments of table 4.1.1 and 4.1.2, paragraph 4.1.1, of results and discussion.

In a dry 50 mL three neck round bottom flask equipped with a reflux condenser under nitrogen atmosphere 10 mL of N,N-dimethylformamide was introduced; before addition of all reagents solvent was degassed by bubbling nitrogen, then Palladium (II) acetate (0.034 g, 0.152 mmol), tri-o-tolylphosphine (0.309 g, 1.017 mmol), 5-bromoindole **(I)** (1 g, 5.08 mmol), phenyl vinyl sulphone **(XXXIV)** (1.28 g, 7.63 mmol) and triethylamine (1.02 g, 10.17 mmol) were added and the mixture was stirred at reflux temperature for 5-16 h. The reaction was monitored by TLC and GC-MS. After completion the reaction mixture was cooled at room temperature, filtered on diatomaceous earth to remove the spent catalyst and evaporated under reduced pressure. The solid obtained was purified by flash-chromatography (eluent: dichloromethane/MeOH/ liquid ammonia 98/2/0.1): the title compound 5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole **(XXXV)** was obtained as a white solid. (1.3 g, 90% yield).

5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole **(XXXV)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 8.52 (broad s, 1H), 7.99-7.97 (m, 2H), 7.85-7.78 (m, 2H), 7.61-7.52 (m, 3H), 7.41-7.25 (m, 3H), 6.83-6.78 (d, J = 15Hz, 1H), 6.60-6.58 (m, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ (ppm): 144.64, 141.45, 137.43, 133.08, 129.76, 129.28, 127.47, 125.75, 124.31, 123.51, 123.28, 121.79; GC-MS m/z : 283 $[M]^+$; 141 $[M, -C_6H_6O_2S]^+$; 115 $[M, -C_8H_8O_2S]^+$.

6.6.1.2 General procedure for the synthesis of 5-(2-(phenylsulfonyl)ethyl)-1H-indole (XXXVII)



XXXV XXXVII

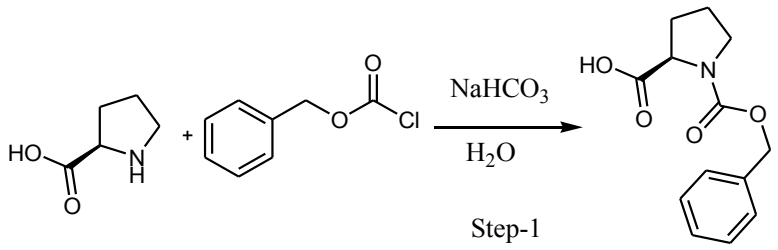
For example, here the procedure adopted for experiments of table 4.1.3, paragraph 4.1.2, of results and discussion.

In a Schlenk tube, (1 g, 3.53 mmol) of 5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole **(XXXV)**, 0.201 g of 0.18 % Rh/Al_2O_3 (substrate **XXXV**/catalyst molar ratio 1000/1) and 10 mL of toluene were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 0.2 Mpa H_2 and stirred for 6.5 h at 80 °C. The reactor was then cooled to room temperature and the residual gases released. The catalyst was filtered off by using a sintered glass filter and the organic solution was analyzed by GC and GC-MS: 96 % conversion of substrate **(XXXV)** into product **(XXXVII)** was detected. Solvent was distilled off and the crude mixture was purified by flash-chromatography (eluent: dichloromethane/MeOH/liquid ammonia 98/2/0.1): the title compound **(XXXVII)** was obtained as a yellowish solid (0.96 g, 96% yield).

The recovered catalyst was washed with diethyl ether (3x10 mL), dried under vacuum and recycled for the synthesis of compound **(XXXVII)** by adopting the above described procedure.

5-(2-(Phenylsulfonyl)ethyl)-1H-indole **(XXXVII)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 8.23 (broad s, 1H), 8.01-8.97 (m, 2H), 7.72-7.57 (m, 3H), 7.38-7.39 (d, 1H), 7.33-7.28 (dd, *J* = 9 Hz, 1H), 7.22-7.20 (m, 1H), 3.47-3.41 (m, 2H), 3.18-3.12 (m, 2H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ (ppm): 139.16, 134.78, 133.71, 129.32, 128.68, 128.20, 128.11, 124.87, 122.41, 120.08, 111.39, 102.30; GC-MS m/z : 285 $[M]^+$; 143 $[M, -C_6H_6O_2S]^+$; 117 $[M, -C_8H_8O_2S]^+$.

6.6.1.3 Synthesis of (R)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid (XLIV)



XLII XLIII XLIV

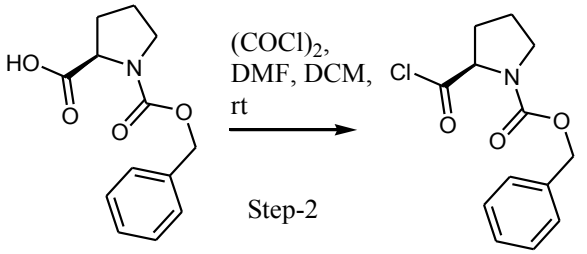
For example, here it is reported experiments of paragraph 4.2.1, of results and discussion.

In a dry 250 mL three necked round bottom flask equipped with dropping funnels, a thermometer and a magnetic stirrer, S-proline **(XLII)** (5 g, 43.47 mmol), $NaHCO_3$ (9.13 g, 108.6 mmol) and 50 mL of water were introduced under an inert atmosphere; then benzylchloroformate **(XLIII)** (8.16 g, 47.82 mmol) was added dropwise at 0 °C and stirred overnight at room temperature. The reaction was monitored by GC and GC-MS. After completion the reaction mixture was washed with di-ethyl ether (2 x 20 mL), the aqueous phase separated and quenched with 1N HCl (pH 2). This solution was extracted with EtOAc (3 x 20 mL) and the combined organic layer washed with brine (1 x 20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give 10.7 g of a colorless oil.

This oil was dissolved in 10 mL of ethyl acetate and 50 mL of petroleum ether and this mixture cooled at 0 °C in an ice bath; the wall of the flask was continuously scratched with a glass rod until the whole oil was crystallized. The crystals were collected on a sintered glass filter and washed with 10 mL of petroleum ether. After drying under vacuum, afford (R)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid **(XLIV)** as a white crystals (10.65 g, 98.42% yield).

(R)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid **(XLIV)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 10.38 (broad s, 1H), 7.30-7.18 (m, 5H), 5.15-5.06 (dd, *J* = 12, 18 Hz, 2H), 4.37-4.28 (m, 1H), 3.59-3.36 (m, 2H), 2.27-1.80 (m, 4H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 178.48, 176.48, 155.87, 154.43, 136.31, 128.53, 128.41, 128.15, 127.97, 127.90, 127.68, 67.54, 67.16, 59.30, 58.64, 46.94, 46.66, 30.91, 29.36, 24.30, 23.46; (lit: ^{13}C NMR: δ 23.07, 23.89, 29.36, 30.49, 46.21, 46.60, 58.38, 58.87, 66.84, 66.99, 127.18, 127.30, 127.45, 127.64, 128.00, 128.09, 136.00, 154.28, 155.07, 176.26, 176.84)[201]; GC-MS m/z : 249 $[M]^+$; 204 [M, -COOH]$^+$; 160 [M, -C_8H_{10}]$^+$; 115 [M, -$C_8H_8O_2$]$^+$; 91 [M, -$C_7H_{11}NO_4$; Melting Point : 70-75 °C; $[\alpha]_D$: -73.57 ° in $CHCl_3$.

6.6.1.4 Synthesis of (R)-benzyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (XLV)

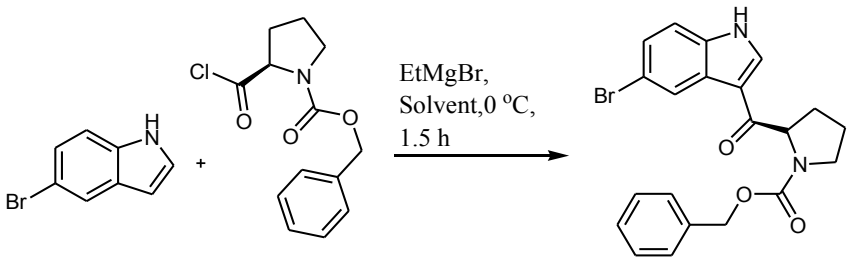


XLIV XLV

For example, here it is reported experiments of paragraph (4.2.1), of results and discussion.

In a dry 250 mL three neck round bottom flask, equipped with a dropping funnel and a magnetic stirring bar, (R)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid **(XLIV)** (5 g, 20.08 mmol) and dry 25 mL of dichloromethane were introduced under an inert atmosphere; oxalyl chloride (3.05 g, 24.09 mmol) was then added dropwise under stirring. When DMF (2 drops) was added, a strong evolution of CO_2 was observed. After the addition the reaction mixture was stirred at room temperature for 30-60 min. The reaction was monitored by TLC after quenching of a small amount of reaction mixture in dry MeOH (methyl ester was formed). After completion of reaction the solution was concentrated to small volume so affording (5.36 g, 100% yield) of (R)-benzyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate **(XLV)** as a pale yellow oil. The crude compound was used as such for the next step.

6.6.1.5 synthesis of (R)-3-carboxylbenzoyl-2-pyrrolidinylcarboxyl)-5-bromo-1H-indole (XLVI)



I XLV XLVI

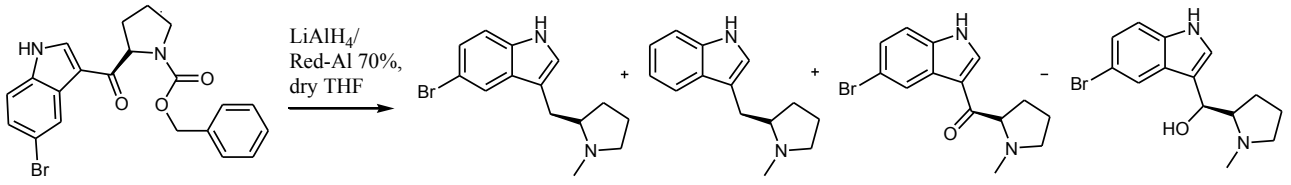
For example, here it is reported experimental of paragraph 4.2.1 of results and discussion.

In a dry 500 mL three neck round bottom flask equipped with a magnetic stirrer 5-beomo-1H-indole **(I)** (5 g, 25.44 mmol) and 25 mL of anhydrous tetrahydrofuran were introduced under an inert atmosphere. The mixture was stirred at room temperature until an homogeneous solution was obtained, then it was cooled to 10-15 °C. A solution of CBZ-prolinoyl chloride **(XLV)** in anhydrous dichloromethane (6.98 g, 25.95 mmol) was added dropwise within 30 minute and then 3M ethyl magnesium bromide in MTBE (6.78 g, 50.87 mmol) was added whilst maintaining the temperature at 10-15 °C.

The resultant slurry was added to a vigorously stirred mixture of conc. HCl (4 mL), demineralised water (30 mL) and THF (25 mL), over 30 minute, while maintaining the temperature below 25 °C. The organic layer was separated, washed with a saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and the solvent evaporated at reduced pressure at a temperature lower than 50 °C. The obtained residue was purified by crystallization using a 1:1 mixture (n-hexane: ethyl acetate) as the eluent. (R)-3-carboxylbenzoyl-2-pyrrolidinylcarboxyl)-5-bromo-1H-indole **(XLVI)** was obtained as a white solid (9.3 g, 85 % yield).

(R)-3-carboxylbenzoyl-2-pyrrolidinylcarboxyl)-5-bromo-1H-indole **(XLVI)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 12.22-12.20 (dd, J = 6 Hz, 1H), 8.52-8.47 (dd, J = 11.1 Hz, 1H), 8.35-8.31 (dd, J = 11.4 Hz, 1H), 7.48-7.36 (m, 5H), 7.11-6.98 (m, 2H), 5.22-5.16 (m, 1H), 5.06-4.86 (m, 2H), 3.54-3.50 (m, 2H), 2.42-2.28 (m, 1H), 1.86-1.85 (m, 3H); ^{13}C NMR (76 MHz, $CDCl_3$) δ (ppm): 192.55, 155.55, 136.62, 134.66, 131.78, 128.55, 128.11, 127.72, 126.25, 124.36 67.28, 62.12, 46.99, 30.76, 24.15; GC-MS m/z : 426 $[M]^+$; 337 $[M, -C_7H_5]^+$; 291 $[M, -C_8H_7O_2]^+$; 204 $[M, -C_{12}H_{14}NO_2]^+$; 91 $[M, -C_{12}H_{12}BrN_2O_3]^+$.

6.6.1.6 Synthesis of 5-Bromo-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole (XLVII)



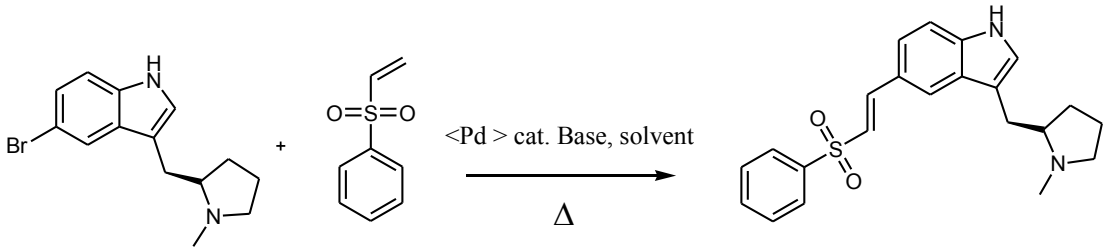
XLVI XLVII XLVIII XLIX L

For example, here it is reported experiments of paragraph 4.2.1, of results and discussion.

In a dry 250 mL three neck round bottom flask equipped with a reflux condenser and a thermometer, under inert atmosphere were introduced (R)-3-carboxylbenzoyl-2-pyrrolidinylcarboxyl)-5-bromo-1H-indole **(XLVI)** (5 g, 11.70 mmol, 1 equiv) and 50 mL of dry toluene; then a 70 % solution of SDMA (Red-Al) in toluene (5.91 g, 29.27 mmol) was added dropwise while maintaining the temperature between 30-40 °C. After the addition the reaction mixture was heated at 50 °C for 1 h, then cooled to 5 °C, and water (5 mL) was carefully added; then a 10 % aqueous solution of NaOH solution (5 mL) and water (25 mL) were added. The resulting mixture was diluted with toluene (25 mL), the organic phase was separated and the aqueous phase was extracted with toluene (2 x 25 mL). The organic solutions were combined, dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated under reduced pressure to give a light yellow oil. This oil was dissolved in toluene and after addition of heptane 5-Bromo-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole **(XLVII)** was obtained as a white solid (3 g, 88 % yield).

5-Bromo-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole **(XLVII) :** ^{1}H-NMR (300MHz, $CDCl_3$) δ ppm: 8.56 (broad s, 1H), 7.73 (s, 1H), 7.30-7.21 (m, 2H), 7.02 (s, 1H), 3.20-3.13 (m, 2H), 2.65-2.57 (m, 1H), 2.49-2.46 (m, 4H), 2.31-2.23 (m, 1H), 1.88-1.51 (m, 4H); ^{13}C-NMR[131] (76 MHz, $CDCl_3$) δ ppm: 134.88, 129.28, 124.65, 123.34, 121.53, 113.70, 112.58, 112.38, 66.18, 57.52, 40.80, 31.45, 29.76, 21.84; GC-MS m/z : 292 $[M]^+$; 207 $[M, -C_5H_{11}N]^+$; 84 $[M, -C_9H_8BrN]$.

6.6.1.7 General procedure for the Synthesis of 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (LI)



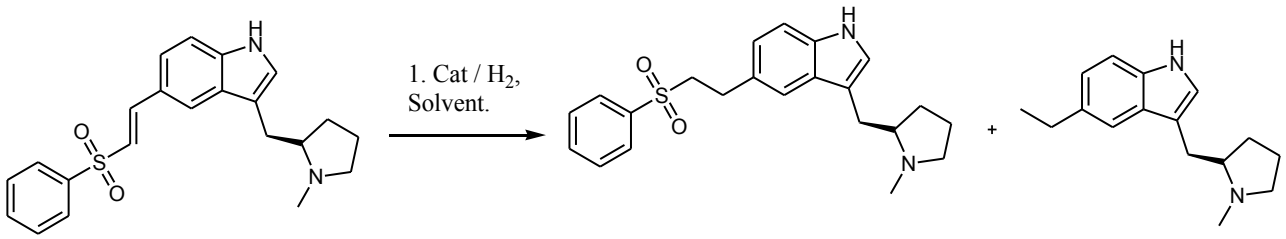
XLVII XXXIV LI

For example, here the procedure adopted for experiments of table 4.2.1, paragraph 4.2.2, of results and discussion.

In a dry 100 mL three neck round bottom flask equipped with a reflux condenser and a thermometer, under inert atmosphere, 10 mL of acetonitrile was introduced; before addition of all reagents solvent was degassed by bubbling dry nitrogen, then Palladium (II) acetate (0.023 g, 0.102 mmol), tri-o-tolylphosphine (0.153 g, 0.476 mmol), 5-bromo-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole **(XLVII)** (1 g, 3.42 mmol), phenyl vinyl sulphone **(XXXIV)** (0.863 g, 5.136 mmol) and triethylamine (0.691g, 6.84 mmol) were added. The reaction mixture was stirred at reflux temperature for 14-16 h. The reaction was monitored by TLC and GC-MS. After completion of reaction, the mixture was cooled at room temperature, filtered on celite to remove the spent catalyst, and the filtrate evaporated under reduced pressure. The solid obtained was purified by flash-chromatography (eluent: dichloromethane/MeOH/ liquid ammonia 98/2/0.1): the title compound 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (**LI**) was obtained as a foam. (0.95 g, 73 % yield).

3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole **(LI)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 8.52 (broad s, 1H), 8.00-7.98 (m, 2H), 7.87-7.85 (dd, 1H) 7.74 (s, 1H), 7.58-7.52 (m, 3H), 7.33 (s, 2H), 7.07 (s, 1H), 6.80-6.77 (d, J = 15.3 Hz, 1H), 3.20-3.16 (q, 2H), 2.65-2.59 (q, 1H), 2.49-2.47 (d, 4H), 2.25-2.21(q, 2H), 1.84-1.69 (m, 4H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 144.84, 142.04, 138.25, 133.73, 130.04, 127.79, 127.34, 125.63, 124.09, 123.52, 122.26, 121.94, 112.64, 112.16, 67.55, 56.61, 40.83, 40.55, 40.27, 39.99, 39.72, 39.44, 39.16, 30.36, 29.79, 27.49, 21.63. (lit: ^{13}C NMR, DMDS: δ 21.72, 28.11, 30.73, 39.29, 39.50, 39.71, 39.92, 40.13, 40.34, 40.55, 56.70, 66.96, 112.56, 113.04, 121.78, 122.29, 123.38, 123.92, 125.30, 127.34, 127.98, 130.02, 133.70, 138.21, 142.04, 144.92) [202]; GC-MS m/z : 380 $[M]^+$; 296 $[M, -C_5H_{10}N]^+$; 154 $[M, -C_{11}H_{16}NO_2S]^+$; 84 $[M, -C_{17}H_{14}NO_2S]^+$

6.6.1.8 General procedure for the synthesis of 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)ethyl)-1H-indole (XL)



LI XL LII

For example, here the procedure adopted for experiments of table 4.2.2 and 4.2.3, paragraph 4.2.3.1 and 4.2.3.2, of results and discussion.

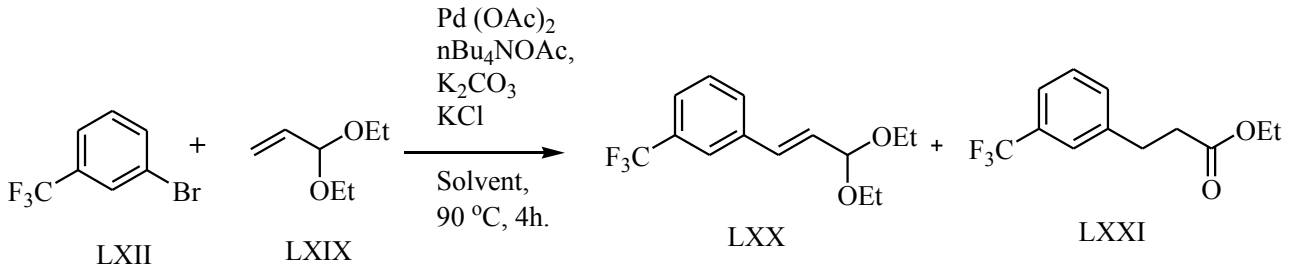
In a dry two neck glass jacketed round bottom flask, under inert atmosphere, 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole **(LI)** (1 g, 2.63 mmol), Pd/Al_2O_3 0.28 % (0.5 g, sub/cat. molar ratio 200/1) and a 10 mL of toluene: methanol mixture (4:1) were introduced. Then the reaction flask was flushed with H_2 and the reaction mixture stirred for 16 h at 40 °C at 0.1Mpa H_2 (balloon pressure). The reaction flask was then cooled to room temperature, the catalyst was filtered off by using a sintered glass filter and the organic solution was analyzed by GC-MS and HPLC: 94 % conversion of substrate **(LI)** into product **(XL)** and ethyl impurity **(LII)** 6% was detected. Solvent was distilled off and the crude mixture was purified by flash-chromatography (eluent: dichloromethane/MeOH/liquid ammonia 98/2/0.1): the title compound 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)ethyl)-1H-indole **(XL)** was obtained as a foam (0.85 g, 85% yield).

3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)ethyl)-1H-indole **(XL)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 8.21 (broad s, 1H), 7.90-7.88 (d, *J* = 7.8 Hz, 1H), 7.52-7.47 (t, J = 15 Hz, 2H), 7.23-7.15 (m, 2H), 6.93 (s, 1H), 6.85-6.82 (d, *J* = 9 Hz, 1H), 3.40-3.32 (m, 2H), 3.11-3.04 (m, 2H), 2.59-2.48 (m, 2H), 2.42-2.39 (m, 4H), 2.23-2.14 (dd, *J* = 17.1 Hz, 2H), 1.79-1.47 (m, 6H),; ^{13}C-NMR data reported in the literature[203]; GC-MS m/z : 382 $[M]^+$; 298 $[M, -C_5H_{10}N]^+$; 156 $[M, -C_{15}H_{21}N_2]^+$; 84 $[M, -C_{17}H_{16}NO_2S]^+$.

5-Ethyl-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole **(LII)** : ^{1}H-NMR and ^{13}C-NMR data are reported in literature[204].

6.6.2 Synthesis of Cinacalcet hydrochloride under conventional condition

6.6.2.1 General procedure for the synthesis of 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene (LXX)



LXII LXIX LXX LXXI

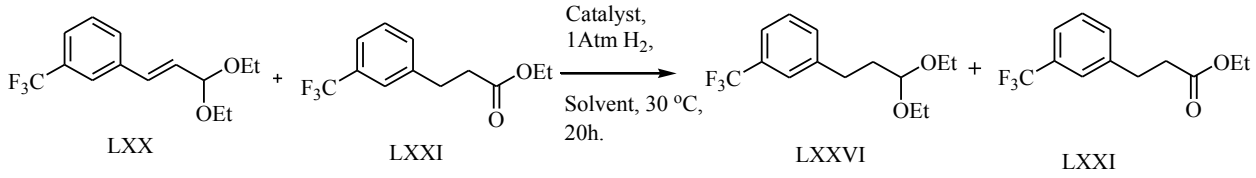
For example, here the procedure adopted for experiments of table 4.4.1, paragraph 4.4.1, of results and discussion.

In a dry 50 mL three neck glass jacket round bottom flask equipped with reflux condenser, thermometer and magnetic stirring bar, under inert atmosphere it was introduced 10 mL of 2-methyl tetrahydrofuran: before the addition of all reagents solvent was degassed by bubbling nitrogen. Then 3-bromobenzotrifluoride **(LXII)** (1 g, 4.44 mmol), acrolein diethyl acetal **(LXIX)** (0.867 g, 6.66 mmol), palladium(II) acetate (0.29 mg, 0.133 mmol), tetra-butylammoniumacetate (2.67 g, 8.88 mmol), potassium chloride (0.331 g, 4.44 mmol) and potassium carbonate (0.919 g, 3.33 mmol) were added and the mixture was stirred at 90 °C for 4 h. The reaction was monitored by GC: 100% conversion of substrate **(LXII)** in to a mixture of product **(LXX)** and **(LXXI)** in the ratio 90:10 was obtained. After completion the reaction, was cooled at room temperature and filtered on diatomaceous earth to remove the spent catalyst. The upper cake was washed with diethyl ether (20 mL) and the filtrate was washed with water (2 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated under reduced pressure to gave a, crude mixture of **(LXX)** and **(LXXI)** 90:10, as a yellowish oil.

1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene **(LXX):** ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 7.66-7.44 (m, 4H), 6.79-6.74 (d, *J* = 15.9 Hz, 1H), 6.33-6.26 (dd, *J* = 16.2, 4.8 Hz, 1H), 5.11-5.09 (dd, *J* = 4.8, 1.2 Hz, 1H), 3.76-3.70 (q, *J* = 6.9, 9.3 Hz), 3.61-3.56 (q, *J*= 7.2, 9.6 Hz, 2H), 1.30-1.25 (t, *J* = 14.1 Hz, 6H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ (ppm): 144.80, 134.83, 131.35, 129.97, 129.61, 129.53, 128.90, 127.55, 125.15, 119.36, 60.69, 14.15; GC-MS m/z: 274 $[M]^+$; 255 $[M, -F]^+$; 229 $[M, -C_2H_5O]^+$; 200 $[M, -C_4H_{10}O]^+$; 172 $[M, -C_5H_{10}O_2]^+$; 103 $[M, -C_6H_{10}F_3O_2]^+$.

Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 7.47-7.37 (m, 4H), 4.18-4.07 (q, *J* = 16.2, 7.2 Hz, 2H), 3.05-3.00 (t, *J* = 16.5, 8.7 Hz, 2H), 2.68-2.62 (t, *J* = 16.8, 7.5 Hz, 2H), 1.26-1.21 (t, *J* = 9.3, 6.9 Hz, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 172.06, 141.20, 131.47, 128.57, 124.61, 122.69, 60.18, 35.21, 13.69; GC-MS m/z: 246 $[M]^+$; 227 $[M, -F]^+$; 201 $[M, -C_2H_5O]^+$; 172 $[M, -C_3H_6O_2]^+$; 172 $[M, -C_5H_{10}O_2]^+$; 103 $[M, -C_6H_{10}F_3O_2]^+$.

6.6.2.2 General procedure for the synthesis of 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene (LXXVI)

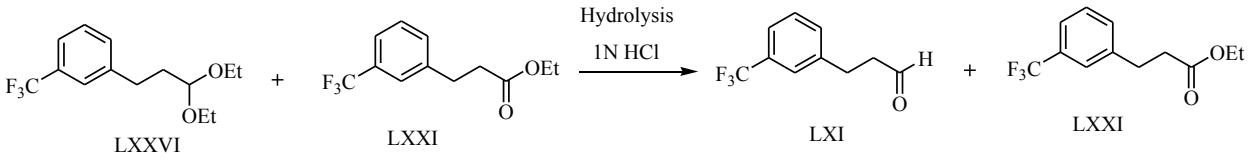


For example, here the procedure adopted for experiments of paragraph 4.1.2, of results and discussion.

In a dry 25 mL single neck round bottom flask equipped with magnetic stirrer bar, under inert atmosphere, was introduced the mixture obtained (from 6.6.2.1), 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene 90% **(LXX)** (1.1 g, 4.01 mmol) and 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene 10% **(LXXI)** in 10 mL of 2-methyl tetrahydrofuran and palladium catalyst 3 mol %, derived from reaction mixture of (6.6.2.1). Then the reaction flask was flushed with H_2 twice and stirred with 0.1 Mpa H_2 (with balloon pressure) for 20 h at 30 °C. The reaction flask was then cooled to room temperature, the catalyst was filtered through diatomaceous earth to remove the spent catalyst by using a sintered glass filter and the organic solution was analyzed by GC. 100 % conversion of substrate **(LXX)** into product **(LXXVI)** was detected and **(LXXI)** remains unreacted in the reaction mixture. Solvent was distilled off to afford a mixture of **(LXXVI)** and **(LXXI)** as a yellowish liquid. Yield: (1.1 g, quantitative yield with respect to compound **(LXX)**).

1-(3,3-Diethoxypropyl)-3-(trifluoromethyl)benzene **(LXXVI)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 7.47-7.37 (m, 4H), 4.52-4.46 (t, *J* = 5.7, 9.9 Hz, 1H), 3.75-3.63 (q, *J* = 7.2, 9.6 Hz, 2H), 3.54-3.43 (q, *J* = 6.9, 9.3 Hz, 2H), 2.81-2.73 (q, *J* = 8.1, 10.2 Hz, 2H), 2.02-1.91 (q, *J* = 8.1, 10.1 Hz, 2H), 1.26-1.22 (t, *J* = 7.2, 11.4 Hz, 6H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm):142.46, 131.57, 128.53, 124.84, 124.76, 122.44, 122.36, 101.67, 60.91, 34.62, 30.43, 14.98; GC-MS m/z : 276 $[M]^+$; 257 $[M, -F]^+$; 231 $[M, -C_2H_5O]^+$; 201 $[M, -C_4H_{11}O]^+$; 183 $[C_4H_{10}FO]$; 103 $[M, -C_6H_{12}F_3O_2]^+$.

6.6.2.3 Procedure for the synthesis of 3-(3-(trifluoromethyl)phenyl)propanal (LXI) from mixture of (LXXVI) and (LXXI)

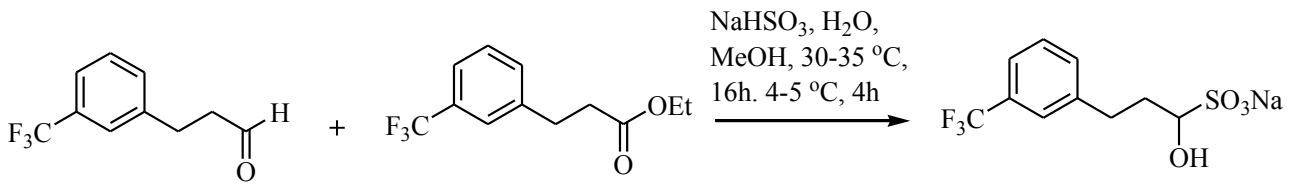


For example, here the procedure adopted for experiments of paragraph 4.1.2, of results and discussion.

In a dry 25 mL single neck round bottom flask the mixture of 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene **(LXXVI)** and 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene **(LXXI)** (1.1 g, 3.98 mmol) (obtained from 5.10.2) was introduced; then 1M HCl aqueous solution was added dropwise, maintaining the temperature below 25 °C till pH = 1-2. Then the mixture stirred for 30 min, (the reaction was monitored by GC), and after completion the reaction mixture was diluted with diethyl ether (20 mL) and washed with water (20 mL x 3). The organic solutions were combined, dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated under reduced pressure to give 3-(3-(trifluoromethyl)phenyl)propanal (**LXI)** as a colorless liquid, (0.790 g, 97 % yield).

3-(3-(Trifluoromethyl)phenyl)propanal **(LXI)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 9.75 (s, 1H), 7.48-7.41 (m, 4H), 3.06-3.01 (t, *J* = 7.5, 15 Hz, 2H), 2.86-2.82 (t, *J* = 7.8, 14.9 Hz, 1H), 2.75-2.20 (t, J = 7.5, 15, 1H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ (ppm): 200.67, 141.33, 131.82, 129.03, 125.02, 123.22, 44.94, 27.76; GC-MS m/z : 202 $[M]^+$; 183 $[M, -F]^+$; 160 $[M, -C_2H_5O]^+$; 133 $[M, -F_3]^+$; 183 $[C_4H_{10}FO]$; 103 $[M, -C_6H_{12}F_3O_2]^+$.

6.6.2.4 Procedure for the purification of the mixture of 3-(3-(trifluoromethyl)phenyl)propanal (LXI) and 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene (LXXI) by Bertagnini salt



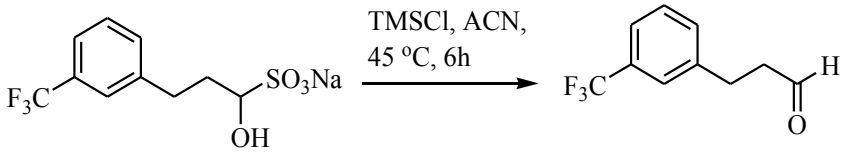
LXI LXXI LXXVII

For example, here the procedure adopted for experiments of paragraph 4.4.3, of results and discussion.

In a dry 50 mL glass jacketed three neck round bottom flask equipped with thermometer and magnetic stirrer, under inert atmosphere, the mixture of crude **(LXI)** and **(LXXI)** (1 g, 4.95 mmol) in 45 mL of ethanol was introduced. The resulting solution was stirred at room temperature for 10 minutes, then a solution of $NaHSO_3$ (0.515g, 4.95 mmol) in 1.8 mL of water was added dropwise within 10 min. Then it was stirred at 35 °C for 16 h and subsequently at 5 °C for 4 h. After completion of reaction the product was filtered, washed with methyl-tert-butyl ether (10 mL x 3) and dried under vacuum to gave sodium 1-hydroxy-3-(3-trifluoromethylphenyl)propane-1-sulfonate **(LXXVII)** as a white powder (1.44 g, 95 % yield).

sodium 1-hydroxy-3-(3-trifluoromethylphenyl)propane-1-sulfonate **(LXXVII)** : ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 7.81-7.25 (m, 4H), 5.52-5.50 (d, J = 6 Hz, 1H), 3.84-3.78 (m, 1H), 2.94-2.81 (m, 1H), 2.76-2.65 (m, 1H), 2.11-2.00 (m, 1H), 1.85-1.73 (m, 1H); ^{13}C-NMR (76 MHz, DMSO-d_6) δ (ppm): 144.17, 133.10, 129.69, 129.25, 126.63, 125.23, 122.87, 82.14, 34.05, 31.57; IR- spectra[205] ; 3267, 1454, 1334, 1220, 1177, 1143, 1108, 1073, 1028, 935, 887, 801, 746, 630 cm^{-1}.

6.6.2.5 Procedure for the regeneration of 3-(3-(trifluoromethyl)phenyl)propanal (LXI), from sodium 1-hydroxy-3-(3-trifluoromethylphenyl)propane-1-sulfonate (LXXVII)

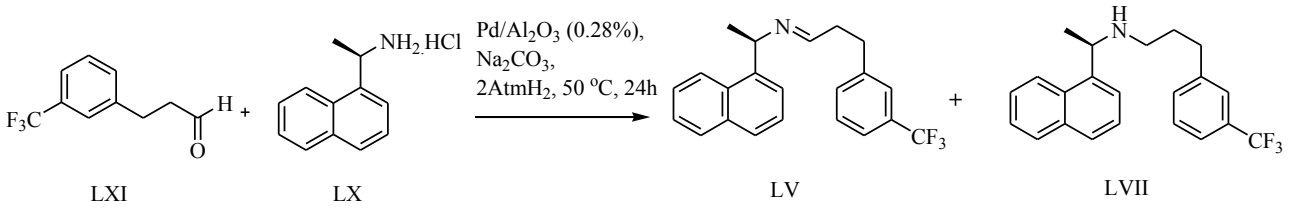


LXXVII LXI

For example, here the procedure adopted for experiments of paragraph 4.4.3, of results and discussion.

In a dry two neck glass jacketed round bottom flask equipped with reflux condenser, thermometer and magnetic stirrer, under inert atmosphere, was introduced sodium 1-hydroxy-3-(3-trifluoromethylphenyl)propane-1-sulfonate **(LXXVII)** (1.44 g, 19.28 mmol), in 15 mL of acetonitrile, and TMS-Cl (1.75 g, 16.1 mmol); after the addition the mixture was stirred at 45 °C for 6 h. Initially the reaction mixture was likely homogeneous but after 6 h it was observed precipitation of NaCl. The reaction was monitored by GC and GC-MS. After completion the reaction mixture was cooled at room temperature, then the resulting mixture was diluted with toluene (20 mL), and washed with water (10 mL x 3) and brine (10 mL x 3). The organic solutions were combined, dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated under reduced pressure to half volume to give a colorless liquid. This aldehyde containing toluene is ready to use for next step.

6.6.2.6 Procedure for the synthesis of 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine (LVII) catalysed by Pd/Al_2O_3, Rh/Al_2O_3, Pt/Al_2O_3



LXI LX LV LVII

For example, here the procedure adopted for experiments of table 4.4.2 and 4.4.3, paragraph 4.4.4 and 4.4.5, of results and discussion.

In a Schlenk tube under inert atmosphere, 3-(3-(trifluoromethyl)phenyl)propanal **(LXI)** (1 g, 4.95 mmol), (R)-1-(Naphthalen-1-yl)ethanamine hydrochloride **(LX)** (1.02 g, 4.95 mmol), sodium carbonate (0.524 g, 4.95 mmol), Pd/Al_2O_3 0.28% (0.188 g, sub/cat ratio 1000/1) and 10 mL of toluene were introduced. Then the Schlenk tube was transferred in to 150 mL stainless steel autoclave under inert atmosphere, pressurized with 0.5 Mpa H_2 and stirred for 24 h at 50 °C. Then the reactor was cooled to room temperature and the residual gas released. The catalyst was filtered off by using a sintered glass filter to recover the catalyst for further use and the organic solution was analyzed by GC and GC-MS: 98 % conversion of substrate **LXI** into product **LVII** and 2 % **LV** of imine intermediate was detected. Then obtained filtrate was diluted with fresh toluene (10 mL); the resulting filtrate was washed with water (10 mL x 2) and brine (10 mL x 2) and the organic solution dried over Na_2SO_3, filtered and concentrated under reduced pressure to gave a yellowish oil. This oil was dissolved in n-pentane (1-2 mL) and 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-5-yl)ethyl)propan-1-amine **(LVII)** precipitated as a white solid (1.67 g, 94% yield).

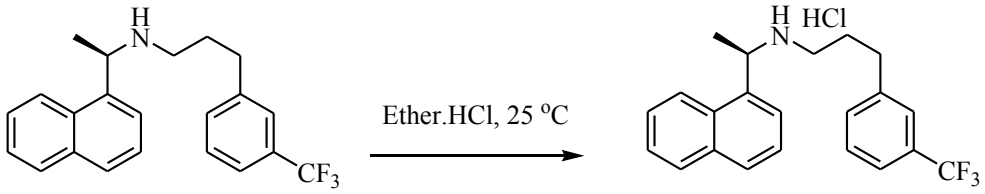
3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine **(LVII)** : ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm)**:** 8.22-8.19 (d, *J* = 9.3 Hz 1H), 7.91-7.88 (dd, *J* = 7.2, 8.1 Hz, 1H), 7.78-7.75 (d, *J* = 8.1 Hz, 1H), 7.68-7.65 (d, *J* = 6.3 Hz, 1H), 7.53-7.33 (m, 6H), 4.68-4.61 (q, *J* = 6.6 Hz, 1H), 2.82-2.56 (m, 4H), 1.91-1.81 (m, 2H), 1.53-1.51 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR data reported in literature[169]; GC-MS m/z : 357 $[M]^+$; 342 $[M, -CH_3]^+$; 155 $[M, -C_{10}H_{11}F_3N]^+$.

6.6.2.7 Procedure for the synthesis of 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine (LVII) catalysed by Aquivion®-M and $NaBH_4$

For example, here the procedure adopted for experiments of table 4.4.4, paragraph 4.4.6, of results and discussion.

In a dry 50 mL two neck round bottom flask were introduced 3-(3-(trifluoromethyl)phenyl)propanal (1 g, 4.95 mmol), Aquivion®-Fe (14 mg, 0.016 mmol), and 20 mL of dichloromethane resulting mixture stirred for 15-20 minute at 30 °C, then it was added (R)-1-(naphthalen-1-yl)ethanamine hydrochloride (1.027 g, 4.96 mmol), Na_2CO_3 (0.524 g, 4.96 mmol), $NaBH_4$ (0.185 g, 4.95 mmol) after all addition obtained reaction mixture stirred at 30 °C for 1h. Then reaction mixture were analyzed by GC-FID shown 100% formation of imine intermediate then it was added MeOH (1 mL) in to reaction mixture to obtained immediately imine to amine, after completion of reaction. The catalyst was filtered off by using a sintered glass filter to recover the catalyst for further use and the organic solution was analyzed by GC and GC-MS: 98 % of product **LVII** and 2% **LV** of imine intermediate was detected. Then obtained filtrate was diluted with fresh dichloromethane (10 mL); the resulting filtrate was washed with water (10 mL x 2) and brine (10 mL x 2) and the organic solution dried over Na_2SO_3, filtered and concentrated under reduced pressure to give a yellowish oil. This oil was dissolved in n-pentane (1-2 mL) and 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine **(LVII)** precipitated as a white solid (1.60 g, 90% yield).

6.6.2.8 Procedure for the synthesis of 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine hydrochloride (LXXV)



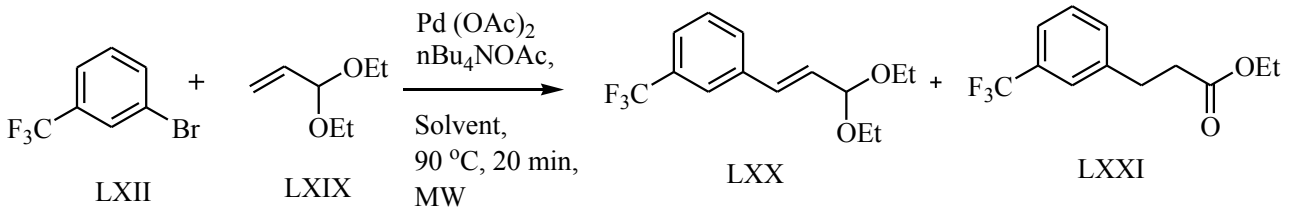
LVII LXXV

In a dry 50 mL two neck round bottom flask under inert atmosphere were introduced 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine **(LVII)** (1.60 g, 4.48 mmol) in 15 mL of dry ether HCl, resulting mixture stirred at 25 °C for 1-2 h: obtained precipitated solid was filtered on buchner funnel; upper solid was washed with (10 mL x 3) of n-pentane to afford 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine hydrochloride **(LXXV)** as a white crystal solid (1.74 g, 99 % yield).

3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine hydrochloride **(LXXV)** : ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm)**:** 10.58 (broad s, 1H), 10.08 (broad s, 1H), 8.26-8.23 (d, J = 9 Hz, 1H), 8.00-7.90 (m, 3H), 7.67-7.56 (m, 3H), 7.35-7.21 (m, 4H), 5.24-5.18 (m, 1H), 2.80-2.72 (m, 2H), 2.59-2.52 (m, 2H), 2.34-2.22 (m, 2H), 2.01-1.99 (d, J = 6 Hz 1H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ (ppm): 140.78, 133.86, 132.09, 131.54, 130.69, 129.57, 129.50, 128.85, 127.35, 126.27, 126.12, 125.00, 124.90, 123.1, 121.25, 53.53, 45.49, 32.50, 27.30, 21.31; ^{19}F-NMR (376 MHz, $CDCl_3$) δ_f (ppm): -63.0 (3F, s, CF_3)[206] (data from literature); GC-MS m/z : 393 $[M]^+$; 378 $[M, -CH_3]^+$; 191 $[M, -C_{10}H_{11}F_3N]^+$.

6.6.3 Synthesis of Cinacalcet hydrochloride under microwave conditions

6.6.3.1 General procedure for the synthesis of 1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene (LXX)

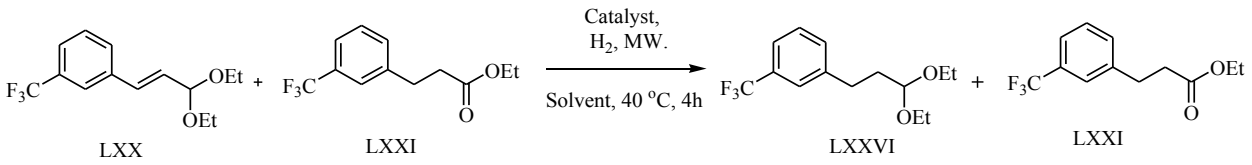


LXII LXIX LXX LXXI

For example, here the procedure adopted for experiments of table 4.5.1 and 4.5.2, paragraph 4.5.1, of results and discussion.

In a dry 10 mL CEM Microwave process vial with magnetic stirrer bar, under inert atmosphere, 2-methyl tetrahydrofuran (2 mL) was introduced. Before addition of all reagents solvent was degassed by bubbling nitrogen; then 3-bromobenzotrifluoride **(LXII)** (0.5 g, 2.22 mmol), acrolein diethyl acetal **(LXIX)** (0.433 g, 6.66 mmol), palladium(II) acetate (14.9 mg, 0.066 mmol,) and tetra-butylammoniumacetate (1.35 g, 4.44 mmol) were added. The mixture containing vial was sealed tightly by using the CEM Discover pressure equipment and placed into the CEM Discover microwave unit; then the reaction mixture was irradiate under MW by following MW method, Pressure-5 W, Ramp time- 5 min, Hold time- 20 min, Temperature- 90 °C, Pressure- 300 psi. After allowing the reaction mixture to cool down to room temperature the reaction mixture was analyzed by GC and GC-MS: 100 % conversion of substrate **(LXII)** into **(LXX)** (90 % yield) and **(LXXI)** (10 % yield) was detected. The resulting reaction mixture was taken for hydrogenation by utilizing the same catalyst.

6.6.3.2 General procedure for the synthesis of 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene (LXXVI)

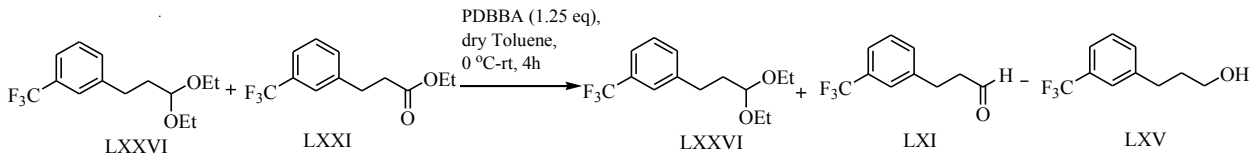


For example, here the procedure adopted for experiments of table 4.5.3, paragraph 4.5.3.1, of results and discussion.

The reaction mixture was performed with CEM Discover single mode microwave reactor equipped with a 300 W power source. A 10 mL fiber optic accessory was equipped with a gas inlet to allow introduction of hydrogen gas to the reaction vessel.

The obtained above Heck reaction mixture (from 6.6.3.1) was introduced into a 10 mL fiber optic accessory, then the reaction vessel was purged three times with hydrogen, pressurized with 0.2 Mpa H_2 and then closed off to the source of hydrogen. The reaction mixture was heated under microwave irradiation at 40 °C with 5 W power and held for 240 min. Upon cooling to room temperature the mixture was analyzed by GC and GC-MS; 100% conversion of **(LXX)** in to **(LXXVI)** was obtained and **(LXXI)** remains as such in to the reaction mixture. Then the catalyst was filtered off by using a sintered glass filter through diatomaceous earth to remove the spent catalyst and the residue washed with diethyl ether (15 mL). The resulting filtrate was evaporated under reduced pressure to afford a mixture of **(LXXVI)** and **(LXXI)** as a yellowish liquid, with quantitative yield.

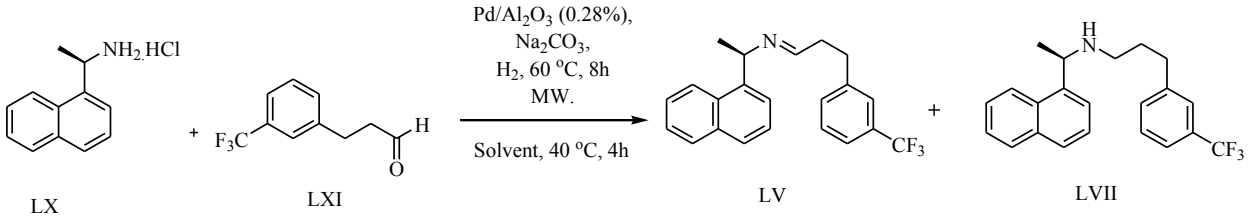
6.6.3.3 Procedure for the synthesis of 3-(3-(trifluoromethyl)phenyl)propanal (LXI) from a mixture of 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene (LXXVI) and 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene (LXXI)



For example, here the procedure adopted for experiments of table 4.6.1, paragraph 4.6.1, of results and discussion.

In a thoroughly oven dried 10 mL single neck round bottom flask, equipped with septum, under inert atmosphere, the mixture of 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene **(LXXVI)** and ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)** (0.120 g, (10.8 mg of **(LXXI)** present in the mixture, 0.043 mmol)) in anhydrous toluene (2 mL), was introduced. This reaction mixture was cooled to 0 °C then a solution of PDBBA (potassium diisobutyl-t-butoxyaluminum hydride) (0.112 mL, 0.5 M in THF: hexane) was added dropwise with a syringe. After the addition, temperature raised to room temperature and the resulting mixture was stirred for 4 h. The reaction mixture was analyzed by GC and GC-MS after quenching a sample with water: only reduction of **(LXXI)** to **(LXI)** occurred and **(LXXVI)** remained as such. 97 % conversion of **(LXXI)** to **(LXI)** and 3 % of **(LXV)** alcohol byproduct was obtained. The resulting reaction mixture was hydrolyzed by adding 1M HCl (5 mL) to pH = 1-2; product was extracted in diethyl ether (10 mL x 2), then organic layer washed with water and brine and the organic phase evaporated and dried over anhydrous Na_2SO_4. Then it was filtered and evaporated under reduced pressure to get product **(LXI)** in 99.2 % purity and the overall content of alcohol impurity is **(LXV)** 0.8 %. The isolated yield of aldehyde **(LXI)** is 87 mg, 99%.

6.6.3.4 Procedure for the synthesis of 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine (LVII)



LX LXI LV LVII

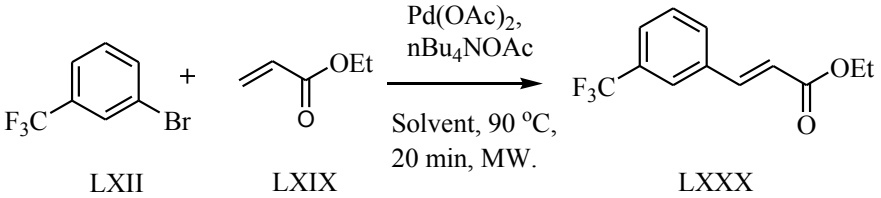
For example, here it is reported an experiment of Table 3.7.5 of paragraph (3.7.4) of results and discussion.

The reaction was performed with CEM Discover single mode microwave reactor equipped with a 300 W power source A 10 mL fiber optic accessory was equipped with a gas inlet to allow introduction of hydrogen gas to the reaction vessel.

In a dry 10 mL CEM Discover microwave vial under inert atmosphere it was introduced 3-(3-(trifluoromethyl)phenyl)propanal **(LXI)** (202 mg, 1 mmol), (R)-1-(Naphthalen-1-yl)ethanamine hydrochloride **(LX)** (207 mg, 1 mmol), sodium carbonate (106 mg, 1 mmol), Pd/Al_2O_3 0.28 % (36.7 mg, sub/cat ratio 1000/1) and toluene (2 mL). Then the reaction vessel was purged three times with hydrogen, pressurized with 0.2 Mpa H_2, and then closed off to the source of hydrogen. The reaction was heated under microwave irradiation at 60 °C with 20 W power and held for 480 min. Upon cooling to room temperature the residual gas was released and the mixture analyzed by GC and GC-MS: 98 % conversion of **(LXI)** to **(LVII)** and 2 % of imine intermediate was detected. Then the catalyst was filtered off by using a sintered glass filter, the upper wet cake washed with THF (10 mL) and the catalyst dried under vacuum for further use. The filtrate was then washed with water (10 mL x 2) and brine (10 mL x 2) and the separated organic phase dried over anhydrous Na_2SO_3, filtered and concentrated under reduced pressure to give a yellowish oil. This oil was dissolved in n-pentane (1-2 mL) and 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)propan-1-amine **(LVII)** precipitated as a white solid (0.337 g, 94 % yield).

6.6.4 Alternative synthesis of 3-(3-(trifluoromethyl)phenyl)propanal (LXI). by Heck, hydrogenation reactions followed by selective reduction of ester by PDBBA complex

6.6.4.1 Procedure for the synthesis of (E)-ethyl 3-(3-(trifluoromethyl)phenyl)acrylate (LXXX)

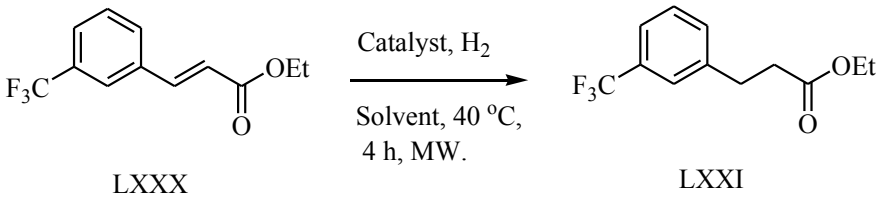


LXII LXIX LXXX

For example, here the procedure adopted for experiments of table 4.8.1, paragraph 4.8.1, of results and discussion.

In a dry 10 mL CEM Microwave process vial equipped with magnetic stirrer bar, under inert atmosphere, 2-methyl tetrahydrofuran (2 mL) was introduced; before addition of all reagents solvent was degassed by bubbling nitrogen. Then 3-bromobenzotrifluoride **(LXII)** (0.5 g, 2.22 mmol), ethylacrylate **(LXIX)** (0.333 g, 3.33 mmol), palladium(II) acetate (14.9 mg, 0.066 mmol) and tetra-butylammoniumacetate (1.35 g, 4.44 mmol) were added and the mixture containing vial was sealed tightly by using the CEM Discover pressure equipment and placed into the CEM Discover microwave unit; then reaction mixture was irradiate under MW by following MW method, Pressure-5 W, Ramp time- 5 min, Hold time- 20 min, Temperature- 90 °C, Pressure- 300 psi. After allowing the reaction mixture to cool down to room temperature the reaction mixture was analyzed by GC and GC-MS; 100 % conversion of substrate **(LXII)** into **(LXXX)** 100 % was obtained. The resulting reaction mixture was taken for hydrogenation by utilizing the same catalyst.

6.6.4.2 Procedure for the synthesis of 1-(3,3-diethoxypropyl)-3-(trifluoromethyl)benzene (LXXI)



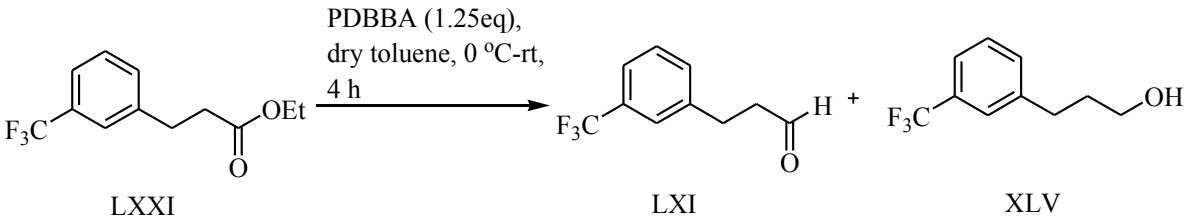
LXXX LXXI

For example, here it is reported an experiment discussed in paragraph 4.8.2, of results and discussion.

The reaction mixture was performed with CEM Discover single mode microwave reactor equipped with a 300 W power source. A 10 mL fiber optic accessory was equipped with a gas inlet to allow introduction of hydrogen to the reaction vessel.

The obtained above Heck reaction mixture (from 6.6.4.1) was introduced into A 10 mL fiber optic accessory containing compound **(LXXX)**, then the reaction vessel was purged three times with hydrogen, pressurized with 0.2 Mpa H_2 and then closed off to the source of hydrogen. The reaction was heated under microwave irradiation at 40 °C with 5 W power and held for 240 min. Upon cooling to room temperature the mixture was analyzed by GC and GC-MS: 100 % conversion of **(LXXX)** to **(LXXI)** was obtained. Then the catalyst was filtered off by using a sintered glass filter through diatomaceous earth to remove the spent catalyst. Then the residue was washed with diethyl ether (15 mL) and the resulting filtrate evaporated under reduced pressure to afford **(LXXI)** as a yellowish liquid, with quantitative yield.

6.6.4.3 Procedure for the synthesis of 3-(3-(trifluoromethyl)phenyl)propanal (LXI) by reduction with potassium diisobutyl-t-butoxyaluminum hydride (PDBBA)



LXXI LXI XLV

For example, here the procedure adopted for experiments of table 4.8.3, paragraph 4.8.3, of results and discussion.

In a thoroughly oven dried 10 mL single neck round bottom flask, equipped with septum, under inert atmosphere, ethyl 3-(3-(trifluoromethyl)phenyl)propanoate **(LXXI)** (0.125 g, 0.5 mmol) in anhydrous toluene (5 mL) was introduced. This reaction mixture was cooled to 0 °C then a solution of PDBBA (potassium diisobutyl-t-butoxyaluminum hydride) (1.3 mL, 0.5 M in THF: hexane) was added dropwise with a syringe; after the addition, temperature raised to room temperature and the resulting mixture was stirred for 4h. The reaction mixture was analyzed by GC and GC-MS: 97 % conversion of **(LXXI)** to **(XLI)** and 3 % of **(XLV)** alcohol was obtained**.** The resulting reaction mixture was hydrolyzed by adding 1M HCl (5 mL) to pH = 1-2 and the product extracted in diethyl ether (10 mL x 2); then the organic layer was washed with water and brine and the organic phase was separated and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get product **(LXI)** (98 mg, 96 % yield).

6.7 List of Abbreviations

APIs	Active Pharmaceutical Ingredients
ATR-FTIR	Attenuated Total Reflectance-Fourier transform Infrared
ACN	Acetonitrile
CPME	Cyclopentylmethylether
DIBAL-H	Diisobutylaluminum hydride
DMF	N,N-dimethylformamide
DCHMA	Dicyclohexylmethylamine
DCM	Dichloromethane
DHTANa	Dihydrothioctic acid sodium salt
DBU	1,8-Diazabicycloundec-7-ene
Et_3N	Triethylamine
EtOH	Ethanol
FDA	Food and drug administrative
FPP	Finished pharmaceutical product
IARC	International Agency for Research on Cancer
IND	Investigational new drug
NDA	New drug application
LAH	Lithium aluminium hydride
LDBBA	Lithium diisobutyl-t-butoxyaluminum hydride
MW	Microwave

MSDS	Material safety data sheet
2-MeTHF	2-Methyltetrahydrfuran
NMR	Nuclear Magnetic Resonance
PDBBA	Potassium diisobutyl-t-butoxyaluminum hydride
PFSA	PerFluoroSulfonic Acid
PTH	Parathyroid hormone
SPC	Supplementary protection certificate
SDBBA	Sodium diisobutyl-t-butoxyaluminum hydride
TBAB	Tetrabutylammonium bromide
TBAA	Tetrabutylammonium acetate
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxi free radical
THF	Tetrahydrofuran
TG-DSC	Thermo gravimetric-Differential Scanning Calorimetry
TMS-Cl	Trimethylsilyl chloride
WHO	World health organization

6.8. Roman Numbers - chemical names

I	5-Bromo-1H-indole
II	Acetic anhydride or acetyl chloride
III	3-Acyl-5-bromo-1H-indole
IV	1,3-Diacyl-5-bromo-indole
V	1-Acyl-5-bromo-indole
VI	Cyclohex-2-en-1-one
VII	Cyclohexanone
VIII	Cyclohexanol
IX	Cyclohex-2-enol
X	(E)-4-phenylbut-3-en-2-one
XI	4-Phenylbutan-2-one
XII	4-Phenylbutan-2-ol
XIII	(E)-4-(2-methoxynaphthalen-6-yl)but-3-en-2-one
XIV	4-(2-Methoxynaphthalen-6-yl)butan-2-one
XV	4-(2-Methoxynaphthalen-6-yl)butan-2-ol
XVI	Cinnamaldehyde
XVII	3-Phenylpropionaldehyde
XVIII	3-Phenylpropan-1-ol
XIX	(E)-3-(benzo[d][1,3]dioxol-6-yl)-2-methylacrylaldehyde
XX	2-Methyl-3-(3,4-methylenedioxyphenyl)propanol

XXI 3-(Benzo[d][1,3]dioxol-6-yl)-2-methylpropan-1-ol

XXII Nitrobenzene

XXIII Aniline

XXIV 1-Nitrosobenzene

XXV 1,2-Diphenyldiazene

XXVI 1,2-Diphenyldiazene-N-oxide

XXVII 1-Iodo-4-nitrobenzene

XXVIII 4-Iodobenzenamine

XXIX 1-Chloro-3-nitrobenzene

XXX 3-Chlorobenzenamine

XXXI 1-Chloro-3-nitrosobenzene

XXXII 1,2-bis(3-Chlorophenyl)diazene

XXXIII 1,2-bis(3-Chlorophenyl)diazene-N-oxide

XXXIV Phenyl vinyl sulfone

XXXV 5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole

XXXVI Indole

XXXVII 5-(2-(Phenylsulfonyl)ethyl)-1H-indole

XXXVIII (R)-1-methylpyrrolidine-2-carbonyl chloride

XXXIX ((S)-1-methylpyrrolidin-2-yl)(5-(2-(phenylsulfonyl)ethyl)-1H-indol-3-yl)methanone

XL 3-(((R)-1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)ethyl)-1H-indole

XLI 3-(((R)-1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)ethyl)-1H-indole hydrobromide

XLII (R)-pyrrolidine-2-carboxylic acid.

XLIII Benzyl chloroformate

XLIV (R)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid

XLV (R)-benzyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate

XLVI Eletriptan step-3 Ketone

XLVII 5-Bromo-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole

XLVIII 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole

XLIX (5-Bbromo-1H-indol-3-yl)((S)-1-methylpyrrolidin-2-yl)methanone

L (S)-(5-bromo-1H-indol-3-yl)((S)-1-methylpyrrolidin-2-yl)methanol

LI 3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole

LII 5-Ethyl-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole

LIII 1-(Naphthalen-5-yl)ethanone

LIV 3-(3-(Trifluoromethyl)phenyl)propan-1-amine

LV (E)-3-(3-(trifluoromethyl)phenyl)-N-(1-(naphthalen-5-yl)ethylidene)propan-1-amine

LVI 3-(3-(Trifluoromethyl)phenyl)-N-(1-(naphthalen-5-yl)ethyl)propan-1-amine

LVII 3-(3-(Trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-5-yl)ethyl)propan-1-amine

LVIII tert-butanesulfinamides

LX (R)-1-(naphthalen-1-yl)ethanamine hydrochloride

LXI 3-(3-(Trifluoromethyl)phenyl)propanal

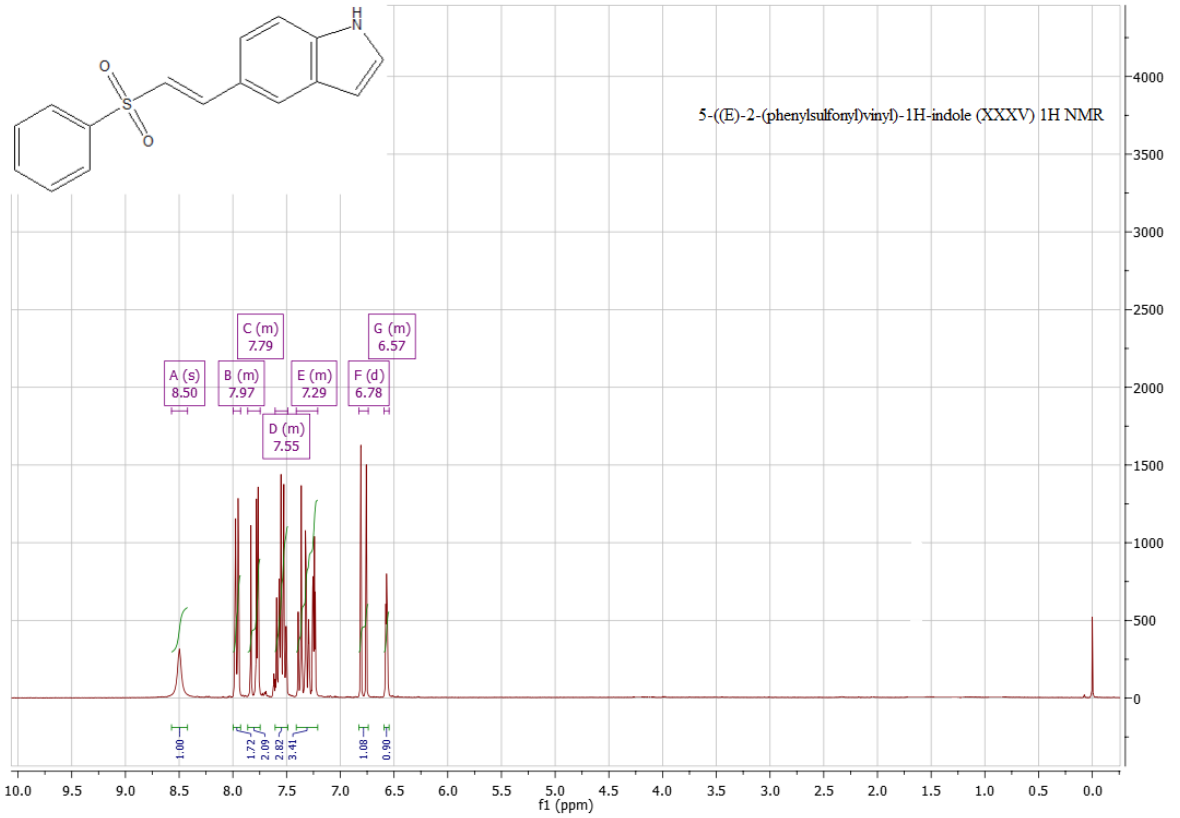
LXII 1-Bromo-3-(trifluoromethyl)benzene

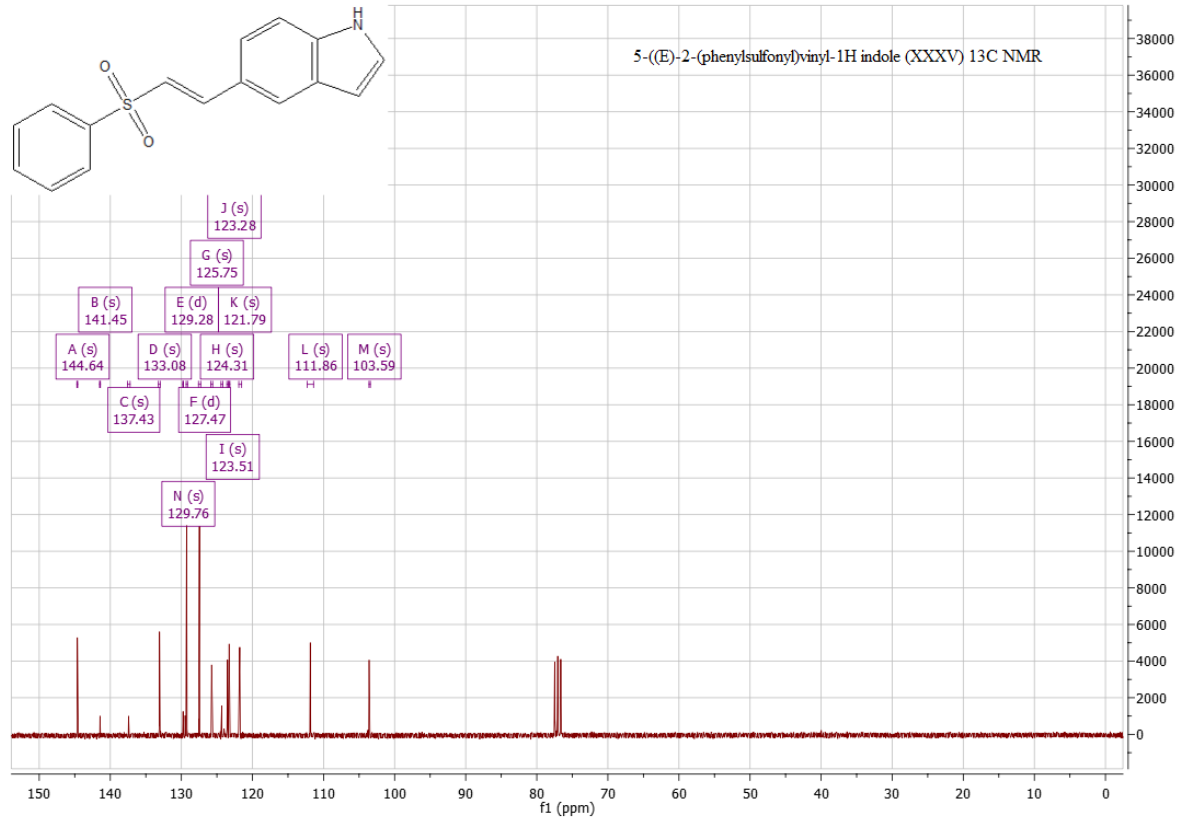
LXIII Prop-2-yn-1-ol

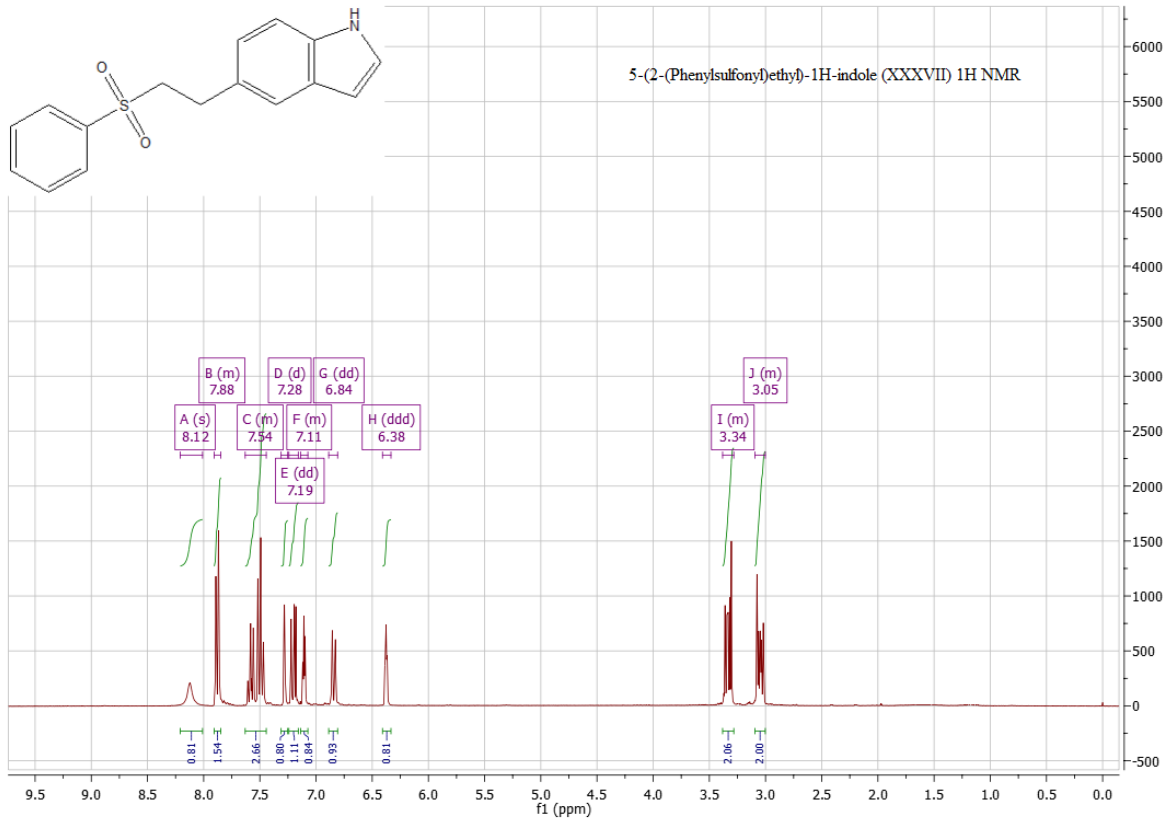
LXIV	3-(3-(Trifluoromethyl)phenyl)prop-2-yn-1-ol
LXV	3-(3-(Trifluoromethyl)phenyl)propan-1-ol
LXVI	(E)-3-(3-(trifluoromethyl)phenyl)acrylic acid
LXVII	3-(3-(Trifluoromethyl)phenyl)propanenitrile
LXVIII	3-(3-(Trifluoromethyl)phenyl)propanenitrile Imine complex
LXIX	Acroline diethyl acetal
LXX	1-((E)-3,3-diethoxyprop-1-enyl)-3-(trifluoromethyl)benzene
LXXI	Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate
LXXII	(E)-3-(3-(trifluoromethyl)phenyl)acrylaldehyde
LXXIII	(E)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol
LXXIV	(E)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol halide derivative
LXXV	3-(3-(Trifluoromethyl)phenyl)-N-((S)-1-(naphthalen-1-yl)ethyl)propan-1-amine hydrochloride
LXXVI	1-(3,3-Diethoxypropyl)-3-(trifluoromethyl)benzene
LXXVII	Sodium 3-(3-(trifluoromethyl)phenyl)-1-hydroxypropane-1-sulfonate
LXXVIII	Palladium complex intermediate
LXXIX	1-(3,3-Diethoxyallyl)-3-(trifluoromethyl)benzene
LXXX	(E)-ethyl 3-(3-(trifluoromethyl)phenyl)acrylate

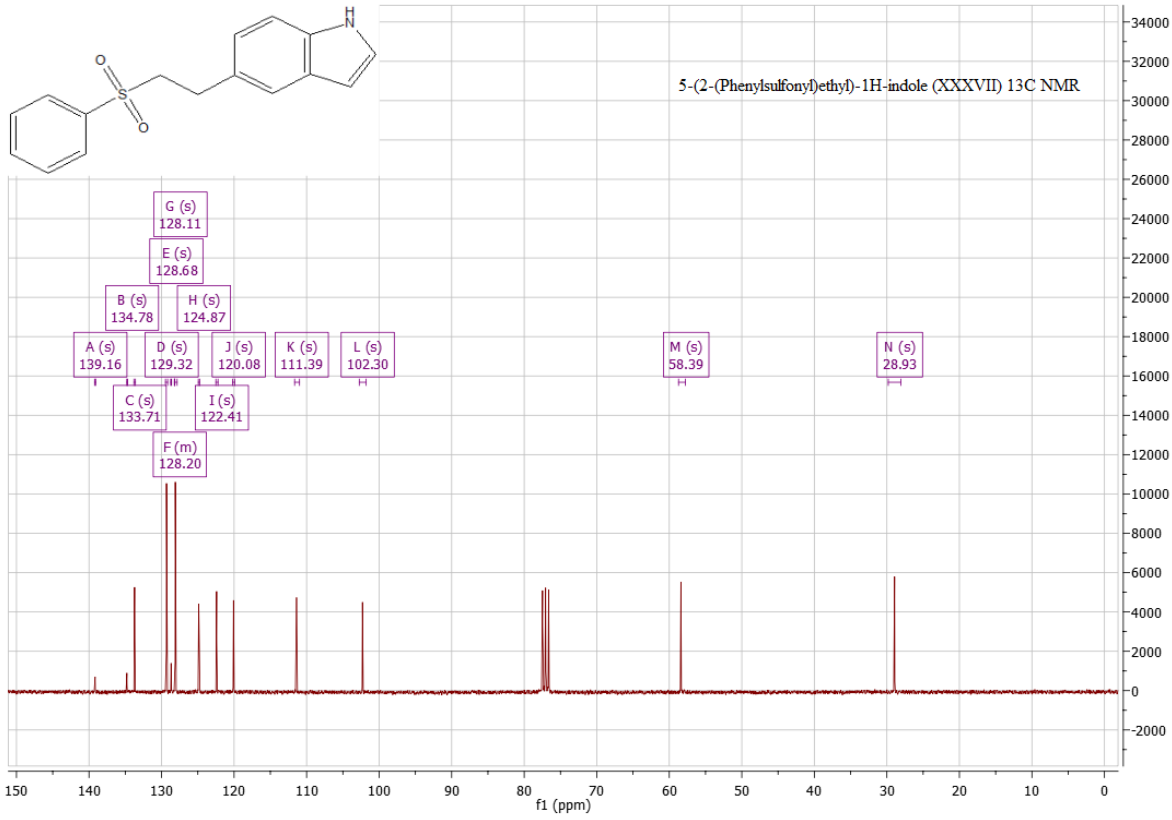
6.9 Appendix

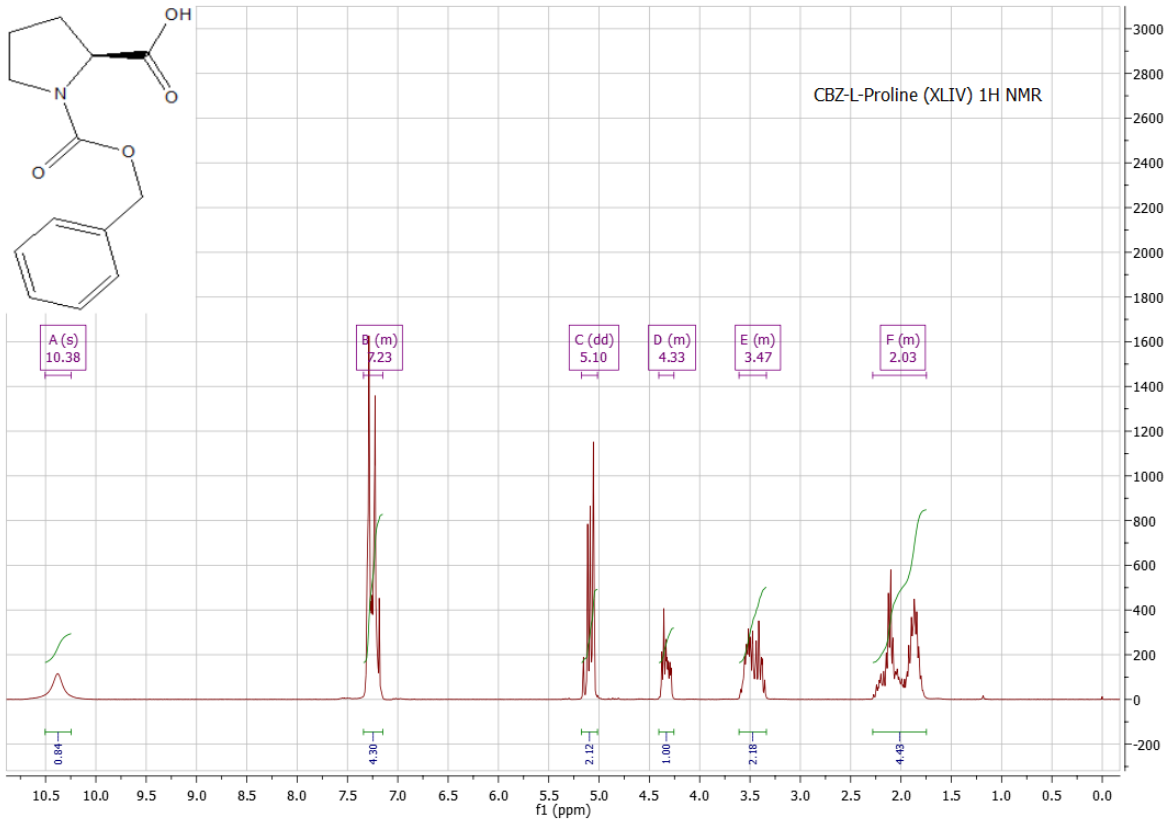
6.9.1 ^{1}H-NMR and ^{13}C-NMR Spectra of Eletriptan

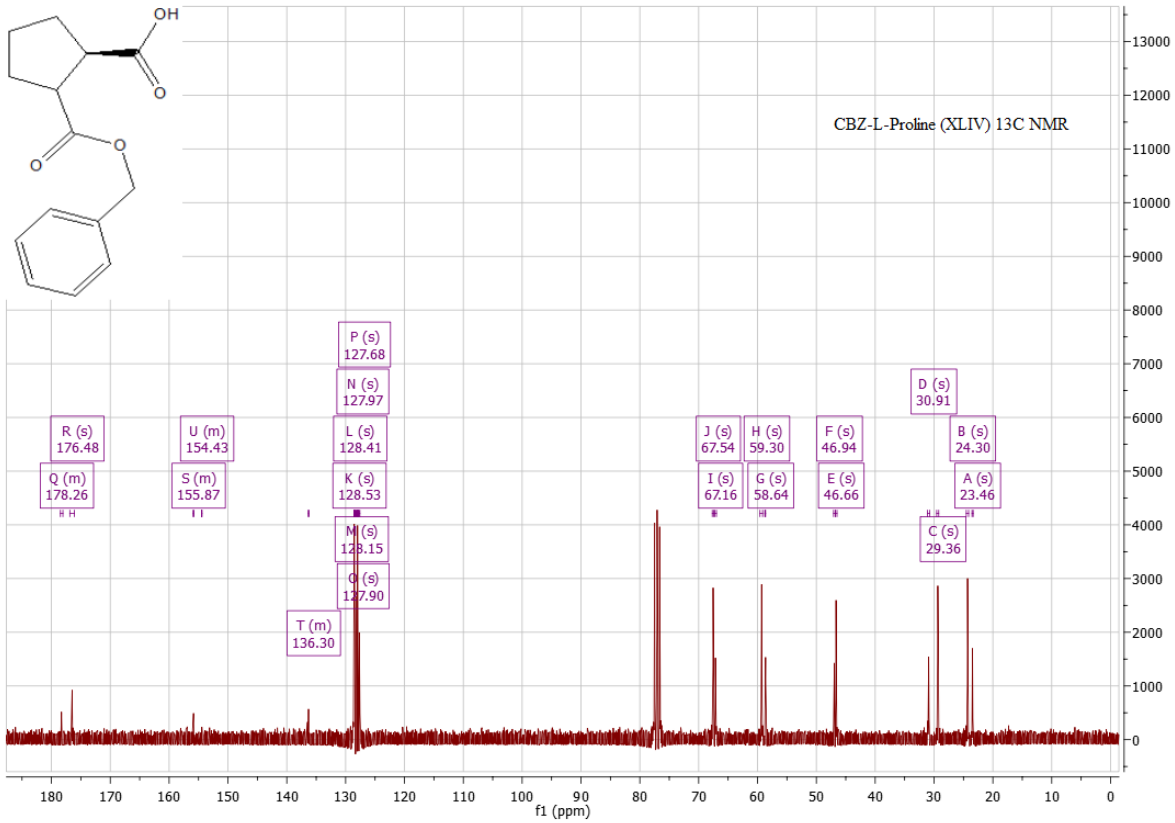


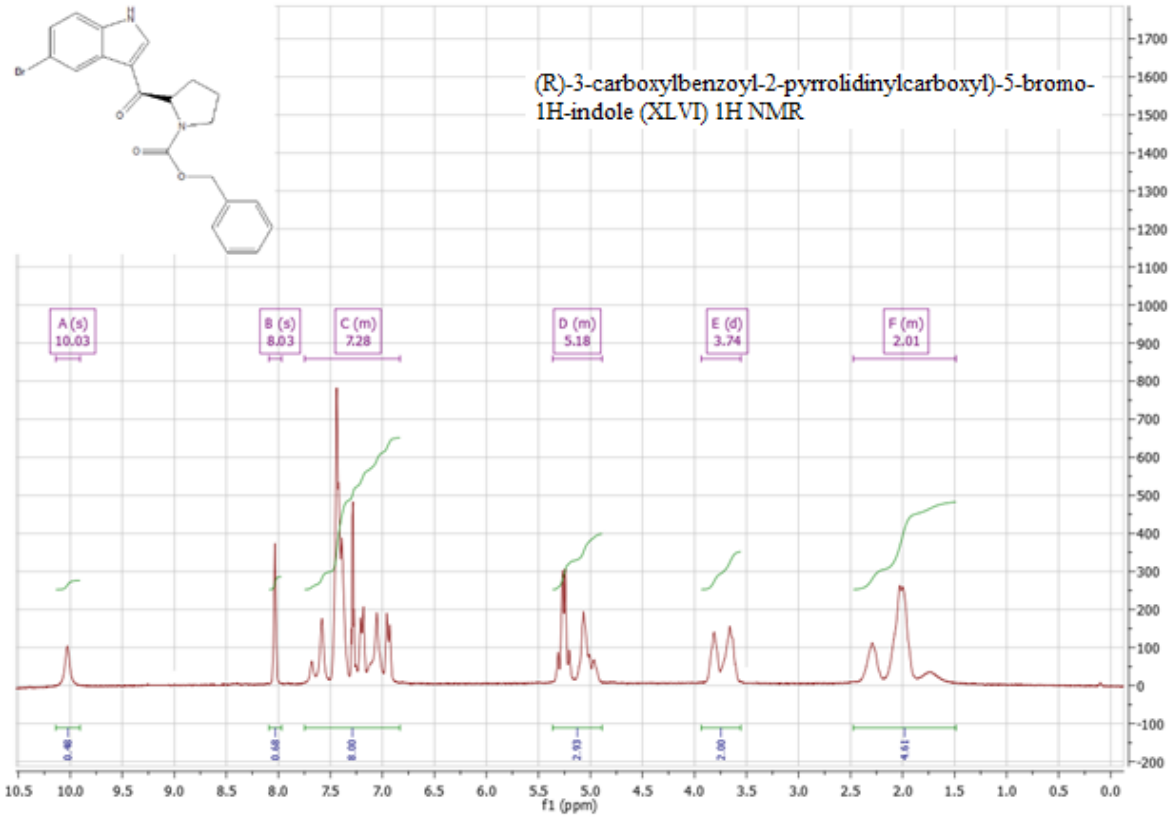


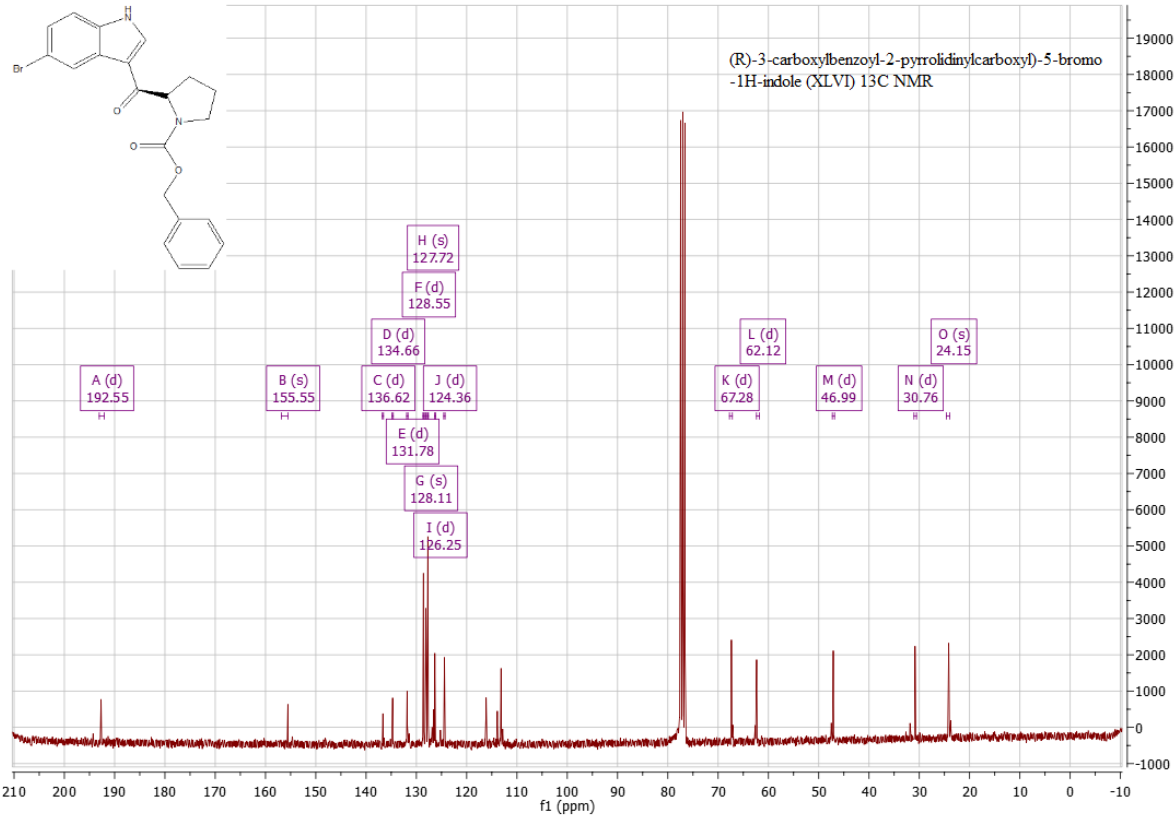

5-(2-(Phenylsulfonyl)ethyl)-1H-indole (XXXVII) 1H NMR
B (m) 7.88
D (d) 7.28
G (dd) 6.84
J (m) 3.05
A (s) 8.12
C (m) 7.54
F (m) 7.11
H (ddd) 6.38
I (m) 3.34
E (dd) 7.19
f1 (ppm)

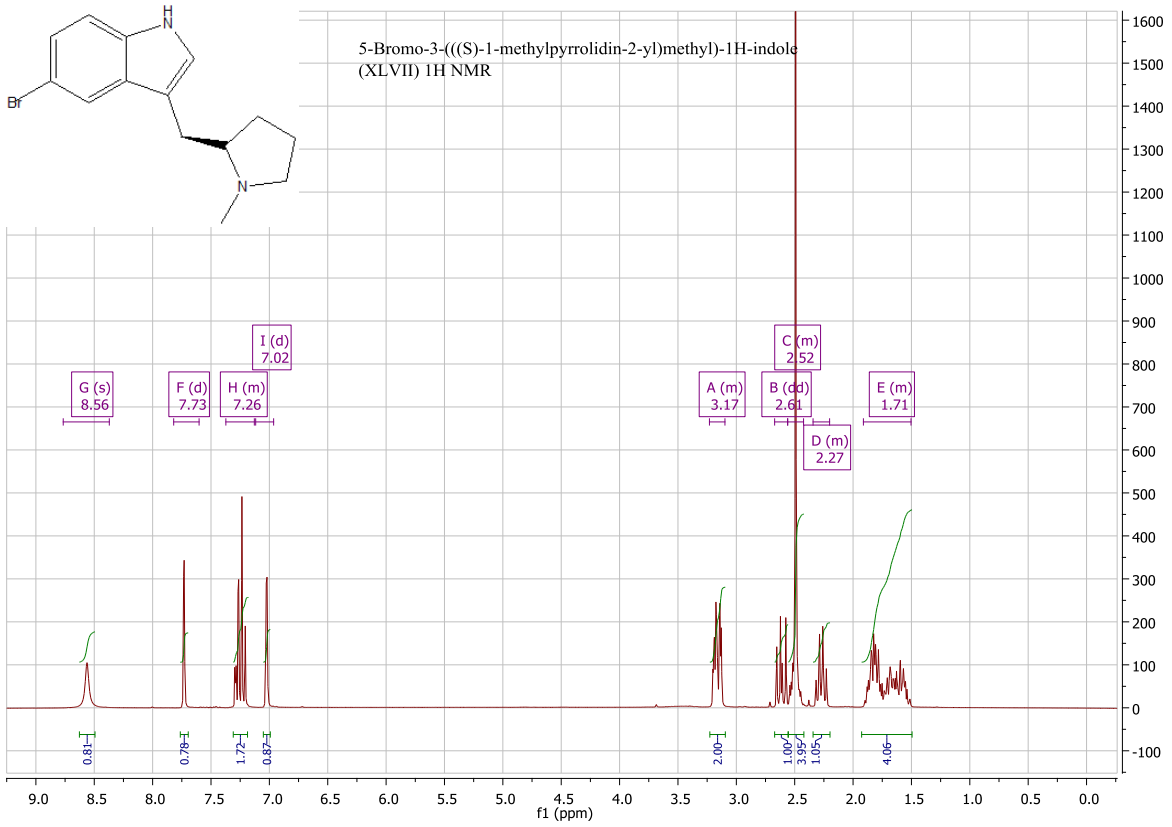

5-(2-(Phenylsulfonyl)ethyl)-1H-indole (XXXVII) 13C NMR
G (s) 128.11
E (s) 128.68
B (s) 134.78
H (s) 124.87
A (s) 139.16
D (s) 129.32
J (s) 120.08
K (s) 111.39
L (s) 102.30
M (s) 58.39
N (s) 28.93
C (s) 133.71
I (s) 122.41
F (m) 128.20
f1 (ppm)

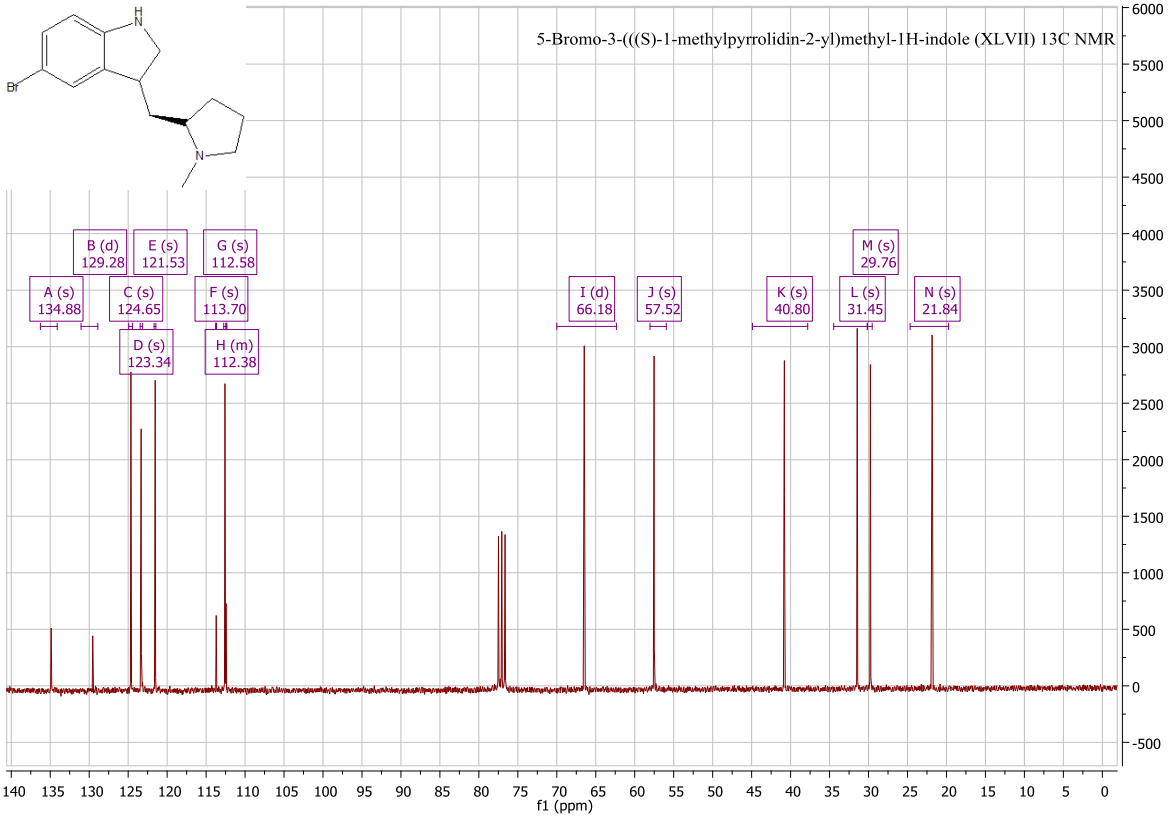

CBZ-L-Proline (XLIV) 1H NMR
OH
N
O
O
O
A (s)
10.38
B (m)
7.23
C (dd)
5.10
D (m)
4.33
E (m)
3.47
F (m)
2.03
0.84
4.30
2.12
1.00
2.18
4.43
f1 (ppm)

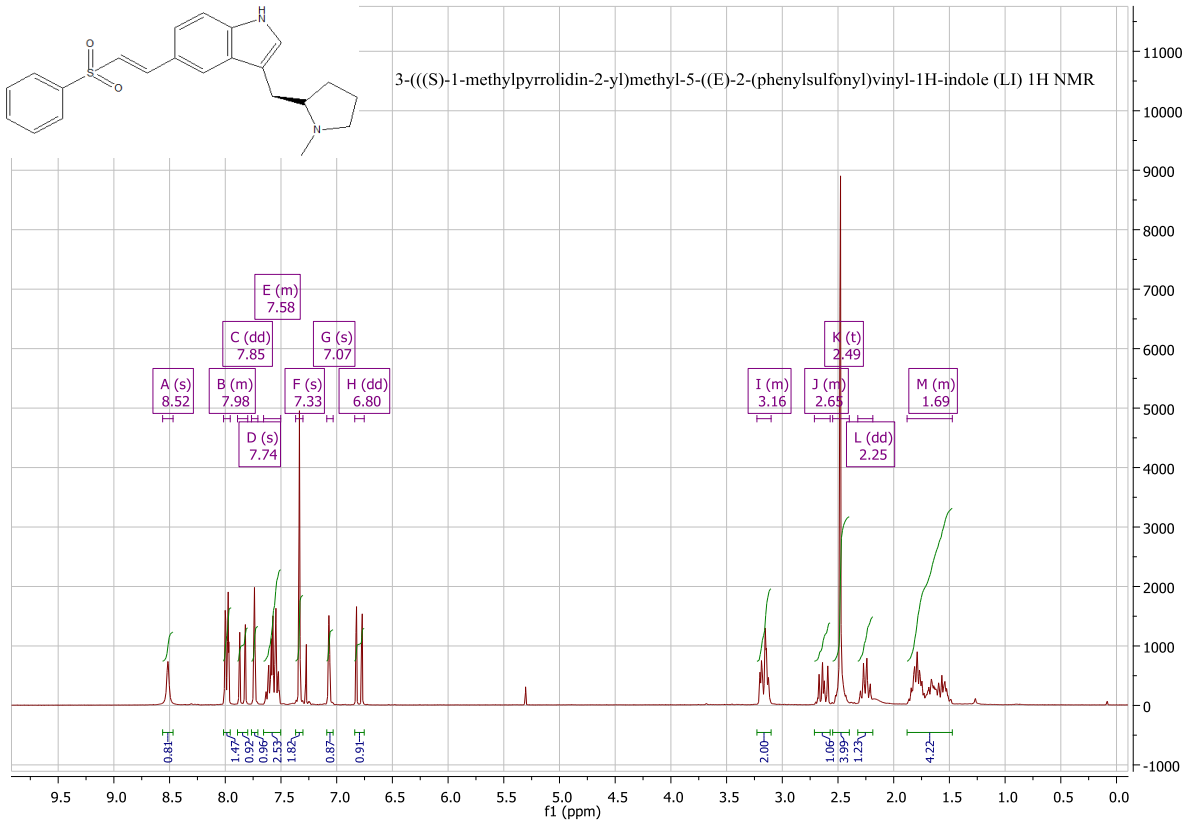

CBZ-L-Proline (XLIV) 13C NMR
OH
O
O
O
P (s)
127.68
N (s)
127.97
R (s)
176.48
U (m)
154.43
L (s)
128.41
J (s)
67.54
H (s)
59.30
F (s)
46.94
D (s)
30.91
B (s)
24.30
Q (m)
178.26
S (m)
155.87
K (s)
128.53
I (s)
67.16
G (s)
58.64
E (s)
46.66
A (s)
23.46
M (s)
128.15
C (s)
29.36
O (s)
127.90
T (m)
136.30
f1 (ppm)

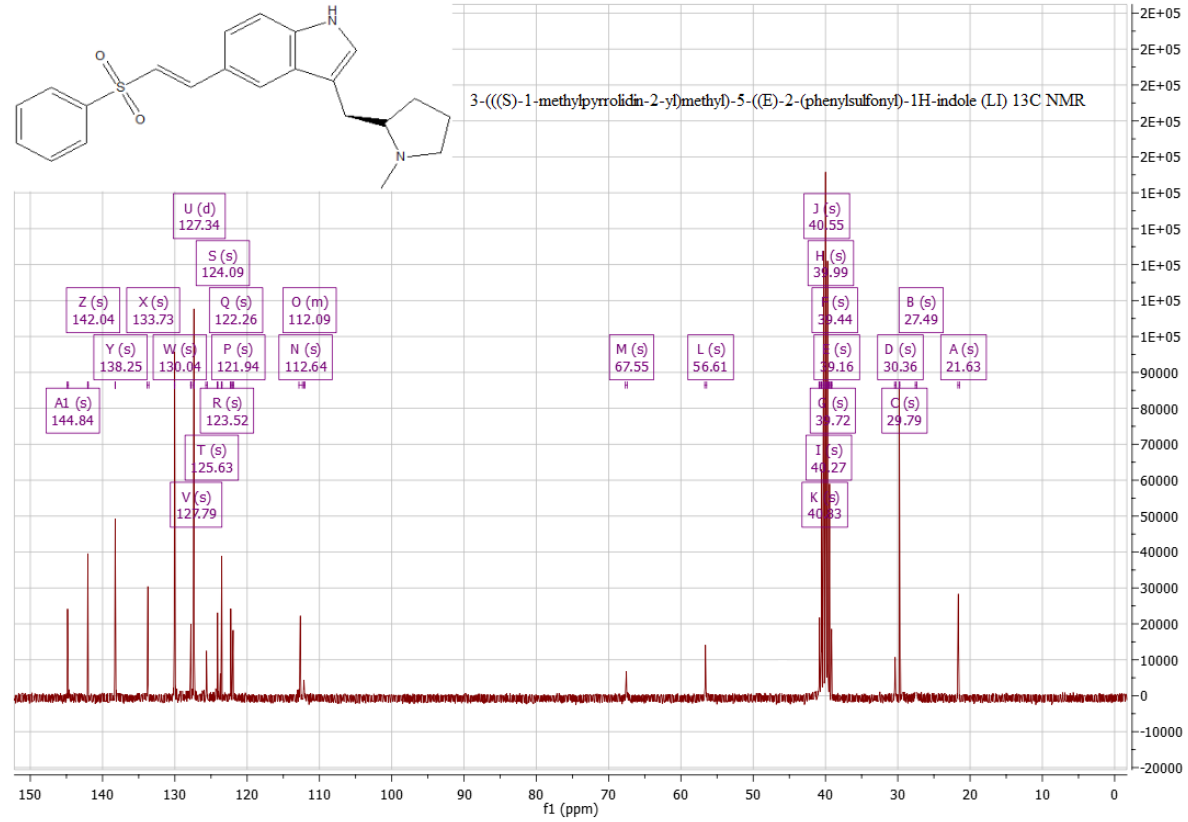

(R)-3-carboxylbenzoyl-2-pyrrolidinylcarboxyl)-5-bromo-1H-indole (XLVI) 1H NMR
A (s) 10.03
B (s) 8.03
C (m) 7.28
D (m) 5.18
E (d) 3.74
F (m) 2.01
f1 (ppm)

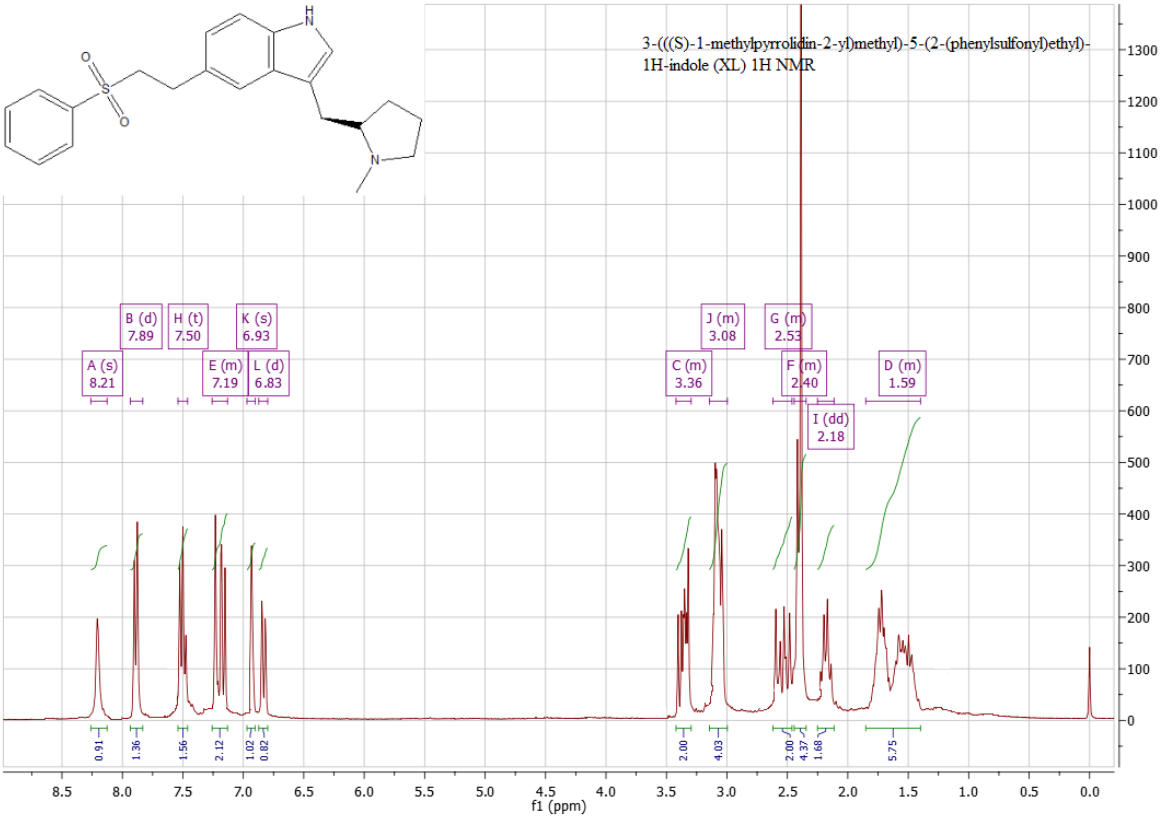

(R)-3-carboxylbenzoyl-2-pyrrolidinylcarboxyl)-5-bromo-1H-indole (XLVI) 13C NMR
A (d) 192.55
B (s) 155.55
C (d) 136.62
D (d) 134.66
E (d) 131.78
F (d) 128.55
G (s) 128.11
H (s) 127.72
I (d) 126.25
J (d) 124.36
K (d) 67.28
L (d) 62.12
M (d) 46.99
N (d) 30.76
O (s) 24.15
f1 (ppm)


5-Bromo-3-(((S)-1-methylpyrrolidin-2-yl)methyl)-1H-indole
(XLVII) 1H NMR
Br
H
N
N
G (s) 8.56
F (d) 7.73
H (m) 7.26
I (d) 7.02
A (m) 3.17
B (dd) 2.61
C (m) 2.52
D (m) 2.27
E (m) 1.71
0.81
0.78
1.72
0.87
2.00
1.00
3.95
1.05
4.06
f1 (ppm)

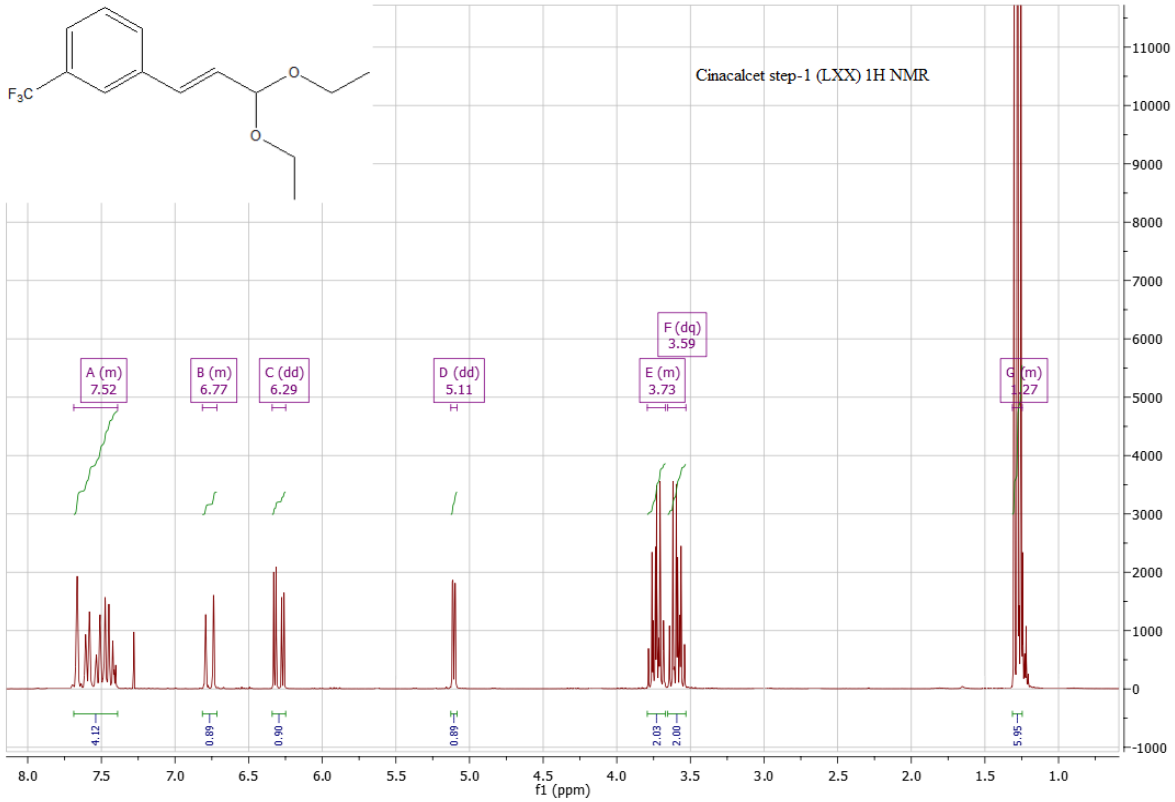

5-Bromo-3-(((S)-1-methylpyrrolidin-2-yl)methyl-1H-indole (XLVII) 13C NMR
Br
H
N
N
A (s) 134.88
B (d) 129.28
C (s) 124.65
D (s) 123.34
E (s) 121.53
F (s) 113.70
G (s) 112.58
H (m) 112.38
I (d) 66.18
J (s) 57.52
K (s) 40.80
L (s) 31.45
M (s) 29.76
N (s) 21.84
f1 (ppm)

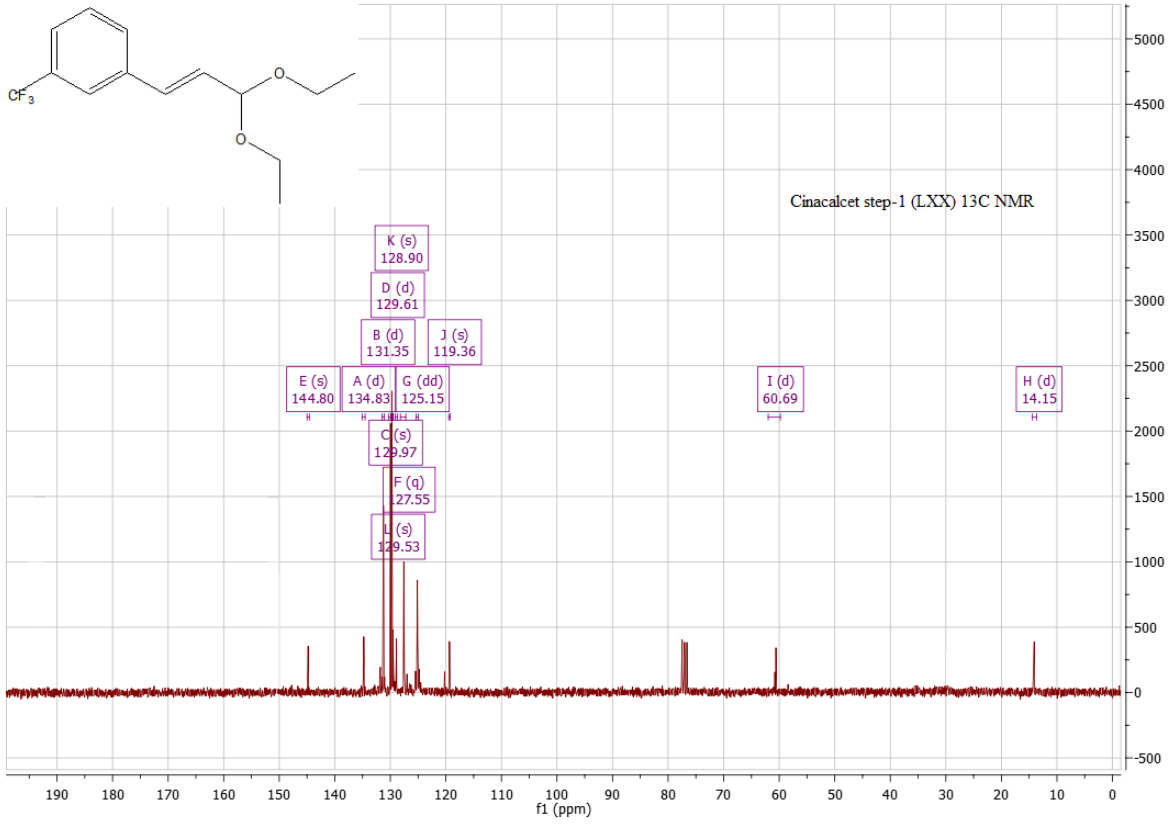

3-(((S)-1-methylpyrrolidin-2-yl)methyl-5-((E)-2-(phenylsulfonyl)vinyl-1H-indole (LI) 1H NMR
A (s) 8.52
B (m) 7.98
C (dd) 7.85
D (s) 7.74
E (m) 7.58
F (s) 7.33
G (s) 7.07
H (dd) 6.80
I (m) 3.16
J (m) 2.65
K (t) 2.49
L (dd) 2.25
M (m) 1.69
f1 (ppm)

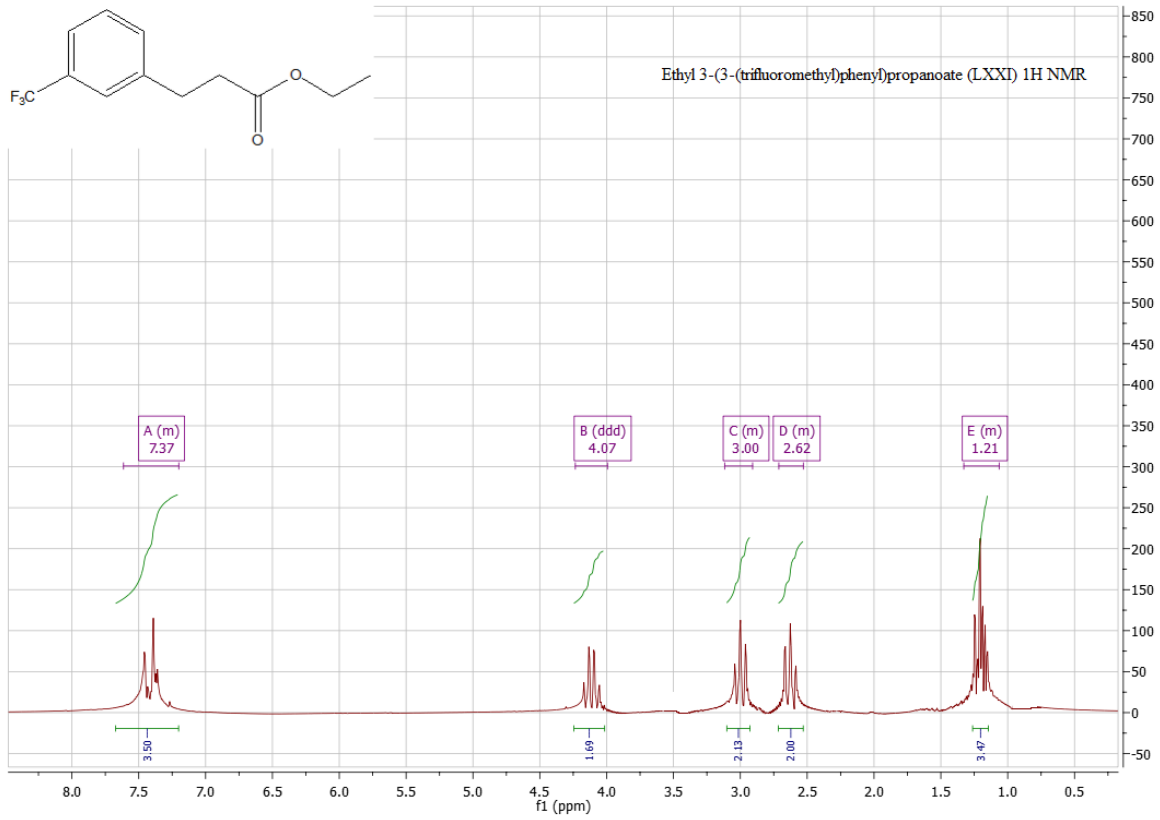

3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-((E)-2-(phenylsulfonyl)-1H-indole (LI) 13C NMR
A (s) 21.63
A1 (s) 144.84
B (s) 27.49
C (s) 29.79
D (s) 30.36
L (s) 56.61
M (s) 67.55
N (s) 112.64
O (m) 112.09
P (s) 121.94
Q (s) 122.26
R (s) 123.52
S (s) 124.09
T (s) 125.63
U (d) 127.34
V (s) 127.79
W (s) 130.04
X (s) 133.73
Y (s) 138.25
Z (s) 142.04
J (s) 40.55
f1 (ppm)

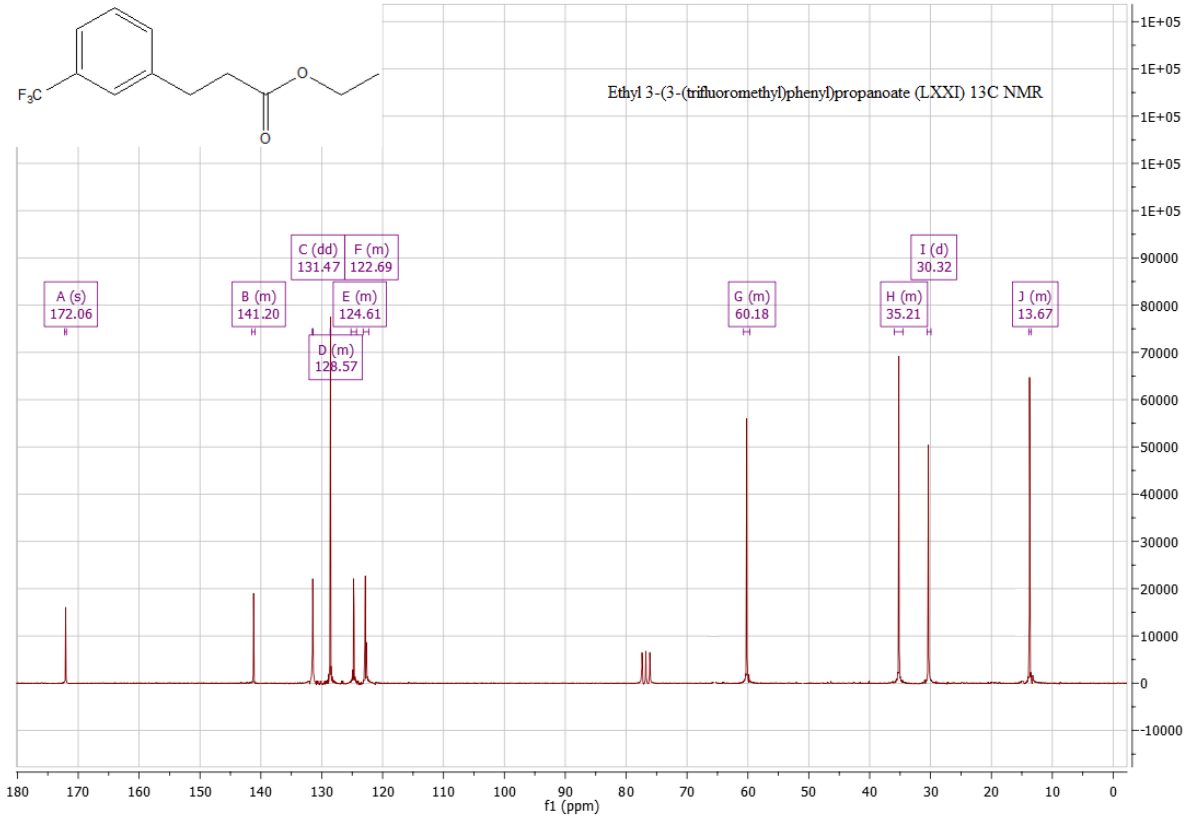

3-(((S)-1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)ethyl)-1H-indole (XL) 1H NMR
A (s) 8.21
B (d) 7.89
H (t) 7.50
E (m) 7.19
K (s) 6.93
L (d) 6.83
C (m) 3.36
J (m) 3.08
G (m) 2.53
F (m) 2.40
I (dd) 2.18
D (m) 1.59
0.91
1.36
1.56
2.12
1.02
0.82
2.00
4.03
2.00
4.37
1.68
5.75
f1 (ppm)

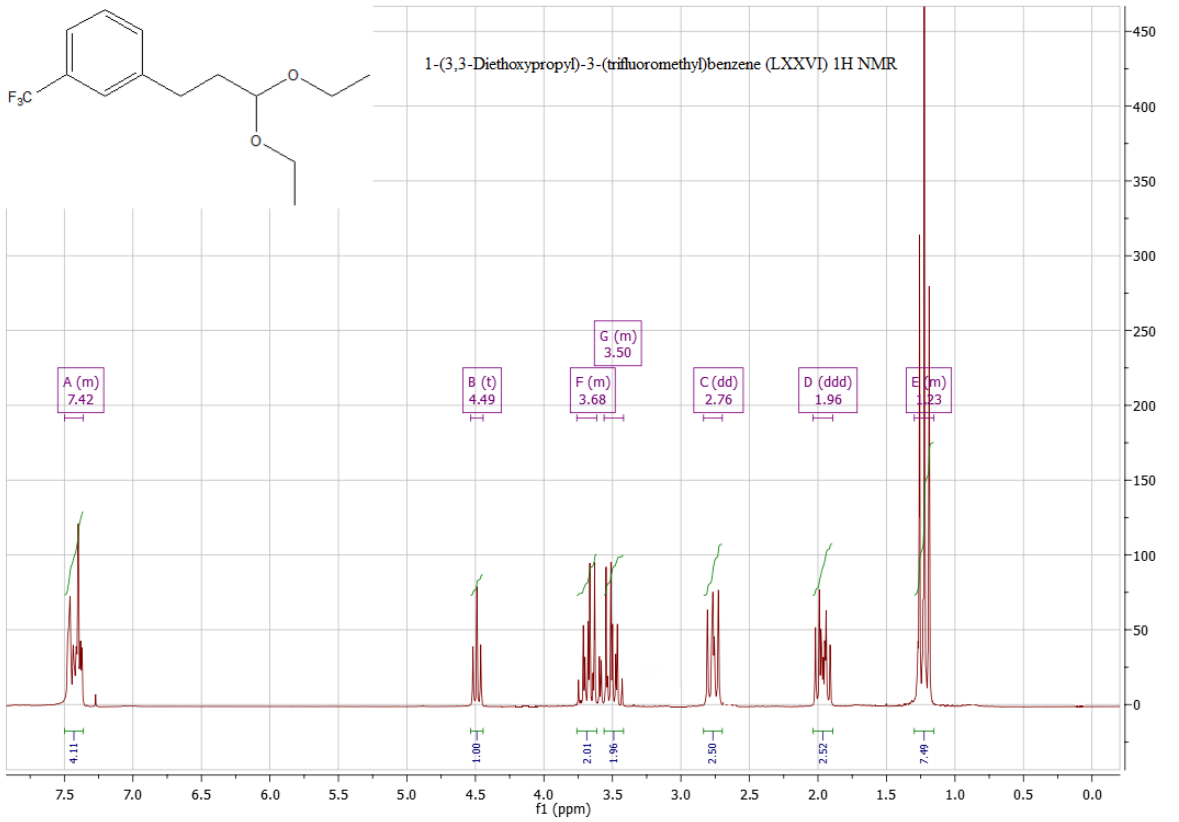
6.9.2 [1]H-NMR and [13]C-NMR spectra of Cinacalcet

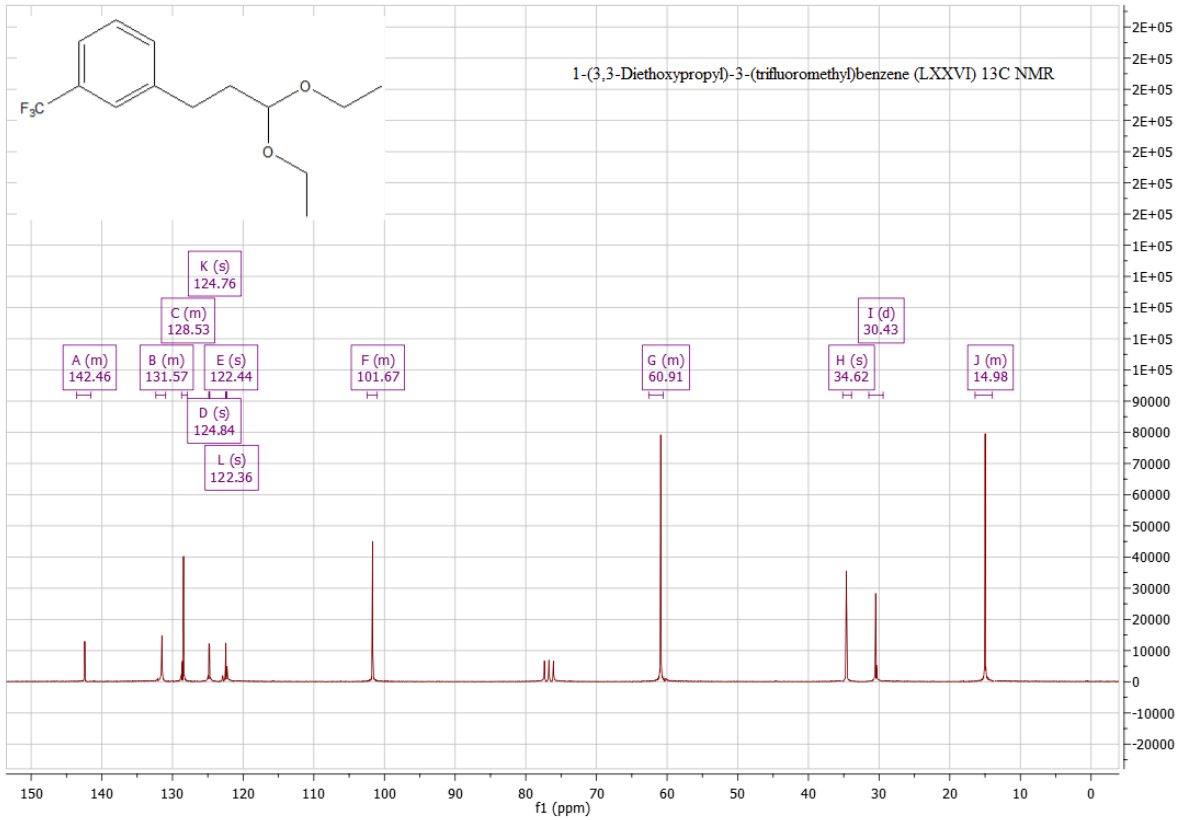


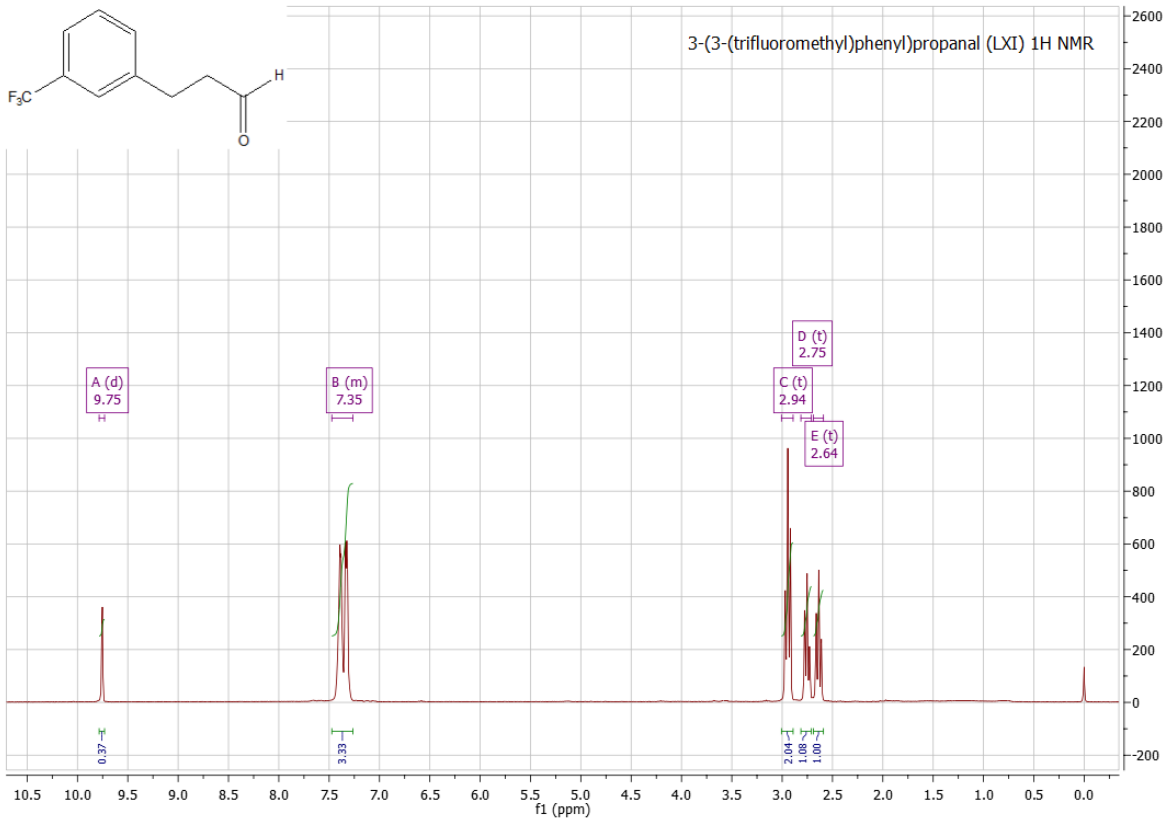


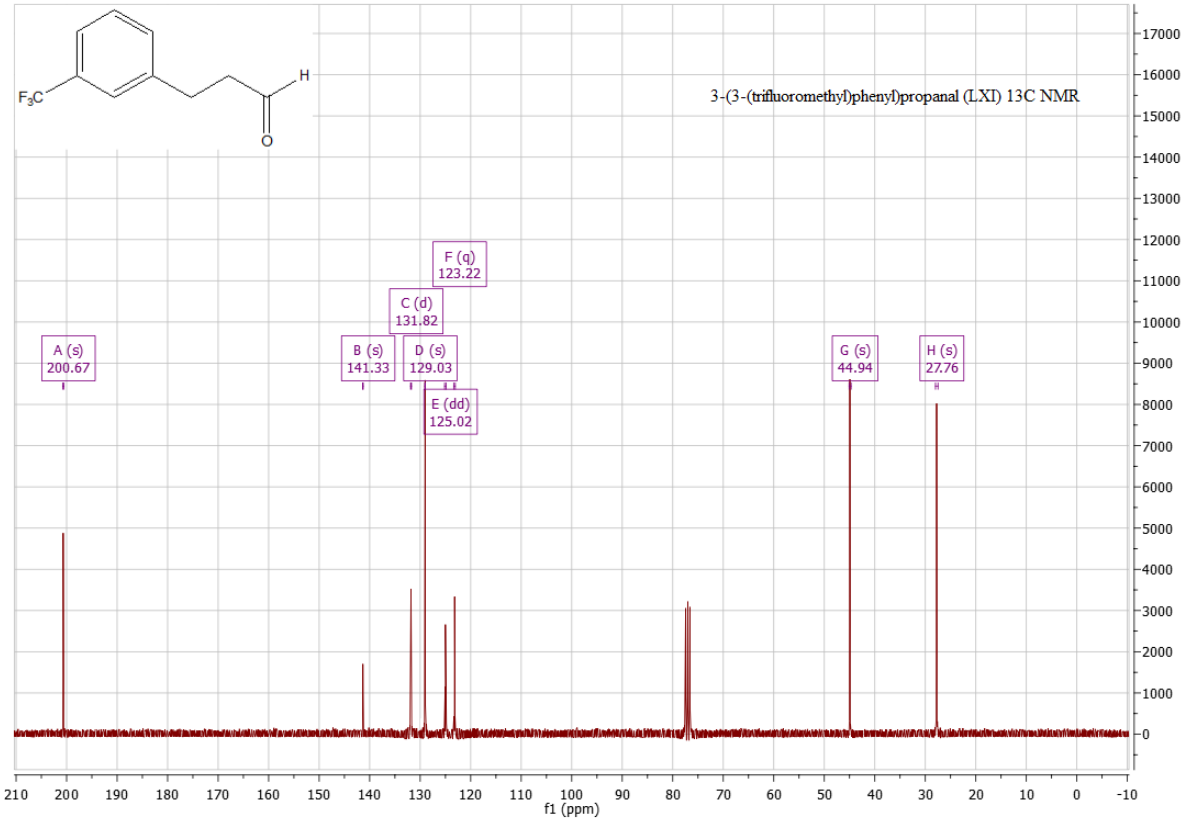

Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate (LXXI) 1H NMR
A (m) 7.37
B (ddd) 4.07
C (m) 3.00
D (m) 2.62
E (m) 1.21
3.50
1.69
2.13
2.00
3.47
f1 (ppm)

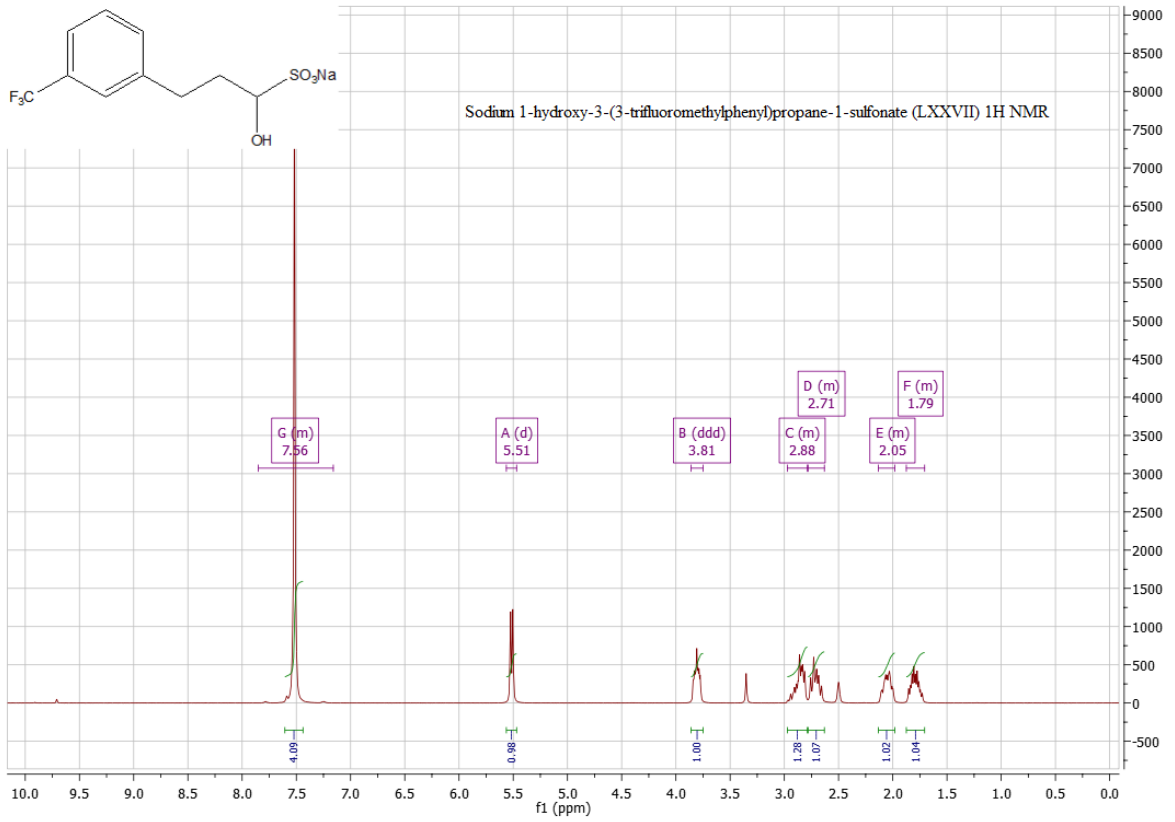

Ethyl 3-(3-(trifluoromethyl)phenyl)propanoate (LXXI) 13C NMR
A (s) 172.06
B (m) 141.20
C (dd) 131.47
F (m) 122.69
E (m) 124.61
D (m) 128.57
G (m) 60.18
I (d) 30.32
H (m) 35.21
J (m) 13.67
f1 (ppm)

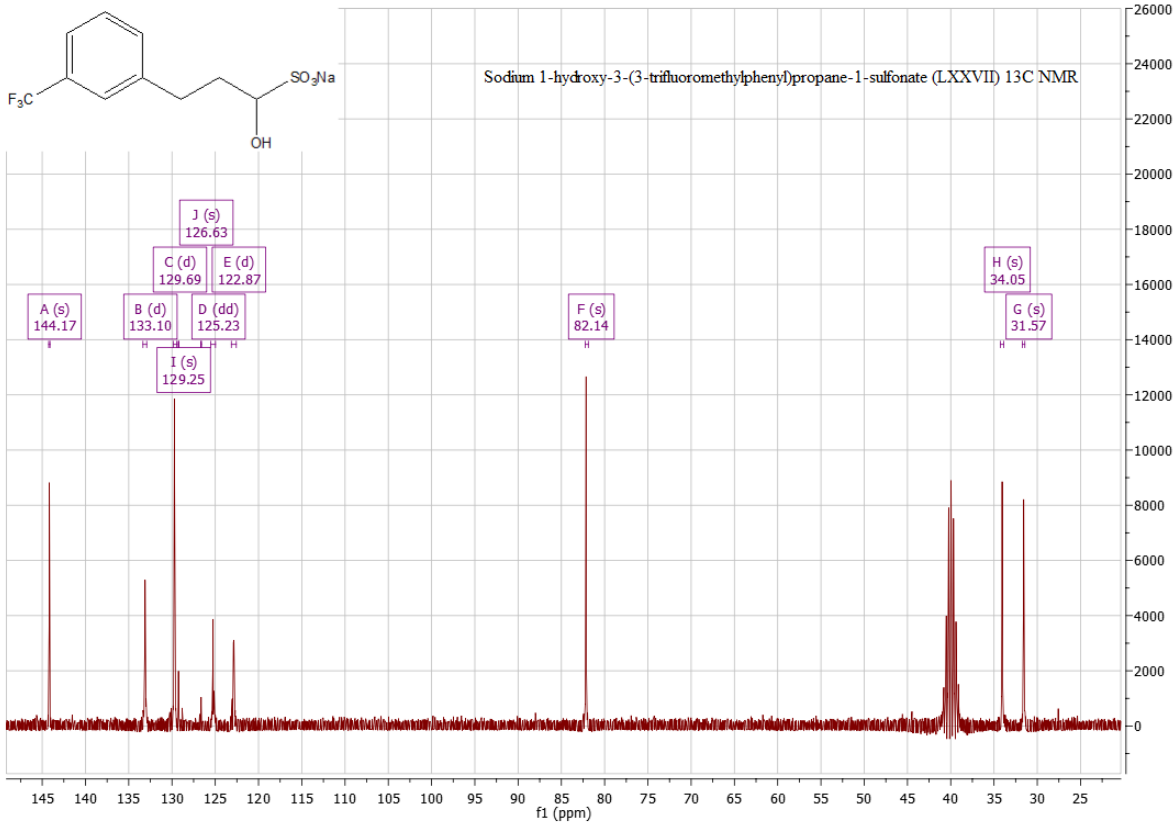

1-(3,3-Diethoxypropyl)-3-(trifluoromethyl)benzene (LXXVI) 1H NMR
F3C
O
O
A (m) 7.42
B (t) 4.49
F (m) 3.68
G (m) 3.50
C (dd) 2.76
D (ddd) 1.96
E (m) 1.23
4.11
1.00
2.01
1.96
2.50
2.52
7.49
f1 (ppm)

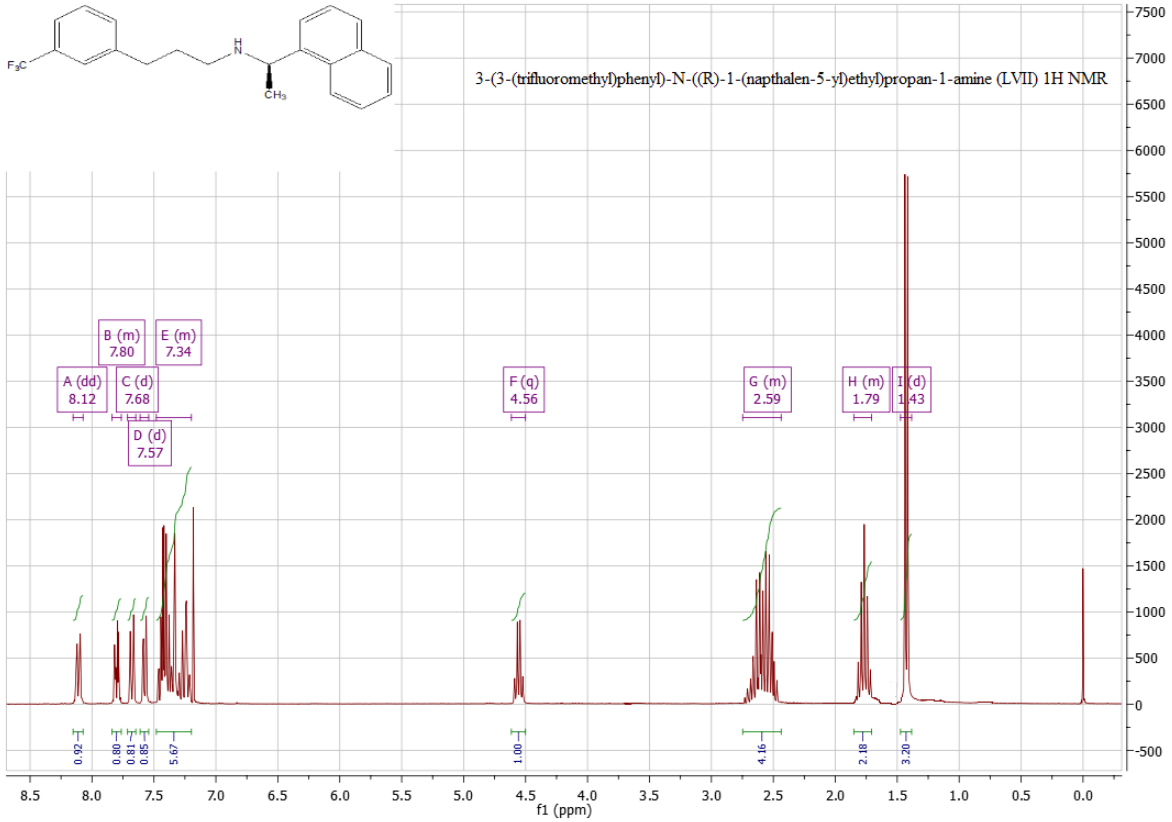

1-(3,3-Diethoxypropyl)-3-(trifluoromethyl)benzene (LXXVI) 13C NMR
F3C
O
O
K (s) 124.76
C (m) 128.53
A (m) 142.46
B (m) 131.57
E (s) 122.44
D (s) 124.84
L (s) 122.36
F (m) 101.67
G (m) 60.91
I (d) 30.43
H (s) 34.62
J (m) 14.98
f1 (ppm)

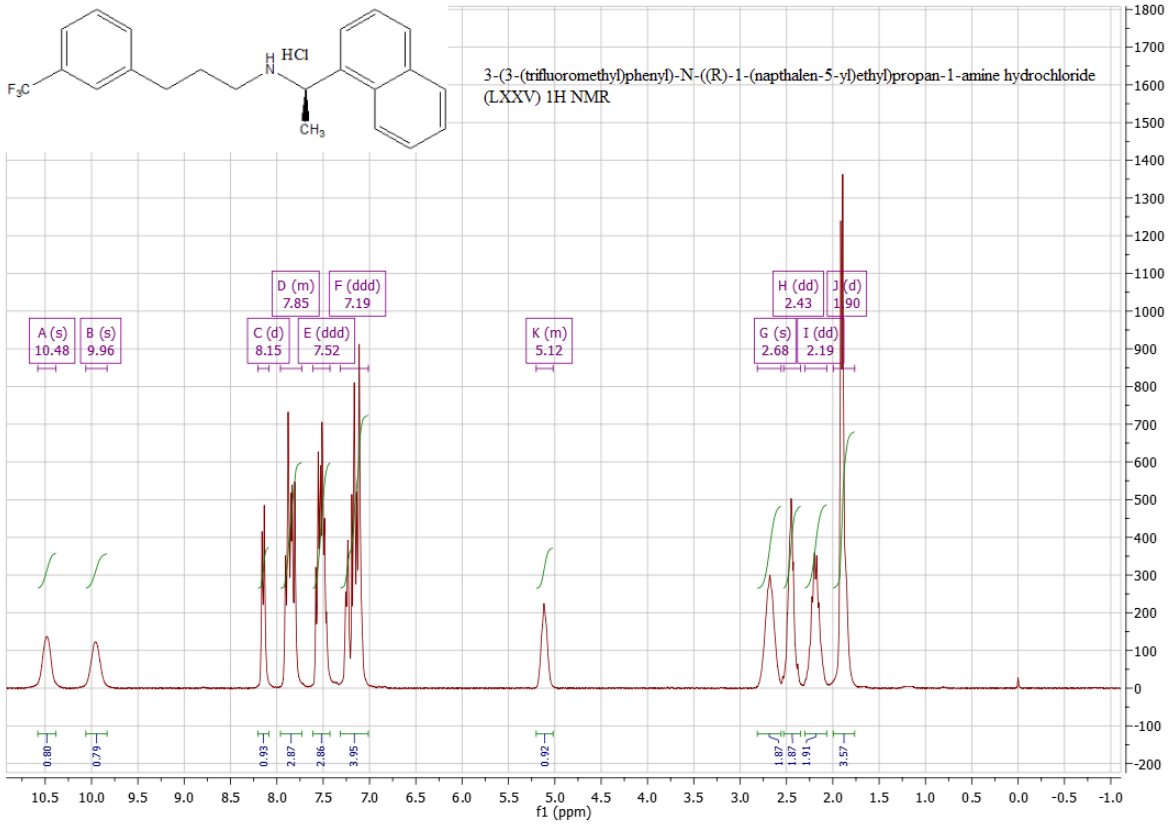

3-(3-(trifluoromethyl)phenyl)propanal (LXI) 1H NMR
A (d)
9.75
B (m)
7.35
C (t)
2.94
D (t)
2.75
E (t)
2.64
f1 (ppm)

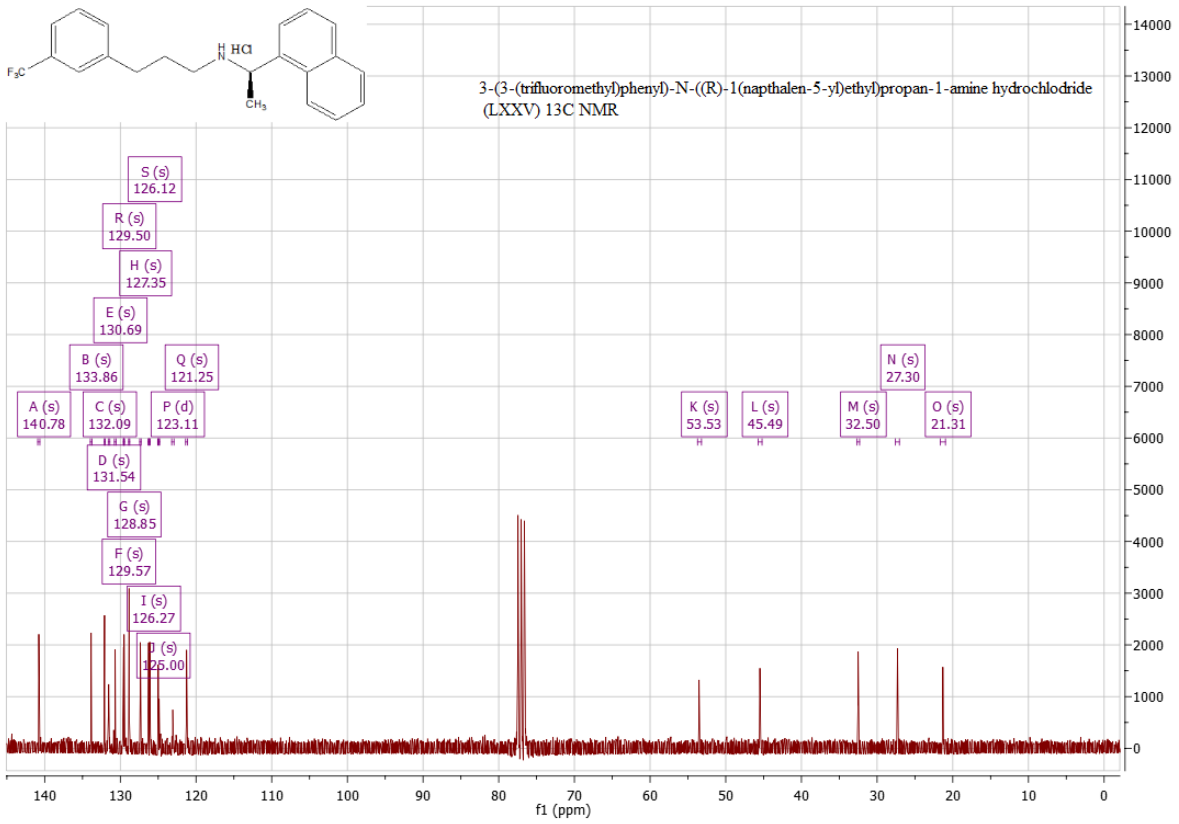

3-(3-(trifluoromethyl)phenyl)propanal (LXI) 13C NMR
A (s)
200.67
B (s)
141.33
C (d)
131.82
D (s)
129.03
E (dd)
125.02
F (q)
123.22
G (s)
44.94
H (s)
27.76
f1 (ppm)


Sodium 1-hydroxy-3-(3-trifluoromethylphenyl)propane-1-sulfonate (LXXVII) 1H NMR
F3C
SO3Na
OH
G (m) 7.56
A (d) 5.51
B (ddd) 3.81
C (m) 2.88
D (m) 2.71
E (m) 2.05
F (m) 1.79
4.09
0.98
1.00
1.28
1.07
1.02
1.04
f1 (ppm)


Sodium 1-hydroxy-3-(3-trifluoromethylphenyl)propane-1-sulfonate (LXXVII) 13C NMR
F3C
SO3Na
OH
A (s) 144.17
B (d) 133.10
C (d) 129.69
D (dd) 125.23
E (d) 122.87
F (s) 82.14
G (s) 31.57
H (s) 34.05
I (s) 129.25
J (s) 126.63
f1 (ppm)


3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(napthalen-5-yl)ethyl)propan-1-amine (LVII) 1H NMR
B (m) 7.80
E (m) 7.34
A (dd) 8.12
C (d) 7.68
D (d) 7.57
F (q) 4.56
G (m) 2.59
H (m) 1.79
I (d) 1.43
f1 (ppm)


3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(napthalen-5-yl)ethyl)propan-1-amine hydrochloride (LXXV) 1H NMR
D (m) 7.85
F (ddd) 7.19
A (s) 10.48
B (s) 9.96
C (d) 8.15
E (ddd) 7.52
K (m) 5.12
H (dd) 2.43
G (s) 2.68
I (dd) 2.19
f1 (ppm)


3-(3-(trifluoromethyl)phenyl)-N-((R)-1(napthalen-5-yl)ethyl)propan-1-amine hydrochlodride
(LXXV) 13C NMR
S (s) 126.12
R (s) 129.50
H (s) 127.35
E (s) 130.69
B (s) 133.86
Q (s) 121.25
A (s) 140.78
C (s) 132.09
P (d) 123.11
D (s) 131.54
G (s) 128.85
F (s) 129.57
I (s) 126.27
J (s) 126.00
K (s) 53.53
L (s) 45.49
N (s) 27.30
M (s) 32.50
O (s) 21.31
f1 (ppm)

Chapter 7: References

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Estratto per riassunto della tesi di Dottorato

Studente: Vikas Damu Rathod, Matricola: 956039

Dottorato: Scienze Chimiche

Ciclo: XXVIII cycle

Titolo della tesi: Synthesis of fine chemicals, such as pharmaceuticals, agrochemicals, fragrances, by using catalytic reactions under homogeneous, heterogeneous and biphasic reaction conditions

Abstract: The aim of this thesis work was the synthesis, characterization and application of new catalysts to be used in reactions as hydrogenation, Heck reaction, Friedel-Crafts acylations, etc., in homogeneous or heterogeneous and/or in biphase systems.

These reactions were applied first on model substrates and then for the synthesis of target pharmaceuticals and for fine chemicals intermediate. In particular it was studied the hydrogenation of carbon-carbon double bonds catalyzed by: 1) new heterogeneous catalysts with a low content of precious metal (Pd 0.28%, Rh 0.18%) on alumina: these catalysts were very easily prepared in a new greener solvent and showed a very high activity and selectivity; 2) Rhodium and Palladium catalysts, with suitable ligands (in particular lactic acid derivatives), able to operate in both aqueous biphasic or homogeneous system. Heck reactions were carried out in homogeneous system by using palladium based catalysts in the presence or absence of suitable phosphino ligands; Friedel-Crafts acylations of heterocyclic compounds were studied by using different metal catalysts, in particular new iron and gallium polymeric fluorosulphonate, easily prepared by a convenient protocol. Most of these reactions were applied for the synthesis of the two target pharmaceuticals, the calcimimetic Cinacalcet and the antimigrane Eletriptan.

Finally, some reactions for the synthesis of Cinacalcet were carried out under microwaves conditions in order to reduce the catalyst amount, the reaction time and to increase the chemical yield. Moreover, these reactions were carried out in more environmentally friendly solvents as Me-THF, CPME and γ-valerolactone. When possible the activity of these new catalysts was compared

to that of commercially available catalyst and in some cases they showed better performances with respect to largely applied industrial catalysts, appearing so suitable for a possible commercial development.

Firma dello studente

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