# Greener Approaches for Chemical Synthesis – Ball Mill and Microwave Assisted Synthesis of Fluoxetine and Duloxetine and Enantioselective Catalysed Addition of Organometallic Reagents to Aldehydes

**Ricard Solà Mestres**

Doctor of Philosophy (PhD)

Division of Chemistry & Environmental Science

School of Science and the Environment

Manchester Metropolitan University

2017

Division of Chemistry & Environmental Science
School of Science and the Environment
Manchester Metropolitan University

# Greener approaches for chemical synthesis – ball mill and microwave assisted synthesis of fluoxetine and duloxetine and enantioselective catalysed addition of organometallic reagents to aldehydes

**Ricard Solà Mestres**

**A thesis submitted in partial fulfilment of the requirements of the Manchester Metropolitan University for the degree of Doctor of Philosophy**

Manchester, May 2017

# ACKNOWLEDGEMENTS

I would like to start thanking my Director of Studies, Dr. Beatriz Maciá-Ruiz, for giving me the opportunity to carry out this exciting and challenging project. Not only I have been working on what I love for the last three years, but also I had the opportunity to grow both personally and professionally, get to know this beautiful country and meet a lot of interesting people that have made a great impact to my life. Thank you for the support and the guideance and I wish you all the happiness to you, Gareth and Evan.

I also want to thank Dr. Marloes Peeters, for all the help and suggestions on the polymer project. A big thank you to all the technicians from the 6$^{th}$ and 7$^{th}$ floors that have always found some free time to help me and sort out any technical problem with a smile on their faces, especially to Lee, Bill, Allan and Helen. To all the people I have shared the lab with, especially the ones I now consider my friends. Thank you to Jimmy, Jay, Sasha and Neyvero for such an amazing time in the lab.

I would like to give a special thank you to all the "Spaniards MMU Fellows". Thank you for the countless conversations during lunch time, all the good and funny moments, the craziest night outs and for being always there. It would not have been the same without all of you. For a friendship that will last a lifetime, best of luck for the near future!

Als meus amics de Calaf, per convertir les meves breus estades en les millors vacances. A la meva família. Al meu germà, l'Adrià per fer-me costat sempre tot i la distància que ens separa. Als meus pares. Gràcies per tot, per donar-me suport, per animar-me a estudiar i per entendre la meva decisió d'anar a viure a l'extranger. Us estimo.

And finally to my partner, to the brightest star, Sylwia. With who I have discovered what love is. Thank you for everyday, for sharing with me all the adventures, for all the good moments and for those that are yet to come. For this journey that has only just begun. Kocham cię.

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| $[\alpha]_D$ | optical rotation, optical activity |
| acac | acetylacetone |
| $Ac_2O$ | acetic anhydride |
| Aq. | aqueous |
| Ar | aromatic group |
| ArCHO | aromatic aldehyde |
| ArOH | substituted phenol |
| BDMAEE | bis(2-dimethylaminoethyl)ether |
| $Boc_2O$ | boc anhydride, di-*tert*-butyl dicarbonate |
| *c* | concentration (g / 100 mL) |
| cat | catalyst |
| CBS | Corey-Bakshi-Shibata |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DCM | dichloromethane |
| *de* | diastereomeric excess |
| DIAD | diisopropyl azodicarboxylate |
| DIPT | diisopropyl tartrate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMSO | dimethyl sulfoxide |
| dppf | 1,1'-bis(diphenylphosphino)ferrocene |
| E | electrophile |
| *ee* | enantiomeric excess |
| Eq. | equivalents |
| ESI | electrospray ionization |
| GC | gas chromatography |
| Hex | hexane |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |

| | |
|---|---|
| HSBM | high speed ball milling |
| $Ipc_2BCl$ | chlorodiisopinocampheylborane |
| IR | infrared spectroscopy |
| K | kelvin |
| LAG | liquid assisted grinding |
| $M_p$ | melting point |
| MS | mass spectrometry |
| MsCl | methanesulfonyl chloride |
| MTBE | methyl *tert*-butyl ether |
| MW | microwave |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| Org. | organic |
| ppm | parts per million |
| psi | pounds per square inch |
| Red-Al | sodium bis(2-methoxyethoxy)aluminumhydride |
| Rf | retention factor |
| rpm | revolutions per minute |
| RT | room temperature |
| SCF | supercritical fluid |
| $S_NAr$ | nucleophilic aromatic substitution |
| SSRI | selective serotonin reuptake inhibitor |
| t | time |
| T | temperature |
| TEEDA | *N,N, N',N'*-tetraethylethylenediamine |
| THF | tetrahydrofuran |
| TMEDA | Tetramethylethylenediamine |
| tol | toluene |
| $t_r$ | retention time |
| TS | transition state |
| TsCl | *p*-toluenesulfonyl chloride |

# ABSTRACT

This PhD thesis focuses on the development of "greener" synthetic methodologies in organic synthesis. Turning chemical production into a more sustainable industry - by reducing the waste generated and the electricity consumption - is highly desired in a world with limited resources and increasing population.
This thesis, in particular, focuses on three of the '12 Principles of Green Chemistry', reducing the amount of solvent and energy consumption in a chemical process, and the use of catalytic reagents instead of stoichiometric.

In the first chapter of this thesis, a greener synthetic route for the preparation of the antidepressant fluoxetine (Prozac) was developed. The use of ball milling allowed a decrease of the solvent used in the process, furthermore, microwave assisted heating provided a more efficient method compared to the traditional heating using an oil bath. Fluoxetine was synthesised with 47% yield through two different synthetic routes (3 and 4 steps respectively). In addition, the scope of the developed methodologies was tested by the attempted synthesis of the antidepressant duloxetine.

The second chapter of this thesis focuses on the catalytic enantioselective synthesis of chiral alcohols. More specifically, two different methodologies for the catalytic enantioselective addition of organolithium reagents to aldehydes were successfully developed, achieving excellent yields and enantioselectivities. Furthermore, a new methodology for the use of organozirconium reagents as nucleophiles in the catalytic enantioselective 1,2-addition of alkenes to aldehydes was also developed. Last, the implementation of a catalytic enantioselective step to the previous syntheses of fluoxetine was attempted.

# GENERAL INTRODUCTION

The Earth has gone through many environmental changes along the years; however, the planet has remained stable for the last 12,000 years in a period that geologists refer as the Holocene.[1] This period of stability that started after the last ice age, is now facing some major and irreversible consequences. Human activities are now leading Earth towards a brand new area called the Anthropocene.[2, 3] This geologic chronological term, which was first used by Eugene F. Stoermer in the late 1980s, defines our current epoch in which human actions are the main cause of global environmental change.

It is well known that the chemical industry has an important role in the current environmental changes, mainly due to the millions of tonnes of waste that chemical manufacturing generates every year. Therefore, it has become a priority to eliminate or minimize the impact of the chemical industry towards the environment. The ideal solution to avoid waste would be to prevent its formation in the first place.[4, 5]

Since the risk associated with a chemical process can be expressed as:[6]

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

by reducing or eliminating the hazard, it is possible to minimize the risk involved in any chemical reaction.

As a result of expanding this idea, the concept of Green Chemistry was formulated at the beginning of the 1990s.[7] Its most common and widely accepted definition is "the design, development and implementation of chemical processes and products to reduce or eliminate substances hazardous to human health and the environment".[6]

Few years later, continuing with the aim of achieving sustainability, Paul Anastas and John Warner expanded its definition by formulating the 12 principles of Green Chemistry (which are shown below).[6]

## The 12 principles of Green Chemistry

1. It is better to prevent waste than to treat or clean up waste after it 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, separation agents, and so forth) should be made unnecessary wherever possible and innocuous when used.

6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.

8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) 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 break down into innocuous degradation products and do not persist in the environment.

11. Analytical methodologies need to be developed further to allow for real-time in-process monitoring and control pior to the formation of hazardous substances.

12. Substances and the form 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.

---

Sheldon's Environmental Impact Factor (E Factor) is used to determine the environmental acceptability of a manufacturing process.[8]

The E Factor is defined as the mass ratio of waste to desired product (kg waste/kg product). In other words, it is the actual amount of waste produced during a chemical process.

*Table 1* summarizes the E factors for some segments of the chemical industry. The higher the E factor is, the greater negative impact to the environment.[8]

*Table 1 – E factors for some segments of the chemical industry*

| Industry segment | Product tonnage | E Factor (kg waste/kg product) |
|---|---|---|
| Oil refining | $10^6$ - $10^8$ | < 0.1 |
| Bulk chemicals | $10^4$ - $10^6$ | < 1 - 5 |
| Fine chemical industry | $10^2$ - $10^4$ | 5 - 50 |
| Pharmaceutical industry | 10 - $10^3$ | 25 - 100 |

Data in *Table 1* shows that the E factor rises dramatically as we move from oil refineries and the bulk chemical industry to the fine chemicals and pharmaceutical industries. The main reasons why the pharmaceutical industry displays the highest E factor are that it is normally based on multi-step syntheses that frequently involve large quantities of solvents, and the use of stoichiometric reagents instead of catalytic ones.[9] A lot of efforts are now being made in order to turn the pharmaceutical industry into a sustainable industry.

Amongst all the strategies that constitute the 12 principles of Green Chemistry, this thesis focuses on principles 5, 6 and 9.

Principle 5 states that the use of solvents should be made unnecessary wherever possible. We will address this by the use of mechanochemistry or ball milling techniques, which allow the performance of chemical reactions in the absence of solvent.

Principle 6 targets the minimization of energy requirements for a chemical process. This issue will be addressed by replacing traditional heating (i.e. oil baths, isomantels, etc) by mechanochemistry and microwave assisted heating.

More in particular, the first chapter of this thesis is based on the use of ball milling techniques and microwave assisted reactions in order to develop greener synthetic routes for the preparation of the active pharmaceutical ingredients fluoxetine and duloxetine, both antidepressant drugs.

Regarding the principle 9, the second chapter of this thesis covers the use of catalytic reagents (instead of stoichiometric ones) for the development of new catalytic asymmetric processes. In particular, we have addressed the enantioselective addition of different organometallic reagents to carbonyl compounds.

# CHAPTER 1

---

Part of the research described in this chapter has been published:

**1.** Solà, R.; Sutcliffe, O. B.; Banks, C. E.; Maciá, B. ***'Ball mill and microwave assisted synthetic routes to Fluoxetine'.*** *Sustainable Chemistry and Pharmacy* **2017**, *5*, 14–21.

# 1.1. Introduction

Pharmaceutical manufacturing is the most solvent-intensive and the least efficient of all chemical industries in terms of waste generated per unit of product. Statistics compiled across the industry point to an average waste-to-product ratio of 200 times. In other words, factories generate 200 kilograms of waste for every kilogram of active pharmaceutical ingredient produced. In particular, 90% of more than 500 million tons of toxic waste that pharmaceutical companies generate each year, is solvent.[10]

According to a recent study carried by GlaxoSmithKline,[11] 85% of the total mass of chemicals that are involved in pharmaceutic manufacturing consists of solvents. Although the typical recovery efficiencies are 50-80%, most of the solvent is incinerated for power, thus contributing to $CO_2$ formation.

Recent studies have identified three "green" approaches that could help the pharmaceutical industry to reduce its ecological impact.

- Alternative feedstocks: use the waste generated in a process as a feedstock or reagent for the next one.[12]
- Non-solvent reactions,[13, 14] and alternative solvents (e.g. utilisation of water,[15] ionic liquids[16, 17] and supercritical fluids (SCF)[18]).
- Alternative synthetic pathways: usage of catalysts instead of stoichiometric reagents, and their recovery and reutilisation after they have been used.

Taking into consideration that solvents are the major cause of waste in the pharmaceutical industry, non-solvent reactions will constitute a relevant area of interest in this work.

## 1.1.1. Non-solvent reactions

The main role of solvents is to provide homogeneity in a chemical reaction. When all the components in a reaction are dissolved, the approach between molecules is favoured, which promotes the interactions between reagents at

a molecular level. Furthermore, solvents can also favour the formation and stability of certain intermediates formed during the reaction, thus allowing the thermodynamic and kinetic control to happen over a chemical process. In addition, solvents can also act as a heat trap, absorbing and dissipating the heat generated during the reaction. When heating is needed for the process, solvent provides additional safety and control since the chemicals will never be heated above the solvent's boiling point.

Despite all the advantages mentioned before, the use of solvents is expensive in production scale. It is not only about the cost of the solvent itself, the disposal and the subsequent treatment are also expensive processes. For this reason, pharmaceutical industry aims to reduce the amount of solvent used in every process. Ideally, the best situation would be a reaction in which no solvent is used at all.

In a reaction without solvent, the challenge is to guarantee a good mixing of the reagents and achieve a homogeneous phase, so the molecules can interact between each other and the reaction can take place. Mechanochemical activation (as simple as grinding two reactants in a pestle and mortar) can facilitate this approach between molecules. Mechanochemical processes can be automated with the use of ball mills, which have the advantage over the pestle and mortar of requiring no physical effort, supplying greater power and being programmable.

During the last decade, numerous protocols have been published using ball milling technologies for the synthesis of many valuable compounds.[19, 20] This powerful method, based on the absorption of mechanical energy, has drawn the attention of many chemists as no solvent is required to carry out the reaction.

Mechanochemistry has already been used for the synthesis of some active pharmaceutical ingredients (APIs) (see some examples in *Figure 1.1*).[21-25] Even though the number of reported mechanochemical syntheses of APIs is

still modest, there is a growing number of mechanochemical procedures for generating pharmaceutically relevant fragments and functionalities.[26]

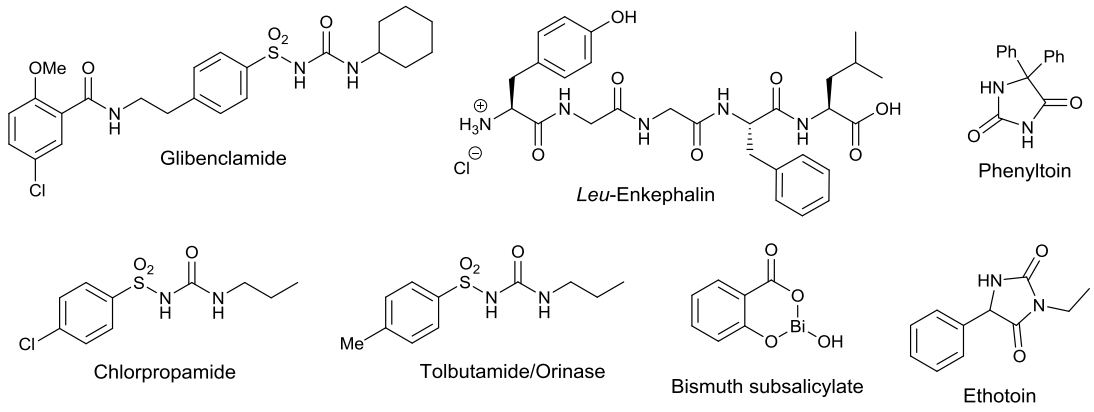



*Figure 1.1 – Mechanochemically synthesised APIs*

More interestingly, it has been recently reported that some reactions are only possible under mechanochemical conditions.[27] For example, in 2013, Friscic et al. reported a new single-step procedure for the preparation of sulfonylguanidines through grinding in a ball mill.[25] Despite all the attempts of his research team at McGill University in Montreal, it was not possible to replicate the process in solution conditions.

However, despite all the recent work on mechanochemistry and solventless chemical transformations, the transition from traditional wet technologies to dry methods for the synthesis of pharmaceuticals is a highly desirable but unexplored area that needs further investigation.[28]

## 1.1.2. Ball Mill

According to IUPAC, a mechanochemical reaction is defined as "a chemical reaction that is induced by the direct absorption of mechanical energy".[29] Its simplest case is grinding two reagents with a pestle and mortar. However, the process can be automatized with the utilisation of ball mills, which can provide greater power and avoid the use of physical energy at the same time.

Ball mills are common equipment in industry, but their applications are usually limited to the grinding of solid materials in order to make thin

powders. However, the idea of using ball mills as efficient reaction vessels for the synthesis of pharmaceuticals has recently become very popular as a possible cleaner technology in the pharmaceutical sector.[30]

Mechanosynthetic methods – grinding of (solid) reactants in a ball mill[26] – avoid the use of solvents and at the same time utilise mechanical energy from the grinding for the formation/breaking of new bonds.[13, 21-26, 31, 32] No solvent would be needed to carry out reactions and the energy required for the formation/breaking of new bonds would be provided by mechanochemical means (grinding).

There are mainly two different kinds of ball mills commercially available for laboratory-scale synthesis, the shaker and the planetary ball mill. The shaker ball mill (*Figure 1.2*), based on a rapid horizontal shaking motion, is provided with a metal ball inside the reaction vessel that impacts against the sides of the grinding jar. The mechanical energy generated in the process is transferred to the reactants and allows the reaction to take place.

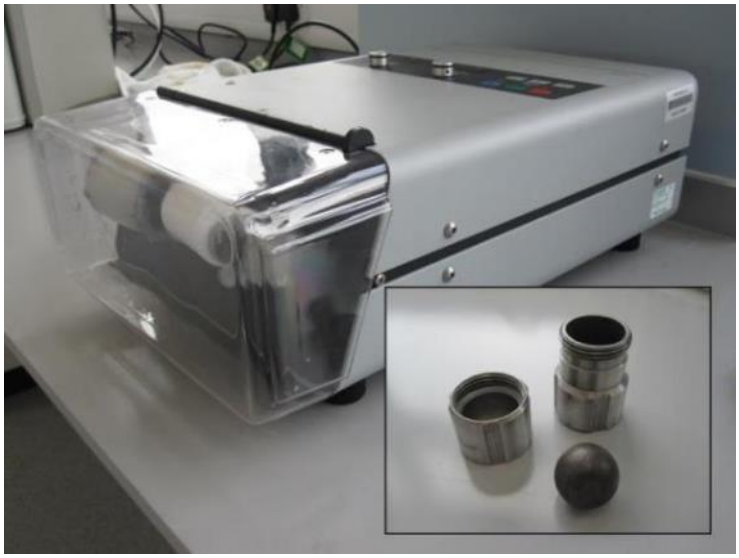


*Figure 1.2 – Shaker mill*

In the planetary ball mill, on the other hand (*Figure 1.3*), the grinding jar mimics the orbit of the planets around the sun (both rotation and revolution movements). It can work either on friction mode (the balls move around the walls of the grinding jar) or impact mode (the balls jump across the grinding

jar and impact against the walls) depending on the relative speeds of the rotation and revolution movement. Planetary mills generally have a lower impact frequency than shaker mills,[33] however the oblique collisions and friction of the balls in the grinding jar produce higher temperatures (higher energy output), which can be beneficial for the reaction.[34]

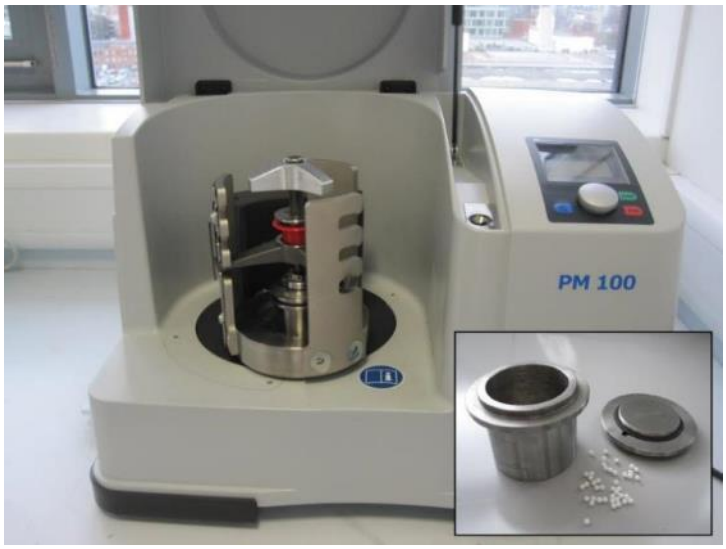



*Figure 1.3 – Planetary ball mill*

Besides the type of ball mill that can be used to perform mechanochemical reactions, there are some parameters that can influence the yield of the reaction and have to be borne in mind: the revolutions per minute (rpm), the grinding time (t), the number and size of the milling balls, and the material both the grinding balls and grinding jar are made of.

The main purpose of the ball mill when performing a mechanochemical reaction is to achieve the biggest energy input possible, so to evaluate the impact of each parameter a reference to the classical equations of kinetic energy ($E_k$) can be done (*Equations 1.1 and 1.2).*[35, 36]

$$E_K = \frac{1}{2}\, m\, v^2 \qquad \textit{Equation 1.1}$$

$$E_k(rot\ or\ osc) = \frac{1}{2}\, I\, w^2 = 2\,\pi^2\, I\, f^2 \qquad \textit{Equation 1.2}$$

The angular velocity ($w$) can be expressed as $w = 2\pi f$ , so it is easier to understand how frequency ($f$) is related to the kinetic energy ($E_k$).

The frequency $(f)$ is the most determining parameter, so the rpm is going to have major contribution to the reaction. The faster the grinding balls move, the greater energy will be provided to the reaction mixture.

On the other hand, the mass $(m)$ depends on the number and the size of the grinding balls used. In other words, it comprises the total surface of grinding material involved in the reaction. Not only the number of balls is important, but the size of them.[36]

The milling material (for both the grinding balls and jar) is also important, as the moment of inertia $(I)$ (*Equation 1.2*) depends on the mass $(m)$, therefore the density of the material is also involved when calculating the kinetic energy ($E_k$). The higher the density of the milling material, the greater energy is transferred to the reaction mixture.

Despite this, it would be wrong to state that a greater energy input will always lead to a higher yield. The activation energy of the reaction and its mechanism have to be considered as well.[37]

If we order all the parameters regarding their influence during the milling process, the sequence would follow this trend: rpm > milling time (t) > size of milling balls > number of milling balls > grinding material.[36]

There are two types of mechanical actions in a ball mill: impact (collision of the grinding ball into the wall) and shear (the layers of the substance are laterally shifted in relation to each other).[38] Impact is the predominant action taking place in the shaker mill, while shear is more distinctive of the planetary mill.

While trying to understand the relationship between these types of mechanical action, it has been observed that two unique zones of different reactivity are present inside the grinding jar.[38, 39] Samples at the milling jar ends (where impact prevails) may have a different concentration than samples from the walls (where shear is the predominant action).

It is also believed that increasing the number of balls in the grinding jar can change the motion of the media,[40] reducing the number of impacts while increasing the shearing action. By using that technique, it would be possible to decrease the number of impacts of a shaker mill and increase the shearing, which is more characteristic of the planetary mill.

In relation to the different types of mechanical action, the phenomenon of tableting or sintering can affect the progress of the reaction during the grinding. This phenomenon is characterised by the formation of a compact layer of the reaction mixture, which consists of particles incapable of further motion.[36, 39] This tablet formed will initially be characterised by large amounts of shearing stress. Nevertheless, as the space between the particles is reduced, a densely packed tablet will be formed in which impact action is going to be dominant.

In order to evaluate which kind of mechanical action is better for a particular reaction, all the reactions carried out during this thesis will be performed in both shaker and planetary ball mills.

#### 1.1.2.1. Mechanism at molecular level

Although many efforts have been done in the area, and many models have been proposed, the mechanism of a mechanochemical reaction is still far from being understood up to date. Each mechanistic model developed has a limited area of applicability, whilst more than one may apply to a given reaction.[13]

Early approaches to understand the mechanism of mechanochemical reactions were based on thermal effects. In particular, it was believed that the chemical reactions were the result of local heating. The most popular mechanisms based on local heating are the hot spot theory and the magma-plasma model.

The hot spot theory, developed by Bowden, Tabor and Yoffe during the 1960's,[41] is based on friction processes for $10^{-4}$ – $10^{-3}$ s that can generate

local temperatures of over 1000 K between two surfaces of about 1 $\mu m^2$. In the case of more brittle (fragile) materials, this process occurs at the tip of the propagating crack.[13, 41]

The magma-plasma model, developed by Thiessen in 1967, is also based on the dramatic increase of the temperature in specific points, but focused on impacts rather than friction between surfaces. It is defined as an energetic impact between two particles that generates a plasma-like state characterized by the emission of electrons and photons. This state, which lasts less than $10^{-7}$ s, results in local temperatures that can reach more than $10^4$ K.[13, 41, 42]

Despite this, the above-mentioned phenomena are too brief and/or too localized to define the entire course of the reaction. Further models have to be developed to understand the processes occurring in areas larger than 1 $mm^2$.[13]

Recent studies have been carried out in order to enlighten the mechanism at molecular level behind solid/solid organic reactions. Some of the reactions studied include: aldol condensations, Baeyer-Villiger oxidation, esterification of alcohols, etc.[43] It has been suggested that those organic reactions, in which a new covalent bond is formed, occur through a liquid eutectic intermediate phase that subsequently solidifies once the product is formed.[43]

This liquid phase involves the formation of a low-melting eutectic mixture that provides particles with the necessary mobility to allow collisions between the two solid reagents. In the cases where heating is required for the phase change, local heating effects could provide the necessary temperature increase.[43]

#### 1.1.2.2. Liquid Assisted Grinding (LAG)

In contrast to conventional chemical synthesis, where the energy dispersion and the transport of chemicals are assured by the action of solvents, the challenge in solvent-free reactions is to achieve good contact between the

different reagents (ideally, a homogeneous phase). In order to avoid the formation of areas of different reactivity, with the aim of achieving a homogeneous phase, liquid assisted grinding (LAG) is getting popular as a variation of neat grinding.[44, 45]

LAG or solvent-drop co-grinding, as its name suggests, is based on the addition of a small amount of liquid phase within the grinding jar. The role of the liquid is still not fully understood, but several theories have been suggested including: influence the mixing of the reagents (dissolving one or more components), modify the surface properties (changing the interactions between the solids), or affecting the dielectric permeability which could induce the polarization of the components.[46]

### 1.1.3. Non-conventional Energy Sources

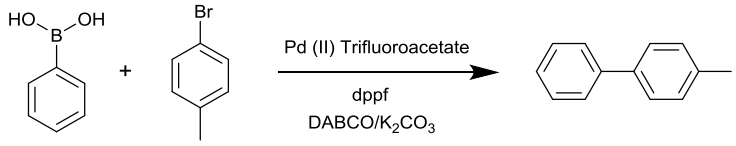
Non-conventional energy sources have gained popularity during the last years. The ones that are generating more interest within the field of organic chemistry are mechanochemistry (see ball mill section above), microwave assisted heating, ultrasound and photochemical activation.

Traditional heating in organic synthesis usually involves the utilisation of an isomantle or an aluminium block, an oil or sand bath, or a jacketed reactor in case the reaction is done at bigger scale; that transfers heat to the solution by convection and conduction. However, these classical ways of heating are considered slow and inefficient as there is a temperature gradient within the reaction flask (heat is transferred from the glass to the solvent). A more efficient way of heating would reduce time and therefore costs in industrial processes.

In this context, microwave heating has been reported to reduce reaction times dramatically, sometimes from hours to minutes, or even seconds.[47] In addition, microwave heating is much more efficient than conventional heating as it heats the reagents and the solvent without heating the vessel.[48]

Comparative studies on the energy consumption from different technologies have been carried out. For example, in 2005, Macquarrie performed a study comparing the preparation of one mole of 4-methyl-1,1'-biphenyl *via* a Suzuki coupling reaction using conventional heating and microwave assisted heating.[49] The results (shown in *Table 1.1*) indicate that microwave heating is more energy efficient than the oil bath.

*Table 1.1 – Energy consumption comparison in a Suzuki coupling*




| Heating source | Solvent | Time (h) | 4-methyl-1,1'-biphenyl yield (%) | Energy (kW/mol) |
|---|---|---|---|---|
| Oil-bath | dioxane | 24 | 56.6 | 5830 |
| Microwave | dioxane | 1 | 40.7 | 1680 |

Not only microwave irradiation provides a more efficient heating, but also it usually allows shorter reactions times, which ranks this technology as a low energy consuming method. For this particular reason, microwave assisted heating has become such an attractive technique for synthetic chemists during the last years.[50]

Despite this, in case of low-boiling point solvents and comparatively short reaction times, classical heating techniques become more energy efficient.[49]

### 1.1.3.1. Microwave Assisted Heating

Microwaves are a form of electromagnetic radiation that lies between infrared and radio frequencies. Microwave wavelengths range from 1 mm to 1 m, corresponding to frequencies between 30 GHz to 300 MHz. The frequency $(f)$ indicates the number of oscillations of the electric or magnetic field in one second, and is inversely proportional to the wavelength $(\lambda_0)$ (see *equation* 1.3 below).

$$\lambda_0 = \frac{c}{f} \qquad \textit{Equation 1.3}$$

In case of electromagnetic radiation, the phase speed is the speed of light $(c)$. In order to avoid interfering with radar transmissions, domestic microwaves are required to operate at 2.45 GHz (12.2 cm).[51]

Microwave domestic ovens have been used to heat food for more than 50 years, the first microwave oven was invented by Percy Spenser in 1946. Despite this, they did not become popular in the field of organic chemistry until middle 90s, due to the lack of reproducibility of the reactions in domestic ovens. Some research groups were using modified microwave domestic ovens and they did not provide the necessary reaction parameters to reproduce the same reaction conditions.[52] Furthermore, there was also a lack of understanding of the microwave dielectric heating.

Nowadays, the dielectric heating process is fully understood and the utilization of monomode irradiation provides the necessary reproducibility for microwaves to become a successful alternative heating technique for organic chemistry.

### 1.1.3.2. Microwave dielectric heating

Microwave dielectric heating is the ability of some substances to transform electromagnetic energy into heat.

An electromagnetic wave, as its name suggests, has both electric and magnetic components. The electric field component is the responsible for the dielectric heating, which happens mainly through two different mechanisms: dipolar polarization and conduction.[53]

#### 1.1.3.2.1. Dipolar Polarization

When a substance is irradiated with microwaves, if the molecule has a dipole moment it will rotate in order to align itself with the electric applied field. The oscillating field will force the molecule to try to realign constantly.[52]

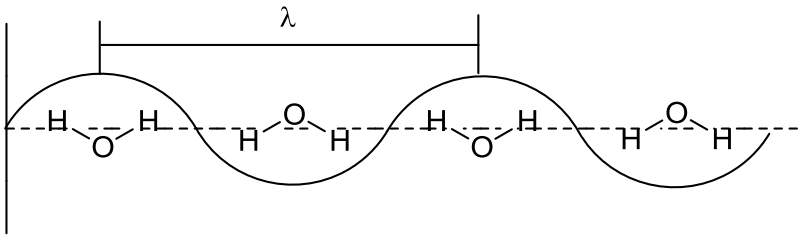



*Figure 1.4 - Water molecule trying to align in an alternating electrical field*

Microwave cannot be used to heat gases as the molecules are too spaced from each other and their rotation is fast.

On the contrary, when a liquid is irradiated with an electromagnetic field, its ability to align with the field will depend on the frequency applied and the viscosity of the liquid. At low frequencies, the molecules will rotate in phase with the oscillating electric field generating low energy, while at high frequencies, the molecules will not have enough time to align with the field, so no rotation will occur.[53]

The ideal situation is when the frequency applied is within the microwave region; low enough so the molecule has time to respond to the electric field and rotate, but not too high so rotation cannot follow the alternating field accurately. During this process energy is lost and transformed into heat because of molecular friction and collisions.

It would be reasonable to think that more polar solvents absorb more energy, so the temperature increase is higher. However, with substances with similar dielectric constants $(\epsilon')$, the dielectric loss $(\epsilon'')$ has to be considered as well.[50, 51]

The loss factor $(\tan\delta)$ is expressed as the quotient of both parameters.

$$\tan\delta = \frac{\epsilon''}{\epsilon'} \qquad \textit{Equation 1.4}$$

The dielectric loss $(\epsilon'')$ is the efficiency in which the electromagnetic radiation is converted into heat, and the dielectric constant $(\epsilon')$ is the ability of the molecules to re-orientate in the electric field.

Depending on the loss factor $(\tan\delta)$, a solvent can be classified as high $(\tan\delta > 0.5)$, medium $(\tan\delta\ 0.1 - 0.5)$ or low microwave absorbing $(\tan\delta < 0.1)$.

Next table shows the loss factor $(\tan\delta)$ for some commonly used solvents.[50]

*Table 1.2 – Loss factor for some common solvents*

| **Solvent** | **tan $\delta$** | **Solvent** | **tan $\delta$** |
|---|---|---|---|
| ethylene glycol | 1.350 | chloroform | 0.091 |
| ethanol | 0.941 | ethyl acetate | 0.059 |
| DMSO | 0.825 | acetone | 0.054 |
| 2-propanol | 0.799 | THF | 0.047 |
| methanol | 0.659 | dichloromethane | 0.042 |
| DMF | 0.161 | toluene | 0.040 |
| water | 0.123 | hexane | 0.020 |

1.1.3.2.2. Conduction

Conduction, the second mechanism of heating, is the movement of ions through the solution because of the effect of the electric field. Therefore, energy is converted into heat because of the increase in collisions.

This mechanism can be easily acknowledged when two samples of tap and distilled water are heated in the microwave. Under the same irradiation conditions, the tap water sample will reach higher temperature due to the presence of ions.

This conductivity effect is of stronger magnitude than the dipolar effect because of its higher heat-generating capacity. This is the reason why ionic liquids are perfect solvents for microwave assisted synthesis.[54]

1.1.3.2.3. Other thermal effects

Apart from the above mentioned thermal effects (*i.e.* dipolar polarization and conduction) there are some other thermal effects associated with the dielectric heating of the microwave.

i) Superheating effect: It has been observed that at early stages of microwave heating, the temperature rise is localized in distinct parts of the reaction vessel and that most organic solvents are superheated above their boiling points.[55] This effect is due to the presence of a vapour embryo trapped inside the bulk of the liquid that is subsequently released as a bubble. Most organic solvents are overheated 13-26 °C above their boiling point.[55]

ii) Hot spots: Formation of hot spots with a temperature 100-200 °C higher than the bulk temperature, caused by an inhomogeneity of the electromagnetic field.[56]

iii) Selective heating: Since only polar substances are heated while non-polar substances do not absorb radiation; solvents, catalysts or reagents can be heated selectively.

iv) Molecular radiators: In case of non-absorbing solvents like benzene, carbon tetrachloride or dioxane, a highly absorbing solute can be added in the solution. This molecule will absorb the electromagnetic radiation and transfer the heat to the solution by convection.

v) Elimination of wall effects: The inverted temperature gradient in the microwave causes the temperature of the whole volume to rise simultaneously. Contrary to conventional heating, the highest temperatures are achieved within the reaction volume. By using an oil bath, the reaction mixture in contact with the vessel wall is heated first and the highest temperatures are achieved on the glass and on the areas where no solvent is present.[50]

### 1.1.3.3. Specific Microwave Effects

Specific or non-thermal microwave effects are defined as accelerations that cannot be achieved or duplicated by dielectric heating. This topic is still controversial and research has to be done in order to fully understand this phenomena.

Some research groups state that microwaves are not energetic enough to induce chemical transformations, so it is reasonable to assume that chemical reactivity in microwave is driven exclusively by thermal effects.[48, 57] This affirmation is based on the fact that the energy transferred by microwaves (<0.3 kcal/mol) is too low to induce any molecular activation and microwave irradiation (2450 MHz) cannot excite rotational transformations.[58]

However, other authors have observed accelerations and selectivities that cannot be rationalized by thermal effects. In most cases, this specific MW effects are masked by the solvent absorption of the electric field, despite this, they can be clearly appreciated in non-polar solvents (in which MW absorption is low).

Several theories have been postulated in order to understand the specific microwave effects.[56, 59]

i) Microwave activation can change the energy of activation of a reaction by increasing the Arrhenius pre-exponential factor $(A)$.

$$k = A\, e^{-\Delta G/RT} \qquad \textit{Equation 1.5}$$

The pre-exponential factor $(A)$ represents the probability of molecular impacts, and it is believed that by changing the orientation of polar molecules it is possible to influence $A$.

ii) The activation energy $(\Delta G)$ is largely reduced. It is predicted that the entropy $(\Delta S)$ for the reaction may increase because of the dipolar polarization. That would result in a decrease of the activation energy.

$$\Delta G = \Delta H - T\Delta S \qquad \textit{Equation 1.6}$$

iii) Reaction's mechanism: It has been previously stated that increasing the polarity of a molecule would result in a higher temperature rise. Therefore the polarity changes during the reaction have to be considered as well.

In case of two competing transition states (TS) with different polarities, the more polar TS will be favoured under microwave radiation, increasing the selectivity of the reaction.

### 1.1.3.4. Irradiation method

There are two different types of microwaves depending on the irradiation method that they use: monomode and multimode.

All domestic microwaves use the multimode technique. When the radiation gets inside the cavity, microwaves are reflected by the walls generating different modes in order to distribute the radiation homogeneously. This prevents the formation of standing waves (a wave that remains in constant position) minimizing the generation of "hot and cold spots". Its major advantage is that several samples can be irradiated at the same time. Despite this, the heating efficiency can change dramatically depending of the position of the sample inside the microwave cavity.[53]

Monomode or single mode, on the other side, is based on a cavity that only allows one mode to be present. This results in a uniform radiation pattern that prevents the formation of "hot and cold spots". Monomode microwave apparatus are used in organic chemistry as they allow the achievement of higher reproducibility and predictability.[53] Their major drawback is that the reaction volume is fixed and it is relatively small. A flow microwave reactor has to be used in order to scale up reactions to industrial levels.[60]

## 1.2. Aim and objectives

This chapter aims to the development of eco-friendly methodologies for the preparation of top selling and commercially available Selective Serotonin Reuptake Inhibitors (SSRIs), a very important class of antidepressants. According to the IMS Health, the antidepressant drugs duloxetine and aripiprazole (commercialized as Cymbalta and Abilify, respectively) were ranked 1st and 4th in a list of the top 100 prescribed medicines by U.S. National Sales in Q3 2013. The application of "greener" methodologies to the development of pharmaceutical processes could decrease the number of technological stages, leading to both the simplification of the procedure and the reduction of costs to the manufacturer and, ultimately, to the consumer.

A well-known antidepressant, fluoxetine (commercialized as Prozac, *Figure 1.5*), was set as a target molecule for the eco-friendly synthesis. The purpose of this research was to develop a new and efficient method for the synthesis of fluoxetine using solvent free conditions and microwave assisted techniques. Both ball mill and microwave technologies were tested in the development of an alternative "greener" strategy that could lead to a simple and more efficient synthesis of fluoxetine.

In order to prove the scope of our synthetic strategy, the synthesis of the structurally similar antidepressant duloxetine (*Figure 1.5*) was also attempted under the optimized conditions.


*Figure 1.5 – Structures of fluoxetine and duloxetine*

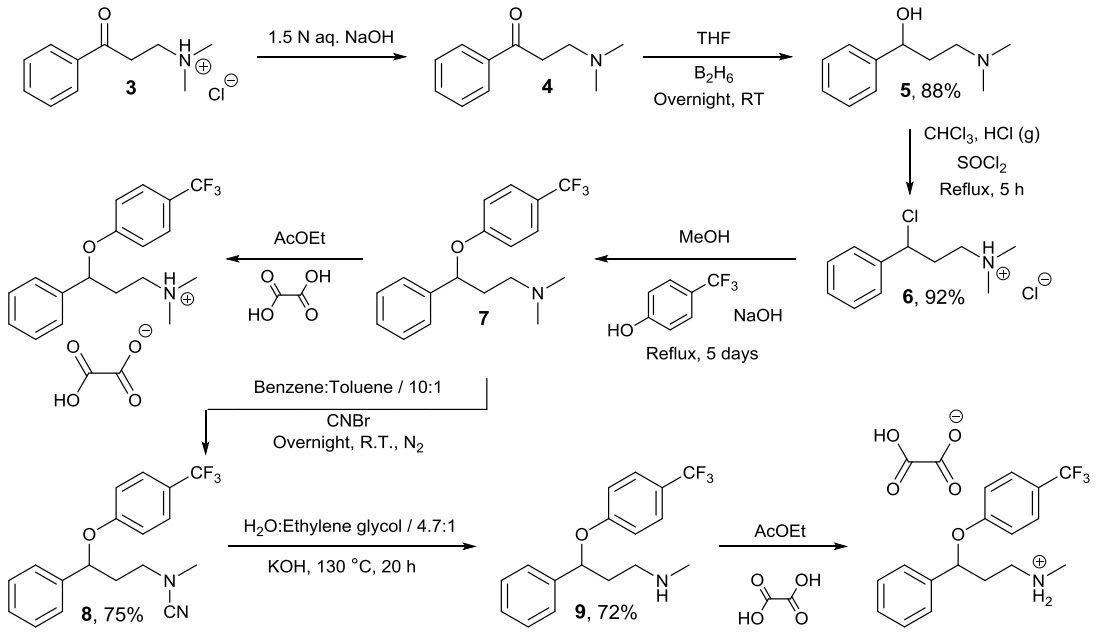
# 1.3. Synthesis of fluoxetine (Prozac)

## 1.3.1. Background

Fluoxetine, commercially known as Prozac, is a selective serotonin reuptake inhibitor (SSRI) widely used for the treatment of depression and anxiety.

Although Prozac is currently sold in its racemic form, some studies have proved that both enantiomers have different activities and metabolic rates.[61, 62] In particular, Robertson et al. in 1988 established that there is a small stereospecificity when it comes to the interactions with the serotonin-uptake carrier, being (*S*)-fluoxetine the enantiomer with the most potent biochemical activity as a serotonin-uptake inhibitor.[61]

Fluoxetine, in its racemic form, was synthesised for the first time by Bryan B. Molloy and Klaus K. Schmiegel in 1982 with an overall yield of about 32%.[63] The process, patented by Eli Lilly and Company, consists on the preparation of fluoxetine's oxalate salt after 7 reaction steps, starting from the commercially available 3-dimethylamino-1-phenyl-propan-1-one hydrochloride (**3**) (*Scheme 1.1*).




*Scheme 1.1 – Fluoxetine's first synthesis by Bryan B. Molloy and Klaus K. Schmiegel*

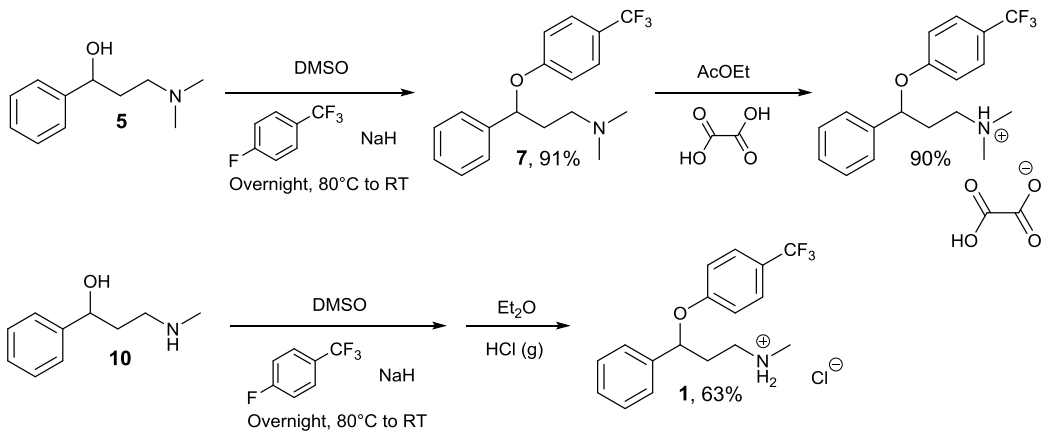
Hydrochloride salt **3** is converted into the free amine **4** by reaction with aqueous sodium hydroxide. Aminoketone **4** is subsequently treated with diborane in THF to provide amino alcohol **5** in 88% yield. Next, compound **5** is dissolved in chloroform saturated with gaseous hydrogen chloride and treated with thionyl chloride to afford **6** in 92% yield. Finally, the reaction of **6** with *p*-trifluoromethylphenol and sodium hydroxide in methanol affords **7** after heating under reflux for 5 days. The yield of this reaction is not provided in the original patent. Compound **7** can be stored as the corresponding oxalate salt, as shown in *Scheme 1.1*, or used directly in the next reaction steps.

In the last part of the synthesis, *N*,*N*-dimethyl-3-(*p*-trifluoromethylphenoxy)-3-phenylpropylamine (**7**) is reacted with cyanogen bromide to generate **8** in 75% yield. The reaction of **8** with potassium hydroxide provides fluoxetine's free amine (**9**) in 72% yield, which is stored as the corresponding oxalate salt.

In 1987, Prozac was the first SSRI to hit the U.S. market. After earning $350 million during 1989, Prozac became the country's most prescribed antidepressant by 1990.[64]

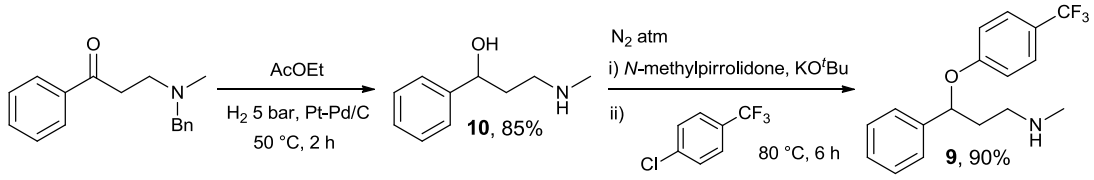
However, Eli Lilly's patented synthetic route suffers from several disadvantages. The *p*-trifluoromethylphenol used for the nucleophilic substitution reaction is not only expensive and unstable, but also unreactive, which makes the *O*-arylation reaction very long (5 day at reflux in methanol). Furthermore, the *N*-demethylation step is difficult and involves the use of the highly toxic CNBr (*Scheme 1.1*).

For these reasons, R. G. Shepherd filed a new patent in 1980 presenting a new alternative method for the etherification reaction, based on the deprotonation of alcohols **5** or **10** with sodium hydride followed by reaction with 1-fluoro-4-(trifluoromethyl)benzene (*Scheme 1.2*).[65] This method avoids the use of the *p*-trifluoromethylphenol and reduces the reaction time of the *O*-arylation reaction from 5 days to overnight.



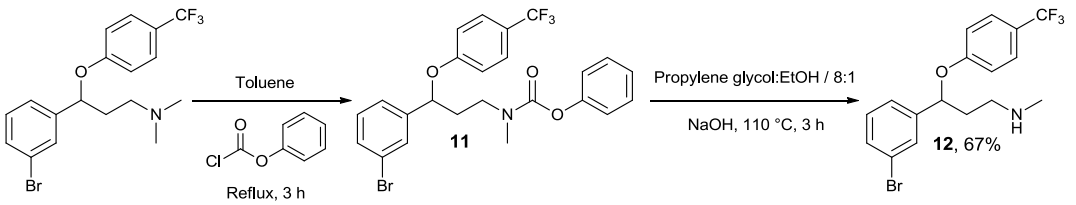

*Scheme 1.2 – Shepherd's patent on the etherification reaction of **5** and **10***

A few years later, Kairisalo et al. patented another synthetic route in which a catalytic hydrogenation followed by an etherification reaction using 1-chloro-4-(trifluoromethyl)benzene and a milder base (i.e. potassium *tert*-butoxide) generates fluoxetine's free amine (**9**) in 87% overall yield over these two last steps.[66] The process is summarised in the scheme below (*Scheme 1.3*). The use of a *N*-protected benzyl derivative instead of a methyl one avoids the challenging demethylation step; the benzyl group being easily removed at the same time as the reduction of the ketone takes place.



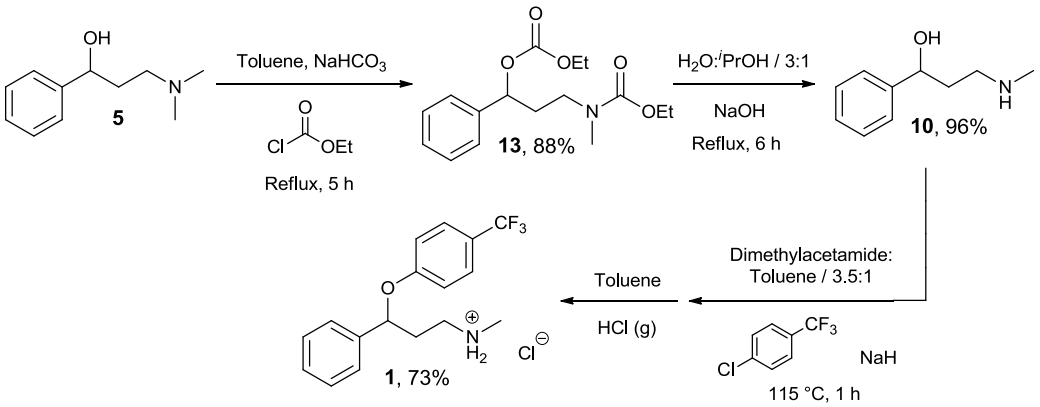

*Scheme 1.3 – Kairisalo's patent on the etherification reaction*

Although Robertson et al. described an early attempt at the *N*-demethylation process in 1987 that avoids the use of cyanogen bromide, the fluoxetine obtained required preparative HPLC for its purification.[67] In that process, cyanogen bromide is replaced by the less toxic phenyl chloroformate and the mixture is refluxed in toluene for 3 h. The carbamate intermediate **11** is then reacted with sodium hydroxide to provide **12** in 67% yield (*Scheme 1.4*). Preparative HPLC is, nevertheless, a too costly purification technique to be carried out on industrial scale.




*Scheme 1.4 – Robertson's N-demethylation process*

It was not until 1993 that Schwartz et al. patented a more efficient methodology for the *N*-demethylation step, based on the reaction sequence depicted in *Scheme 1.5*.[68] Thus, the reaction of 3-dimethylamino-1-phenyl-propan-1-ol (**5**) with ethyl chloroformate and sodium bicarbonate under reflux of toluene for 5 h, provides **13** in 88% yield. This carbamate intermediate **13** is consequently treated with sodium hydroxide to afford amino alcohol **10** in 96% yield. Last, the reaction of **10** with sodium hydride and 4-chlorobenzotrifluoride provides fluoxetine hydrochloride salt (**1**) in 73% yield, after reaction with hydrogen chloride gas in toluene.

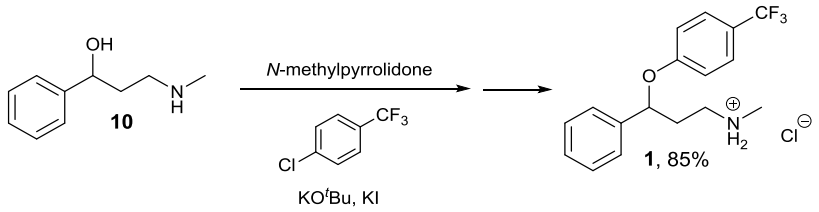



*Scheme 1.5 – Schwartz's N-demethylation process*

Amongst all the patented fluoxetine syntheses, the etherification step has probably been the most challenging and controversial one. Many research groups have argued about which method is the most suitable to carry out this transformation in industrial scale. The most prominent methodologies are detailed below.

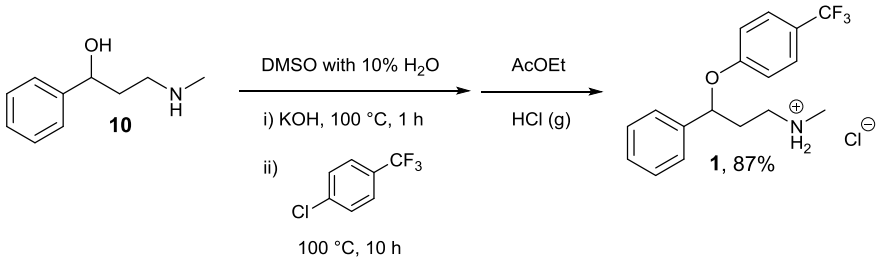
A Hungarian patent by K. P. Juhani in 1992 details the reaction of **10** with 4-chlorobenzotrifluoride in *N*-methylpyrrolidone in the presence of potassium

*tert*-butoxide and potassium iodide to afford fluoxetine (**1**) in 85% yield (*Scheme 1.6*).[69]



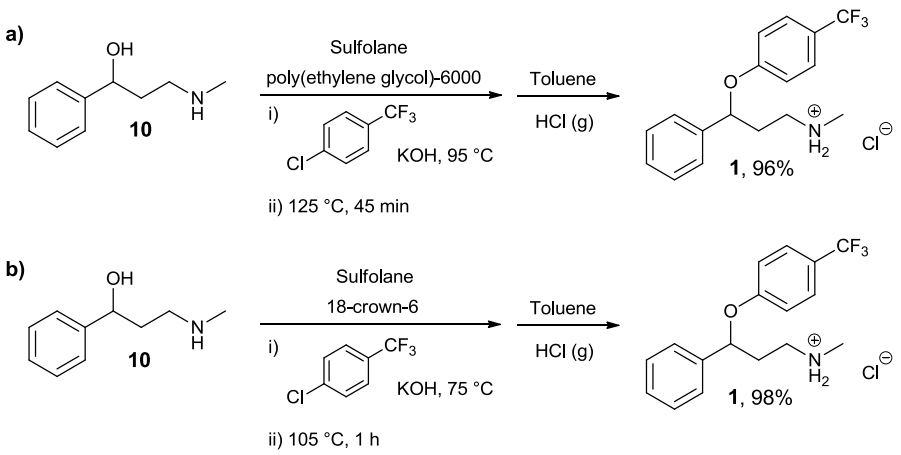

*Scheme 1.6 – Juhani's etherification process*

Two years later, R. G. Vegyészeti et al. published another method using potassium hydroxide as a base in dimethylsulfoxide.[70] Despite of the long reaction time, they were able to use a milder base and obtain fluoxetine hydrochloride (**1**) in 87% yield (*Scheme 1.7*).




*Scheme 1.7 – Vegyészeti's etherification process*

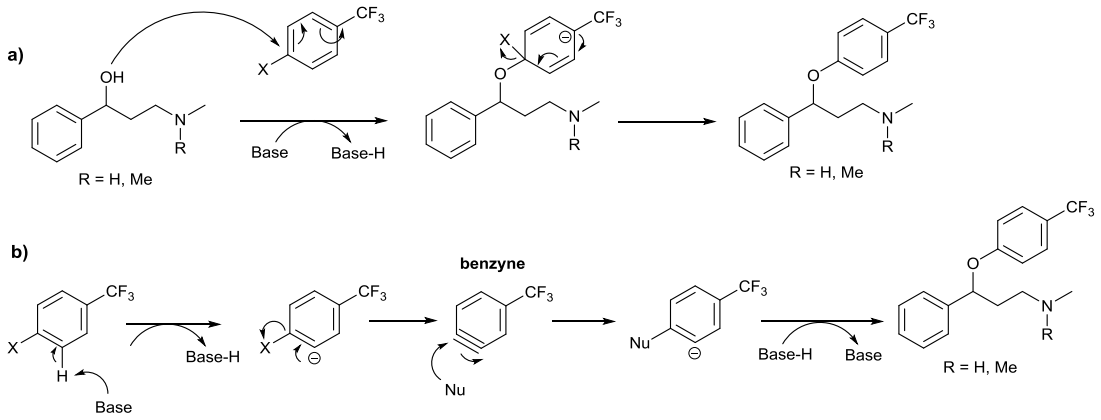
In 2004, Kumar et al. patented a new method for the *O*-arylation step with 4-chlorobenzotrifluoride, using potassium hydroxide as a base. The reaction is performed in sulfolane as a solvent and additives such us poly(ethylene glycol)-6000 (**a**) or 18-crown-6 (**b**), that act as solubility enhancers, are needed (*Scheme 1.8*). This methodology allows high yields in short reaction times.[71]




*Scheme 1.8 – Kumar's etherification process*

Although the mechanism of the arylation reaction for the previous reactions has not been studied in much detail, it is believed to go *via* a nucleophilic aromatic substitution ($S_NAr$).[72] The reaction of the alcohol with the base generates the corresponding alkoxide, which acts as a nucleophile towards the aryl halide to form the *O*-arylated product (*Scheme 1.9 a*).

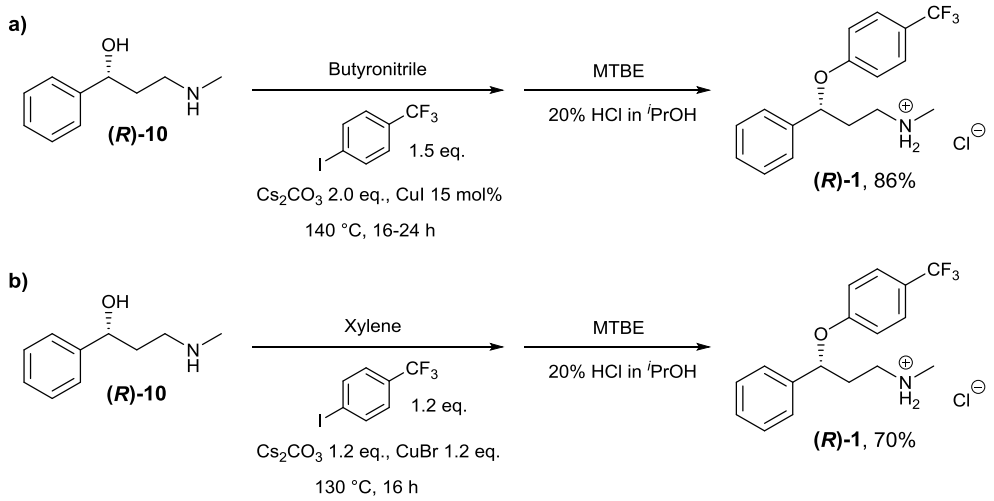
Despite this, in the cases where a strong base is used (e.g. sodium hydride), the formation of benzyne could be considered as well. The removal of the proton in *ortho* to the halide, followed by the elimination of the halide, generates an unstable benzyne intermediate, which is rapidly intercepted by the nucleophile (the hydroxyl group), to generate the corresponding *O*-arylated product (*Scheme 1.9 b*).




*Scheme 1.9 – Mechanism of the O-arylation reaction*

However, the fact that a loss of regioselectivity has never been observed, suggests that the $S_NAr$ is the most plausible mechanism.

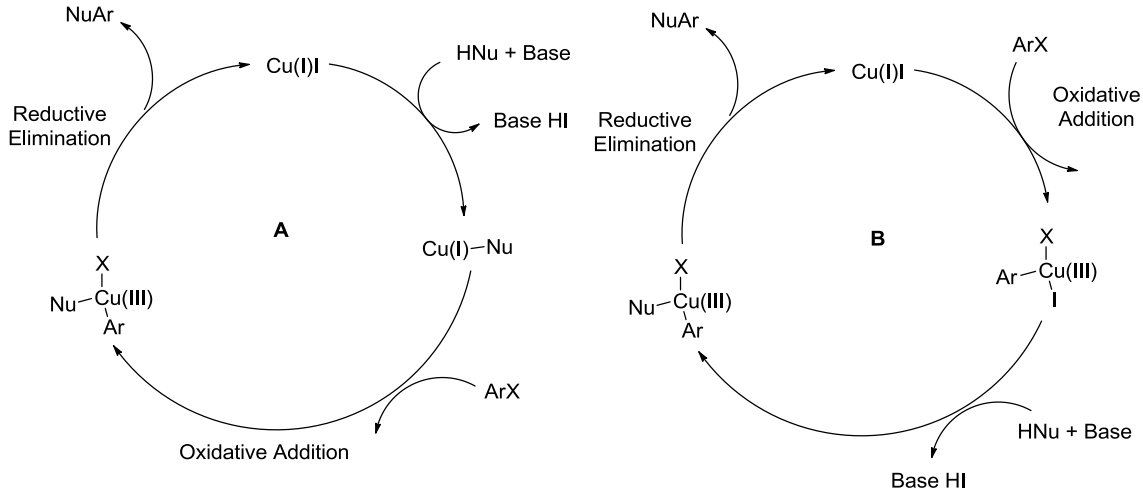
A more recent patent from Wang et al. in 2007 describes the copper (I) coupling reaction between the optically pure (*R*)-*N*-methyl-3-hydroxy-3-phenylpropylamine ((*R*)-**10**) with 4-iodobenzotrifluoride, using cesium carbonate as a base (*Scheme 1.10*).[73]




*Scheme 1.10 – Wang's Cu(I) coupling reaction*

The reaction can be carried out either in butyronitrile, using a catalytic amount of copper iodide (*Scheme 1.10* **a**) or in xylene with stoichiometric amounts of copper bromide (*Scheme 1.10* **b**). Once the coupling reaction is finished, after 16-24 h, the crude is dissolved in methyl *tert*-butyl ether and treated with a 20% hydrogen chloride solution in isopropanol to generate the corresponding hydrochloride salt (*R*)-**1**.

The reaction mechanism for this copper catalysed coupling reaction can be rationalised *via* the Ullmann type reaction catalytic cycle (*Scheme 1.11*).



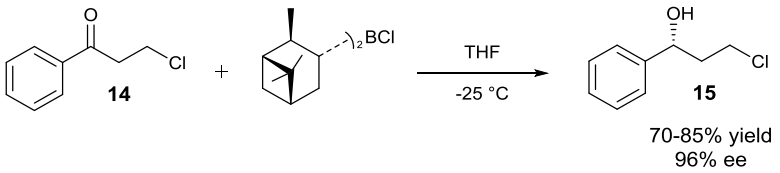

*Scheme 1.11 – Ullmann type reaction catalytic cycle*

The reaction mechanism is believed to proceed through a Cu(I)/Cu(III) catalytic cycle as shown in the previous scheme. However, there are two possible mechanistic pathways that can take place (*Scheme 1.11*).[74] In the first proposal (**A**), the halide on copper is exchanged for the nucleophile and an oxidative addition on the aryl halide forms the copper (III) intermediate. Finally, a reductive elimination step releases the coupling product and regenerates the catalyst. The second route (**B**) starts with the oxidative addition, followed by the exchange for the nucleophile and ends with the reductive elimination.

Although the order of the first two steps is uncertain, recent literature favours route **A**, in which the reaction with the nucleophile takes places before the oxidative addition step.[74]

Although this chapter focuses on the racemic synthesis of fluoxetine, many enantioselective syntheses have been described in the literature since fluoxetine's first patent in 1982. A detailed discussion of those syntheses will not be covered in this thesis; however, some of the asymmetric steps are worth mentioning.

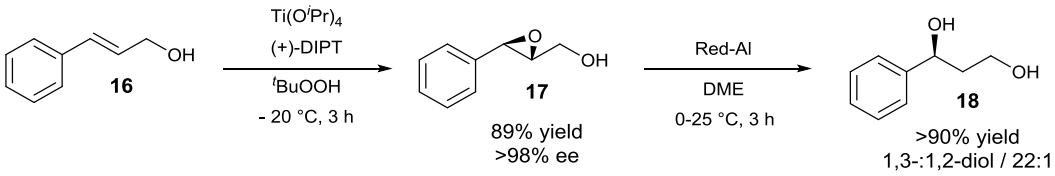
The first chiral synthesis of fluoxetine was published by Brown at al. in 1987.[75] Brown's group carried out the asymmetric reduction of haloalkyl aryl ketones using $Ipc_2BCl$ in THF at –25 °C (*Scheme 1.12*).




*Scheme 1.12 – Brown's asymmetric step for the synthesis of fluoxetine*

Both enantiomers of the corresponding chloro alcohol **15** can be accessed by using the diisopinocampheylchloroborane derived from (+)-α-pinene or (-)-α-pinene.

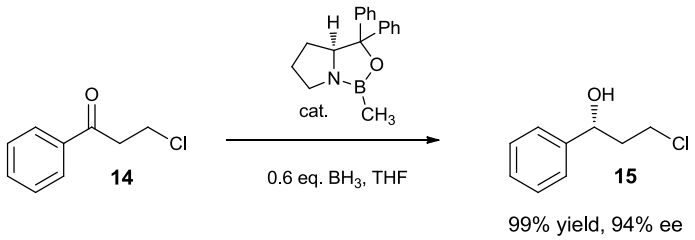
Later, Sharpless et al. published a new asymmetric synthesis of fluoxetine based on an asymmetric epoxidation followed by the selective reduction with Red-Al (*Scheme 1.13*).[76, 77]




*Scheme 1.13 – Sharpless's asymmetric step for the synthesis of fluoxetine*

The asymmetric epoxidation of cinnamyl alcohol (**16**) with (+)-DIPT, titanium tetraisopropoxide and tert-butyl peroxide, leads to the optically pure (2*S*,3*S*)-2,3-epoxycinnamyl alcohol (**17**) in excellent yield and ee. Next, the subsequent reduction of **17** with Red-Al in DME at 0 °C allows the synthesis of **18** in high selectivity (22:1) and excellent yield.

In 1989, Corey et al. reported another enantioselective route to fluoxetine which involves a CBS catalytic reduction process (*Scheme 1.14*).[78] The reduction of **14** with borane (0.6 eq.) in the presence of catalytic amounts of (*S*)-oxazaborolidine (0.1 eq.), in THF at 0 °C, allows the synthesis of the corresponding alcohol **15** in excellent yield (99%) and enantioselectivity (94%).

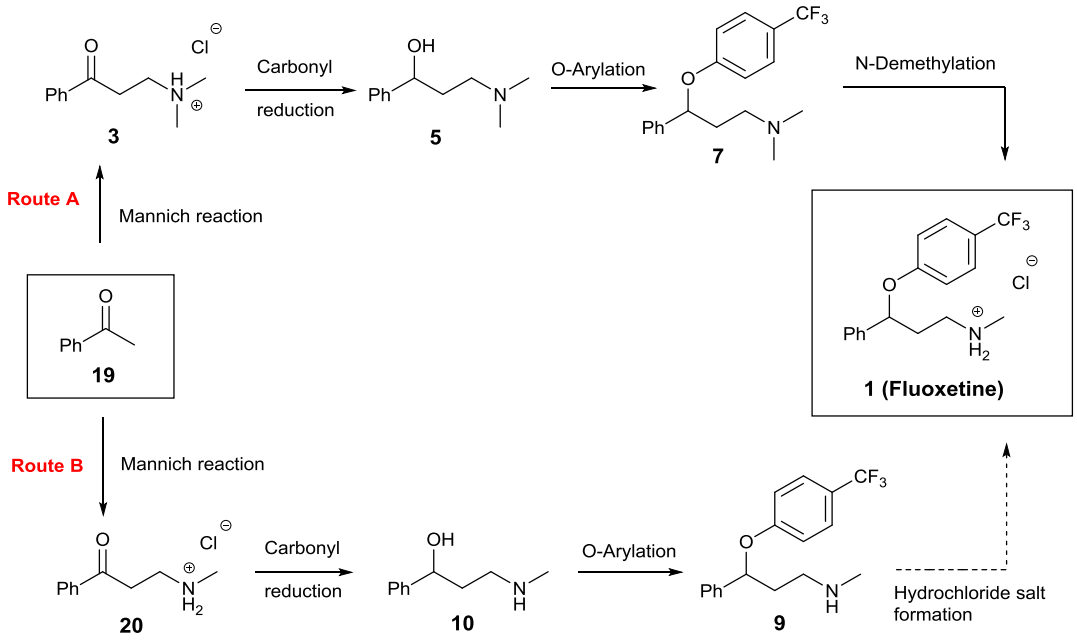



*Scheme 1.14 – Corey's asymmetric step for the synthesis of fluoxetine*

Apart from the above mentioned methods, other procedures for the preparation of optically pure fluoxetine have been reported. Some of the most relevant asymmetric strategies include: enantioselective hydroxylation,[79] enzymatic reduction of ketones and β-ketoesters,[80, 81] stereoselective coupling reaction,[82] and enzymatic[83] or chemical[84] resolution of benzylic alcohols.

## 1.3.2. Results and discussion

Two different synthetic routes (A and B, *Scheme 1.15*)[63, 85-87] were proposed for the synthesis of fluoxetine. Both pathways consist on: (i) a Mannich condensation, (ii) a carbonyl reduction and (iii) an *O*-arylation. In the case of Route A, an additional (iv) *N*-demethylation step is needed in order to obtain fluoxetine hydrochloride. (*Scheme 1.15*)




*Scheme 1.15 – Proposed synthesis for fluoxetine*

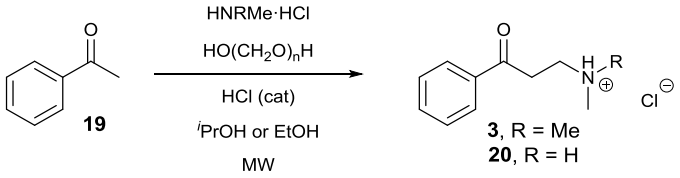
### 1.3.2.1. Step 1 - Mannich Condensation

The Mannich condensation between acetophenone (**19**) and dimethyl- or methylamine hydrochlorides in the presence of paraformaldehyde has been previously described under conventional heating conditions, to provide adducts **3**[88-91] and **20**,[92] respectively.

The analogous Mannich reactions were first attempted under mechanochemical conditions, using both shaker and planetary ball mills. A wide screening of various grinding parameters was performed; including size, number and material of grinding balls, reaction scale and solvent assisted grinding with EtOH and $^{i}$PrOH. The reaction was also performed using different reaction conditions; changing the equivalents of hydrochloride salt and paraformaldehyde. Unfortunately, no conversion higher than 10% was achieved in any case for either **3** or **20**.

When the reactions were performed under microwave irradiation, they provided higher yields in shorter times than the corresponding reactions under conventional heating, which range from 29-86% with reaction times between 1-5 h (*Table 1.3*).[88-92] Thus, the reaction of **19** with 1.25 eq. of dimethylamine hydrochloride and 1.50 eq. of paraformaldehyde in isopropanol, provided the hydrochloride salt **3** in 65% yield in only 1 h at 110 $^{o}$C (*entry 1, Table 1.3*). Longer reaction times did not improve the yield of the reaction (*entry 2*). Similarly, the synthesis of **20** was achieved in 40% yield, using ethanol as solvent and microwave assisted heating at 130 °C (*entry 3*). In this case, the yield of the reaction could be improved to 57% with longer reaction times (5 h, *entry 4*).

*Table 1.3 – MW assisted Mannich reaction for the synthesis of **3** and **20**.*

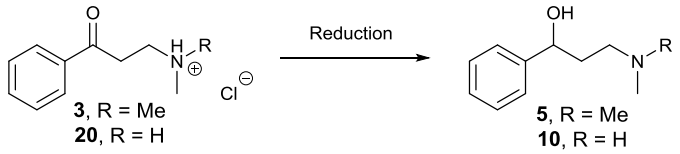



| Entry | Product | HNRMe (eq.) | $HO(CH_2O)_nH$ (eq.) | Solvent | T (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **3** | $HNMe_2$ (1.25) | 1.50 | $^i$PrOH | 110 | 1 | 65 |
| 2 | **3** | $HNMe_2$ (1.25) | 1.50 | $^i$PrOH | 110 | 4 | 59 |
| 3 | **20** | $H_2NMe$ (1.10) | 1.40 | EtOH | 130 | 2 | 40 |
| 4 | **20** | $H_2NMe$ (1.10) | 1.40 | EtOH | 130 | 5 | 57 |

[a] Reaction Conditions: **19** (1 eq.), HNRMe, paraformaldehyde, solvent, MW . [b] Isolated yield.

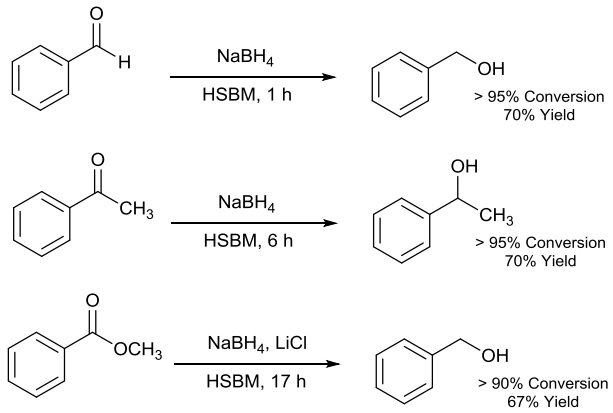
## 1.3.2.2. Step 2 - Carbonyl Reduction

Next, we studied the reduction of **3** and **20** to their corresponding alcohols **5** and **10** (*Scheme 1.16*).



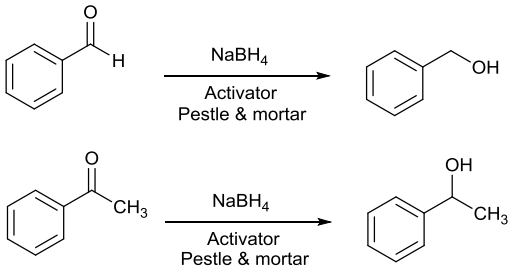

*Scheme 1.16 – Carbonyl reduction reaction*

James Mack et al. described a solvent-free method for the reduction of carbonyl compounds (aldehydes, ketones and esters) using high-speed ball milling (HSBM) technique, in 2007.[93] Their method consisted of the use of $NaBH_4$ as a reducing agent. High conversions (>95%) and isolated yields (up to 70%) for aromatic aldehydes and ketones were achieved under these conditions. In addition, this methodology also allows the reduction of aromatic esters (>90% conversion and up to 67% isolated yield) when lithium chloride is added to the reaction mixture, in order to generate lithium borohydride *in situ* (*Scheme 1.17*).[94]




*Scheme 1.17 – Reduction of carbonyl compounds using HSBM by Mack et al.*

A similar method was developed by B. T. Cho et al. in a pestle and mortar, using $NaBH_4$ as a reducing agent in presence of some activators (*Scheme 1.18*).[95] The results point out that the utilisation of solid acid-activated sodium borohydride shortens the reaction times for the reduction of both aromatic aldehydes and ketones, leading to high yields. However, the use of pestle and mortar requires physical effort and results are hard to reproduce as the energy supplied will depend on the person grinding.

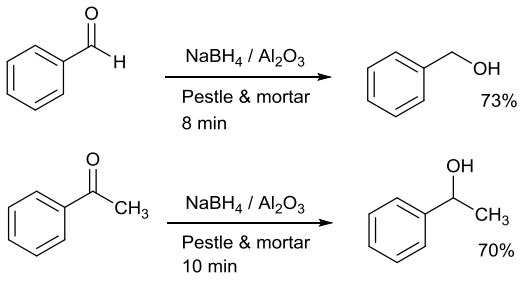



| Activator | Time (min) | Yield (%) |
|---|---|---|
| None | 10 | >99 |
| $H_3BO_3$ | 5 | >99 |
| $PhCO_2H$ | 5 | >99 |
| PTSA[a] | 5 | >99 |
| None | 120 | 18 |
| $H_3BO_3$ | 10 | >99 |
| $PhCO_2H$ | 50 | >99 |
| PTSA[a] | 50 | 70 |

[a] PTSA = *p*-toluenesulfonic acid monohydrate

*Scheme 1.18 – Carbonyl reduction in pestle and mortar using activated $NaBH_4$*

Few years later, in 2010, H. Shalbaf developed a faster method for the reduction of aromatic aldehydes and ketones in a pestle and mortar. This methodology is based on the utilisation of $NaBH_4$ as a reducing agent and $Al_2O_3$ as a solid support (*Scheme 1.19*).[96] Using alumina as a solid inorganic support to immobilize (probably by adsorption) the reagents, generates active sites that are homogeneously dispersed through the reaction mixture. An easy work-up allows the recyclability of this porous solid support.




*Scheme 1.19 – Reduction of carbonyls in pestle and mortar using $NaBH_4/Al_2O_3$*

Inspired by these methodologies described in the literature, we envisioned that the development of a ball milling methodology for the reduction of the fluoxetine precursors **3** and **20** under solvent-free conditions could be feasible.

Thus, the reduction reaction of **3** and **20** was attempted in both a shaker and a planetary ball mill. Different parameters were optimised in order to get the highest yield and shorter reaction times:

a) Type of ball mill: planetary and shaker mills were tested.

   We observed that it was harder to obtain a homogeneous phase in the planetary ball mill due to the large surface that the grinding balls had to cover. Furthermore, it was harder for larger grinding balls to reach the chemicals accumulated in the corners. On the contrary, the round shape of the shaker mill provided a most homogeneous reaction mixture, which, ultimately, led to higher yields compared to the planetary mill.

b) Type of grinding jar/number, size and material of the grinding balls:

   In the case of the planetary ball mill, a 50 mL stainless steel grinding jar was used. Different sizes of stainless steel grinding balls were tested, as well as Zr grinding balls. The best results and most homogeneous phase was obtained when using a 2.5 and a 1.0 cm diameter stainless steel grinding balls simultaneously.

   The shaker mill was tested with both a 25 mL stainless steel grinding jar and a 2 mL plastic Eppendorf inserted in the corresponding holder.

Different combinations of stainless steel grinding balls were tested in the 25 mL stainless steel grinding jar. However, a single 2.5 cm diameter stainless steel grinding ball provided the best fit and the most homogeneous phase.

The reaction in a plastic Eppendorf could only be carried out using Zr grinding balls, since stainless steel balls were damaging/breaking the Eppendorf. Even though we previously stated that the grinding material was the least important parameter in a milling process, in this case, plastic was not a suitable material to use together with stainless steel. This highlights the fact that the density of the materials used has to be considered always.

Full conversion was only obtained when using a 2.5 cm diameter stainless steel grinding ball in the shaker mill. When smaller grinding balls were used in any kind of grinding jar, the reaction did not reach full conversion because the grinding balls got trapped in the reaction mixture. That hampered the grinding and prevented the reaction from continuing.

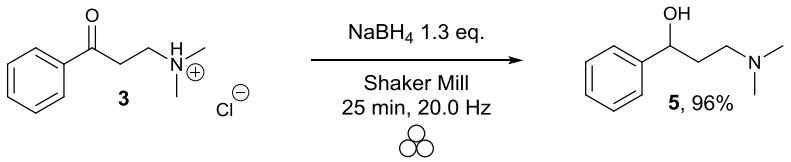
c) Reaction scale: the best way to prevent the grinding balls from becoming fouled in the reaction mixture was to use the 25 mL steel grinding jar in the shaker with a single grinding ball of 2.5 cm diameter. Furthermore, the amount of reagents inserted in the grinding jar has to be limited so the grinding ball can move freely. We found out that the optimal amount of solid inside the grinding jar is 132 mg (all reagents included). In case of our substrate **3**, this equals to work in a 0.5 mmol scale.

d) Solvent assisted reaction: the reduction of substrate **3** with 1.3 eq. of sodium borohydride in the presence of a small amount of MeOH (50 µL per 107 mg of ketone) was tested in the shaker mill. Unfortunately, results were not better than under solvent free

conditions, and the reaction did not reach full conversion after 1 h of shaking at 20.0 Hz.

e) Reaction work-up: when the crude reaction mixture from the reduction of **3** was simply dissolved in ethyl acetate and washed with water, a mixture of the desired product **5** and its corresponding boronate was obtained. An acid/base extraction work-up, however, allowed the hydrolysis of the boronate, and pure product **5** was easily obtained.

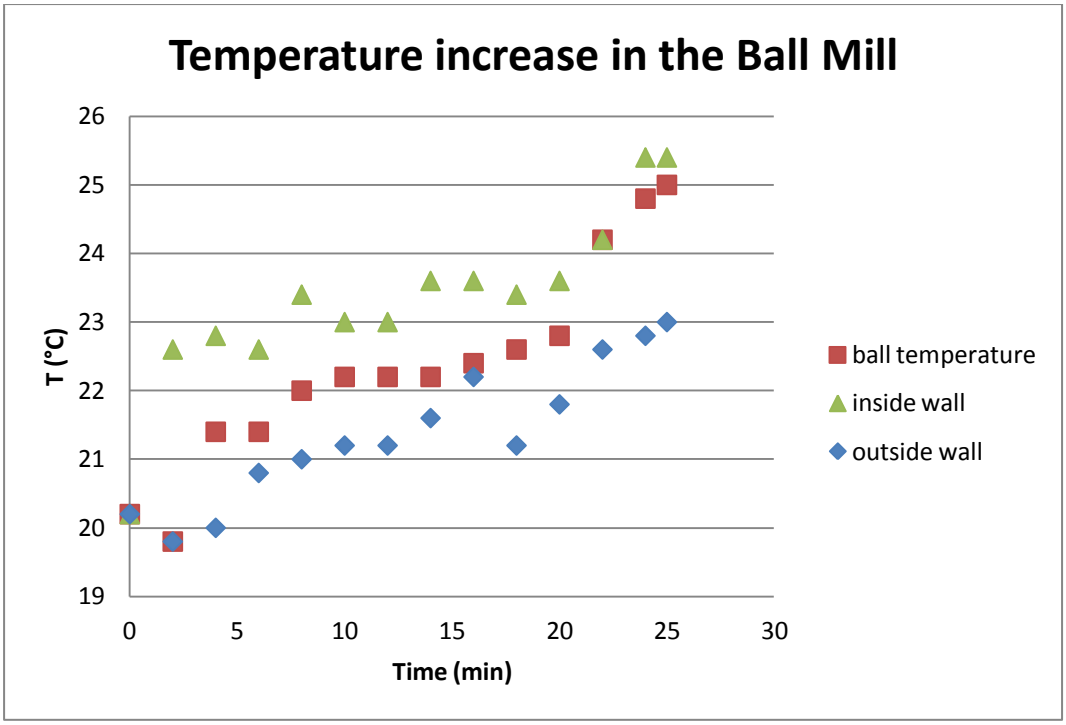
The optimised reaction conditions for the racemic reduction of **3** (Route A) allowed the synthesis of **5** in 96% yield (*Scheme 1.20*). The reaction reached full conversion after grinding at 20.0 Hz for 25 min, using a 25 mL stainless steel grinding jar provided with one stainless steel grinding ball with a diameter of 2.5 cm. No additional reagents or additives were necessary, which allowed a simply purification of **5** by acid/base extraction.




*Scheme 1.20 – Optimised conditions for the racemic reduction of **3***

This new methodology reduces the reaction time to only 25 min of shaking, compared to 15 h reaction time in the solution-based reactions described in the literature.[87, 97] Furthermore, no solvent has to be used for the reaction.

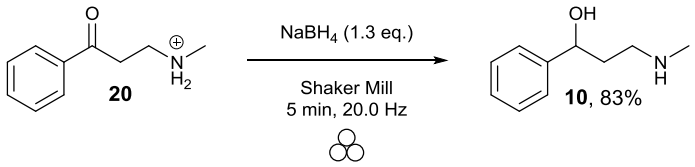
Additionally, in order to know if the temperature was an important parameter for this reaction, an IR thermometer was used to measure the temperature of the grinding ball and the inside and outside walls of the grinding jar every 2 minutes until the reaction was finished. Results are represented in *Graph 1.1* below.




*Graph 1.1 – Temperatures of the ball, inside wall and outside wall of the grinding jar every 2 min of reaction.*

The average increase of temperature for the grinding ball and the inside and outside walls of the grinding jar during the 25 min of reaction is only 4.5 °C. We believe this increase is not significantly high and it is not a determining factor for the reaction.

When the same reaction conditions (1.3 eq. of $NaBH_4$, 20.0 Hz of frequency) were used for the reduction of **20** (Route B), using a 25 mL stainless steel grinding jar provided with one stainless steel grinding ball with a diameter of 2.5 cm, the reaction reached full conversion after only 5 min of grinding, providing 83% yield after purification by acid/base extraction workup (*Scheme 1.21*).

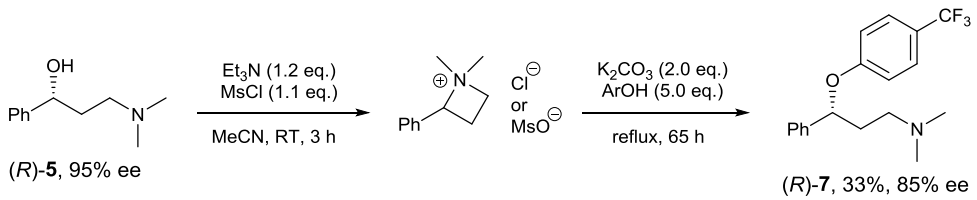



*Scheme 1.21 – Optimised conditions for the racemic reduction of **20***

The yield obtained through this new methodology is similar to the one reported in the literature (90%).[92] However, the reaction time has been shortened from 1 h to only 5 min. Furthermore, our method has the advantage of not requiring any solvent for the reaction.

### 1.3.2.3. Step 3 – *O*-Arylation

In the search of new routes for fluoxetine's syntheses, in 2002, Peter O'Brien developed a methodology to access 3-aryloxy-3-aryl-1-propanamines.[98] This approach is based on the mesylation of the corresponding aminoalcohol **5**, followed by an intramolecular substitution reaction that leads to an azetidinium ion intermediate. A second $S_N2$ reaction where the corresponding phenol acts as nucleophile provides the *O*-arylated product (*R*)-**7** in 33% yield and 85% ee, with overall retention of the configuration (*Scheme 1.22*).[98] The small loss of the enantiopurity is attributed to the ring opening of the azetidinium intermediate.[98]




*Scheme 1.22 – Synthesis of 3-aryloxy-3-aryl-1-propanamines via azetidinium ion intermediate*

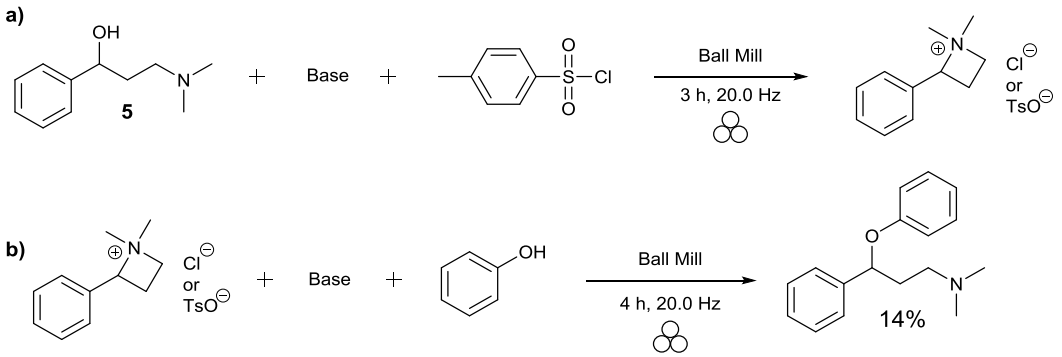
We decided to investigate the effect of ball milling in this reaction, in an attempt to increase the yield. Due to the high toxicity of methanesulfonyl chloride (MsCl), *p*-toluenesulfonyl chloride (TsCl) was used instead in our experiments, using phenol as nucleophile for the preliminary tests (*Scheme 1.23*).

Both shaker and planetary mills were explored for this reaction, using different grinding ball sizes, shaking frequencies/rpm, and reaction times for both steps of the reaction sequence. In all experiments, the planetary mill was used with the 50 mL stainless steel grinding jar while the shaker mill was used with the 25 mL stainless steel grinding jar. The use of plastic

Eppendorfs as grinding jars was discarded and not tested in the shaker mill, based on the previous negative results during the reduction reaction.

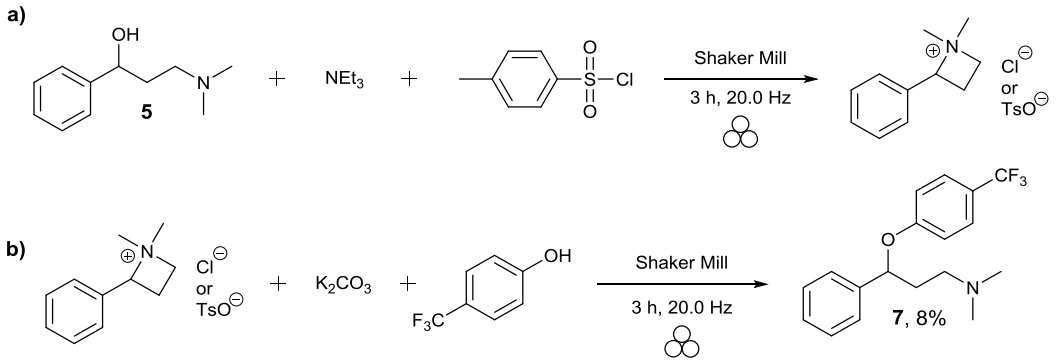
Different bases were also evaluated ($Et_3N$, $K_2CO_3$, DMAP). After a through optimization process, the best conditions for the step 1 (*Scheme 1.23a*) resulted in the use of the shaker mill with the 25 mm diameter stainless steel grinding ball, triethylamine as base (1.2 eq.) and 1.1 eq. of *p*-toluenesulfonyl chloride. Full conversion was achieved (disappearance of **5** confirmed by GC-MS) after 3 h of shaking at 20.0 Hz. Next, the grinding jar was opened and potassium carbonate and phenol were added.

The optimization of step 2 (*Scheme 1.23b*) was therefore carried out in the shaker mill with the 25 mm diameter stainless steel grinding ball. Different bases ($K_2CO_3$ and $NEt_3$) and equivalents of nucleophile (phenol) were tested. The optimal conditions found consisted of the use of potassium carbonate (2.0 eq.) and 5 eq. of phenol. The azetidinium ion intermediate is not visible by GC-MS, so it was not possible to track the progress of the reaction. An overall yield of 14% from **5** was obtained after 4 h of shaking at 20.0 Hz and purification by column chromatography.




*Scheme 1.23 – Tosylation reaction and reaction with phenol*

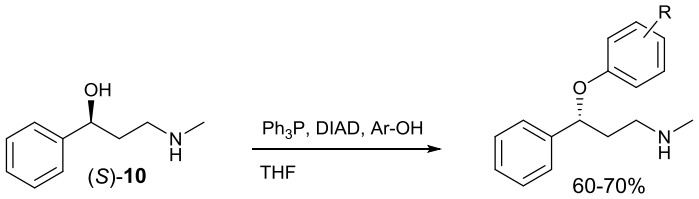
When the optimised conditions were applied using *p*-trifluoromethylphenol as arylating agent, the corresponding product **7** (fluoxetine's precursor) was obtained in 8% overall yield from **5** after 6 h of milling at 20.0 Hz and purification by column chromatography (*Scheme 1.24*). Longer reaction times or different bases ($NEt_3$) in the second step of the reaction were tested, but, unfortunately, higher yields could not be achieved.




*Scheme 1.24 – Tosylation reaction and substitution with phenol derivative*

In spite of all our efforts, the yield of the fluoxetine precursor **7** was very low with this strategy, so we decided to explore new strategies for the *O*-arylation step.

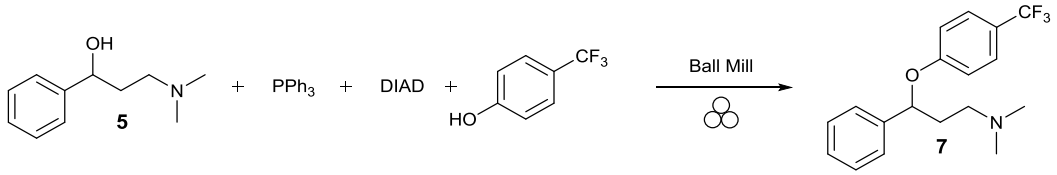
Rej et al. reported, in 2013, a 9 steps asymmetric synthesis of fluoxetine using benzaldehyde as starting material, with 23% overall yield.[99] Their *O*-arylation step consisted on a Mitsunobu reaction, that leads to the corresponding arylated product with inversion of configuration and a yield of 60-70% (*Scheme 1.25*).[99]




*Scheme 1.25 – Mitsunobu reaction with inversion of configuration*

This same strategy was explored in neat conditions using both planetary and shaker ball mills at different frequencies and rpm, testing several grinding ball sizes (*Scheme 1.26*). After optimisation of reaction times and equivalents of each reagent, we concluded that the best results were obtained in the shaker mill, using a single 2.5 cm diameter stainless steel grinding ball at 20.0 Hz for 3h 30min. Thus, the use of triphenylphosphine (1 eq.), diisopropyl azodicarboxylate (1 eq.) and *p*-trifluoromethylphenol (1 eq.), provided 44% conversion and 25% isolated yield of **7**, after purification by column chromatography).

As comparison, when the reaction was carried out in the planetary ball mill, using a 50 mL stainless steel grinding jar provided with both a 2.5 cm and a 1.0 cm diameter stainless steel grinding balls at 250 rpm for 14 h, only 25% conversion of **7** was achieved (determined by GC-MS). Under analogous reaction conditions, liquid assisted grinding was also attempted in the planetary ball mill, using 100 µL of dichloromethane for 0.25 mmol of substrate. Only 15% conversion was obtained after 6 h of grinding at 250 rpm.



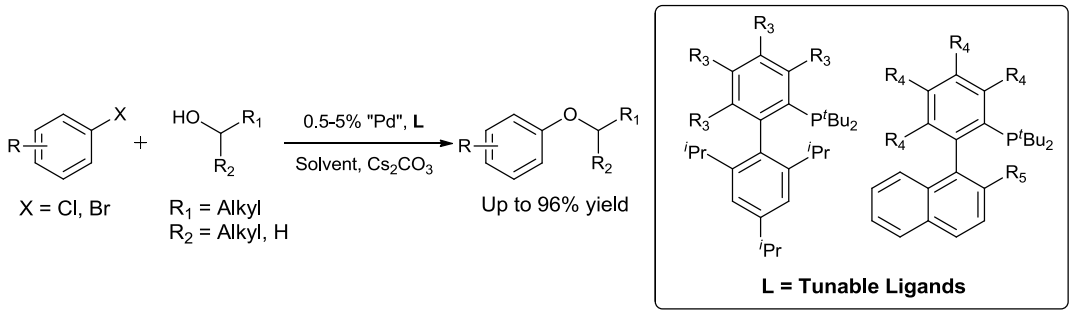

*Scheme 1.26 – Mitsunobu reaction in the ball mill*

Although the yield of **7** obtained with this approach was higher than the previous tosylation strategy, it is still not satisfactory enough to use in a pharmaceutical synthesis. In addition, the fact that a purification by column chromatography is needed is not feasible in a commercially production scale.

As a matter of fact, both previous methodologies generate considerable amounts of waste. In the case of the tosylation reaction, two reaction steps are required and a total of 5 reagents are involved in the reaction. On the other hand, the Mitsunobu procedure is based on stoichiometric amounts of reagents that generate undesired waste such us triphenylphosphine oxide.

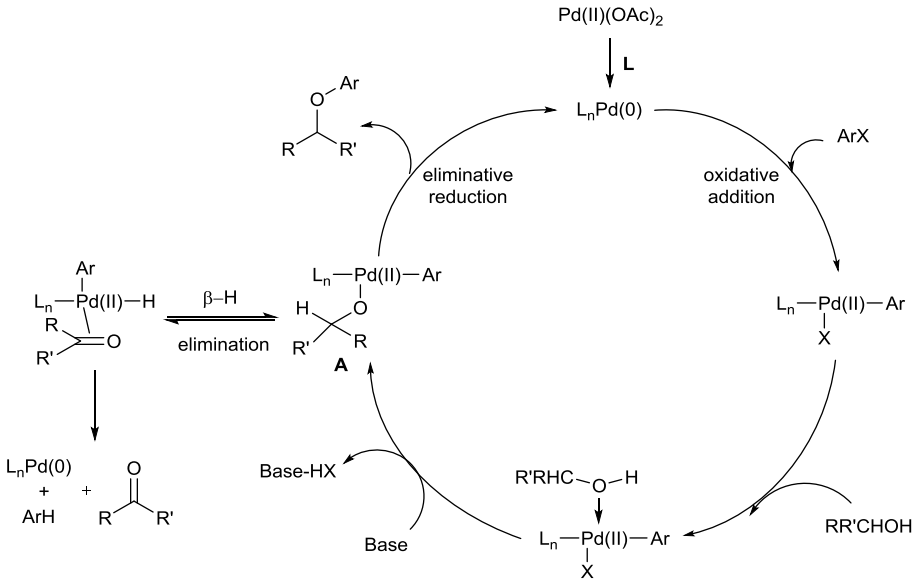
For this particular reasons, we decided to change the approach and look for a catalytic and more sustainable strategy.

Amongst the *O*-arylation reactions present in the literature, the palladium catalysed coupling developed by S. L. Buchwald drew our attention for being a catalytic process with minimal generation of waste (*Scheme 1.27*).[100, 101]




*Scheme 1.27 – Buchwald's palladium catalysed coupling*

The coupling of primary and secondary alcohols with aryl halides is based on the utilisation of $Pd(OAc)_2$, a phosphine ligand and $Cs_2CO_3$ as a base. The catalytic cycle for the process is represented in *Scheme 1.28*.

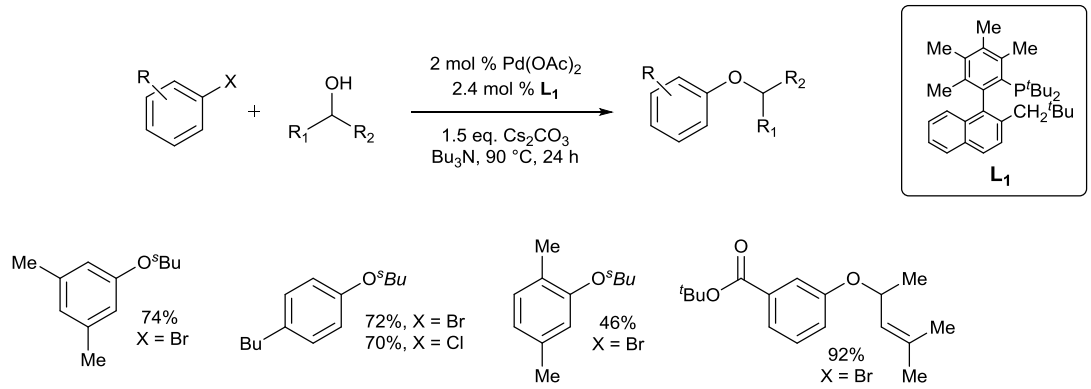



*Scheme 1.28 – Pd catalysed cycle for the O-arylation of secondary alcohols*

As reported by Buchwald et al., the success of this catalytic cycle depends on the ability of the alkoxide intermediate **A** to undergo a reductive elimination, avoiding a β-hydride elimination reaction that would lead to the oxidised product. The best way to prevent β-hydride elimination is the use bulky ligands (see some examples in *Scheme 1.27*) and activated aryl halides.[101]

*Scheme 1.28* below shows some results reported by Buchwald et al. using this methodology. The authors describe a 24 h reaction in tributylamine as solvent, cesium carbonate as base and palladium acetate/**$L_1$** as catalyst. The use of these conditions allows a low catalyst loading (2 mol%) and leads to

yields up to 92%. Satisfyingly, the use of the bulky phosphine **$L_1$** completely suppresses the formation of any β-hydride elimination product. Many functionalities are allowed in the aryl halide coupling partner, however, hindered alcohols provide lower yields.



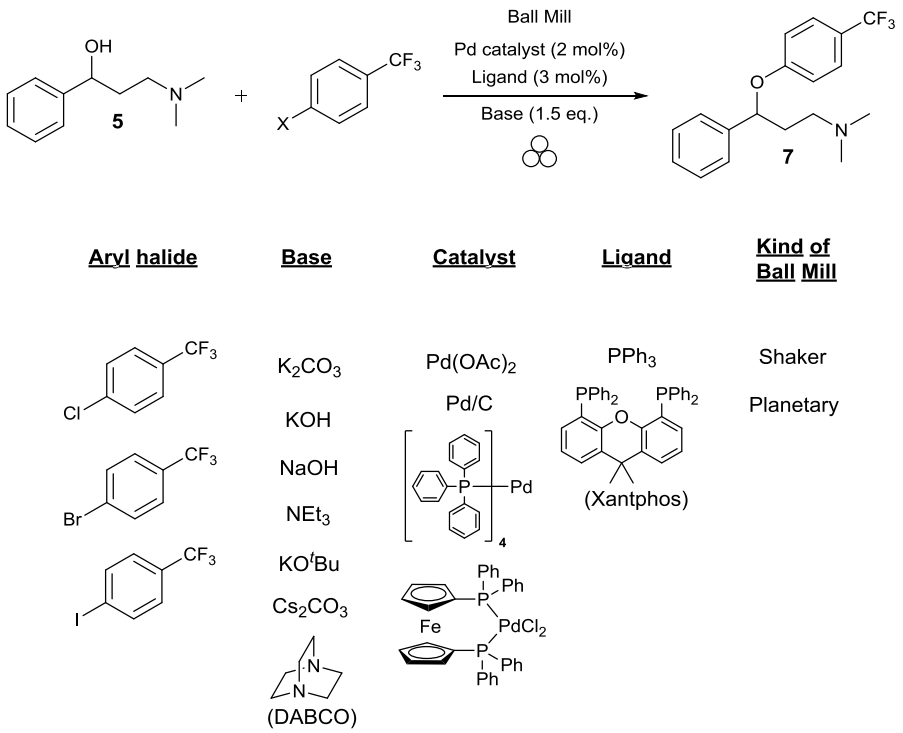

*Scheme 1.28 – Buchwald's methodology results for different secondary alcohols and aryl halides*

Inspired by these results, we tested the Pd catalysed *O*-arylation reaction for our substrate **5** in the ball mill under solvent free conditions. Different bases, Pd sources and phosphine ligands* were evaluated in both the shaker and planetary mill (see *Table 1.4* for further details). In case of the shaker mill, a single 2.5 cm diameter stainless steel grinding ball was used, whereas in the planetary ball mill a 2.5 cm and a 1.0 cm diameter stainless steel grinding balls were used together.

A through screening of different conditions and catalyst combinations was performed, but no product **7** was obtained in any case and the starting material was always recovered.

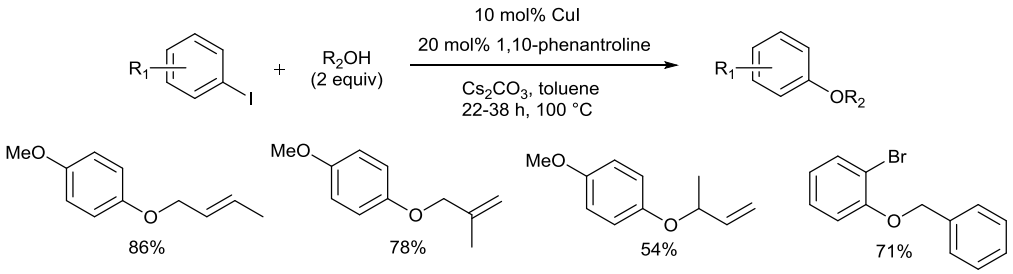
* None of the bulky Buchwald ligands were available in our laboratories and were not tested.

*Table 1.4 – Pd based coupling reaction in solvent free conditions*




We were aware that the use of deactivated *para*-$CF_3$ aryl halides as coupling partners was an extra challenge for this coupling reaction, that would hamper the oxidative addition step. For this reason, we also performed several reactions using iodobenzene as coupling partner instead, however, no *O*-arylation product was observed in any case either.

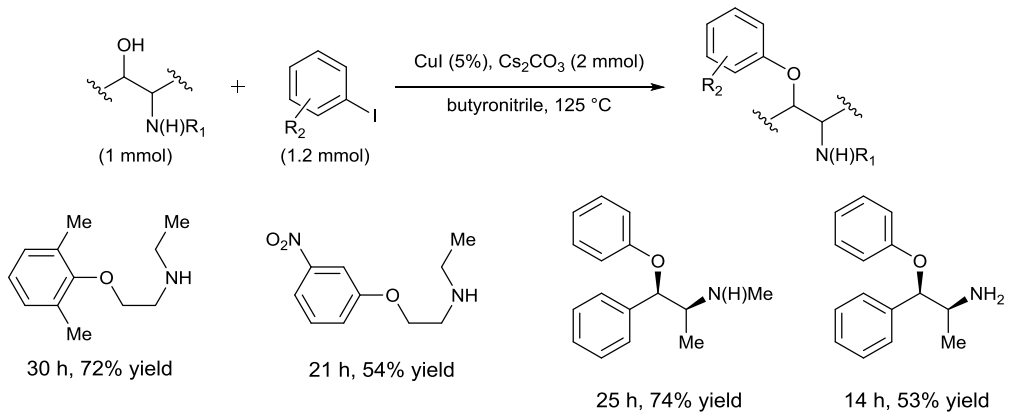
Based on Ullmann's ether synthesis,[102, 103] Buchwald et al. developed another *O*-arylation methodology using CuI as a catalyst and 1,10-phenanthroline as a ligand (*Scheme 1.29*). Thus, the coupling reaction between an aliphatic alcohol (primary or secondary) and an aryl iodide is performed in neat alcohol, or, if the alcohol is a precious compound, the reaction can be carried out in toluene using only 2 eq. of the alcohol.[104] Good yields are obtained using only 10 mol% of CuI and 20 mol% of phenanthroline, using cesium carbonate as base (2 eq.), as depicted in the examples in *Scheme 1.29*.




*Scheme 1.29 – Results of the CuI methodology for different alcohols and aryl iodides*

A few years later, in 2009, Tao et al. extended this methodology to the use of both aryl bromides and chlorides as coupling partners, by using 3,4,7,8-tetramethyl-1,10-phenanthroline as ligand.[105] However, their scope only included the *O*-arylation of benzylic alcohols.

Buchwald et al. also developed a ligand-free copper-catalysed arylation of β-amino alcohols in which the reaction site could be controlled by tuning the reaction conditions.[106] Thus, selective *O*-arylation of amino alcohols with several aryl iodides (1.2 eq.) can be achieved in the presence of CuI (5 mol%), $Cs_2CO_3$ (2 eq.) in butyronitrile at 125 °C (*Scheme 1.30*).



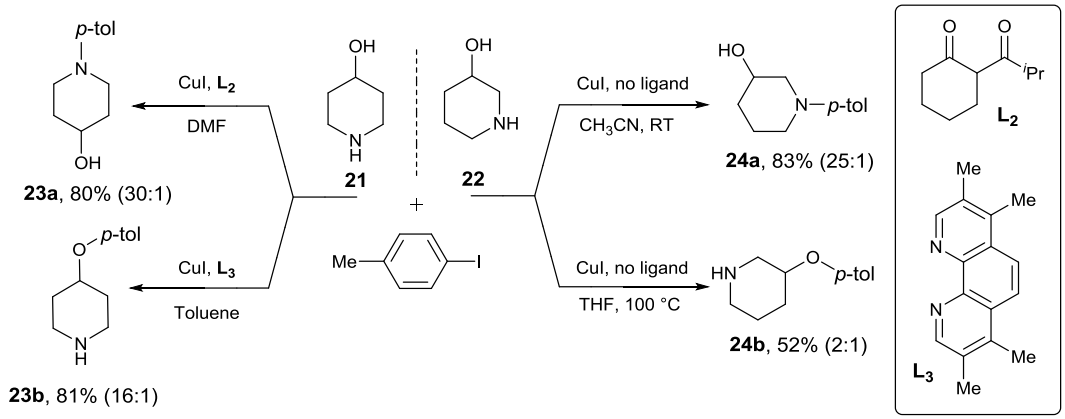

*Scheme 1.30 – Buchwald's selective O-arylation of amino alcohols*

The reaction requires long reaction times (14-48 h), but the method does not require the use of any ligand and allows the synthesis of the *O*-arylated product in moderated to good yields (50-80%). Reactions with primary β-amino alcohols (primary amine) exhibit higher *N*/*O*-arylation ratio and/or higher diaryl byproduct formation compared to the secondary ones.[106]

The absolute lack of reactivity of simple alcohols (e.g. 1-octanol) under these conditions points out that the presence of a neighbouring amine group is necessary for the activation of the alcohol.[106] In fact, the selective ligand free arylation of amino alcohols is only possible because of the formation of a *five-membered* chelate ring (see *Scheme 1.31, formation of products* **24a** and **24b**).[107, 108]

As represented in *Scheme 1.31*, the solvent plays a crucial role in regards the *N*/*O*-arylation selectivity of aminoalcohols where the formation of a five-membered chelate ring is possible. For example, in the presence of CuI as catalyst, the substrate **22** undergoes *N*-arylation with 1-iodo-4-methylbenzene (in good selectivity) when the reaction is carried in acetonitrile, while *O*-arylation is observed (in moderate selectivity) when the THF is used as solvent (*Scheme 1.31*).[107]

For aminoalcohols where it is not possible to form a *five-membered* chelate ring (substrate **21**, *Scheme 1.31*), the use of the ligands $\mathbf{L_2}$ and $\mathbf{L_3}$ allows the selective *N*- or *O*-arylation, respectively.

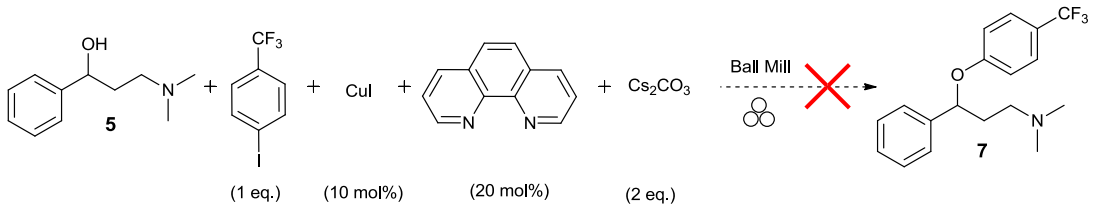



*Scheme 1.31 – Buchwald's N- vs O-arylation of aminoalcohols catalysed by CuI*

With this background, we envisioned that the development of a copper catalysed *O*-arylation reaction for the fluoxetine synthesis could be a good approach and decided to evaluate the reaction with and without a ligand.

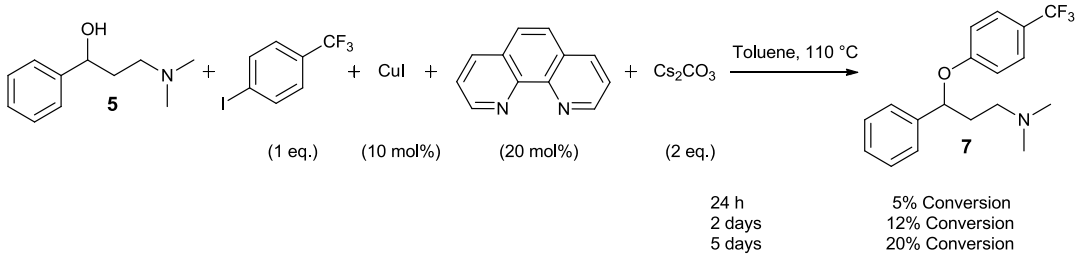
We attempted the *O*-arylation reaction of **5** using ball milling techniques (*Scheme 1.32*) under solventless conditions. The reaction was attempted in

the shaker mill at 20.0 Hz using a 25 mm diameter stainless steel grinding ball, and in the planetary ball mill at 250 rpm using a 25 mm and a 10 mm diameter stainless steel grinding balls. Unfortunately, no product was obtained and starting material was recovered in all cases (0% conversion).




*Scheme 1.32 – CuI coupling reaction in the ball mill*

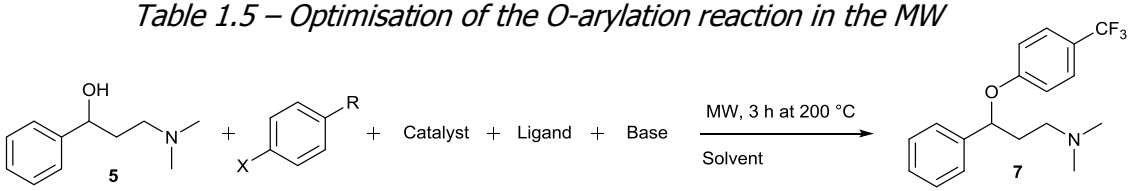
As a mode of comparison, we performed the *O*-arylation reaction of **5** under classical conditions (reflux in toluene, *Scheme 1.33*), using 1 eq. of the aryl iodide, 10 mol% of CuI, 20 mol% of 1,10-phenanthroline and 2 eq. of cesium carbonate. Surprisingly, we observed very low conversion (20%) after 5 days of reaction time (*Scheme 1.33*).




*Scheme 1.33 – CuI coupling reaction in solvent conditions*

However, we were pleased to find out that the reaction of **5** (0.1 M in toluene) and 1-iodo-4-(trifluoromethyl)benzene (1 eq), with 10 mol% of CuI, 20 mol% of 1,10-phenanthroline and 2 eq. of cesium carbonate gave 75% conversion when carried out with MW assisted heating with only 3 h at 200 °C (*entry 1, Table 1.5*). With this preliminary results in hand, we performed an extensive optimization screening in order to find the best conditions for this synthetic step (*Table 1.5*).

*Table 1.5 – Optimisation of the O-arylation reaction in the MW*




| Entry | Aryl halide | Catalyst | Ligand | Base | Solvent | Conc. of 5 | Conv.[b] |
|---|---|---|---|---|---|---|---|
| 1 | X = I, R = $CF_3$ | CuI (10 mol%) | 1,10-phenanthroline (20 mol%) | $Cs_2CO_3$ | toluene | 0.1 M | 75% |
| 2 | X = I, R = H | CuI (10 mol%) | 1,10-phenanthroline (20 mol%) | $Cs_2CO_3$ | toluene | 0.1 M | 60% |
| 3 | X = I, R = H | CuI (10 mol%) | 2,2'-bipyridine (20 mol%) | $Cs_2CO_3$ | toluene | 0.1 M | 73% |
| 4 | X = I, R = H | CuI (10 mol%) | 2,2'-bipyridine (20 mol%) | KOH | toluene | 0.1 M | 0% |
| 5 | X = I, R = H | CuI (10 mol%) | 2,2'-bipyridine (20 mol%) | $KO^tBu$ | toluene | 0.1 M | 0% |
| 6 | X = I, R = H | CuI (10 mol%) | 2,2'-bipyridine (20 mol%) | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 96% |
| 7 | X = I, R = H | CuI (10 mol%) | 2,2'-bipyridine (20 mol%) | $Cs_2CO_3$ | 1,2-dichlorobenzene | 0.1 M | 63% |
| 8 | X = I, R = H | CuI (10 mol%) | 2,2'-bipyridine (20 mol%) | $Cs_2CO_3$ | DMF | 0.1 M | 64% |
| 9 | X = I, R = H | CuI (10 mol%) | 2,2'-bipyridine (20 mol%) | $Cs_2CO_3$ | ethylbenzene | 0.1 M | 81% |
| 10 | X = I, R = $CF_3$ | CuI (10 mol%) | 2,2'-bipyridine (20 mol%) | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 98% |
| 11 | X = I, R = $CF_3$ | no catalyst | no ligand | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 10% |
| 12 | X = I, R = $CF_3$ | CuI (20 mol%) | 2,2'-bipyridine (40 mol%) | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 92% |
| 13 | X = I, R = $CF_3$ | CuI (5 mol%) | 2,2'-bipyridine (10 mol%) | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 90% |
| 14 | X = I, R = $CF_3$ | CuI (10 mol%) | no ligand | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 99% |
| 15 | X = I, R = $CF_3$ | CuI (10 mol%) | no ligand | $Cs_2CO_3$ | xylene (isomer mixture) | 0.1 M | 80% |
| 16 | X = I, R = $CF_3$ | CuI (10 mol%) | no ligand | $Cs_2CO_3$ | *p*-xylene | 0.1 M | 68% |
| 17 | X = I, R = $CF_3$ | CuI (20 mol%) | no ligand | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 99% |
| 18 | X = I, R = $CF_3$ | CuCl (10 mol%) | no ligand | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 99% |
| 19 | X = I, R = $CF_3$ | $CuCl_2$ (10 mol%) | no ligand | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 74% |
| 20 | X = I, R = $CF_3$ | CuI (10 mol%) | no ligand | $Cs_2CO_3$ | *o*-xylene | 0.2 M | 76% |
| 21 | X = Br, R = $CF_3$ | CuI (10 mol%) | no ligand | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 51% |
| 22 | X = Cl, R = $CF_3$ | CuI (10 mol%) | no ligand | $Cs_2CO_3$ | *o*-xylene | 0.1 M | 1% |

*[a] Reaction Conditions: **5** (1.0 eq.), aryl halide (1.1 eq.), base (2.0 eq.) [b] Conversion determined by GC-MS after heating for 3h at 200 °C*

Our optimization studies started by evaluating the reaction of **5** with iodobenzene using 1,10-phenanthroline and 2,2'-bipyridine as ligands (*entries 2 and 3* respectively), using $Cs_2CO_3$ (2 eq.) as base in toluene. The later ligand, 2,2'-bipyridine, provided higher conversion (73%*, entry 3*, versus 60%, *entry 2*), so it was selected for the next reactions.

Other bases such as KOH and KO$^t$Bu were tested (*entries 4* and *5*) but no product **7** was obtained at all. We also screened different solvents (*entries 6-9*); *o*-xylene providing the highest conversion (96%, *entry 6*). The method seemed robust and similar result was obtained when 4-iodobenzotrifluoride was used as coupling parter (98% conversion, *entry 10*).

In the absence of any copper salt and ligand, the *O*-arylation reaction of **5** with 4-iodobenzotrifluoride led only to 10% conversion (*entry 11*). Higher loadings of CuI and ligand (20 and 40 mol%, respectively) did not improve the conversion of the reaction (*entry 12*) while lower CuI/ligand loadings (5 and 10 mol%, respectively) lead to an small drop in conversion (entry *13*).

Gratifyingly, the *O*-arylation of **5** with 4-iodobenzotrifluoride worked in the presence of 10 mol% of CuI without any ligand (*entry 14*), reaching full conversion after 3 h.

It is important to note that when an isomeric mixture of xylene was used as solvent, instead of *o*-xylene, the conversion was lower (80%, *entry 15,* versus 99%, *entry 14*), and when the reaction was performed in *p*-xylene, only a 68% conversion was obtained after 3 h (*entry 16*). We believe this could be due to the decrease of the dipole moment of the *p*-xylene compared to the other isomers of the molecule.

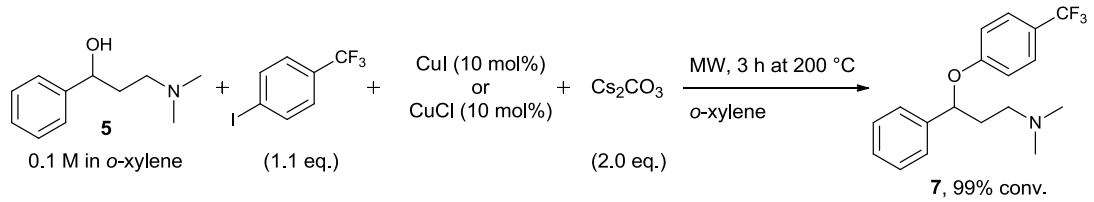
Doubling the amount of CuI to 20 mol% did not shorten the reaction time (*entry 17*).

In addition, we screened different copper sources (*entries 18* and *19*). CuCl proved to be as efficient as CuI (99% conversion, *entry 17*) whilst with $CuCl_2$ (*entry 19*), lower conversion was obtained (74%).

Next, we evaluated the concentration of substrate **5** in the reaction. Unfortunately, higher concentrations than the original 0.1 M led to lower conversions (*entry 20*).

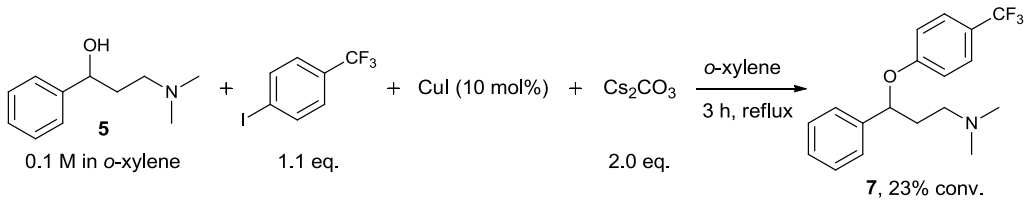
Last, we applied our optimised conditions for the *O*-arylation of **5** with 4-bromobenzotrifluoride and 4-chlorobenzotrifluoride (*entries 21* and *22* respectively). However, low conversion (51%) was obtained in the case of the corresponding aryl bromide and no reaction took place when the aryl chloride was used as coupling partner.

To summarise, the best conditions to carry out the *O*-arylation of **5** (Route A) are shown in the scheme below (*Scheme 1.34*). This methodology allows the synthesis of the fluoxetine's precursor ***7*** in 99% conversion after 3 h of MW dielectric heating.




*Scheme 1.34 – Optimised conditions for the O-arylation reaction of **5** under MW irradiation*

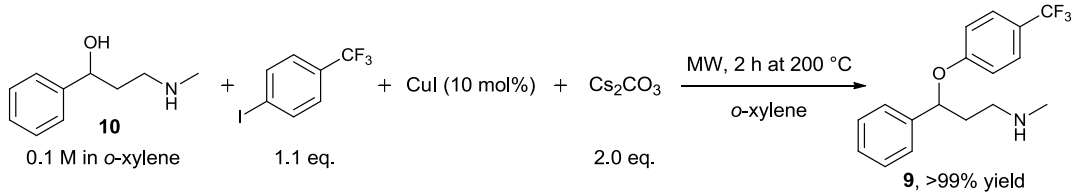
When the analogous reaction, under the same conditions, was carried out in solution (using an oil bath) only 23% of conversion was reached after 3 h of heating to reflux at 145 °C (see *Scheme* below). This result points out the advantages of using MW assisted heating, supporting the higher rates of reaction previously described in the literature.[47]




*Scheme 1.35 – O-arylation reaction of **5** under traditional heating*

Next, we applied the optimised reaction conditions to the *O*-arylation of **10** (Route B). Satisfyingly, the reaction reached full conversion after only 2 h of

microwave assisted heating and a simple filtration through a plug of Celite® allowed us to obtain **9** in a quantitative yield (*Scheme 1.36*).




*Scheme 1.36 - Optimised conditions for the O-arylation reaction of **10***

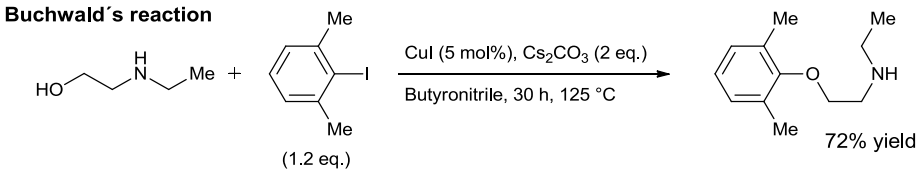
1.3.2.3.1. *O*-Arylation – Scope of the reaction

Being aware of the potential of the methodology just developed, we decided to expand the scope of the reaction using different amino alcohols and aryl iodides. As a reference, the results would be compared to the ones previously described by Buchwald's research group.[106-108]

Our aim was to proof that MW assisted heating would decrease the long reaction times described by Buchwald and, at the same time, analyse if our methodology would lead to higher N/O selectivities.

The *O*-arylation of 2-(methylamino)ethanol with 2-iodo-1,3-dimethylbenzene was chosen as model reaction (*Scheme 1.38*).

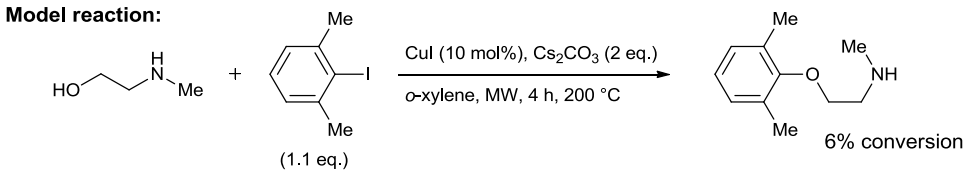
Under Buchwald´s reaction conditions[106] (5 mol% CuI, 1.2 eq. of aryl iodide and 2 eq. of cesium carbonate) the *O*-arylation of 2-(ethylamino)ethanol proceeds in 72% yield after 30 h, using butyronitrile as solvent, under classical reflux conditions (*Scheme 1.37*).




*Scheme 1.37 – Buchwald O-arylation reaction of 2-(ethylamino)ethanol under classical reflux conditions*

When our optimised conditions for the *O*-arylation reaction of **5** (*Scheme 1.34*) were applied to our model reaction with 2-(methylamino)ethanol, 6%

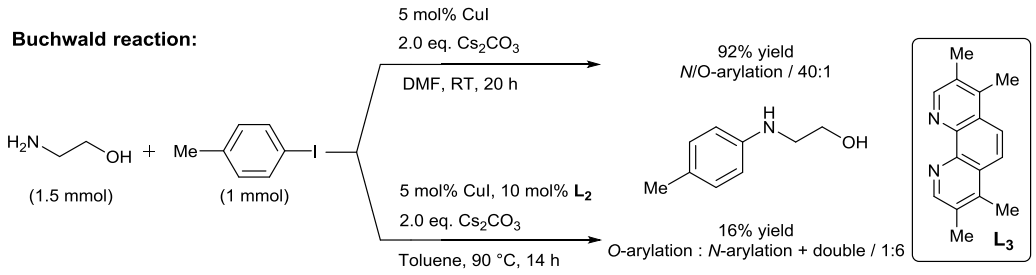
conversion was obtained after 4 h of MW assisted heating (*Scheme 1.38*). Even though we only observed *O*-arylation product, the reaction was much slower compared to the one developed by Buchwald's group (*Scheme 1.37* vs *Scheme 1.38*).




*Scheme 1.38 – O-arylation reaction of 2-(methylamino)ethanol under MW irradiation*

Next, we decided to examine the difference in the *N*/*O*-arylation ratio when using primary amines as substrates. We chose the coupling of ethanolamine with *p*-iodotoluene as model reaction (*Scheme 1.40*).

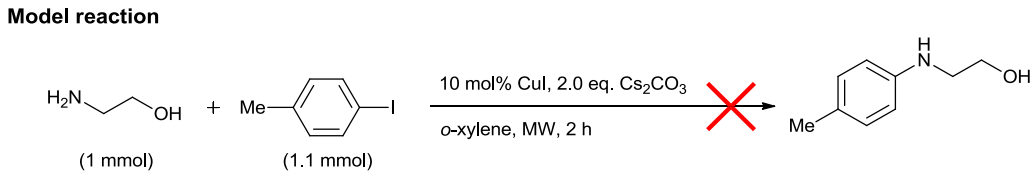
Buchwald described the reaction between ethanolamine and *p*-iodotoluene under two different reaction conditions (*Scheme 1.39*).[107] The ligand free reaction in dimethylformamide at room temperature leads to the *N*-arylated product in high yield (92%). However, when toluene is used as a solvent at 90 °C, together with ligand **$L_3$** (Buchwald's optimal conditions for *O*-arylation) the desired *O*-arylation product is obtained with poor selectivity and low yield (16%, *Scheme 1.39*).




*Scheme 1.39 – Buchwald O-arylation reaction of ethanolamine under classical reflux conditions*

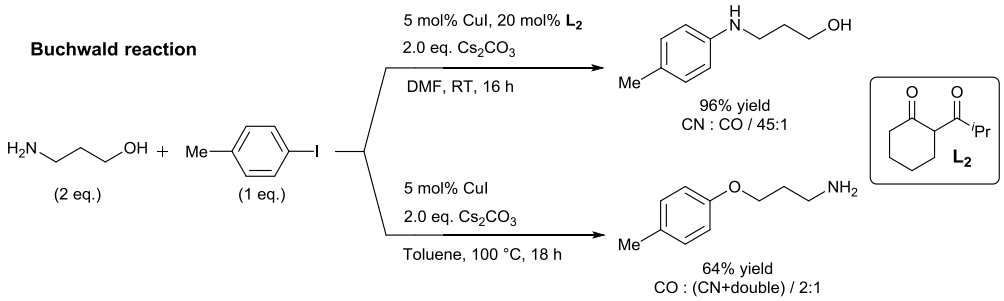
In an attempt to improve Buchwald´s results, we carried out the *O*-arylation reaction of ethanolamine using our coupling optimised conditions in the microwave. However, in spite of increasing our catalyst loading up to 10

mol%, no product was observed after 2 h of heating under MW conditions (*Scheme 1.40*).



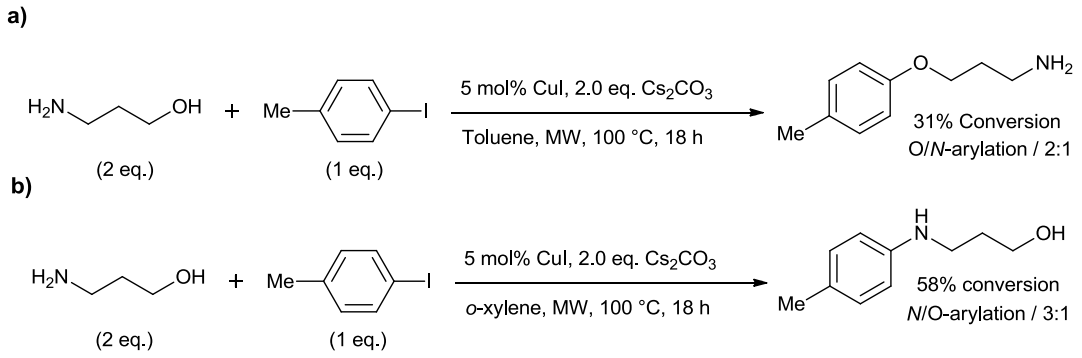

*Scheme 1.40 – O-arylation reaction of ethanolamine under MW irradiation*

Next, we studied the reaction of 3-aminopropan-1-ol with *p*-iodotoluene. Under Buchwald´s conditions,[107] the reaction, in the presence of **$L_2$** and dimethylformamide as solvent affords the corresponding *N*-arylated product in excellent yield and selectivity (96%, 45:1) at room temperature (*Scheme 1.41*). When the same reaction is executed in toluene at 100 °C in the absence of any ligand, the *O*-arylated product is only obtained in moderate yield (64%) and low selectivity (2:1, *Scheme 1.41*).




*Scheme 1.41 – O-Arylation reaction of 3-aminopropan-1-ol under classical Buchwald conditions*

We attempted the same reaction conditions using MW assisted heating instead of classical reflux conditions (*Scheme 1.42*). Unfortunately, we obtained the same *O*/*N*-arylation selectivity (2:1) and lower conversion (31%, *Scheme 1.42a*) than Buchwald´s report.[107] Interestingly, when *o*-xylene was used as solvent, a switch in the *N*/*O*-arylation selectivity was observed (*N*/*O* 3:1), although the conversion for this reaction was only 58% (*Scheme 1.42b*).

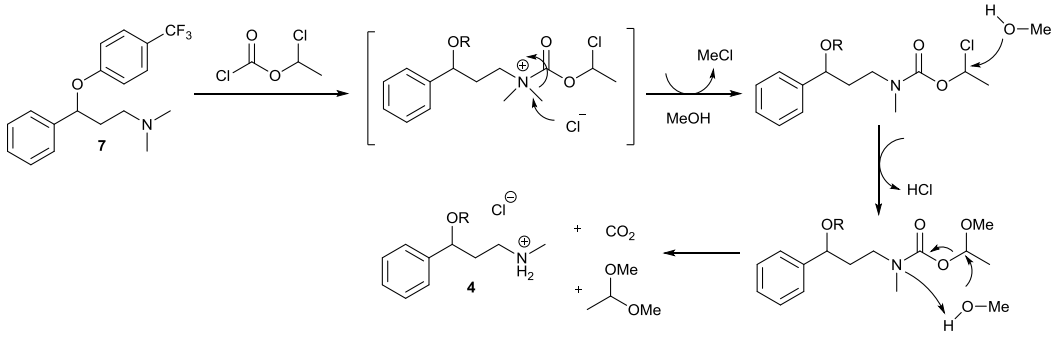



*Scheme 1.42 – O-Arylation reaction of 3-aminopropan-1-ol under MW irradiation*

The switch in *N*/*O*-arylation selectivity that the solvent provided is an interesting fact. With further optimization, and perhaps with the aid of some ligands, the reaction could reach good levels of selectivities under MW irradiation, in shorter reaction times than Buchwald´s methodology. More work needs to be carried out in this area.

### 1.3.2.4. Step 4 - *N*-Demethylation

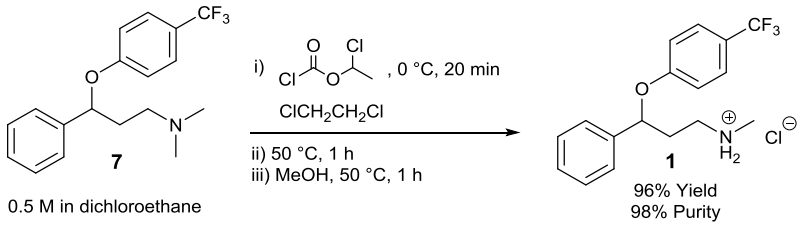
In 1984, Olofson, Senet et al. described the use of $\alpha$-chloroethyl chloroformate for the selective *N*-dealkylation of tertiary amines.[109] The tertiary amine reacts with $\alpha$-chloroethyl chloroformate, and the carbamate intermediate is subsequently treated with methanol. The mechanism of the process is described below (*Scheme 1.43*).




*Scheme 1.43 – Mechanism for the N-dealkylation reaction with $\alpha$-chloroethyl chloroformate*

Some years later, in 2000, R. Noyori et al. successfully applied this methodology to the *N*-demethylation of **7**, leading to fluoxetine

hydrochloride (**1**) in 96% yield.[110] The reaction conditions are described in *Scheme 1.44* below.




*Scheme 1.44 – Reaction conditions for the N-dealkylation of **7** by R. Noyori*

Many attemps were done in order to reproduce Noyori's reaction (*Scheme 1.44*) but unfortunatelly none of them were successful.

The demethylation of **7** with α-chloroethyl chloroformate was first attempted in dichloromethane (0.1 M) under the above described reaction conditions, but only 2% conversion was observed after the treatment of the corresponding carbamate with methanol.

The reaction was also attempted under reflux conditions. Unfortunately, refluxing a mixture of **7** and α-chloroethyl chloroformate during 15 h in dichloromethane, followed by the addition of methanol and subsequent stirring at 50 °C for 1 h; did not improve the conversion (4%). When the concentration of **7** was increased to 0.5 M in dichloromethane, the reaction only reached 7% conversion.

The reaction was then carried out in dichloroethane as solvent (0.1 M and 0.5 M of **7**), under the same conditions reported in the literature,[110] but no improvement in conversion (*c.a.* 7%) was observed after 6 h of classical reflux.

A neat reaction in 5 eq. of α-chloroethyl chloroformate was also carried out, but the reflux of the mixture for 3 h only led to decomposition products.

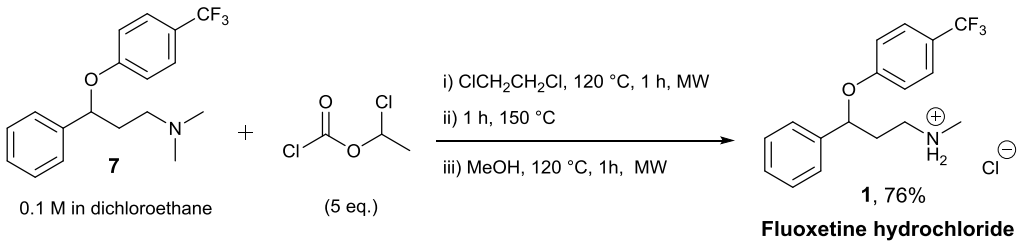
After these unsuccessfull attemps to carry out this reaction under classical heating conditions, ball milling technologies and microwave assisted reactions were also assayed.

The reaction was tried in the planetary ball mill using a 25 mm and a 10 mm diameter stainless steel grinding balls in the 50 mL stainless steel grinding jar. A mixture of **7**, α-chloroethyl chloroformate (1 eq.) and methanol (5 eq.) were ground for 21 h at 250 rpm, but the reaction only led to 3% conversion.

Surprisingly, when the same reaction was performed with microwave assisted heating using 5 eq. of α-chloroethyl chloroformate, 89% conversion was obtained after heating for 2 h in dichloroethane (1 h at 120 °C and 1 h at 150 °C), followed by the addition of methanol and subsequent heating for 1 h at 120 °C.

Longer reaction times with MW irradiation did not increase the conversion. After 1 h at 120 °C and 3 h at 150 °C in dichloroethane and 1 h at 120 °C in methanol, the conversion of **7** into **1** was still 88%.

After the *N*-demethylation reaction, a recrystallisation in AcOEt:hexane led to 76% yield of pure fluoxetine hydrochloride (**1**, 66 mg) (*Scheme 1.45*).

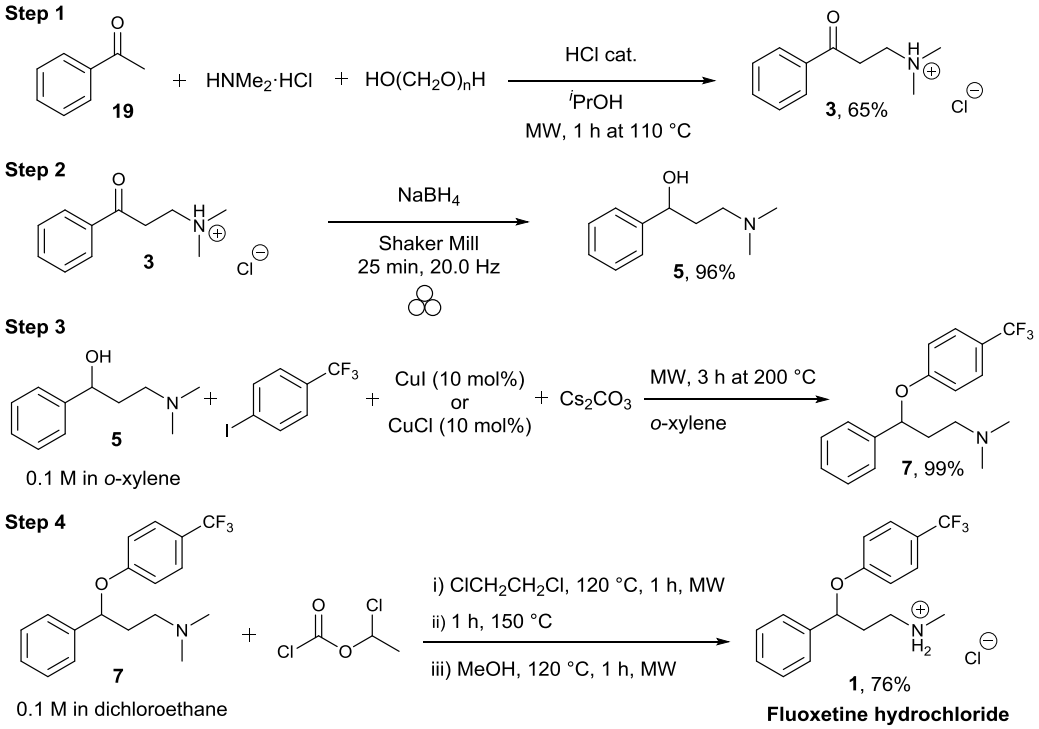



*Scheme 1.45 – N-Demethylation reaction with MW assisted heating*

## 1.3.3. Conclusions

A greener synthesis of fluoxetine has been developed. Fluoxetine hydrochloride (**1**) has been obtained with an overall yield of 47% through both Routes A or B.

The developed synthesis of fluoxetine through Route A is summarized below (*Scheme 1.46*).




*Scheme 1.46 – Route A, greener synthesis for the preparation of fluoxetine hydrochloride*

- The Mannich condensation of acetophenone (**19**) led to the aminoketone **3** in 65% yield after only 1 h of heating in the microwave (Step 1). This shortens considerably the Mannich reaction times previously described in the literature.[88-91]

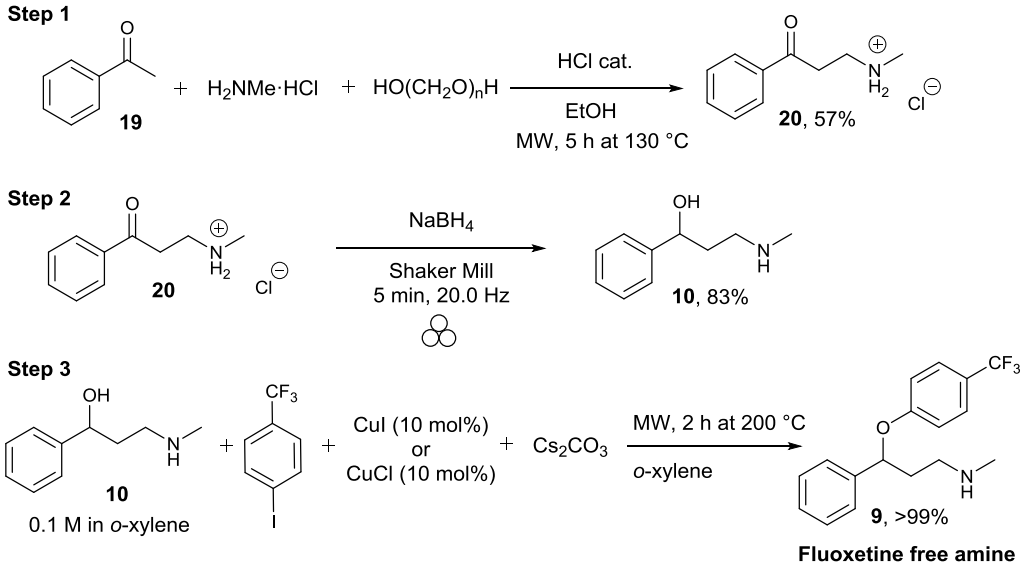
- The carbonyl reduction of **3** in the ball mill afforded **5** in 96% yield. No solvent was needed for the reaction, which finished after only 25 min of grinding in a shaker ball mill (Step 2). The reaction time of the solution based reaction described in the literature is 15 h.[87, 97]

- The *O*-arylation reaction was fully optimised, reaching 99% yield after 3 h of heating in the microwave (Step 3). When the reaction was done under classical reflux conditions, only 23% conversion was reached after 3 h.

- Although it was not possible to replicate the literature reaction conditions[110] for the *N*-demethylation of **7** in solution, the reaction in

the microwave proved to be reproducible and provided **1** in 76% yield after 3 h (Step 4).

The developed synthesis of fluoxetine through Route B is summarized below. (*Scheme 1.47*)




*Scheme 1.47 – Route B, greener synthesis for the preparation of fluoxetine*

- The Mannich condensation of acetophenone (**19**) afforded aminoketone **20** in 57% yield after 5 h of microwave assisted heating (Step 1). Although this Mannich reaction proved to be harder than the one in Route A, the result is still an improvement when compared it to the 20 h reaction described in the literature.[111]

- The carbonyl reduction of **20** in the ball mill afforded **10** in 83% yield (Step 2). The non-solvent reaction finished after only 5 min of shaking in the shaker mill. The reaction time of the solution based reaction described in the literature is 1 h.[92]

- The *O*-arylation reaction was fully optimised, reaching >99% yield after 2 h of heating in the microwave (Step 3).

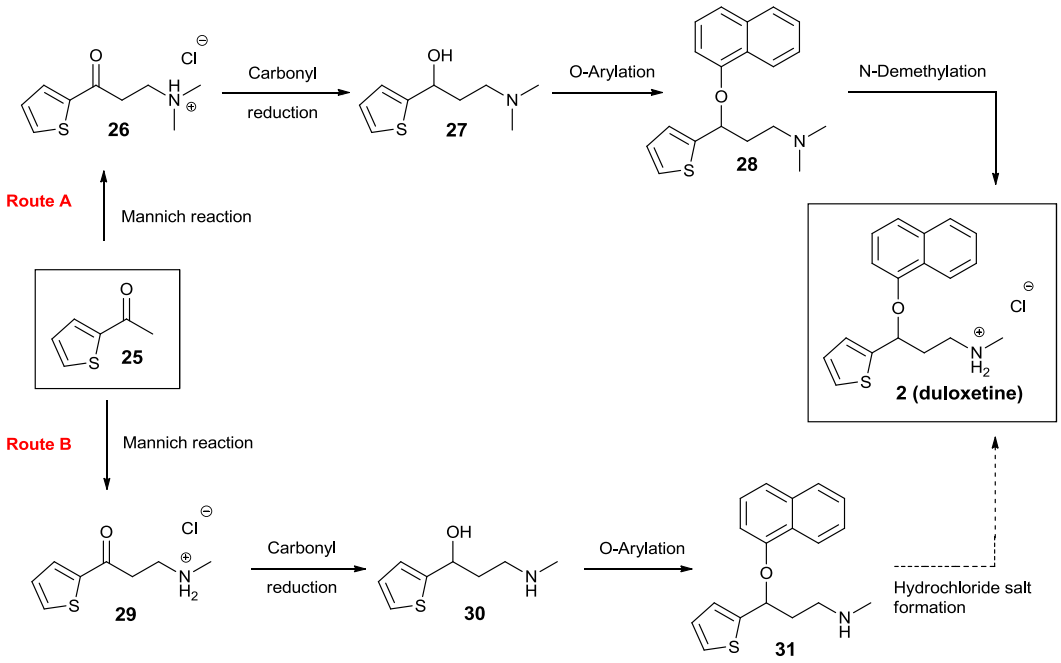
In conclusion, the use of ball milling and microwave assisted heating represented a substantial improvement compared to the previously described synthetic methodologies based on conventional heating methods, not only by

allowing higher yields and shorter reaction times, but also by reducing the amount of solvent and diminishing the number of process operations. This leads to a potential reduction of the production costs of fluoxetine, that could ultimately decrease the price of the drug for the consumers.

# 1.4. Synthesis of duloxetine (Cymbalta)

## 1.4.1. Results and discussion

With the ball mill and MW optimised conditions for the synthesis of fluoxetine in hand, we decided to expand the scope of our synthetic strategy to the synthesis of duloxetine. Due to their structural similarities, we thought it would be feasible to carry out both synthetic routes (A and B) for the new target (Scheme 1.48).




*Scheme 1.48 – Proposed synthesis for duloxetine*

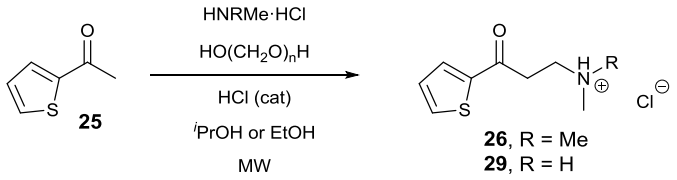
### 1.4.1.1. Step 1 – Mannich Condensation

The reaction between acetylthiophene (**25**) and dimethyl- or methylamine hydrochlorides in the presence of paraformaldehyde was studied under MW assisted heating. The optimised conditions for the Mannich condensation used in the synthesis of fluoxetine (section 3.2.1 of this thesis) were chosen as our starting point for this new reaction.

Mechanochemistry was not evaluated in this case because of the low conversions obtained in the condensation of acetophenone with dimethyl- or methylamine hydrochlorides (synthesis of fluoxetine, section 3.2.1).

Thus, under MW irradiation, the reaction of **25** with 1.25 eq. of dimethylamine hydrochloride and 1.50 eq. of paraformaldehyde in isopropanol, provided the hydrochloride salt **26** in 74% yield after only 1 h at 110 °C (*entry 1, Table 1.6*). The yield of the reaction could not be improved with longer reaction times (2h, *entry 2)*. Similarly, the synthesis of **29** was achieved in 44% yield, using ethanol as solvent and microwave assisted heating at 130 °C (*entry 3*). Longer reaction times did not lead to higher yields (*entry 4*).

*Table 1.6 – MW assisted Mannich reaction for the synthesis of **26** and **29**.*




| Entry | Product | HNRMe (eq.) | $HO(CH_2O)_nH$ (eq.) | Solvent | T (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **26** | $HNMe_2$ (1.25) | 1.50 | $^{i}$PrOH | 110 | 1 | 74 |
| 2 | **26** | $HNMe_2$ (1.25) | 1.50 | $^{i}$PrOH | 110 | 2 | 70 |
| 3 | **29** | $H_2NMe$ (1.10) | 1.40 | EtOH | 130 | 4 | 44 |
| 4 | **29** | $H_2NMe$ (1.10) | 1.40 | EtOH | 130 | 5 | 34 |

[a] Reaction Conditions: **25** (1 eq.), HNRMe, paraformaldehyde, solvent, MW . [b] Isolated yield.

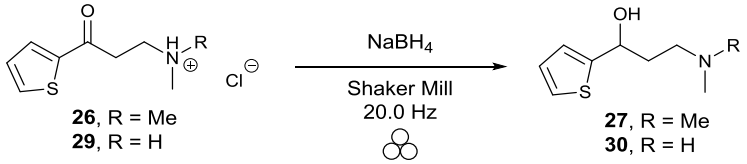
## 1.4.1.2. Step 2 – Carbonyl Reduction

The reduction of **26** and **29** was carried out in the shaker mill, using a 25 mL stainless steel grinding jar provided with a 25 mm diameter stainless steel grinding ball. The reduction of **26** with 1.3 eq. of sodium borohydride for 25 min at 20.0 Hz led to the reduced product **27** in 88% yield (*entry 1, table 1.7*). The yield of the reaction could be improved to 92% with longer reaction times (*entry 2*). In an attempt to increase the yield even further, we

increased the equivalents of sodium borohydride to 2.0, obtaining 95% yield after 1 h (entry 3) and 97% yield after 2 h of reaction (entry 4).

On the other hand, the reduction of ketone **29** with 1.3 eq. of sodium borohydride for 25 min, led to the corresponding alcohol **30** in 74% yield (*entry 5*). Unfortunately, in this case, increased amounts of sodium borohydride and longer reaction times did not improve the yield of the reaction (entry 6).

*Table 1.7 – Carbonyl reduction for the synthesis of **26** and **29**.*




**26**, R = Me
**29**, R = H

**27**, R = Me
**30**, R = H

| Entry | Product | $NaBH_4$ (eq.) | Time (min) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **27** | 1.3 | 25 | 88 |
| 2 | **27** | 1.3 | 90 | 92 |
| 3 | **27** | 2.0 | 60 | 95 |
| 4 | **27** | 2.0 | 120 | 97 |
| 5 | **30** | 1.3 | 25 | 74 |
| 6 | **30** | 2.0 | 120 | 72 |

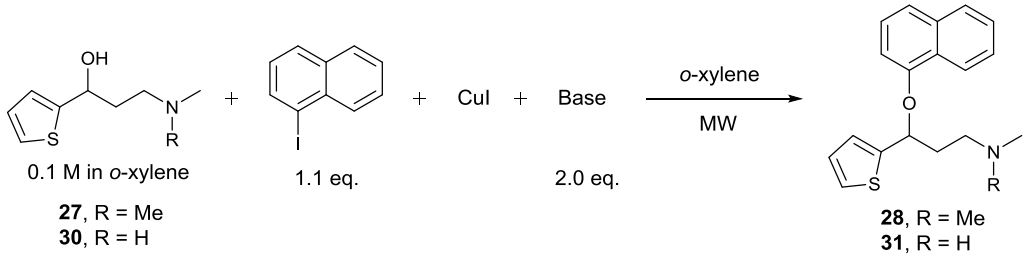
[a] Reaction Conditions: **26** or **29** (1 eq.). [b] Isolated yield.

### 1.4.1.3. Step 3 – *O*-Arylation

The *O*-arylation reaction of both **27** and **30** with 1-iodonaphthalene was first carried out in the microwave reactor using the optimised conditions that were previously optimized for the *O*-arylation of fluoxetine (see section 3.2.3). Unfortunately, the MW irradiation at 200 °C, in *o*-xylene as solvent, of the corresponding amino alcohol (**27** or **30**) and 1-iodonaphthalene (1.1 eq.), in the presence of copper iodide (10 mol%) and caesium carbonate

(2.0 eq.), did not provide any *O*-arylated product **28** or **31** after 5 h (*Table 1.8, entries 1 and 2*).

*Table 1.8 – O-Arylation reaction of* **27** and **30** *in the MW*




| Entry | R | CuI (%mol) | Base | T (°C) | Time (h) | Conversion (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Me | 10 | $Cs_2CO_3$ | 200 | 5 | - |
| 2 | H | 10 | $Cs_2CO_3$ | 200 | 5 | - |
| 3 | H | 30 | $Cs_2CO_3$ | 200 | 2 | - |
| 4 | H | 10 | KOH | 200 | 2 | - |
| 5 | Me | 10 | KO$^t$Bu | 200 | 2 | - |
| 6 | Me | 10 | NaOH | 200 | 2 | - |
| 7 | Me | 10 | NaOMe | 200 | 2 | - |
| 8 | Me | 10 | $K_2CO_3$ | 200 | 2 | 2 |
| 9 | H | 10 | $Cs_2CO_3$ | 60 | 8 | - |

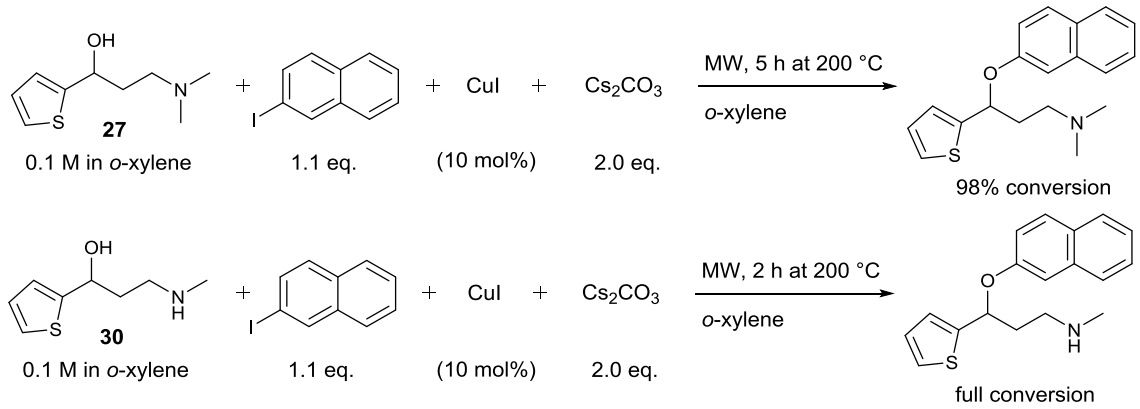
[a] Reaction Conditions: **27** or **30** (1.0 eq.), 1-iodonaphthalene (1.1 eq.), base (2.0 eq.) [b] Conversion determined by GC-MS.

Higher catalyst loadings (30 mol% CuI), did not improve the conversion for the reaction with **30** (*entry 3*). Different bases (potassium hydroxide, potassium *tert*-butoxide, sodium hydroxide and sodium methoxide; *entries 4-7*) were also screened, without any success. Only potassium carbonate gave 2% conversion in the reaction of **30** after 2 h of MW irradiation at 200 °C (*entry 8*).

Concerned about the idea that the starting material was decomposing at the reaction temperature (200 °C), we tested the reaction of **30** at lower

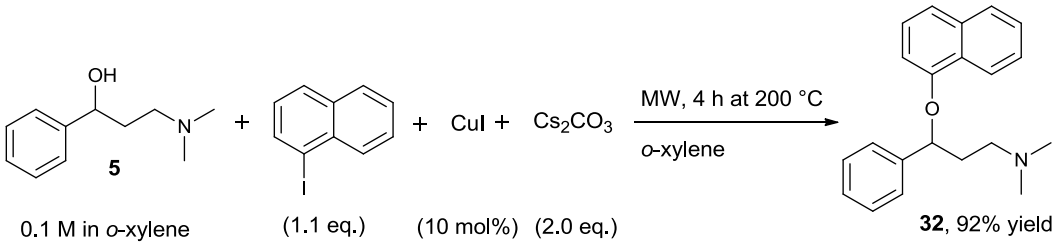
temperature (60 °C). Unfortunately, no conversion was observed after 8 h (*entry 9*).

As a mode of comparison, we performed the reaction with 2-iodonaphthalene as coupling partner. Surprisingly, the reaction of both **27** and **30**, in the presence of copper iodide (10 mol%) and cesium carbonate (2.0 eq.), reached full conversion under MW irradiation at 200 °C, using *o*-xylene as a solvent, in less than 5 h (*Scheme 1.49*).




*Scheme 1.49 – O-Arylation reaction of **27** and **30** with 2-iodonaphthalene*

Furthermore, in order to rule out the possibility of 1-iodonaphthalene not being stable at high temperatures, we attempted the coupling reaction of fluoxetine precursor **5** with 1-iodonaphthalene. To our surprise, the reaction of **5** with 1-iodonaphthalene in the presence of copper iodide (10 mol%) and cesium carbonate (2.0 eq.), reached full conversion in 4 h under MW irradiation at 200 °C, using *o*-xylene as a solvent. (*Scheme 1.50).* The corresponding product **32** was obtained in 92% yield after purification by column chromatography.



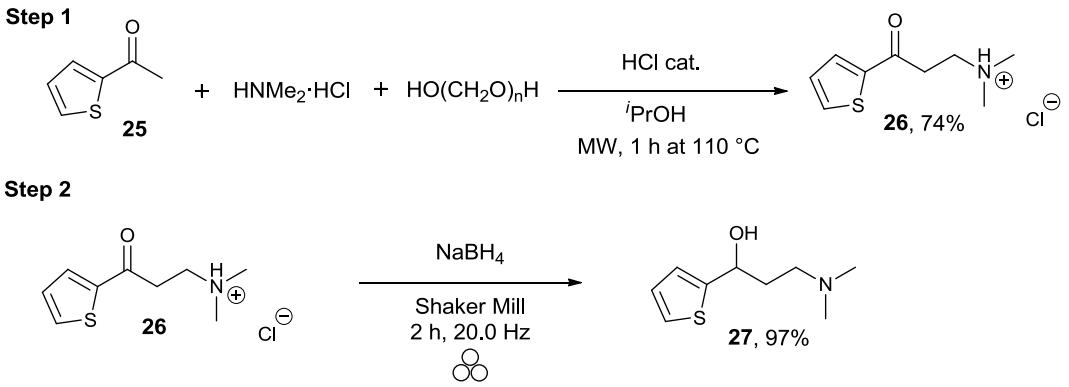

*Scheme 1.50 – O-Arylation reaction of fluoxetine's precursor **5** with 1-iodonaphthalene*

More work needs to be done to optimise the *O*-arylation reaction step in the synthesis of duloxetine. Different solvents, copper sources and ligands could be evaluated in the future.

## 1.4.2. Conclusions

It has not been possible to develop a complete synthesis for the preparation of the antidepressant duloxetine. The *O*-arylation of both intermediates **27** and **30** was not possible under the optimised conditions for the previous synthesis of fluoxetine.

The optimized first two steps in the synthesis of duloxetine through Route A are summarized below (*Scheme 1.51*).



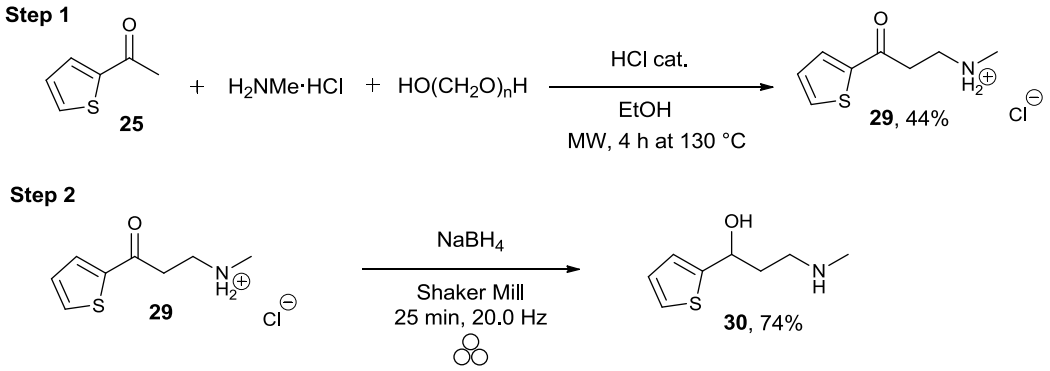

*Scheme 1.51 – Route A, greener synthesis for the preparation of duloxetine's precursor*

- The Mannich condensation of 2-acetylthiophene (**25**) led to the aminoketone **26** in 74% yield after only 1 h of heating in the microwave (Step 1). This shortens the reaction time of the Mannich reactions previously described in the literature (6-24 h of reaction), although the yield obtained is not as high as the ones reported (90-94%).[112, 113]

- The carbonyl reduction of **26** in the ball mill afforded **27** after 2 h, in 97% yield. Both reaction time and yield are similar to the ones described in the literature (2-7 h, 90-95% yield),[114, 115] but our

method has the advantage of avoiding the use of solvent for the reaction.

The optimized first two steps in the synthesis of duloxetine through Route B are summarized below. (*Scheme 1.52*)




*Scheme 1.52 – Route B, greener synthesis for the preparation of duloxetine's precursor*

- The Mannich condensation of acetophenone (**25**) afforded the aminoketone **29** in 44% yield after 4 h of microwave assisted heating (Step 1). Although this result shortens the 9 h reaction time of the procedure described in the literature,[116] the yield obtained is much lower (44% cf. 71%).

- The carbonyl reduction of **29** in the ball mill afforded **30** in 74% yield (Step 2). The non-solvent reaction finished after only 25 min of shaking in the shaker mill. Although the yield reported in the literature is slightly higher (86%),[112] our method shortens considerably their 4 h reaction time and has the advantage of avoiding the use of solvent in the reaction.

# 1.5. Experimental Part

## 1.5.1. General instrumentation

**TLC:** Thin layer chromatography (TLC) was run on silica gel 60 aluminium sheets, 0.25 mm thick ($F_{254}$ *Merck KGaA*®). The components were visualized by UV light (254 nm), phosphomolybdic acid or $KMnO_4$ staining solutions.

**IR:** IR spectra were recorded on *Nicolet*® 380 FT/IR – Fourier Transform Infrared Spectrometer. Only the most significant frequencies have been considered for the characterisation, and have been reported in $cm^{-1}$.

**NMR:** $^{1}H$ NMR, $^{13}C$ NMR and $^{19}F$ NMR were recorded on a *JEOL*® ECS-400 (400, 100.6 and 376.5 MHz, respectively) using $CDCl_3$ or $CD_3OD$ as solvent. Chemical shift values are reported in ppm with TMS as internal standard ($CDCl_3$: δ 7.26 for $^{1}H$-NMR, δ 77.0 for $^{13}C$-NMR). Data are reported as follows: chemical shifts, multiplicity (s= singlet, br s = broad singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad), coupling constants (Hz), and integration.

**Flash chromatography:** Column chromatography was carried out using *Geduran*® Silica gel 60, 40-63 microns RE.

**Melting points:** Melting points were measured in a *Stuart*® SMP10 melting point apparatus and are not corrected.

**GCMS:** Low resolution mass spectra were recorded on a GC-MS spectrometer (*Hewlett Packard*® HP 5890 Series II GC System) equipped with a DB-5 column (*J&W Scientific*®, 30 m × 0.32 mm), connected to a *Hewlett Packard*® HP 5972 Series Mass Selective Detector. Helium was used as carrier gas at 10 psi, and the samples were ionized by an electronic impact (EI) source at 70 eV.

**HRMS:** High resolution mass spectra were obtained on a *Agilent Technologies*® 6540 Ultra-High-Definition (UHD) Accurate-Mass equipped with a time of flight (Q-TOF) analyzer and the samples were ionized by ESI

techniques and introduced through a high pressure liquid chromatography (HPLC) model *Agilent Technologies*® 1260 Infinity Quaternary LC system. Samples were eluted with mixture of MeOH and 0.1% formic acid, with a flow of 0.2 ml/min.

**Shaker ball mill:** Reactions in the shaker ball mill were carried out in a *Retsch*® MM200 (shaker mill) using a 25 mL stainless steel grinding jar provided with one stainless steel grinding ball of 2.5 cm of diameter.

**Planetary ball mill:** Reactions in the planetary ball mill were carried out in a *Retsch*® PM100 using a 50 mL stainless steel grinding jar and different sets of the grinding balls: (a) 2 stainless steel grinding balls of 1.5 cm diameter each, (b) 5 stainless steel grinding balls of 1 cm diameter each, (c) 10 stainless steel grinding balls of 0.8 cm diameter each, (d) 10 stainless steel grinding balls of 0.7 cm diameter each, (e) 5 stainless steel grinding balls of 0.6 cm diameter each, (f) 10 stainless steel grinding balls of 0.4 cm diameter each, or (d) 20 zirconium-coated grinding balls of 0.3 cm diameter each.

**MW:** The microwave irradiation was carried out in an *Anton Paar*® Monowave 300, Microwave Synthesis Reactor, using 10 and 30 mL glass vials sealed with a PTFE-coated silicone septum and closed with a snap cap made of PEEK.

## 1.5.2. General methods and considerations

All commercially available reagents were purchased from Aldrich, Acros, Alfa Aesar, Manchester Organics, Fisher and Maybridge and used without further purification, unless stated otherwise.

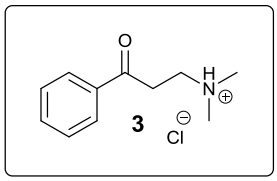
**Ball mill reactions:** Before starting the grinding process, the grinding jar was flushed for 0.5 min with a stream of argon after all the reagents were added.

**MW reactions:** A dry MW-glass vial was filled with argon and sealed with a rubber septum. All the chemicals were added under argon atmosphere. The

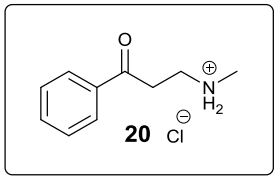
septum was quickly changed for a snap cap before inserting the vial inside the Microwave Synthesis Reactor.

## 1.5.3. Experimental procedure and data of compounds

### 1.5.3.1. Mannich reactions under MW irradiation

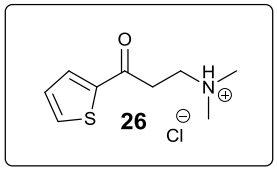



**3-(Dimethylamino)propiophenone hydrochloride (3).**[117] Concentrated HCl (40 µL, 0.5 mmol) was added dropwise to a solution of acetophenone (961 mg, 8.0 mmol), dimethylamine hydrochloride (832 mg, 10.0 mmol) and paraformaldehyde (360 mg, 12.0 mmol) in $^{i}$PrOH (4 mL) at RT under Ar atmosphere, in a 30 mL MW glass tube. The mixture was heated in the MW to 110 °C for 60 min and a solid precipitated inside the glass tube. The resulting solid was removed by filtration, washed with acetone and dried under vacuum. Pure 3-(dimethylamino)propiophenone hydrochloride (**3**) was obtained as a white solid (1.10 g, 65%). $\mathbf{M_p}$ = 153–156 °C [lit.[118] $\mathbf{M_p}$ = 153–154 °C]. **IR** (ATR) 3400 (br), 2946, 2662, 1674, 1334, 1222, 958 cm$^{-1}$. **$^{1}$H NMR** (400 MHz, $CD_3OD$) δ 8.80–7.20 (m, 5H), 4.45–2.25 (m, 4H), 3.75 (s, 6H). **$^{13}$C NMR** (100.6 MHz, $CD_3OD$) δ 198.3, 137.2, 135.0, 129.9, 129.3, 54.4, 43.9, 34.2. Data in agreement with the literature.

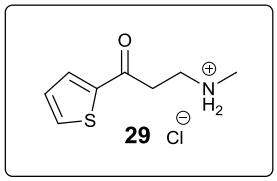



**3-(Methylamino)-1-phenylpropan-1-one hydrochloride (20).**[111] Concentrated HCl (125 µL, 1.5 mmol) was added dropwise to a solution of acetophenone (3.00 g, 25.0 mmol), methylamine hydrochloride (1.86 g, 27.5 mmol) and paraformaldehyde (1.05 g, 35.0 mmol) in EtOH (12.5 mL) at RT under Ar atmosphere, in a 30 mL MW glass tube. The mixture was heated in the MW to 130 °C for 5 h. The solvent was then removed under vacuum and the crude product was purified by recrystallization ($^{i}$PrOH/AcOEt) to afford pure 3-(methylamino)-1-phenylpropan-1-one hydrochloride (**20**) as a white solid (2.82 g, 57%). $\mathbf{M_p}$ = 113–118 °C [lit.[111] $\mathbf{M_p}$ = 113–115 °C]. **IR** (ATR) 3390 (br), 2941, 2694, 2448, 1679, 1373, 1223, 749 cm$^{-1}$. **$^{1}$H NMR** (400 MHz, $CD_3OD$) δ 8.10–7.45

(m, 5H), 3.58–3.35 (m, 4H), 2.77 (s, 3H). **$^{13}$C NMR** (100.6 MHz, $CD_3OD$) δ 198.6, 137.2, 135.0, 129.9, 129.3, 45.5, 35.5, 34.1. Data in agreement with the literature.



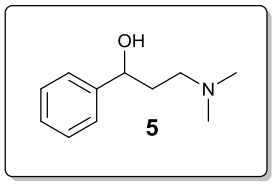

**3-(Dimethylamino)-1-(2-thienyl)-1-propanone hydrochloride (26).**[112] Concentrated HCl (40 µL, 0.5 mmol) was added dropwise to a solution of acetylthiophene (864 mg, 8.0 mmol), dimethylamine hydrochloride (832 mg, 10.0 mmol) and paraformaldehyde (360 mg, 12.0 mmol) in $^{i}$PrOH (4 mL) at RT under Ar atmosphere, in a 30 mL MW glass tube. The mixture was heated in the MW to 110 °C for 60 min and a solid precipitated inside the glass tube. The resulting solid was removed by filtration, washed with acetone and dried under vacuum. Pure 3-(dimethylamino)-1-(2-thienyl)-1-propanone hydrochloride (**26**) was obtained as a white solid (1.31 g, 74%). **$M_p$** = 184–187 °C [lit.[118] **$M_p$ =** 184–185 °C]. **IR** (ATR) 3078, 2960, 2552, 2444, 1650, 1412, 1224 $cm^{-1}$. **$^{1}$H NMR** (400 MHz, $CD_3OD$) δ 8.15–7.95 (m, 1H), 7.85–7.95 (m, 1H), 7.28–7.20 (m, 1H), 3.62–3.50 (m, 4H), 2.95 (s, 6H). **$^{13}$C NMR** (100.6 MHz, $CD_3OD$) δ 191.1, 143.9, 136.3, 135.0, 129.7, 54.1, 43.9, 35.3. Data in agreement with the literature.



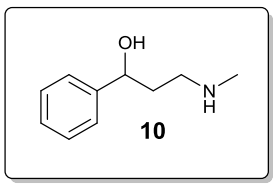

**3-Methylamino-1-thiophen-2-yl-propan-1-one hydrochloride (29).**[111] Concentrated HCl (125 µL, 1.5 mmol) was added dropwise to a solution of acetylthiophene (3.16 g, 25.0 mmol), methylamine hydrochloride (1.86 g, 27.5 mmol) and paraformaldehyde (1.05 g, 35.0 mmol) in EtOH (12.5 mL) at RT under Ar atmosphere, in a 30 mL MW glass tube. The mixture was heated in the MW to 130 °C for 4 h. The solvent was then removed under vacuum and the crude product was purified by recrystallization ($^{i}$PrOH/AcOEt) to afford pure 3-methylamino-1-thiophen-2-yl-propan-1-one hydrochloride (**29**) as a pale brown solid (2.28 g, 44%). **$M_p$** = 140–142 °C [lit.[111] **$M_p$ =** 139–141 °C]. **IR** (ATR) 3383 (br), 2970, 2736, 2450, 1650, 1411, 755 $cm^{-1}$. **$^{1}$H NMR** (400 MHz, $CD_3OD$) δ 7.98–7.95 (m,

1H), 7.92–7.86 (m, 1H), 7.25–7.20 (m, 1H), 3.52–3.35 (m, 4H), 2.76 (s, 3H). **$^{13}$C NMR** (100.6 MHz, $CD_3OD$) δ 191.4, 143.9, 136.2, 134.9, 129.7, 45.4, 35.7, 34.0. Data in agreement with the literature.

### 1.5.3.2. Carbonyl reduction in the shaker mill

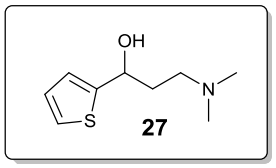



**3-Dimethylamino-1-phenylpropan-1-ol (5).**[119] Aminoketone hydrochloride **3** (107 mg, 0.5 mmol) and $NaBH_4$ (25 mg, 0.7 mmol) were added into a 25 mL stainless steel grinding jar with a 25 mm Ø stainless steel ball. The grinding jar was flushed with a stream of argon and the mixture was shaken at 20.0 Hz for 25 min. The reaction crude was dissolved with water and acetone and transferred into a separating funnel. Concentrated HCl (5 mL) was added and the aqueous layer was washed with $CH_2Cl_2$ (3 × 20 mL) and the organic layer was discarded. A solution of NaOH 5 N (15 mL) was added to the aqueous layer, and was subsequently extracted with $CH_2Cl_2$ (4 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. To afford pure 3-dimethylamino-1-phenylpropan-1-ol (**5**) as a white solid (86 mg, 96%). **$M_p$** = 45–47 °C [lit.[120] **$M_p$ =** 47–48 °C]. **$R_f$** (MeOH) = 0.25. **IR** (ATR) 3076 (br), 2970, 2821, 1602, 1450, 1027, 700 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.15 (m, 5H), 4.93 (dd, *J* = 7.6, 4.0 Hz, 1H), 2.68–2.44 (m, 2H), 2.30 (s, 6H), 1.85–1.78 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 145.1, 128.1, 126.8, 125.5, 75.8, 58.4, 45.3, 34.5. Data in agreement with the literature.



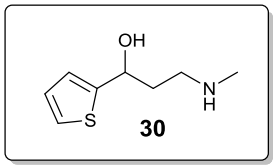

**3-Methylamino-1-phenylpropan-1-ol (10).**[121] Aminoketone hydrochloride **20** (105 mg, 0.5 mmol) and $NaBH_4$ (39 mg, 1.0 mmol) were added into a 25 mL stainless steel grinding jar with a 25 mm Ø stainless steel ball. The grinding jar was flushed with a stream of argon and the mixture was shaken at 20.0 Hz for 5 min. The reaction crude was dissolved with water and acetone and transferred into a separating funnel. Concentrated HCl (5 mL) was added and the aqueous layer was washed with $CH_2Cl_2$ (3 × 20 mL) and the organic layer was discarded. A solution of NaOH

5 N (15 mL) was added to the aqueous layer, and was subsequently extracted with $CH_2Cl_2$ (4 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum to afford pure 3-methylamino-1-phenylpropan-1-ol (**10**) as a white solid (73 mg, 83%). $\mathbf{M_p}$ = 66–73 °C [lit.[122] $\mathbf{M_p}$ = 50–60 °C]. $\mathbf{R_f}$ (AcOEt/MeOH 1:1) = 0.20. **IR** (ATR) 3281, 2927, 2793, 1600, 1450, 1080, 1080 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 4.94 (dd, *J* = 8.8, 3,2 Hz, 1H), 3.95 (br s, 1H), 2.94–2.83 (m, 2H), 2.45 (s, 3H), 1.90–1.73 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 145.1, 128.2, 126.9, 125.6, 75.6, 50.5, 36.8, 36.0. Data in agreement with the literature.



27

**3-Dimethylamino-1-(2-thienyl)propan-1-ol (27).**[123] Aminoketone hydrochloride **26** (113 mg, 0.5 mmol) and $NaBH_4$ (39 mg, 1.0 mmol) were added into a 25 mL stainless steel grinding jar with a 25 mm Ø stainless steel ball. The grinding jar was flushed with a stream of argon and the mixture was shaken at 20.0 Hz for 2 h. The reaction crude was dissolved with water and acetone and transferred into a separating funnel. Concentrated HCl (5 mL) was added and the aqueous layer was washed with $CH_2Cl_2$ (3 × 20 mL) and the organic layer was discarded. A solution of NaOH 5 N (15 mL) was added to the aqueous layer, and was subsequently extracted with $CH_2Cl_2$ (4 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. To afford pure 3-dimethylamino-1-(2-thienyl)propan-1-ol (**27**) as a white solid (89 mg, 97%). $\mathbf{M_p}$ = 71–73 °C [lit.[123] $\mathbf{M_p}$ = 71–73 °C]. **IR** (ATR) 3080, 2942, 2826, 1467, 1076, 844 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.24–7.18 (m, 1H), 7.00–6.94 (m, 1H), 6.94–6.88 (m, 1H), 5.19 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.70–2.51 (m, 2H), 2.29 (s, 6H), 2.20–1.85 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 149.8, 126.5, 123.6, 122.2, 72.2, 58.1, 45.3, 34.5. Data in agreement with the literature.



30

**3-methylamino-1-(2-thienyl)-1-propanol (30).**[121] Aminoketone hydrochloride **29** (103 mg, 0.5 mmol) and $NaBH_4$ (25 mg, 0.7 mmol) were added into a 25 mL stainless steel grinding jar with a 25 mm Ø stainless steel ball. The grinding jar was flushed with a stream of argon and the mixture was shaken at 20.0 Hz for 5 min. The reaction crude was dissolved with water and acetone and transferred into a separating funnel. Concentrated HCl (5 mL) was added and the aqueous layer was washed with $CH_2Cl_2$ (3 × 20 mL) and the organic layer was discarded. A solution of NaOH 5 N (15 mL) was added to the aqueous layer, and was subsequently extracted with $CH_2Cl_2$ (4 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum to afford pure 3-methylamino-1-(2-thienyl)-1-propanol (**30**) as a white solid (64 mg, 74%). $\mathbf{M_p}$ = 58–61 °C [lit.[111] $\mathbf{M_p}$ = 61–63 °C]. $\mathbf{R_f}$ (AcOEt/MeOH/$NEt_3$ 10:10:1) = 0.30. **IR** (ATR) 3282, 2859, 2662, 1473, 1311, 1074 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.20–7.18 (m, 1H), 7.00–6.88 (m, 2H), 5.17 (dd, *J* = 8.8, 3.6 Hz, 1H), 4.00 (br s, 1H), 2.98–2.80 (m, 2H), 2.41 (s, 3H), 2.02–1.80 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 149.7, 126.5, 123.7, 122.3, 71.9, 50.1, 36.8, 35.9. Data in agreement with the literature.

### 1.5.3.3. Carbonyl reduction in solution

To a well stirred solution of the aminoketone hydrochloride (**3**, **20**, **26** or **29**, 4.0 mmol) in $H_2O$ (25 mL) at 0 °C was added $NaBH_4$ (201 mg, 5.2 mmol) in two portions. The solution was warmed to r.t. and stirred for 15-24 h.

The solution was treated with acetone and concentrated HCl (5 mL). The aqueous layer was washed with $CH_2Cl_2$ (3 x 20 mL) and the organic layer was discarded. A solution of NaOH 5 N (15 mL) was added to the aqueous layer, and was subsequently extracted with $CH_2Cl_2$ (4 x 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The corresponding aminoalcohol **5**, **10**, **27** or **30**, respectively, were obtained pure in excellent yields (90-99%).

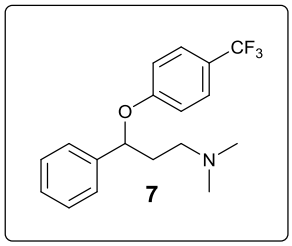
### 1.5.3.4. Tosylation reaction and substitution in the shaker mill

3-Dimethylamino-1-phenyl-propan-1-ol (**5**) (46 mg, 0.25 mmol), $NEt_3$ (42 µL, 0.30 mmol) and 4-toluenesulfonyl chloride (53 mg, 0.28 mmol) were added into a 25 mL stainless steel grinding jar with a 25 mm Ø stainless steel ball. The grinding jar was flushed with argon and the mixture was shaken at 20.0 Hz for 3 h. After the 3 h, $K_2CO_3$ (69 mg, 0.50 mmol) and 4-(trifluoromethyl)phenol (209 mg, 1.25 mmol) were added in the grinding jar, which was flushed with Ar again. The new mixture was shaken at 20.0 Hz for 3 h. The content of the grinding jar was dissolved with $Et_2O$ (25 mL) and an aqueous solution of NaOH 2M (10 mL). The organic layer was washed with $H_2O$ (10 mL) and the aqueous layers were extracted with $CH_2Cl_2$ (4 x 15 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The resulting crude oil was purified with column chromatography ($CH_2Cl_2$/MeOH 95:5) to afford 7 mg (8%) of 3-dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (**7**, see analytical data below).

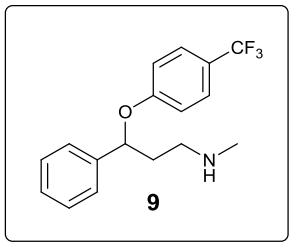
### 1.5.3.5. Mitsunobu reaction in the shaker mill

3-Dimethylamino-1-phenyl-propan-1-ol (**5**) (45 mg, 0.25 mmol), triphenylphosphine (69 mg, 0.25 mmol), diisopropyl azodicarboxylate (50 µL, 0.25 mmol) and 4-(trifluoromethyl)phenol (42 mg, 0.25 mmol) were added into a 25 mL stainless steel grinding jar with a 25 mm Ø stainless steel ball. The mixture was shaken at 20.0 Hz for 3 h 30 min. The content of the grinding jar was dissolved with $CH_2Cl_2$ and concentrated under vacuum. The resulting crude oil was purified with column chromatography ($CH_2Cl_2$/MeOH 95:5) to afford 21 mg (25%) of 3-dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (**7**, see analytical data below).

## 1.5.3.6. MW assisted copper catalysed *O*-arylation

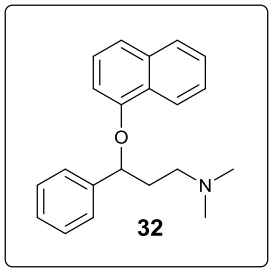



**3-Dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (7).**[124] 4-Iodobenzotrifluoride (40 µL, 0.275 mmol) was added dropwise to a solution of amino alcohol **5** (45 mg, 0.250 mmol), CuI (5 mg, 0.025 mmol) and $Cs_2CO_3$ (163 mg, 0.500 mmol) in *o*-xylene (2.5 mL) at RT under Ar atmosphere, in a 10 mL MW glass tube. The mixture was heated in the MW using the following heating program: 120 °C for 10 min, then 150 °C for 10 min and last 200 °C for 3 h. After that time, GC-MS analysis confirmed 99% conversion. The resulting solution was filtered through a plug of Celite® and eluted with EtOAc. After concentrating the solvent under vacuum, pure 3-dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (**7**) was obtained as a brown oil (84 mg, 99%). $\mathbf{R_f}$ ($CH_2Cl_2$/MeOH 95:5) = 0.25. **IR** (ATR) 2946, 2768, 1614, 1517, 1323, 1248, 1108 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.45–6.88 (m, 9H), 5.28 (dd, *J* = 8.4, 5.2 Hz, 1H), 2.50–2.36 (m, 2H), 2.25 (s, 6H), 2.30–1.94 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 160.6, 141.1, 128.7, 127.8, 126.7 (q, *J* = 15.2 Hz), 125.8, 123.0, 122.7 (q, *J* = 129.6 Hz), 115.8, 78.5, 55.7, 45.4, 36.7. **$^{19}$F NMR** (376.5 MHz, $CDCl_3$) δ –61.52. **HRMS** (+ESI): *m/z* calculated for $C_{18}H_{21}NOF_3$ $[M+H]^+$: 324.1575. Found: 324.1572. Data in agreement with the literature.




**N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine (9)**.[125] 4-Iodobenzotrifluoride (40 µL, 0.275 mmol) was added dropwise to a solution of amino alcohol **10** (41 mg, 0.250 mmol), CuI (5 mg, 0.025 mmol) and $Cs_2CO_3$ (163 mg, 0.500 mmol) in *o*-xylene (2.5 mL) at RT under Ar atmosphere, in a 10 mL MW glass tube. The mixture was heated in the MW using the following heating program: 120 °C for 10 min, then 150 °C for 10 min and last 200 °C for 2 h. After that time, GC-MS analysis confirmed full conversion. The resulting solution was filtered through a plug of Celite® and

eluted with EtOAc. After concentrating the solvent under vacuum, pure *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine (**9**) was obtained as a yellow oil (81 mg, >99%). $\mathbf{R_f}$ ($CH_2Cl_2$/MeOH 95:5) = 0.25. **IR** (ATR) 2927, 2849, 1613, 1516, 1323, 1107 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.37–6.82 (m, 9H), 5.27 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.03 (br s, 1H), 2.82–2.70 (m, 2H), 2.41 (s, 3H), 2.30–1.98 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 160.3, 140.5, 128.8, 128.0, 126.8 (q, *J* = 15.2 Hz), 125.7, 122.9 (q, *J* = 130.0 Hz), 115.8, 78.2, 47.8, 37.7, 35.7, 30.9. **$^{19}$F NMR** (376.5 MHz, $CDCl_3$) δ –61.44. Data in agreement with the literature.



32

***N,N*-dimethyl-3-(α-naphthyloxy)-3-phenylpropylamine (32).**[126] 1-Iodonaphthalene (40 µL, 0.275 mmol) was added dropwise to a solution of amino alcohol **5** (45 mg, 0.250 mmol), CuI (5 mg, 0.025 mmol) and $Cs_2CO_3$ (163 mg, 0.500 mmol) in *o*-xylene (2.5 mL) at RT under Ar atmosphere, in a 10 mL MW glass tube. The mixture was heated in the MW using the following heating program: 120 °C for 10 min, then 150 °C for 10 min and last 200 °C for 4 h. After that time, GC-MS analysis confirmed full conversion. The resulting solution was filtered through a plug of Celite® and eluted with EtOAc.

After concentrating the solvent under vacuum, the crude oil was dissolved in $CH_2Cl_2$ (20 mL) and transferred into a separating funnel. Concentrated HCl (1.5 mL) and water (25 mL) were added and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 15 mL), the organic layer was discarded. A solution of NaOH 1 N (25 mL) was added to the aqueous layer, and was subsequently extracted with $CH_2Cl_2$ (4 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The product obtained was still not satisfyingly pure, so it was subsequently purified with column chromatography (AcOEt/MeOH 95:5) to afford 71 mg (92%) of pure *N,N*-dimethyl-3-(α-naphthyloxy)-3-phenylpropylamine (**32**). $\mathbf{R_f}$ (AcOEt/MeOH 95:5) = 0.35. **IR** (ATR) 2940, 2764, 1576, 1461, 1264, 1095 $cm^{-1}$. **$^1$H NMR**

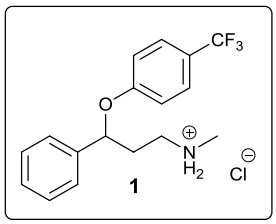
(400 MHz, $CDCl_3$) δ 8.48–6.60 (m, 12H), 5.45 (dd, *J* = 8.4, 4.8 Hz, 1H), 2.60–2.52 (m, 2H), 2.27 (s, 6H), 2.40–2.05 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 153.5, 141.8, 134.5, 128.6, 127.5, 127.5, 126.2, 125.9, 125.8, 125.7, 125.1, 122.1, 120.0, 78.2, 56.1, 45.5, 37.0. Data in agreement with the literature.

### 1.5.3.7. *O*-Arylation – Scope of the reaction

**General procedure:** *p*-Iodotoluene or 2-iodo-1,3-dimethylbenzene (0.275 mmol) was added dropwise to a solution of the corresponding amino alcohol (0.250 mmol), CuI (5 mg, 0.025 mmol) and $Cs_2CO_3$ (163 mg, 0.500 mmol) in toluene or *o*-xylene (2.5 mL) at RT under Ar atmosphere, in a 10 mL MW glass tube. The mixture was heated in the MW using the following heating program: 120 °C for 10 min, then 150 °C for 10 min and last 200 °C for the described reaction time. After that time, the conversion and the N/O-arylation ratio was determined by $^1$H-NMR of the reaction crude.

All the N/O-arylated products have been previously described in the literature by Buchwald et al.[106, 107]

### 1.5.3.8. *N*-demethylation




***N*-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpro pylamine hydrochloride / Fluoxetine hydrochloride (1).**[127] α-Chloroethyl chloroformate (108 µL, 1.00 mmol) was added dropwise to a solution of 3-dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (**7**) (81 mg, 0.25 mmol) in dichloroethane (2.5 mL) at RT under argon atmosphere, in a 10 mL MW glass tube. The mixture was heated in the MW at 120 °C for 1 h and at 150 °C for 1 h. The resulting solution was concentrated under vacuum and heated (MW) with MeOH (2.5 mL) at 120 °C for 1 h. The crude oil was purified by recrystallization (EtOAc/hexane) to afford of pure fluoxetine hydrochloride (**1**) (66 mg, 76%) as a white solid. **$M_p$** = 152–154 °C [lit.[128] **$M_P$ =** 156–158 °C]. **$R_f$** ($CH_2Cl_2$/MeOH 95:5) = 0.30). **IR** (ATR) 2858, 2730, 2450, 1614,

1517, 1325, 1241, 1107 $cm^{-1}$. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.69 (br s, 2H), 7.45–6.85 (m, 9H), 5.46 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.20–3.05 (m, 2H), 2.63 (s, 3H), 2.58–2.37 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 159.6, 139.0, 129.0, 128.4, 126.8 (q, *J* = 15.2 Hz), 125.7, 123.3 (q, *J* = 129.6 Hz), 122.8, 115.8, 76.9, 46.1, 34.5, 33.0. **$^{19}$F NMR** (376.5 MHz, $CDCl_3$) δ –61.54. Data in agreement with the literature.

# 1.6. References

1. Dansgaard, W.; Johnsen, S. J.; Clausen, H. B.; Dahljensen, D.; Gundestrup, N. S.; Hammer, C. U.; Hvidberg, C. S.; Steffensen, J. P.; Sveinbjornsdottir, A. E.; Jouzel, J.; Bond, G., *Nature* **1993**, *364* (6434), 218-220.

2. Rockstrom, J.; Steffen, W.; Noone, K.; Persson, A.; Chapin, F. S., III; Lambin, E. F.; Lenton, T. M.; Scheffer, M.; Folke, C.; Schellnhuber, H. J.; Nykvist, B.; de Wit, C. A.; Hughes, T.; van der Leeuw, S.; Rodhe, H.; Sorlin, S.; Snyder, P. K.; Costanza, R.; Svedin, U.; Falkenmark, M.; Karlberg, L.; Corell, R. W.; Fabry, V. J.; Hansen, J.; Walker, B.; Liverman, D.; Richardson, K.; Crutzen, P.; Foley, J. A., *Nature* **2009**, *461* (7263), 472-475.

3. Steffen, W.; Crutzen, P. J.; McNeill, J. R., *Ambio* **2007**, *36* (8), 614-621.

4. Clark, J. H., *Green Chem.* **1999**, *1* (1), 1-8.

5. Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T., *Science* **2002**, *297* (5582), 807-810.

6. Anastas, P. T.; Warner, J., *Green Chemistry Theory and Practice*. Oxford Univ. Press: Oxford, **1998**.

7. Collins, T. J., A Very Early Definition of Green Chemistry. In *Macmillan Encyclopedia of Chemistry*, Simon and ShusterMacmillan: New York, **1997**; Vol. 2, p 691-697.

8. Sheldon, R. A., *Green Chem.* **2007**, *9* (12), 1273-1283.

9. Sheldon, R. A., *Green Chem.* **2005**, *7* (5), 267-278.

10. Rockwell Automation, *Pharmaceutical Solvent Recovery* **2009**.

11. Jimenez-Gonzalez, C.; Curzons, A. D.; Constable, D. J. C.; Cunningham, V. L., *Int. J. Life Cycle Assess.* **2004**, *9* (2), 114-121.

12. Gross, R. A.; Kalra, B., *Science* **2002**, *297* (5582), 803-807.

13. James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C., *Chem. Soc. Rev.* **2012**, *41* (1), 413-447.

14. Beyer, M. K.; Clausen-Schaumann, H., *Chem. Rev.* **2005**, *105* (8), 2921-2948.

15. Li, C. J.; Chan, T. H., *Comprehensive Organic Reactions in Aqueous Media*. 2nd ed.; John Wiley & Sons: Hoboken, New Jersey, **2007**.

16. Sheldon, R., *Chem. Commun.* **2001**, (23), 2399-2407.

17. Welton, T., *Chem. Rev.* **1999**, *99* (8), 2071-2083.

18. Jessop, P. G.; Ikariya, T.; Noyori, R., *Chem. Rev.* **1999**, *99* (2), 475-493.

19. Rodriguez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C., *Adv. Synth. Catal.* **2007**, *349* (14-15), 2213-2233.

20. Chauhan, P.; Chimni, S. S., *Beilstein J. Org. Chem.* **2012**, *8*, 2132-2141.

21. Andre, V.; Hardeman, A.; Halasz, I.; Stein, R. S.; Jackson, G. J.; Reid, D. G.; Duer, M. J.; Curfs, C.; Duarte, M. T.; Friscic, T., *Angew. Chem. Int. Ed.* **2011**, *50* (34), 7858-7861.

22. Bonnamour, J.; Metro, T. X.; Martinez, J.; Lamaty, F., *Green Chem.* **2013**, *15* (5), 1116-1120.

23. Konnert, L.; Reneaud, B.; de Figueiredo, R. M.; Campagne, J. M.; Lamaty, F.; Martinez, J.; Colacino, E., *J. Org. Chem.* **2014,** *79* (21), 10132-10142.

24. Konnert, L.; Dimassi, M.; Gonnet, L.; Lamaty, F.; Martinez, J.; Colacino, E., *RSC Adv.* **2016**, *6* (43), 36978-36986.

25. Tan, D.; Strukil, V.; Mottillo, C.; Friscic, T., *Chem. Commun.* **2014**, *50* (40), 5248-5250.

26. Tan, D.; Loots, L.; Friscic, T., *Chem. Commun.* **2016**, *52* (50), 7760-7781.

27. Lim, X., Grinding Chemicals Together in an Effort to be Greener. *The New York Times,* **2016**.

28. Cave, G. W. V.; Raston, C. L.; Scott, J. L., *Chem. Commun.* **2001**, (21), 2159-2169.

29. *IUPAC Compendium of Chemical Technology (the "Gold Book")*. 2nd ed.; Blackwell Scientific Publications: Oxford, **1997**.

30. Cernansky, R., *Nature* **2015**, *519* (7543), 379-80.

31. Baig, R. B. N.; Varma, R. S., *Chem. Soc. Rev.* **2012**, *41* (4), 1559-1584.

32. Jones, W.; Eddleston, M. D., *Farad. Discuss.* **2014**, *170*, 9-34.

33. Garay, A. L.; Pichon, A.; James, S. L., *Chem. Soc. Rev.* **2007**, *36* (6), 846-855.

34. Takacs, L.; McHenry, J. S., *J. Mater. Sci.* **2006**, *41* (16), 5246-5249.

35. Schneider, F.; Szuppa, T.; Stolle, A.; Ondruschka, B.; Hopf, H., *Green Chem.* **2009**, *11* (11), 1894-1899.

36. Schneider, F.; Stolle, A.; Ondruschka, B.; Hopf, H., *Org. Process Res. Dev.* **2009**, *13* (1), 44-48.

37. Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B., *Chem. Soc. Rev.* **2011**, *40* (5), 2317-2329.

38. Michalchuk, A. A. L.; Tumanov, I. A.; Drebushchak, V. A.; Boldyreva, E. V., *Farad. Discuss.* **2014**, *170*, 311-335.

39. Michalchuk, A. A. L.; Tumanov, I. A.; Boldyreva, E. V., *CrystEngComm* **2013**, *15* (32), 6403-6412.

40. McKissic, K. S.; Caruso, J. T.; Blair, R. G.; Mack, J., *Green Chem.* **2014**, *16* (3), 1628-1632.

41. Balaz, P., *Mechanochemistry in Nanoscience and Minerals Engineering*. Springer-Verlag, Berlin Heidelberg: **2008**.

42. Takacs, L., *Chem. Soc. Rev.* **2013**, *42* (18), 7649-7659.

43. Rothenberg, G.; Downie, A. P.; Raston, C. L.; Scott, J. L., *J. Am. Chem. Soc.* **2001**, *123* (36), 8701-8708.

44. Friscic, T.; Jones, W., *Cryst. Growth Des.* **2009**, *9* (3), 1621-1637.

45. Friscic, T.; Trask, A. V.; Jones, W.; Motherwell, W. D. S., *Angew. Chem. Int. Ed.* **2006**, *45* (45), 7546-7550.

46. Boldyreva, E., *Chem. Soc. Rev.* **2013**, *42* (18), 7719-7738.

47. Cho, H.; Torok, F.; Torok, B., *Green Chem.* **2014**, *16* (7), 3623-3634.

48. Rosana, M. R.; Hunt, J.; Ferrari, A.; Southworth, T. A.; Tao, Y. C.; Stiegman, A. E.; Dudley, G. B., *J. Org. Chem.* **2014**, *79* (16), 7437-7450.

49. Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J., *Org. Process Res. Dev.* **2005**, *9* (4), 516-518.

50. Kappe, C. O., *Angew. Chem. Int. Ed.* **2004**, *43* (46), 6250-6284.

51. Mingos, D. M. P.; Baghurst, D. R., *Chem. Soc. Rev.* **1991**, *20* (1), 1-47.

52. Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A., *Green Chem.* **2004**, *6* (3), 128-141.

53. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J., *Tetrahedron* **2001,** *57* (45), 9225-9283.

54. Leadbeater, N. E.; Torenius, H. M., *J. Org. Chem.* **2002**, *67* (9), 3145-3148.

55. Baghurst, D. R.; Mingos, D. M. P., *J. Chem. Soc., Chem. Commun.* **1992**, (9), 674-677.

56. de la Hoz, A.; Diaz-Ortiz, A.; Moreno, A., *Chem. Soc. Rev.* **2005**, *34* (2), 164-178.

57. Chen, P. K.; Rosana, M. R.; Dudley, G. B.; Stiegman, A. E., *J. Org. Chem.* **2014**, *79* (16), 7425-7436.

58. Larhed, M.; Hallberg, A., *Drug Discov. Today* **2001**, *6* (8), 406-416.

59. Perreux, L.; Loupy, A., *Tetrahedron* **2001,** *57* (45), 9199-9223.

60. Morschhauser, R.; Krull, M.; Kayser, C.; Boberski, C.; Bierbaum, R.; Puschner, P. A.; Glasnov, T. N.; Kappe, C. O., *Green Process. Synth.* **2012**, *1* (3), 281-290.

61. Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D., *J. Med. Chem.* **1988**, *31* (7), 1412-1417.

62. Robertson, D. W.; Jones, N. D.; Swartzendruber, J. K.; Yang, K. S.; Wong, D. T., *J. Med. Chem.* **1988**, *31* (1), 185-189.

63. Molloy, B. B.; Schmiegel, K. K. US Pat. 4,314,081, **1982**.

64. Fitzpatrick, L., A brief history of antidepressants. *Time* **2010**.

65. Shepherd, R. G. UK Pat. 2,060,618A, **1982**.

66. Kairisalo, P. J.; Hukka, P. J.; Jarvinen, A. H. US Pat. 5,166,437, **1992**.

67. Robertson, D. W.; Krushinski, J. H.; Wong, D. T.; Kau, D., *J. Labelled Comp. Radiopharm.* **1987**, *24* (11), 1397-1404.

68. Schwartz, E.; Kaspi, J.; Itov, Z.; Pilarski, G. US Pat. 5,225,585, **1993**.

69. Juhani, K. P.; Juhani, H. P.; Anitta, J. H. HU Pat. 204,769, **1992**.

70. Ágainé, C. É.; Drexler, F.; Aracsné, T. Z.; Harsányi, K.; Újvári, B.; Vargáné, G. Á. L. G. WO. 94/00416, **1994**.

71. Kumar, N.; Vijayaraghavan, B.; Ramana, K. V.; Sathyanarayana, S. US Pat. 6,677,485 B2, **2004**.

72. Ahmed-Omer, B.; Sanderson, A. J., *Org. Biomol. Chem.* **2011**, *9* (10), 3854-3862.

73. Wang, Z. X.; Raheem, M.; Weeratunga, G.; Guntoori, B. US Pat. 2007/0010678 A1, **2007**.

74. Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G., *Dalton Trans.* **2010**, *39* (43), 10338-10351.

75. Srebnik, M.; Ramachandran, P. V.; Brown, H. C., *J. Org. Chem.* **1988**, *53* (13), 2916-2920.

76. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B., *J. Am. Chem. Soc.* **1987**, *109* (19), 5765-5780.

77. Gao, Y.; Sharpless, K. B., *J. Org. Chem.* **1988**, *53* (17), 4081-4084.

78. Corey, E. J.; Reichard, G. A., *Tetrahedron Lett.* **1989,** *30* (39), 5207-5210.

79. Pandey, R. K.; Fernandes, R. A.; Kumar, P., *Tetrahedron Lett.* **2002**, *43* (25), 4425-4426.

80. Boaz, N. W., *J. Org. Chem.* **1992**, *57* (15), 4289-4292.

81. Schneider, M. P.; Goergens, U., *Tetrahedron: Asymmetry* **1992**, *3* (4), 525-528.

82. Miles, W. H.; Fialcowitz, E. J.; Halstead, E. S., *Tetrahedron* **2001,** *57* (50), 9925-9929.

83. Master, H. E.; Newadkar, R. V.; Rane, R. A.; Kumar, A., *Tetrahedron Lett.* **1996**, *37* (51), 9253-9254.

84. Ali, I. S.; Sudalai, A., *Tetrahedron Lett.* **2002**, *43* (31), 5435-5436.

85. Fuller, R. W.; Wong, D. T.; Robertson, D. W., *Med. Res. Rev.* **1991**, *11* (1), 17-34.

86. Wirth, D. D.; Miller, M. S.; Boini, S. K.; Koenig, T. M., *Org. Process Res. Dev.* **2000**, *4* (6), 513-519.

87. Jakobsen, P.; Drejer, J. US Pat. 4,962,122 A, **1990**.

88. Abid, M.; Azam, A., *Bioorg. Med. Chem.* **2005**, *13* (6), 2213-2220.

89. Borah, A.; Goswami, L.; Neog, K.; Gogoi, P., *J. Org. Chem.* **2015**, *80* (9), 4722-4728.

90. Cablewski, T.; Faux, A. F.; Strauss, C. R., *J. Org. Chem.* **1994**, *59* (12), 3408-3412.

91. Kaiser, S.; Smidt, S. R.; Pfaltz, A., *Angew. Chem. Int. Ed.* **2006**, *45* (31), 5194-5197.

92. Liu, D.; Gao, W. Z.; Wang, C. J.; Zhang, X. M., *Angew. Chem. Int. Ed.* **2005**, *44* (11), 1687-1689.

93. Mack, J.; Fulmer, D.; Stofel, S.; Santos, N., *Green Chem.* **2007**, *9* (10), 1041-1043.

94. Brown, H. C.; Narasimhan, S., *J. Org. Chem.* **1982**, *47* (8), 1604-1606.

95. Cho, B. T.; Kang, S. K.; Kim, M. S.; Ryu, S. R.; An, D. K., *Tetrahedron* **2006**, *62* (34), 8164-8168.

96. Shalbaf, H., *Asian J. Chem.* **2010**, *22* (9), 6761-6764.

97. Kellogg, R. M.; Nieuwenhuijzen, J. W.; Pouwer, K.; Vries, T. R.; Broxterman, Q. B.; Grimbergen, R. F. P.; Kaptein, B.; La Crois, R. M.; de

Wever, E.; Zwaagstra, K.; van der Laan, A. C., *Synthesis (Stuttg.)* **2003**, (10), 1626-1638.

98. O'Brien, P.; Phillips, D. W.; Towers, T. D., *Tetrahedron Lett.* **2002**, *43* (41), 7333-7335.

99. Rej, R. K.; Das, T.; Hazra, S.; Nanda, S., *Tetrahedron:Asymmetry* **2013**, *24* (15-16), 913-918.

100. Wu, X. X.; Fors, B. P.; Buchwald, S. L., *Angew. Chem. Int. Ed.* **2011**, *50* (42), 9943-9947.

101. Vorogushin, A. V.; Huang, X. H.; Buchwald, S. L., *J. Am. Chem. Soc.* **2005**, *127* (22), 8146-8149.

102. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M., *Chem. Rev.* **2002**, *102* (5), 1359-1469.

103. Beletskaya, I. P.; Cheprakov, A. V., *Coord. Chem. Rev.* **2004**, *248* (21-24), 2337-2364.

104. Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L., *Org. Lett.* **2002**, *4* (6), 973-976.

105. Tao, C. Z.; Liu, W. W.; Sun, J. Y., *Chin. Chem. Lett.* **2009**, *20* (10), 1170-1174.

106. Job, G. E.; Buchwald, L., *Org. Lett.* **2002**, *4* (21), 3703-3706.

107. Shafir, A.; Lichtor, P. A.; Buchwald, S. L., *J. Am. Chem. Soc.* **2007**, *129* (12), 3490-3491.

108. Yu, H. Z.; Jiang, Y. Y.; Fu, Y.; Liu, L., *J. Am. Chem. Soc.* **2010**, *132* (51), 18078-18091.

109. Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T., *J. Org. Chem.* **1984**, *49* (11), 2081-2082.

110. Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R., *J. Am. Chem. Soc.* **2000**, *122* (27), 6510-6511.

111. Hu, Q. P.; Zhang, Z. F.; Liu, Y. G.; Imamoto, T.; Zhang, W. B., *Angew. Chem. Int. Ed.* **2015**, *54* (7), 2260-2264.

112. Chen, X.; Liu, Z. Q.; Lin, C. P.; Zheng, Y. G., *Bioorg. Chem.* **2016**, *65*, 82-89.

113. Deeter, J.; Frazier, J.; Staten, G.; Staszak, M.; Weigel, L., *Tetrahedron Lett.* **1990**, *31* (49), 7101-7104.

114. Biswas, S.; Trivedi, A.; Kharbanda, M.; Dubey, S.; Singla, S.; Yogiraj, M. B.; Vir, D. WO 2011/033366 A2, **2011**.

115. Fujima, Y.; Ikunaka, M.; Inoue, T.; Matsumoto, J., *Org. Process Res. Dev.* **2006**, *10* (5), 905-913.

116. Dominique, M. WO 2004/005239 A1, **2004**.

117. Istanbullu, H.; Erzurumlu, Y.; Kirmizibayrak, P. B.; Erciyas, E., *Lett. Drug Des. Discov.* **2014**, *11* (9), 1096-1106.

118. Roman, G.; Mares, M.; Nastasa, V., *Arch. Pharm.* **2013**, *346* (2), 110-118.

119. Xu, W.; Langer, R., *Dalton Trans.* **2015**, *44* (38), 16785-16790.

120. Miyano, S.; Lu, L. D. L.; Viti, S. M.; Sharpless, K. B., *J. Org. Chem.* **1985**, *50* (22), 4350-4360.

121. Calow, A. D. J.; Fernandez, E.; Whiting, A., *Org. Biomol. Chem.* **2014**, *12* (32), 6121-6127.

122. Mathad, V.; Ghanta, M.; Govindan, S.; Macharla, P.; Nalivela, V. US Pat. 034860, **2008**.

123. Chen, S. R.; Li, A. J.; Chen, M. M., *Asian J. Chem.* **2012**, *24* (4), 1680-1684.

124. Andersen, J.; Stuhr-Hansen, N.; Zachariassen, L. G.; Koldso, H.; Schiott, B.; Stromgaard, K.; Kristensen, A. S., *Mol. Pharmacol.* **2014**, *85* (5), 703-714.

125. Siddappa, R. K. G.; Chang, C. W.; Chein, R. J., *Tetrahedron Lett.* **2014**, *55* (5), 1031-1035.

126. Bymaster, F. P.; Beedle, E. E.; Findlay, J.; Gallagher, P. T.; Krushinski, J. H.; Mitchell, S.; Robertson, D. W.; Thompson, D. C.; Wallace, L.; Wong, D. T., *Bioorg. Med. Chem. Lett.* **2003**, *13* (24), 4477-4480.

127. Chang, M. Y.; Lin, C. Y.; Pai, C. L., *Tetrahedron Lett.* **2006**, *47* (15), 2565-2568.

128. Srivastava, S.; Bhandari, K.; Shankar, G.; Singh, H. K.; Saxena, A. K., *Med. Chem. Res.* **2004**, *13* (8-9), 631-642.

# CHAPTER 2

---

Part of the research described in this chapter has been published:

**1.** Veguillas, M.; Solà, R.; Fernández-Ibáñez, M. A.; Maciá, B. ***'Catalytic Enantioselective Addition of Methyltriisopropoxytitanium to Aldehydes'*.** *Tetrahedron Asymmetry* **2016**, *27*, 643–648.

**2.** Veguillas, M.; Solà, R.; Shaw, L.; Maciá, B. ***'Catalytic Asymmetric Addition of Organolithium Reagents to Aldehydes'*.** *European Journal of Organic Chem*istry **2016**, *9*, 1788–1794. [Highlighted in Synfacts **2016**, *12* (6), 0622.].

**3.** Collados, J. F.; Solà, R.; Harutyunyan, S. R.; Maciá, B. **'Catalytic Synthesis of Enantiopure Chiral Alcohols via Addition of Grignard Reagents to Carbonyl Compounds'.** *ACS Catalysis* **2016**, *6*, 1952−1970.

**4.** Solà, R.; Veguillas, M.; Maciá, B. ***'Tandem Hydrozirconation-Catalytic Enantioselective Addition of Alkenes to Aldehydes'***. *Manuscript in preparation.*

# 2.1. Introduction

## 2.1.1. Background

The enantioselective synthesis of chiral secondary alcohols is a recurring chemical transformation for both academia and industry.[1-7] As a matter of fact, there is a countless amount of natural products and pharmaceutical compounds that incorporate this fragment in their structures (*Figure 2.1*).

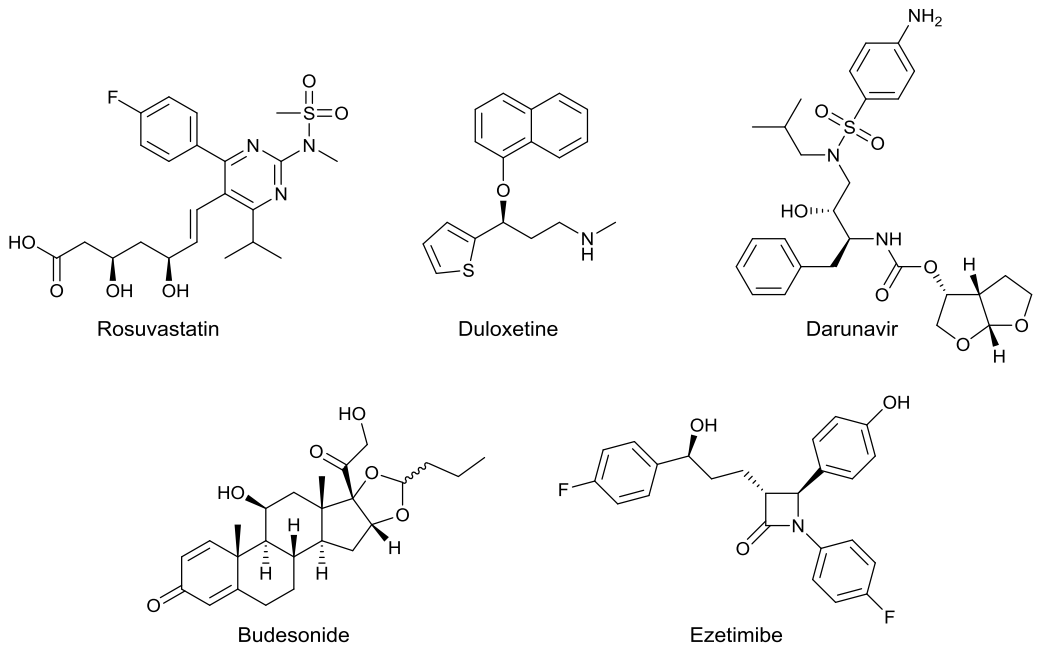



*Figure 2.1 – Structures of top selling pharmaceuticals with a chiral secondary alcohol (or derivative) in their structure*

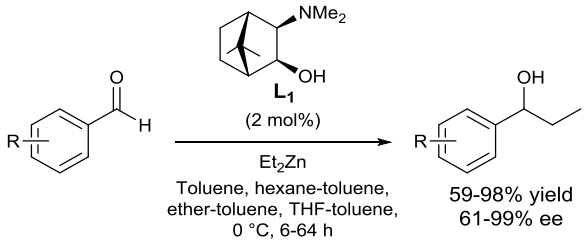
The enantioselective hydrogenation of ketones and the enantioselective addition of organometallic reagents to aldehydes are among the most popular catalytic approaches for the synthesis of non-racemic secondary alcohols.[1, 2, 8-14] This chapter, however, will focus exclusively on the catalytic enantioselective addition of organometallic reagents to aldehydes.

As stated previously in the 12 principles of Green Chemistry, "catalytic reagents are superior to stoichiometric reagents". By using catalytic methodologies, it is possible to decrease the amount of waste generated

in a chemical transformation, in an effort to turn the chemical industry into a more sustainable sector.

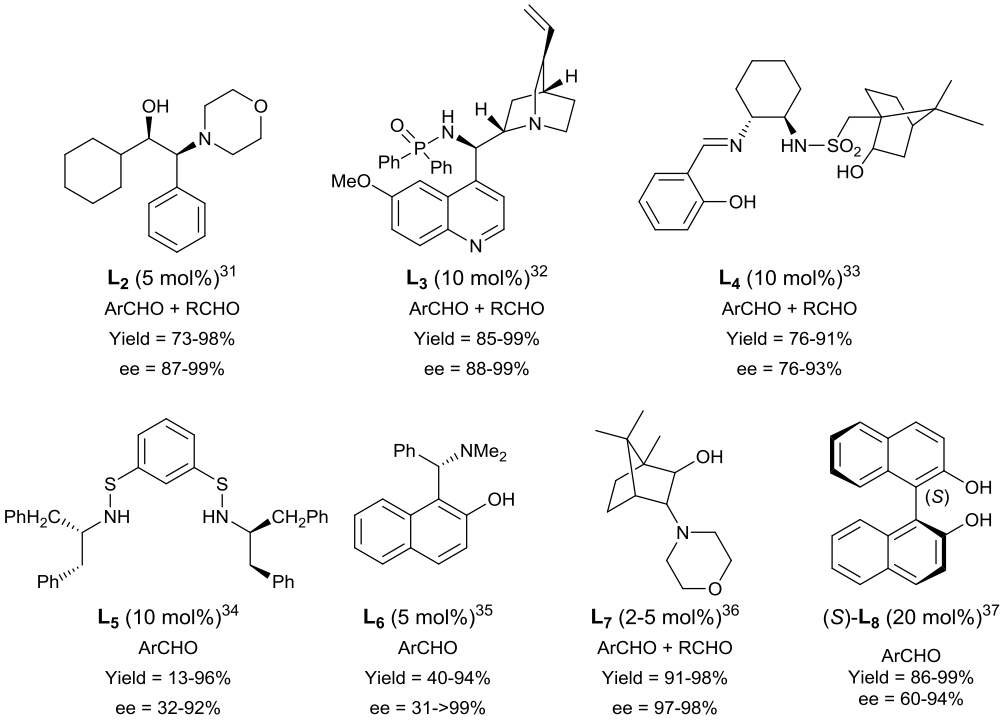
The catalytic enantioselective addition of organometallic reagents to aldehydes has been vastly studied for organometallic species of low to medium reactivity, such as organozinc reagents.[15-28] It is known that organozinc compounds are unreactive towards aldehydes,[29, 30] nonetheless, the use of chelating ligands (e.g. aminoalcohols) can alter their geometry and increase their reactivity so the addition to the carbonyl group can take place.[29]

The first catalytic enantioselective addition of organozinc reagents to carbonyl compounds was described by Noyori et al. in 1986.[16] Their work focused on the asymmetric alkylation of aromatic aldehydes using diethylzinc as nucleophile, in the presence of catalytic amounts of the chiral amino alcohol ligand **$L_1$** (*Scheme 2.1*).




*Scheme 2.1 – Noyori's addition of $Et_2Zn$ to aromatic aldehydes*

Following Noyori's work and the success of the 3-exo-dimethylaminoisoborneol (**$L_1$**) as ligand, the transformation became very popular and a lot of research was done in that field. During the last 20 years, more than 200 different ligands have been reported for the enantioselective addition of diethylzinc to benzaldehyde (see some representative examples in *Figure 2.2*).[31-37]




**L₂** (5 mol%)[31]
ArCHO + RCHO
Yield = 73-98%
ee = 87-99%

**L₃** (10 mol%)[32]
ArCHO + RCHO
Yield = 85-99%
ee = 88-99%

**L₄** (10 mol%)[33]
ArCHO + RCHO
Yield = 76-91%
ee = 76-93%

**L₅** (10 mol%)[34]
ArCHO
Yield = 13-96%
ee = 32-92%

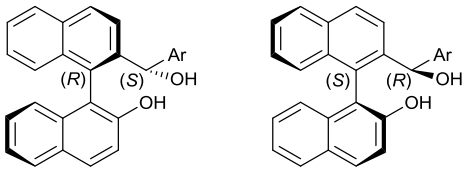
**L₆** (5 mol%)[35]
ArCHO
Yield = 40-94%
ee = 31->99%

**L₇** (2-5 mol%)[36]
ArCHO + RCHO
Yield = 91-98%
ee = 97-98%

(*S*)-**L₈** (20 mol%)[37]
ArCHO
Yield = 86-99%
ee = 60-94%

*Figure 2.2 – Chiral ligands used for the enantioselective addition of $Et_2Zn$ to aldehydes*

Also, recently, Ar-BINMOL ligands have proven to be efficient in the addition of diethylzinc to aromatic aldehydes (Figure 2.3).[38]



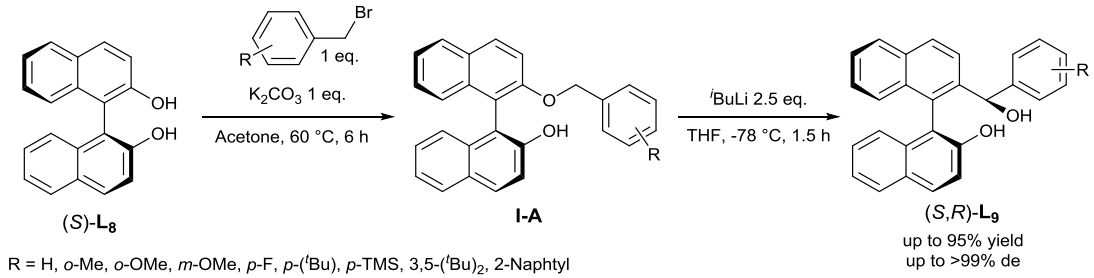

(*R*,*S*)-**L₉** (*S*,*R*)-**L₉**

*Figure 2.3 – Ar-BINMOL ligands (R,S)-**L₉** and (S,R)-**L₉***

Ar-BINMOL ligands were synthesised for the first time by Kiyooka et al. in 1996,[39] *via* a [1,2]-Wittig rearrangement. Although the ligands were obtained in excellent diastereoselectivities (up to >99% *de*) from enantiopure (*R*)- or (*S*)-BINOL, the yields reported were only moderate (up to 55% yield over 2 steps).

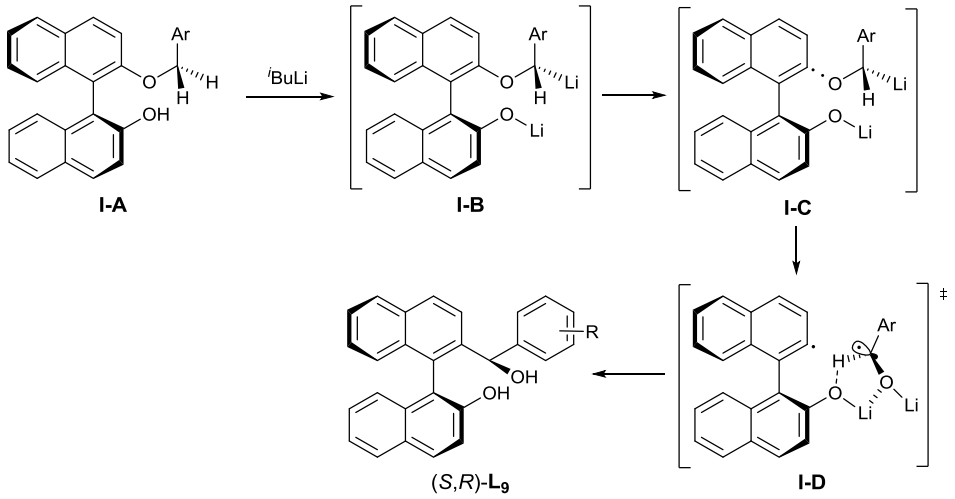
It was not until 2011 that the synthesis of Ar-BINMOLs was improved by Xu and co-workers.[40] The new optimised strategy was also based on a two-step sequence, starting from the commercially available enantiopure (*S*)-BINOL (*Scheme 2.2*). The benzylation of (*S*)-BINOL (**L₈**) with an aryl

bromide, in the presence of potassium carbonate provides the corresponding ether intermediate **I-A**, which is subsequently treated with *i*-butyllithium to afford the corresponding Ar-BINMOL (**L$_9$**) in excellent yield and diastereoselectivity.




*Scheme 2.2 – Xu's synthesis of Ar-BINMOL ligands*

The second step of the transformation is a lithium-assisted [1,2]-Wittig rearrangement. The mechanism of this transformation is shown in *Scheme 2.3* below.

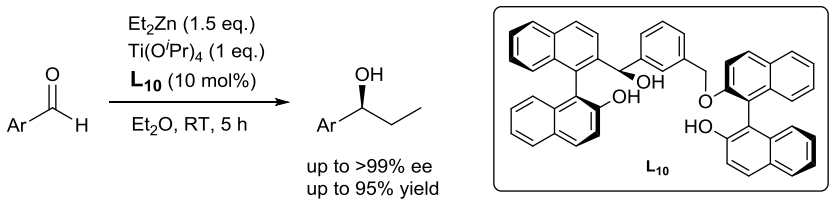



*Scheme 2.3 – Mechanism of the lithium-assisted [1,2]-Wittig rearrangement*

The intermediate **I-A** is deprotonated twice in the presence of *i*-butyllithium, providing the dilithiated species **I-B**. A homolytic dissociation of the C-O bond in **I-B** generates intermediate **I-C**. Next, a radical recombination ([1,2]-Wittig rearrangement) takes place providing the corresponding Ar-BINMOL ligand (***L$_9$***) *via* the intermediate **I-D**. The axial chirality from the (*S*)-BINOL starting material induces the radical recombination to happen in an enantioselective manner. The newly

formed $sp^3$ chiral center holds, exclusively, (*R*) configuration (>99% *de* obtained in the process).

As briefly mentioned above, Xu's et al. successfully used Ar-BINMOL ligands in the catalytic addition of $Et_2Zn$ to aromatic aldehydes.[38] Excellent yields and enantioselectivities are reported in the presence of catalytic amounts of **$L_{10}$** and 1 eq. of titanium tetraisopropoxide (*Scheme 2.4*).




*Scheme 2.4 – Xu's asymmetric addition of $Et_2Zn$ to aromatic aldehydes*

The exact mechanism for the transformation above is not known, however, authors propose that an alkyl group from the organozinc reagent must be transferred to one of the titanium atoms that, in coordination with the chiral ligand, are forming the catalytic complex.[38]

Even though the results obtained by Xu et al. using this methodology were excellent, the use of organozinc reagents has several disadvantages. First of all, their atom economy is poor since only one of the alkyl groups is transferred into the product. Additionally, organozinc reagents are expensive and generally difficult to prepare and to handle.[20]

The use of organometallic species of higher availability and lower cost would be a more attractive option to carry out this transformation. Both organomagnesium and organolithium compounds meet these requirements, but due to their higher reactivity and strong basicity, which leads to the loss of chemo-, regio- and enantioselectivity, they have been studied much less in the enantioselective additions to carbonyl compounds.

## 2.1.2. Catalytic enantioselective addition of Grignard reagents to carbonyl compounds

### 2.1.2.1. Catalytic enantioselective addition of Grignard reagents to aldehydes

The first Grignard reagent was prepared in 1900 by Françoise Auguste Victor Grignard, who was awarded the Nobel Prize for his work in 1912.[41] This world's famous transformation has the ability of turning an electrophile (alkyl or aryl halide) into a nucleophile (alkyl or arylmagnesium halide) by the reaction with magnesium metal in the appropriate solvent.

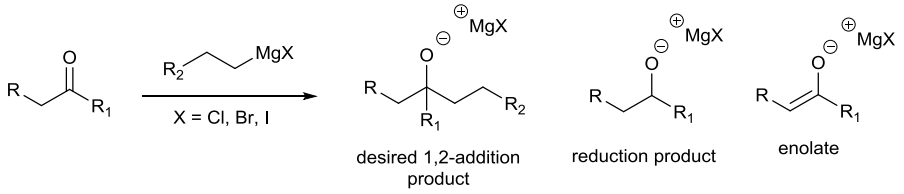
Organomagnesium or Grignard compounds can be divided into two different categories: i) complete compounds, like dialkyl or diarylmagnesium with the formula $R_2Mg$ and ii) mixed compounds, like alkyl or arylmagnesium halides with the formula RMgX. When a Grignard reagent is in solution, both species are in equilibrium (Schlenk equilibrium, *Scheme 2.5*).

*Scheme 2.5 – Schlenk equilibrium*

Grignard reagents are one of the cheapest and most commonly used organometallic reagents in both academic laboratories or industry. When compared to organozinc compounds, Grignard reagents have better atom economy, since all the R groups are transferred from the nucleophile to the product. Additionally, they offer other advantages like lower cost, wider commercial availability and being more tuneable and easier to prepare.

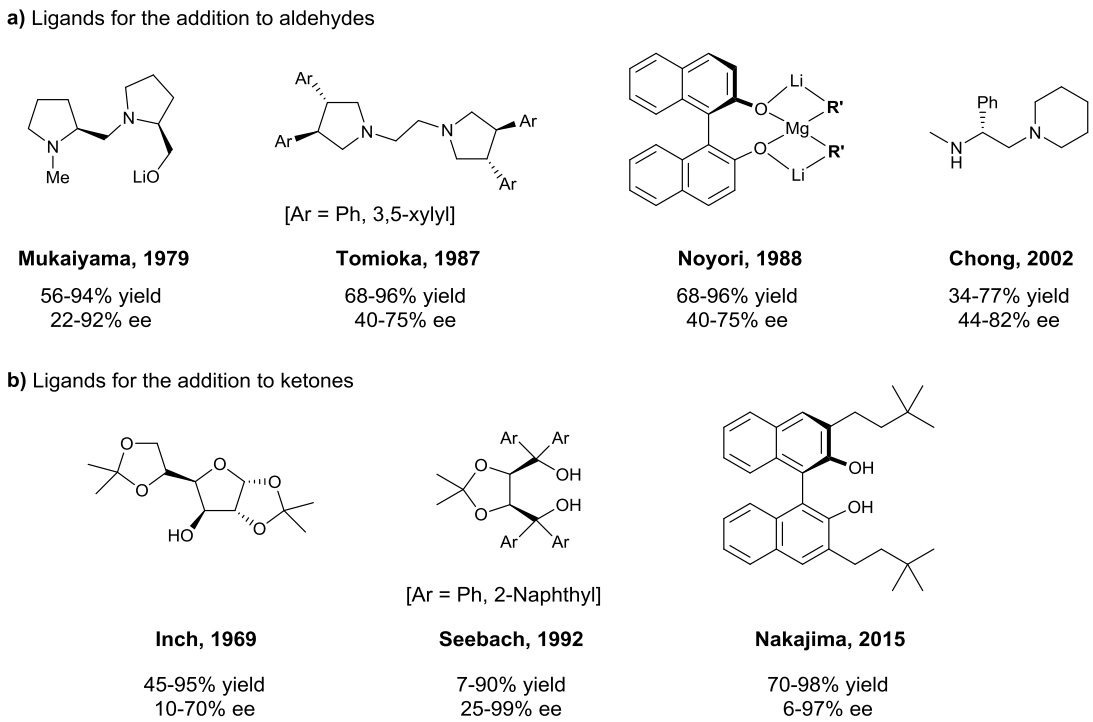
Due to their high reactivity, the use of Grignard reagents in asymmetric catalysis has been limited. The enantioselective addition of Grignard reagents to aldehydes or ketones is difficult due to the competition with the background uncatalysed reaction that leads to the racemic alcohol.[8, 42-

[44] Additionally, due to their high basic character, Grignard reagents can deprotonate enolizable aldehydes and ketones to form the corresponding enolate (*Scheme 2.6*). Furthermore, alkyl Grignard reagents with a hydrogen atom in the β-position easily undergo β-hydride elimination, causing the reduction of the carbonyl group in the starting material (see *Scheme 2.6* below).



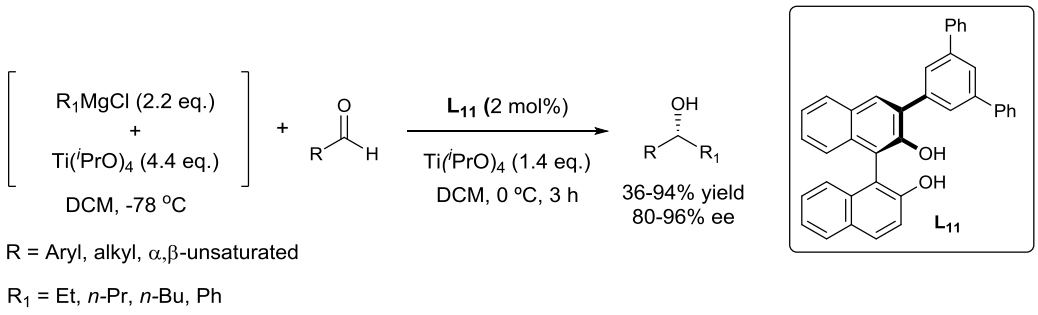

*Scheme 2.6 – Possible products of the Grignard reaction*

For these reasons, most of the enantioselective methodologies described in the literature for the addition of Grignard reagents to carbonyl compounds involve (super)stoichiometric amounts of a chiral ligand and very low temperatures (–78 to –110 °C).[1-8, 42-44] Some of these ligands have been depicted in *Scheme 2.7* below.




*Scheme 2.7 – Ligands used for the (super)stoichiometric addition of Grignard reagents to aldehydes (**a**) and ketones (**b**)*

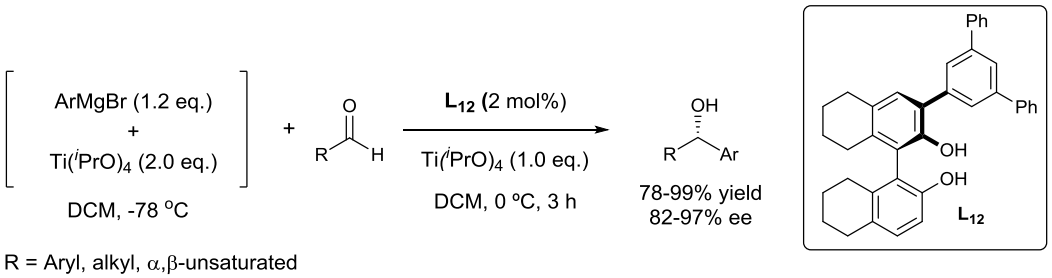
The first highly enantioselective addition of Grignard reagents to a carbonyl compound using catalytic amounts of ligand was reported in 2008 by Harada et al.[45] The reported method involves the initial treatment of an alkyl Grignard reagent with an excess of $Ti(O^iPr)_4$ at –78 °C, which is then slowly added to the reaction mixture at 0 °C. Only 2 mol% of the ligand **$L_{11}$** is needed to obtain excellent levels of enantioselectivity (*Scheme 2.8*).




*Scheme 2.8 – Harada's enantioselective catalytic addition of alkyl Grignard reagents to aldehydes*

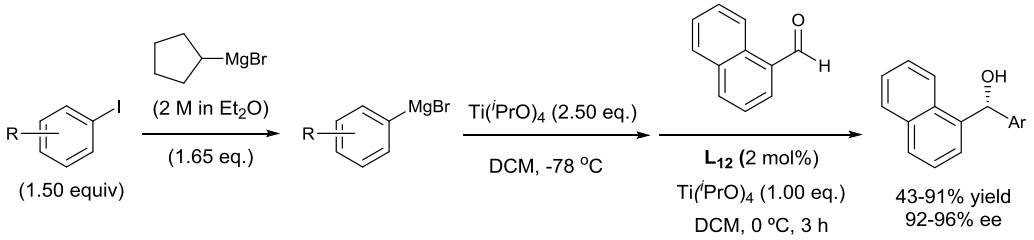
It is worth noting that the addition of the very valuable MeMgCl to 1-naphthaldehyde using this methodology only provided a 28% *ee* of the corresponding methyl carbinol. As it will be explained later (section 2), methyl carbinol units are especially interesting for their abundance in natural products.

For the addition of aromatic Grignard reagents to both aromatic and heteroaromatic aldehydes, the partially hydrogenated ligand **$L_{12}$** proved to be more efficient than **$L_{11}$** (*Scheme 2.9*).[46, 47] The only limitation of this reaction is the addition of PhMgBr to *o*-anisaldehyde, which only provides 66% yield and 9% *ee*, probably due to steric problems.




*Scheme 2.9 – Harada's enantioselective catalytic addition of aromatic Grignard reagents to aldehydes catalysed by* ***L12***

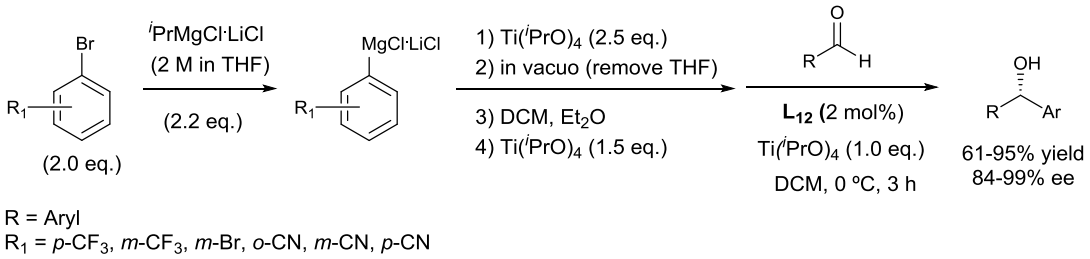
This methodology also allows the addition of functionalised Grignard reagents that have been prepared *in situ* using Knochel's procedure.[48] The reaction of the corresponding iodoarene with *c*-$C_5H_9MgCl$ allows the formation of the corresponding Grignard reagent, which is subsequently treated with $Ti(O^iPr)_4$ at –78 °C. Next, the reaction mixture is slowly added to a solution of the aldehyde in the presence of **L12** at 0 °C. The corresponding secondary alcohols are obtained in good yields and enantioselectivities (*Scheme 2.10*).




*Scheme 2.10 – Harada's catalytic addition of in situ prepared Grignard reagents to 1-naphthaldehyde*

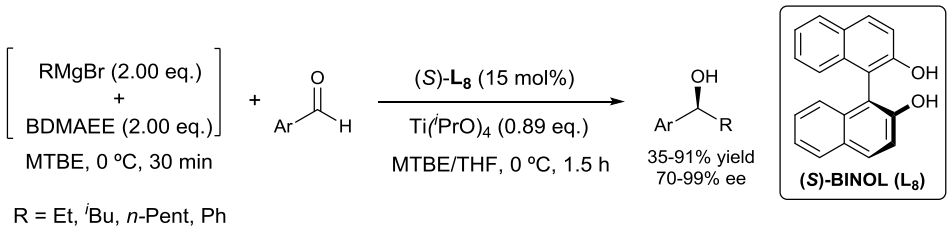
Alternatively, Grignard reagents can be prepared by reaction of an aryl bromide (more desirable precursor than iodoarenes since they offer greater stability, wider availability and lower price) with the commercially available $^iPrMgCl$ in THF.[49-52] Nonetheless, in this particular case, the THF involved in the preparation of the Grignard reagent must be removed *in vacuo* and replaced with dichloromethane in order to obtain the desired secondary alcohols in good yields and enantioselectivities (*Scheme 2.11*).[53] Unfortunately, the reaction with aliphatic aldehydes, such as

cyclohexanecarbaldehyde, only leads to moderate yield (54%) and enantioselectivity (63%).




*Scheme 2.11 – Harada's catalytic addition of in situ prepared Grignard reagents to aldehydes*

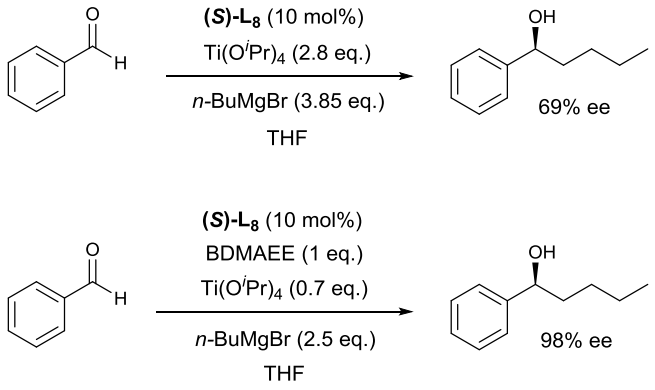
Da et al. have demonstrated that the catalytic use of (*S*)-BINOL as ligand, with stoichiometric amounts of *bis*[2-*N*,*N*-dimethylamino)ethyl]ether (BDMAEE) as additive, is a successful combination for the enantioselective addition of Grignard reagents to aldehydes.[54, 55] The usage of this chelating additive, which is able to coordinate the metal (i.e. magnesium) and decrease its reactivity, improves the reaction conditions (temperature of 0 °C and lower amount of $Ti(O^iPr)_4$ required) compared to Harada's methodology (*Scheme 2.12*).




*Scheme 2.12 – Da's enantioselective addition of Grignard reagents to aldehydes*

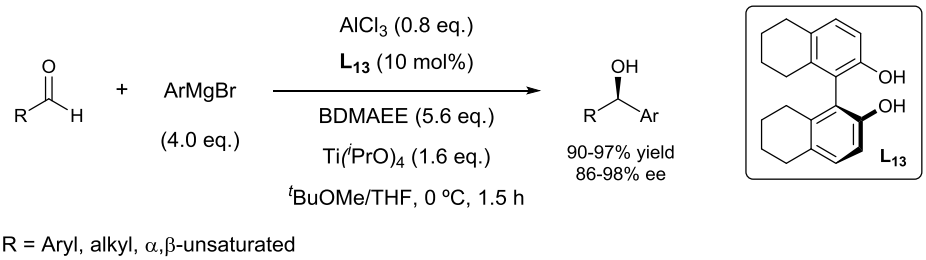
As proposed by Da et al., and in corroboration with the studies of Bolm and Walsh,[56, 57] BDMAEE is not only able to coordinate to the Grignard reagent and decrease its reactivity, but also to trap the magnesium salts ($MgBr_2$ and/or $Mg(O^iPr)Br$) formed during the Schlenk equilibrium and/or the transmetalation process. The coordination of these salts to the oxygen atom of the carbonyl group in the substrate would promote the uncatalysed reaction, thus favouring the formation of the corresponding racemic alcohol.

The following *Scheme 2.13* shows the Ti(O$^i$Pr)$_4$ assisted addition of $^n$BuMgBr to benzaldehyde in the presence and absence of BDMAEE.[55] It is worth noting that BDMAEE not only increases of the enantioselectivity of the reaction up to 98% *ee*, but also allows a substantial reduction of the amount of Ti(O$^i$Pr)$_4$ and Grignard reagent required to perform the transformation.




*Scheme 2.13 – Enantioselective addition of n-butylmagnesium bromide to benzaldehyde with and without the additive BDMAEE.*

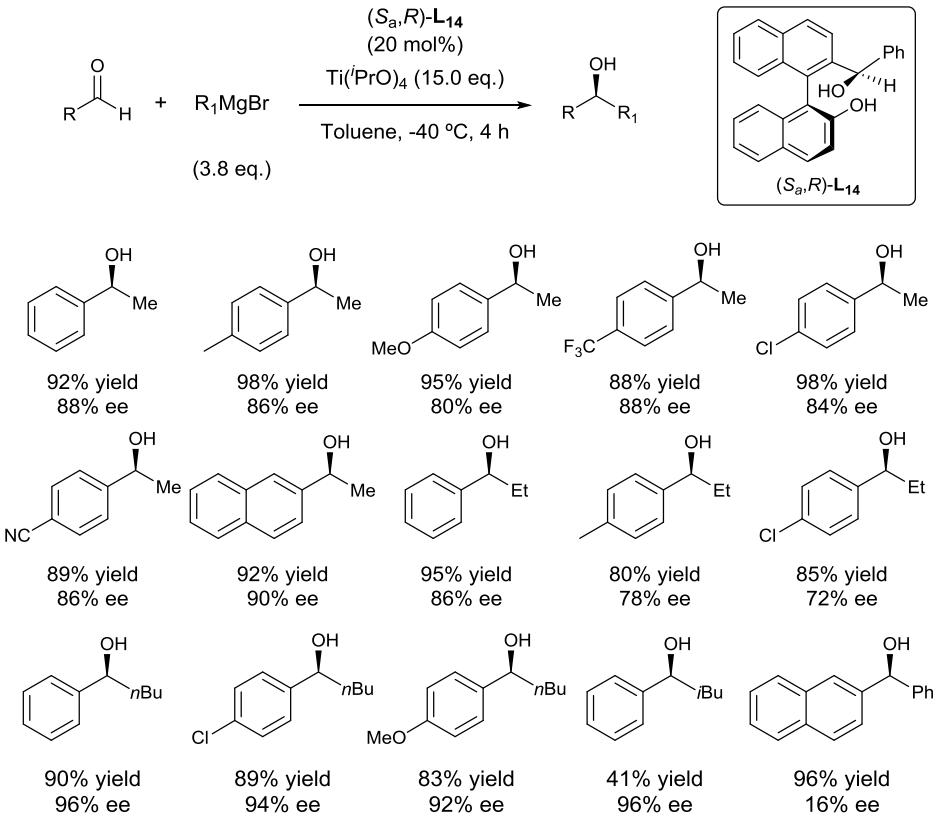
In 2010, Da et al. reported a new methodology that allows the addition of aromatic Grignard reagents to aldehydes in excellent yields and enantioselectivities.[58] The procedure involves the treatment of the corresponding Grignard reagent with $AlCl_3$, to provide a less reactive triarylaluminium intermediate *in situ*. Next, ligand **L$_{13}$** is added, followed by Ti(O$^i$Pr)$_4$ and the aldehyde in the last place (*Scheme 2.14*). The corresponding alcohols are obtained in good yields and enantioselectivities, working at higher and more convenient temperatures (0 $^o$C) than Harada's previous methodology (−78 $^o$C).




R = Aryl, alkyl, α,β-unsaturated

*Scheme 2.14 – Da's enantioselective addition of aromatic Grignards to aldehydes in the presence of AlCl$_3$*

In 2011, our research group published a new methodology for the addition of Grignard reagents to aldehydes catalysed by Ar-BINMOLs ligands (*Scheme 2.15*).[59] The methodology allows the direct addition of Grignard reagents to carbonyl compounds in a one-pot reaction and without the need of performing a slow addition of the nucleophile (main disadvantage of Harada's methodology).[45-47]

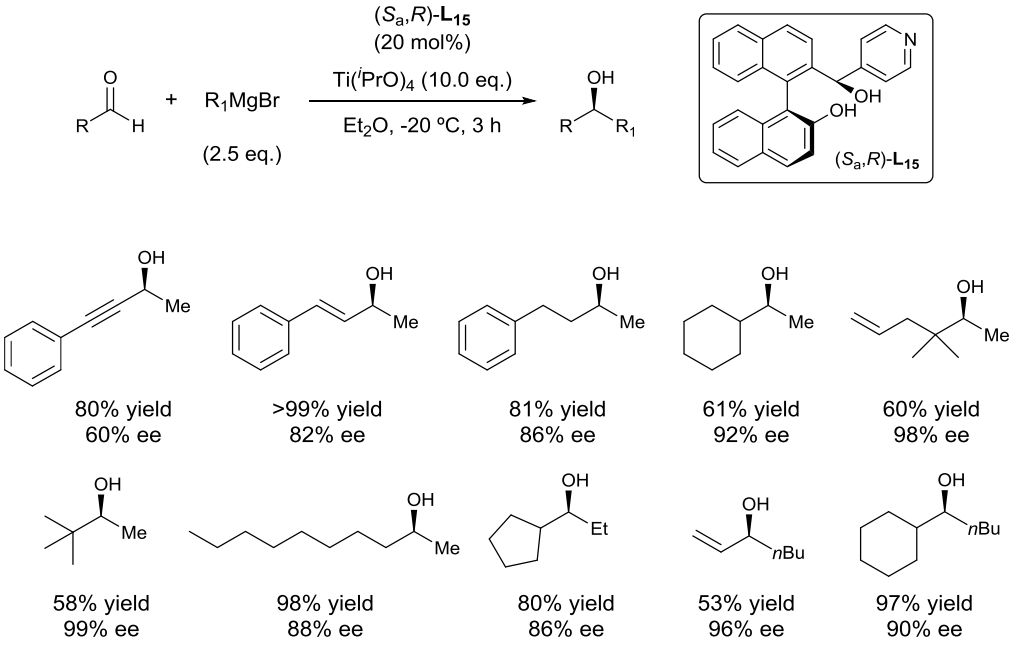



*Scheme 2.15 – Maciá and Yus' addition of Grignard reagents to aldehydes*

Even though the experimental procedure requires a large excess of $Ti(O^iPr)_4$ and low temperatures (–40 °C), the whole process can be done one-pot and good yields and enantioselectivities are obtained for the addition of the challenging methyl Grignard to aromatic aldehydes (85-99% yield, 58-90% ee). The reaction has to be carried out in $Et_2O$ as THF causes a decrease in the enantioselectivities.

The addition of PhMgBr to 2-naphthaldehyde proceeded in a very low enantioselectivity (16% ee) and the reaction with aliphatic aldehydes only provided moderate enantioselectivities (50-70% ee). A simple switch to

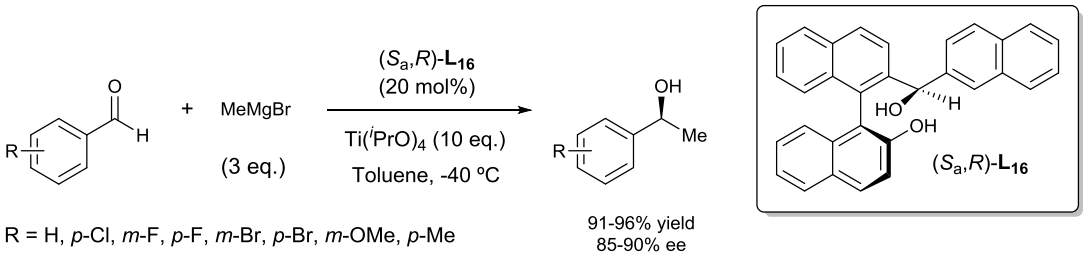
the chiral ligand (*S*$_a$,*R*)-**L$_{15}$**, however, allows the addition of Grignard reagents to aliphatic aldehydes in good yields (61-99%) and enantioselectivities (60-99%) (*Scheme 2.16*).[60]




*Scheme 2.16 – Maciá and Yus' addition of Grignard to aliphatic aldehydes*

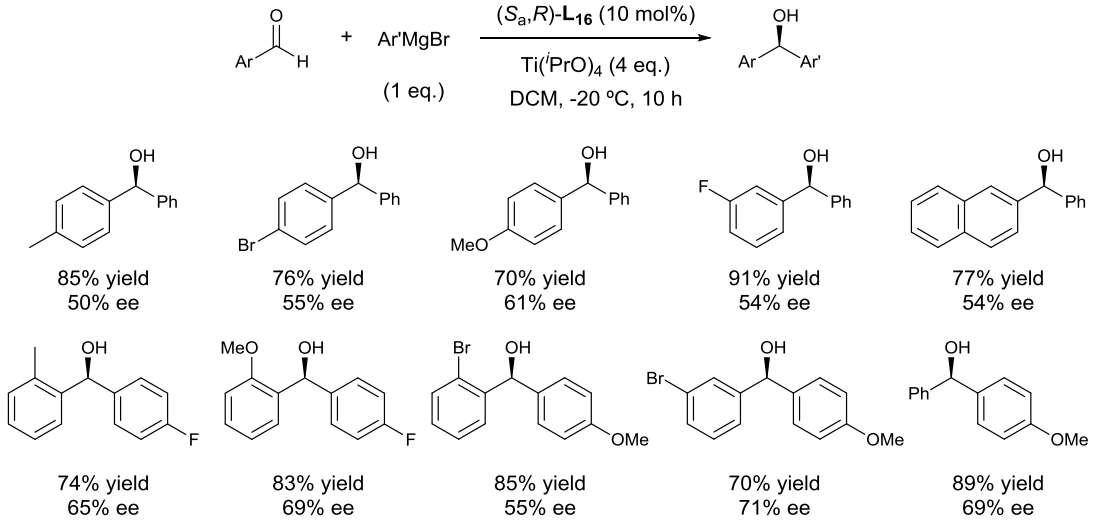
This catalytic system described in *Scheme 2.16* provides unprecedented yields and enantioselectivities for the synthesis of aliphatic chiral secondary alcohols under mild conditions. Additionally, ligand **L$_{15}$** can be easily recovered from the reaction mixture by a simple acid/base extraction (60% recovery yield) and subsequently reused without any loss of activity.

Soon after this methodology was published by our group, Xu et al. reported the use of a new Ar-BINMOL ligand for the addition of MeMgBr to aromatic aldehydes.[61] The utilisation of the ligand **L$_{16}$** allows the synthesis of chiral methyl carbinol products in excellent yields (91-96%) and enantioselectivities (85-90%). Furthermore, this new ligand allows a slight reduction in the amounts of MeMgBr (3.0 vs 3.8 eq.) and Ti(O$^i$Pr)$_4$ (10.0 vs 15.0 eq.), compared to our previous methodology (*Scheme 2.17*).




*Scheme 2.17 – Xu's addition of methylmagnesium bromide to aromatic aldehydes*

Xu and co-workers have also demonstrated that ligand **$L_{16}$** is effective for the addition of aryl Grignard reagents to aromatic aldehydes.[61] The reaction in dichloromethane at –20 °C affords the corresponding chiral secondary alcohols in moderate yields (70-92%) and enantioselectivities (50-71%) (*Scheme 2.18*).



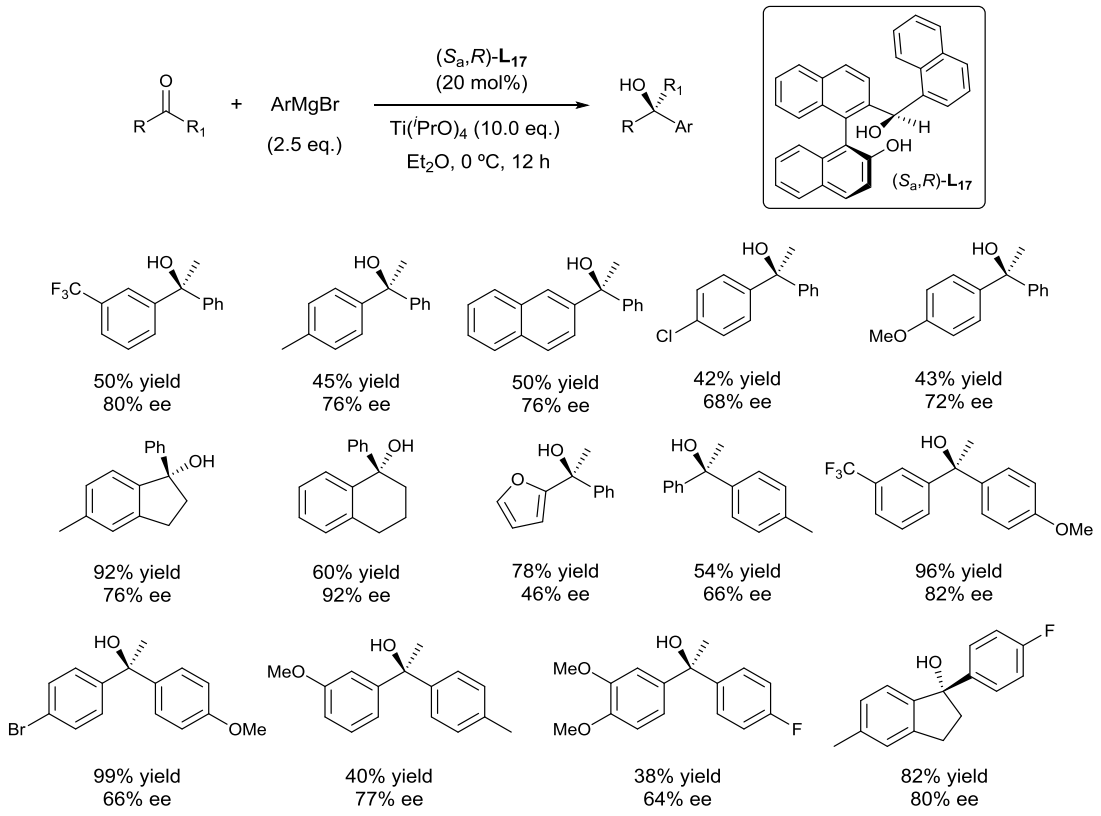

*Scheme 2.18 – Xu's addition of aryl Grignard reagents to aromatic aldehydes*

## 2.1.2.2. Catalytic enantioselective addition of Grignard reagents to ketones

The addition of Grignard reagents to ketones is a very challenging reaction due to the lower reactivity of ketones and the greater steric hindrance around the carbonyl group.

In 2014, our research group published a titanium based methodology for the enantioselective addition of aromatic Grignard reagents to ketones.[62] The use of catalytic amounts of the Ar-BINMOL ligand **$L_{17}$**, in the presence

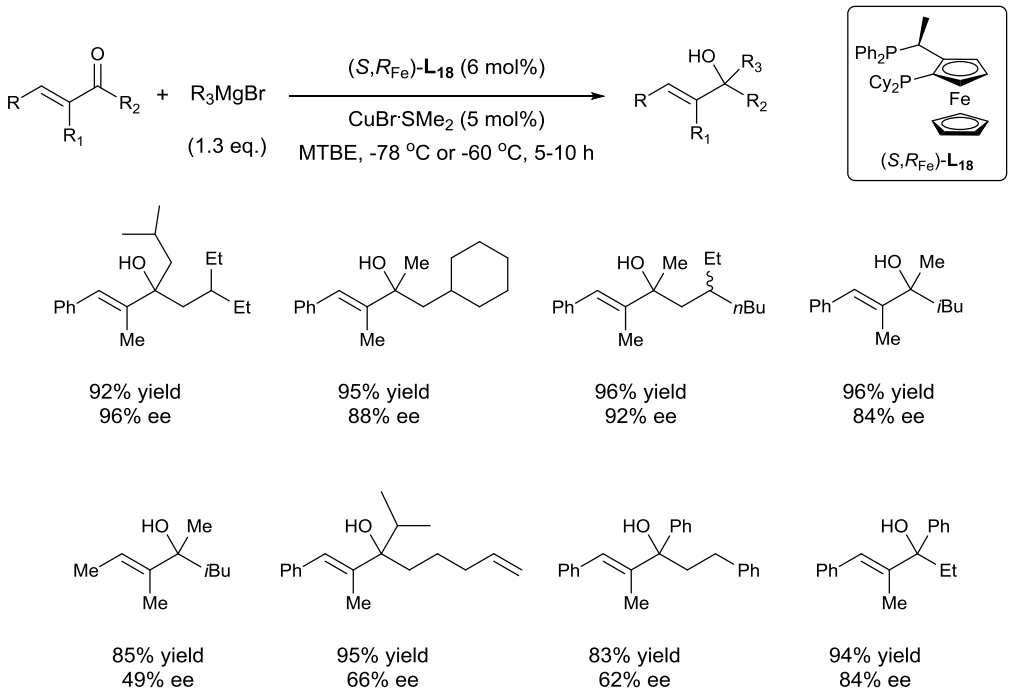
of an excess of $Ti(O^iPr)_4$ (10 eq.), in ether at 0 °C, provides the corresponding chiral tertiary alcohols in moderate to excellent yields (35-99%) and good enantioselectivities (46-92%). Unfortunately, the reaction with bulky substrates such as *o*-methylacetophenone, only leads to a 12% conversion (*Scheme 2.19*).




*Scheme 2.19 – Maciá and Yus' addition of aromatic Grignard reagents to ketones*

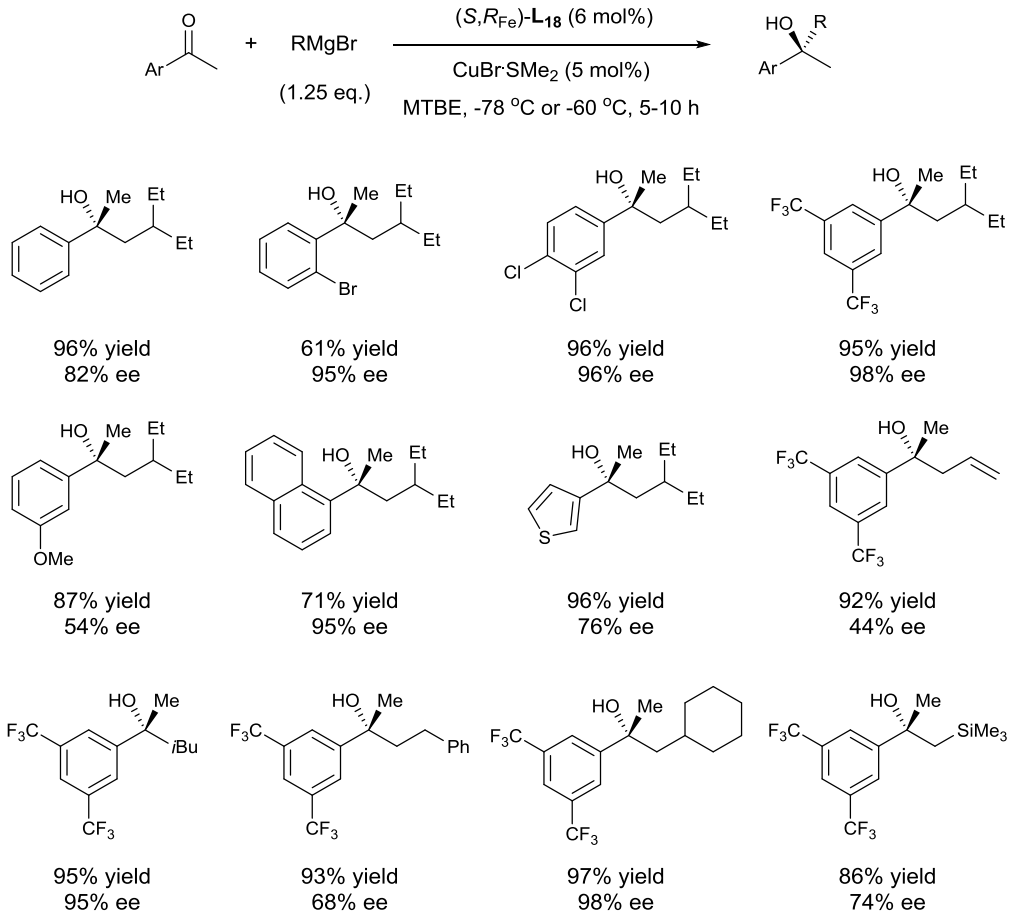
In 2012, the groups of Harutyunyan and Minnaard developed the first catalytic enantioselective 1,2-addition of Grignard reagents to α-substituted α,β-unsaturated ketones based on a copper (I)-diphosphine complex, without the use of any additive (*Scheme 2.20*).[63] The desired chiral tertiary alcohols are obtained in high yields (81-96%) and enantioselectivities (42-96%) when $CuBr{\cdot}SMe_2$ and the ferrocenyl diphosphine rev-Josiphos (**$L_{18}$**) are used as catalysts, in *tert*-butylmethyl ether as solvent (*Scheme 2.20*). Although the scope of the reaction is limited to bulky β-branched Grignard reagents, this methodology is especially relevant, since it breaks the old paradigm that organocopper

compounds favour the 1,4-addition to electron-deficient carbonyl compounds.



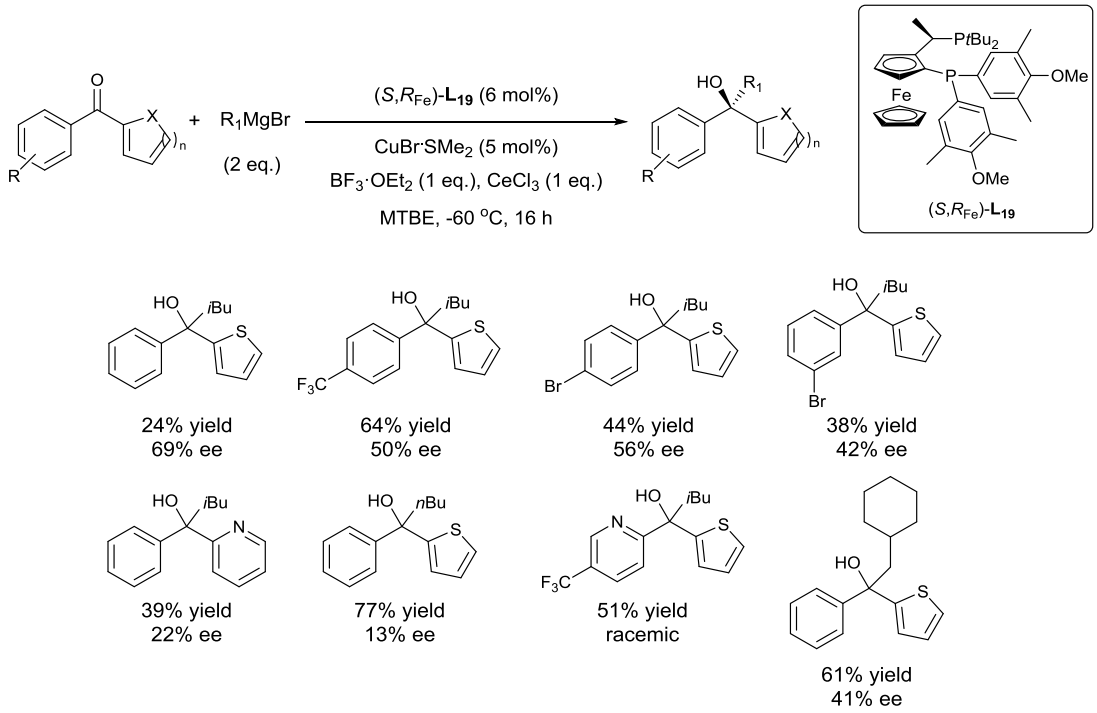

*Scheme 2.20 – Harutyunyan's 1,2-addition of Grignard reagents to α,β-unsaturated ketones*

Harutyunyan and Minnaard's research groups have also successfully applied this methodology to the alkylation of aryl alkyl ketones.[64] The reaction affords the corresponding benzylic tertiary alcohols in high yields and excellent enantioselectivities (*Scheme 2.21*). As observed in the previous case, β-branched Grignard reagents lead to higher enantioselectivities, whilst linear Grignard reagents provide lower enantiomeric excesses. MeMgBr does not react.




*Scheme 2.21 – Harutyunyan's 1,2-addition of Grignard reagents to aryl alkyl ketones*

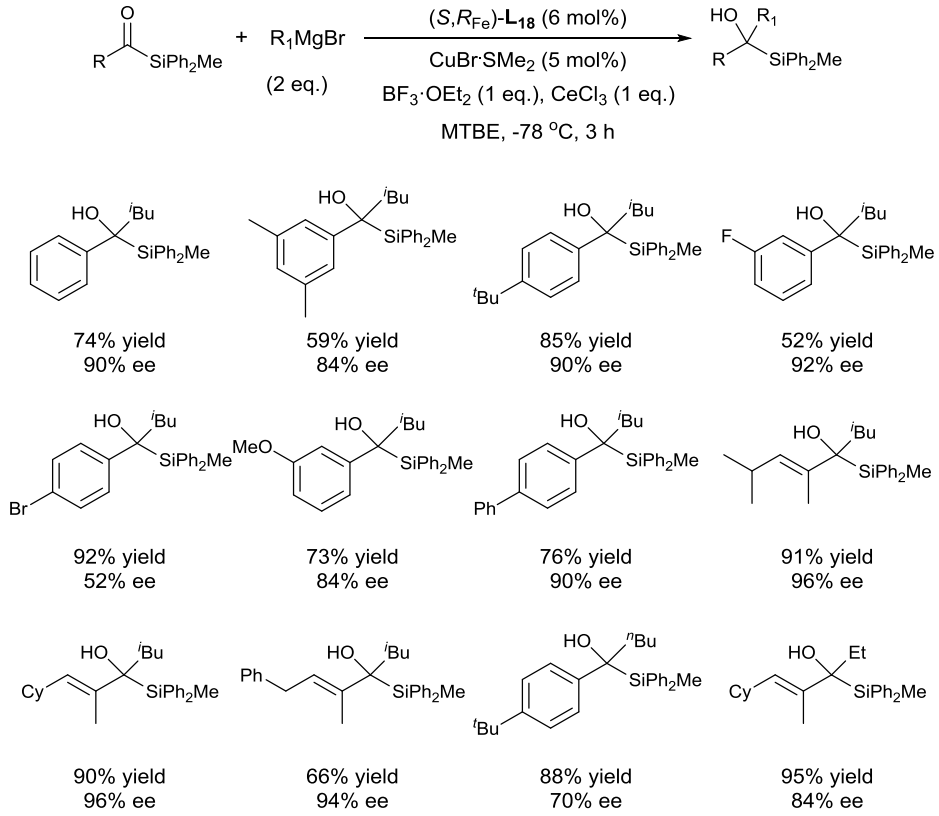
A similar catalytic system, based on CuBr·$SMe_2$/Josiphos ligand **$L_{19}$** proved to be efficient for the alkylation of several aryl heteroaryl ketones (*Scheme 2.22*).[65] The access to tertiary aryl heteroaryl methanols is very attractive because of the presence of this motif in biologically active structures.[66] In this case, however, a mixture of the Lewis acids $BF_3$·$OEt_2$/$CeCl_3$ (1:1) is required in order to improve the reactivity and outcompete the undesired reduction product *via* Meerwein-Pondorf-Verley reaction. The role of the two Lewis acids is not clearly understood, but it would be reasonable to think that they prevent the coordination of the magnesium atom to the oxygen of the carbonyl group, which would promote the undesired β-hydride transfer generating the reduction product.




*Scheme 2.22 – Harutyunyan's addition of Grignard reagents to aryl heteroaryl ketones*

The low stability of both the alkoxide and the diarylmethanol product leads to the formation of the dehydration product during the reaction and purification. For this reason, the yields obtained in this reaction are only moderate. Additionally, the difficult enantiodiscrimination provides low to moderate enantioselectivities (*Scheme 2.22*). Nevertheless, this is the first example of direct asymmetric alkylation of diaryl ketones reported in the literature.

The alkylation of acyl silanes (relevant compounds in medicinal chemistry)[67, 68] with Grignard reagents, has also been evaluated using this methodology.[69, 70] The reaction affords excellent yields and an excellent enantiodiscrimination between the two moieties of the carbonyl group (*Scheme 2.23*).




*Scheme 2.23 – Harutyunyan's addition of Grignard reagents to acyl silanes*

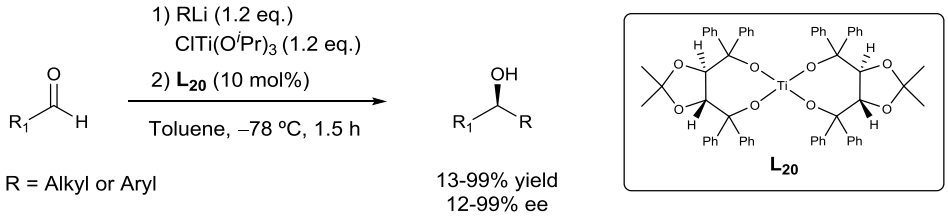
Both the chemo- and enantioselectivity of this reaction depend strongly on the bulkiness of the silyl group. When the reaction was attempted with $SiPh_3$ and $SiEt_3$ ketones, only reduction product was obtained, whilst $SiPh_2Me$ or $SiPhMe_2$ substituents afforded the desired 1,2-addition product with good yields and enantioselectivities. Additionally, the mixture of the two Lewis acids ($BF_3{\cdot}OEt_2/CeCl_3$ 1:1) is necessary in order to obtain good enantiomeric excesses and chemoselectivities. The addition of $^{i}$BuMgBr to phenylsilylketone using this boron/cerium system provides the desired tertiary alcohol in good chemoselectivity (5:1, carbonyl addition/reduction product) and 90% ee.[69, 70]

## 2.1.3. Catalytic enantioselective addition of organolithium reagents to carbonyl compounds

Organolithium compounds were discovered by Wilhelm Schlenk in 1917.[71] Since then, organolithium reagents have become common bench chemicals in any organic synthetic laboratory.

Their use in asymmetric synthesis is a very attractive option due to their great availability and low cost.[72, 73] However, their high reactivity and strong basicity can often lead to the loss of chemo-, regio- and enantioselectivity. For these reasons, their application in enantioselective catalysis is challenging and it usually involves (super)stoichiometric amounts of a chiral ligand together with extremely low temperatures.

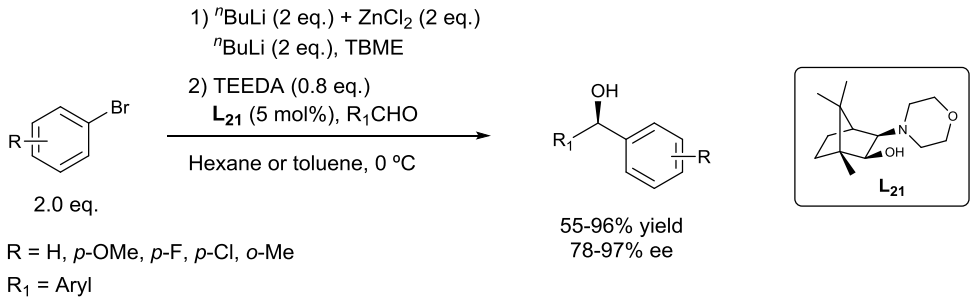
The first catalytic enantioselective addition of organolithium reagents to aldehydes was reported by Seebach et al. in 1994.[74] Their methodology describes the use of the chiral titanium TADDOLate **$L_{20}$** in toluene at –78 °C (*Scheme 2.24*). When $^{n}$BuLi is added to benzaldehyde in the presence of 1.2 eq. of $ClTi(O^{i}Pr)_3$, only 60% *ee* is obtained. However, when the LiCl is removed from the reaction mixture, by a tedious filtration procedure, and the corresponding organotitanium compound isolated, the enantioselectivity increases to 98%. This fact proves that the lithium salts formed during the transmetallation step can act as Lewis acids and promote the undesired uncatalysed reaction.




*Scheme 2.24 – Seebach's enantioselective addition of organolithium reagents to aldehydes*

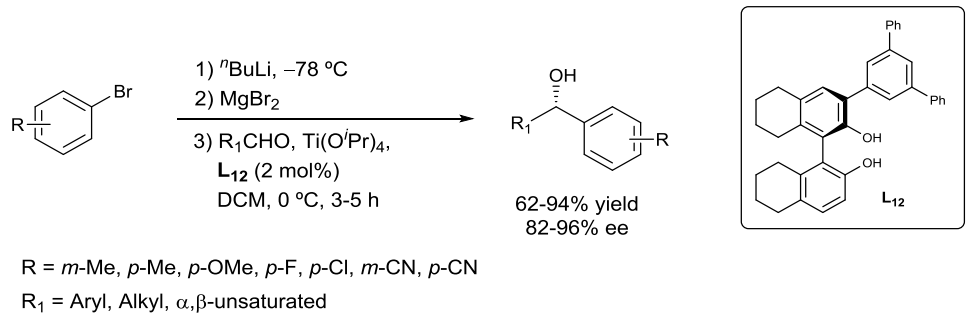
In 2009, Walsh et at. developed a new methodology for the enantioselective addition of organozinc compound to aldehydes catalysed

by **L21** (*Scheme 2.25*).[75] The organozinc compound is prepared by transmetallation of the corresponding organolithium reagent (prepared *in situ* by reaction of an aryl bromide and $^{n}$BuLi) with $ZnCl_2$. The use of TEEDA (0.8 eq.) is necessary to chelate the lithium salts formed during the transmetallation process.




*Scheme 2.25 – Walsh's addition of aryllithium reagents to aldehydes*

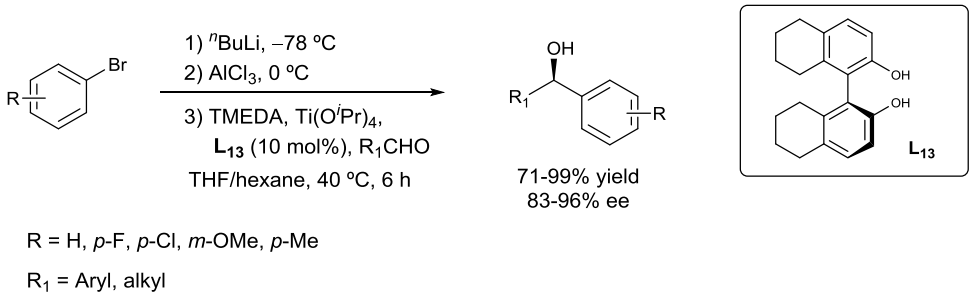
In 2010, Harada et al. described a methodology for the enantioselective addition of Grignard reagents to aldehydes, catalysed by the BINOL derivative ligand **L12** (*Scheme 2.26*).[76] Again, the Grignard reagent is prepared by transmetallation of the corresponding organolithium reagent, which is prepared from reaction between an aryl bromide and *n*-butyllithium. An excess of $Ti(O^{i}Pr)_4$ is necessary to achieve good enantioselectivities in the addition to different aldehydes.




*Scheme 2.26 – Harada's addition of aryllithium reagents to aldehydes*

In 2014, Da et al. reported a procedure for the titanium assisted addition of organoaluminum reagents to aldehydes using the partially hydrogenated (*S*)-BINOL **L13** as chiral ligand (*Scheme 2.27*).[77] The organoaluminum reagents are prepared by transmetallation of the corresponding aryllithium reagents with $AlCl_3$. These aryllithium reagents

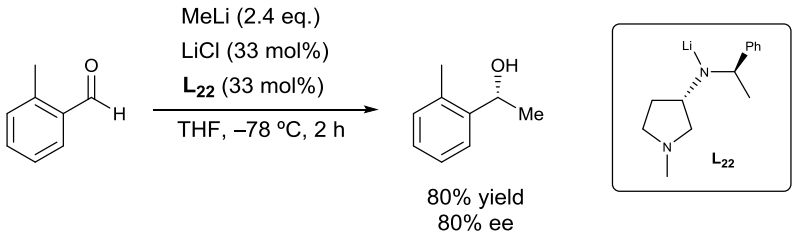
are generated *in situ* from an aryl bromide and *n*-butyllithium. The additive TMEDA is required in order to achieve good enantioselectivities. Authors postulate that the role of the TMEDA is to trap by chelation the lithium salts generated during transmetallation.




*Scheme 2.27 – Da's addition of aryllithium reagents to aldehydes*

As described above, the use of organolithium reagents as nucleophiles in enantioselective catalysis is very challenging, and many groups have opted for their transmetallation into less reactive organometallic species, such as organotitanium, organoaluminum, organozinc or organomagnesium reagents.

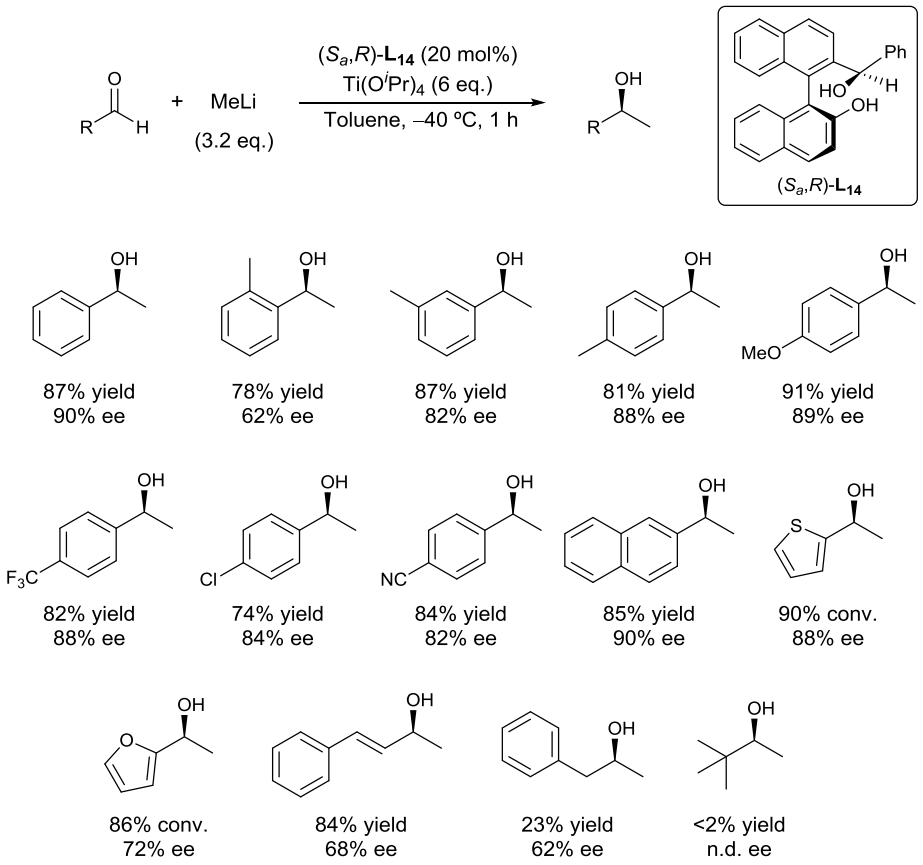
The first substoichiometric direct addition of an organolithium to an aldehyde was not achieved until 2011, by the group of Maddaluno.[78] The direct addition of methyllithium to *o*-methylbenzaldehyde was carried out using a 33 mol% of the chiral ligand **$L_{22}$** and a 33 mol% of LiCl. The corresponding secondary alcohol was obtained in 80% yield and 80% ee (*Scheme 2.27*).




*Scheme 2.28 – Maddaluno's enantioselective direct addition of MeLi to o-methylbenzaldehyde*

In 2012, our research group published a new methodology that allows the direct addition of organolithium reagents to aldehydes by using catalytic

amounts of the Ar-BINMOL ligand ($S_a$,*R*)-**L14** in the presence of an excess of Ti(O$^i$Pr)$_4$ (*Scheme 2.29*).[79]

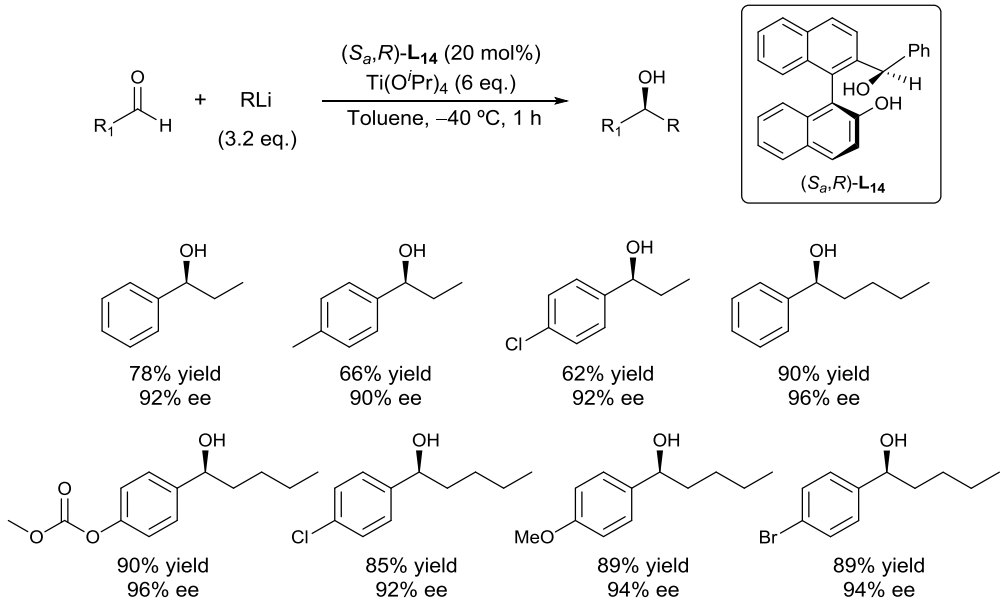



*Scheme 2.29 – Maciá and Yus' enantioselective addition of methyl lithium to aldehydes catalysed by ($S_a$,R)-**L14***

In general, the addition of the very versatile methyllithium proceeds with good yields and enantioselectivities. The lower yield (78%) and enantioselectivity (62%) obtained for the reaction with *o*-methylbenzaldehyde might be due to higher steric hindrance close to the carbonyl group. The reaction with aliphatic aldehydes, such as phenylacetaldehyde and pivaldehyde, provided low conversions.

It is worth mentioning that no additives and no tedious salt filtrations or slow addition procedures are required with this methodology. Furthermore, no by-product formation is observed, and both the non-reacted starting material and the ligand can be easily recovered from the reaction mixture. The recovered ligand **L14** can be used in other reactions without any loss of its activity.

The methodology can be successfully extended to other alkyl lithium reagents using a wide range of aromatic aldehydes, providing the corresponding secondary alcohols in good yields (62-90%) and excellent enantioselectivities (92-96%) (*Scheme 2.30*).[79]




*Scheme 2.30 – Maciá and Yus' enantioselective addition of alkyllithium to aromatic aldehydes catalysed by ($S_a$,R)-**L14***

The main limitations of this methodology are (i) the addition of bulky organolithium reagents (e.g. $^{i}$BuLi only provides 8% yield and 62% ee in the addition to benzaldehyde, together with considerable amounts (40%) of the reduction product phenylmethanol), (ii) the addition of aryllithium reagents (e.g. phenyllithium affords high yields (92-96%) but low enantioselectivities (17-39%) in the addition to different aromatic aldehydes) and (iii) aliphatic aldehydes provide low yields and enantioselectivities.

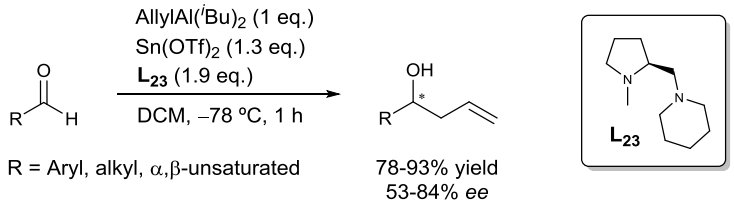
In addition, other disadvantages of this methodology, which hamper its application in industrial processes, are the high loadings of $Ti(O^{i}Pr)_4$ and the low temperatures required in order to obtain high enantioselectivities.

## 2.1.4. Catalytic enantioselective addition of organoaluminium reagents to carbonyl compounds

The discovery of organoaluminium compounds by Karl Ziegler and Giulio Natta in 1953,[80] was closely related to the development of the catalytic olefin polymerisation procedure for which, ten years later, they would be awarded the Nobel Prize.

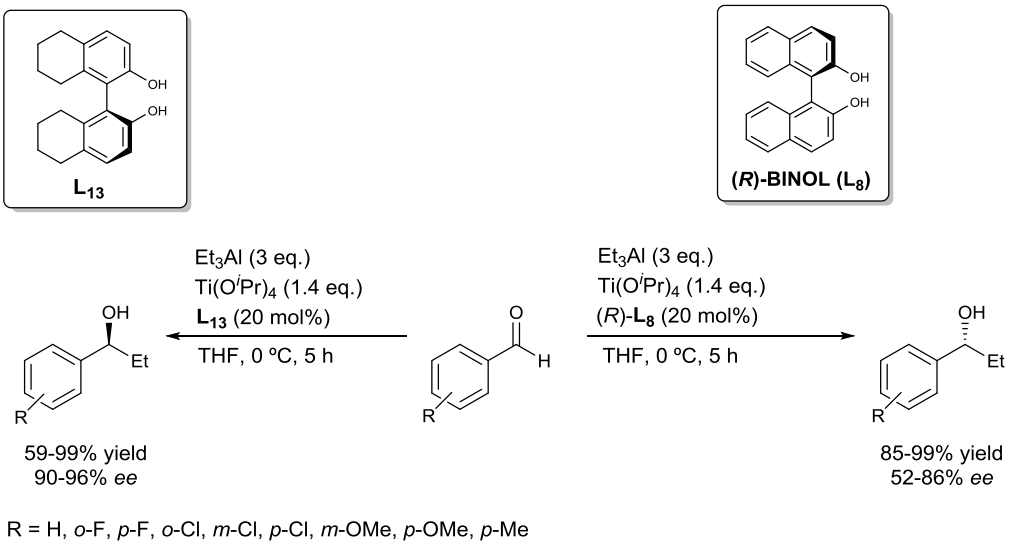
Ever since their discovery, the application of organoaluminium reagents in asymmetric catalysis has increased during the years due to their great stability and low toxicity.

The first enantioselective alkylation of aldehydes with organoaluminium reagents was reported in 1986 by Mukaiyama et al.[81] Their methodology consists in the allylation of aldehydes using Allyl($^i$Bu)$_2$Al as a nucleophile, Sn(OTf)$_2$ as an additive and superstoichiometric amounts of the chiral diamine **L$_{23}$** as ligand. The reaction is carried out in dichloromethane at –78 °C (*Scheme 2.31*).



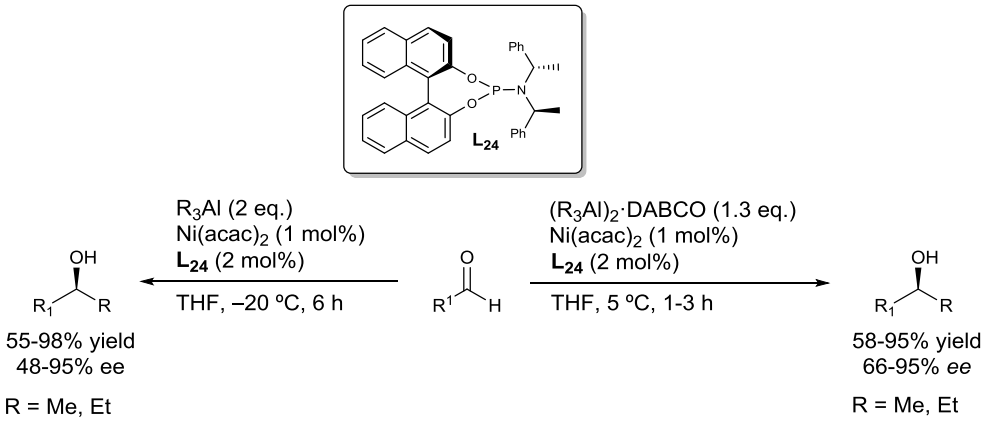

*Scheme 2.31 – Mukaiyama's addition of organoaluminium reagents to aldehydes*

In 1997, Chan et al. developed the first enantioselective addition of Et$_3$Al to aromatic aldehydes using a catalytic amount of a BINOL ligand and an excess of Ti(O$^i$Pr)$_4$.[82] The corresponding chiral secondary alcohols are obtained in good to excellent yields (59-99%) and enantioselectivities (52-96%) (*Scheme 2.32*).




*Scheme 2.32 – Chan's catalytic enantioselective addition of $Et_3Al$ to aldehydes*

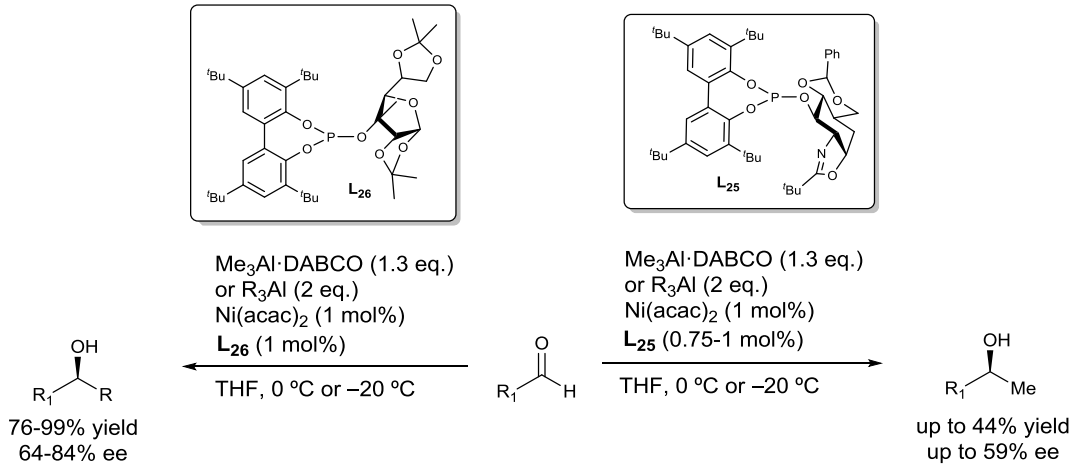
Few years later, in 2005, Woodward et al. developed a new methodology for the methylation and ethylation of aldehydes with organoaluminium reagents using the chiral phosphoramidite **$L_{24}$** and $Ni(acac)_2$ as catalyst.[83] The high stability of the complex $(R_3Al)_2$·DABCO as a nucleophile, compared to $R_3Al$ species, allows the use of milder reaction conditions (5 °C vs –20 °C) and shorter reaction times (1-3 h vs 6 h) (*Scheme 2.33*). Unfortunately, both nucleophiles only give moderate selectivities when the reaction is carried out with aliphatic aldehydes.




*Scheme 2.33 – Woodward's addition of organoaluminium reagents to aldehydes*

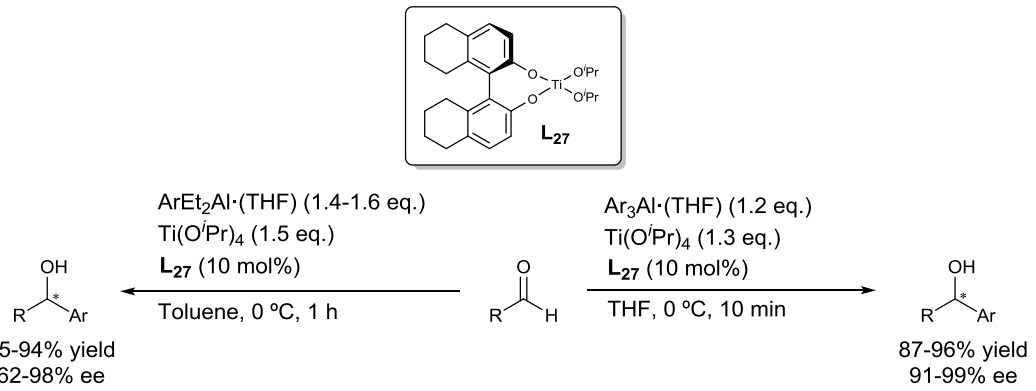
In an attempt to improve the above mentioned methodology, Pàmies and Diéguez's research group, in collaboration with Prof. Woodward, performed a very extensive screening of a new type of chiral sugar

phosphate-oxazoline ligands in the addition of both $(R_3Al)_2$·DABCO and $R_3Al$ to different aldehydes.[84] Although only poor yields and enantioselectivities were obtained during the initial attempts using ligand **$L_{25}$** (*Scheme 2.34*), ligand **$L_{26}$** has proven more efficient, providing the corresponding secondary alcohols in good yields (76-99%) and enantioselectivities (64-84%) (*Scheme 2.34*).[85]



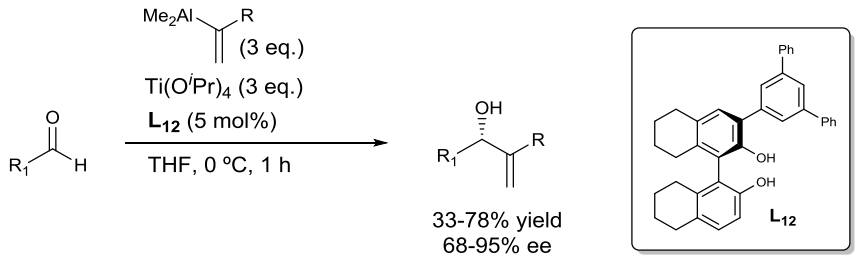

*Scheme 2.34 – Pàmies and Diéguez's addition of organoaluminium reagents to aldehydes*

The first catalytic enantioselective arylation of aldehydes using organoaluminium reagents was developed by Gau et al. in 2006.[86] The use of the BINOLate ligand **$L_{27}$** in catalytic amounts, in the presence of 1.3 eq. of $Ti(O^iPr)_4$ affords excellent yields (87-96%) and enantioselectivities (91-99%) in the addition of $Ar_3Al$·(THF) to different aromatic aldehydes (*Scheme 2.35*). Additionally, the methodology can be successfully extended to aliphatic aldehydes when $ArEt_2Al$·(THF) is used as a nucleophile (*Scheme 2.35*).[87]



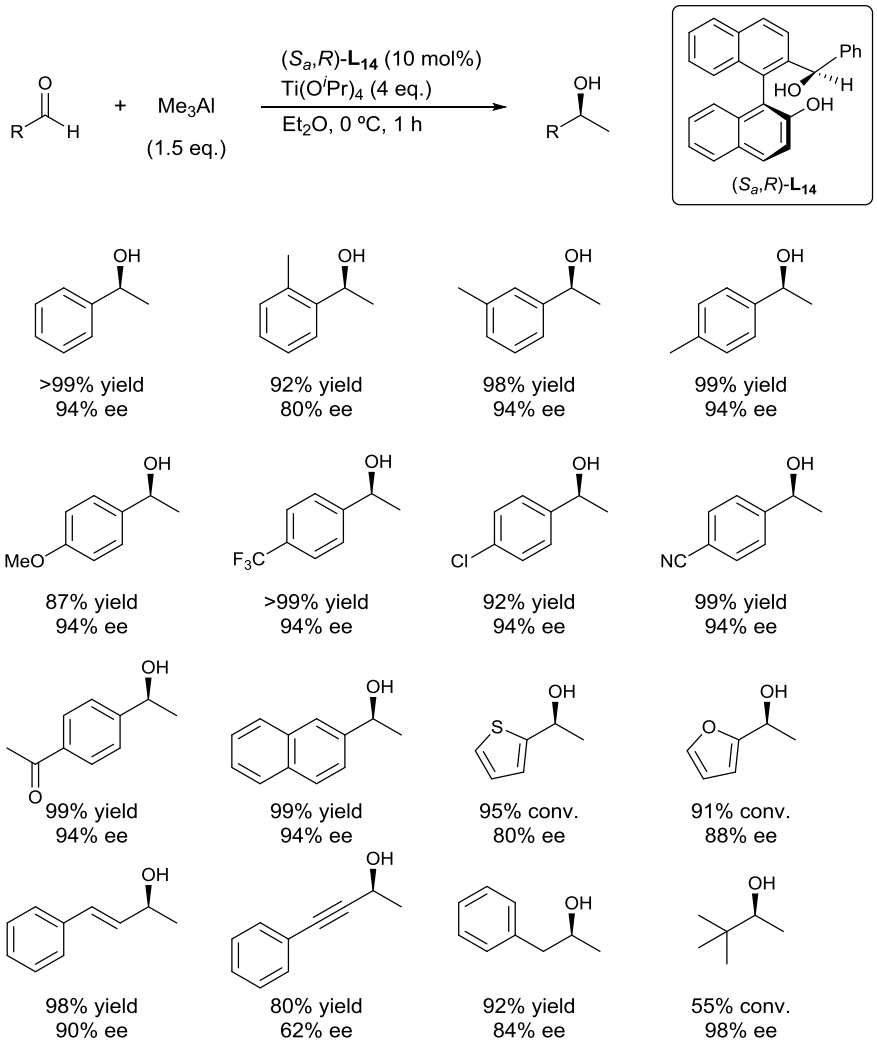

*Scheme 2.35 – Gau's catalytic enantioselective arylation of aldehydes*

In 2013, the first catalytic enantioselective vinylation of aldehydes using organoaluminium reagents was reported by Harada et al., using the chiral binaphthol ligand **$L_{12}$**.[88] The reaction reaches high levels of enantioselectivity (68-95%) even though yields are only moderated (33-78%, *Scheme 2.36*). The organoaluminium reagents are prepared from the corresponding alkyne *via* a hydroalumination reaction, using $Me_2AlH$ (3 eq.) in the presence of [Ni(dppp)$Cl_2$] (3 mol%).



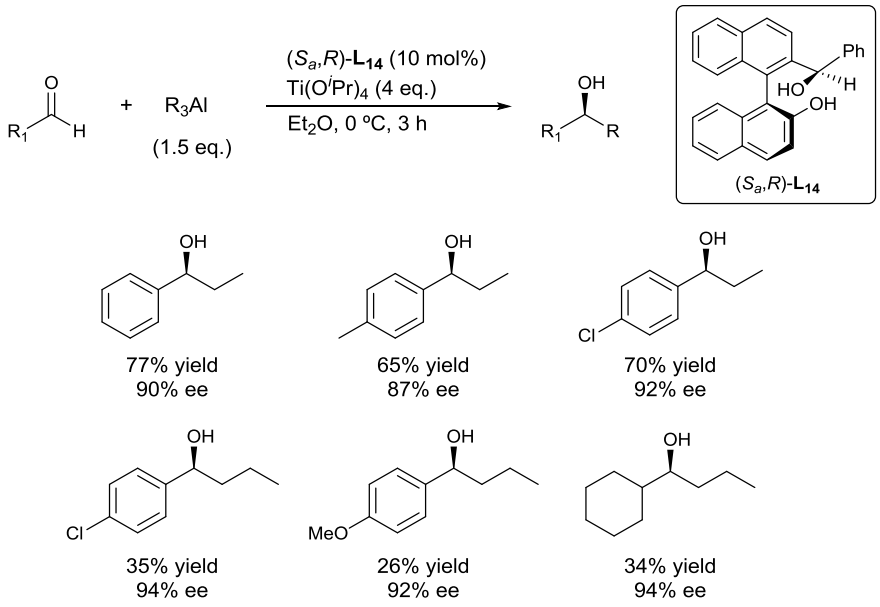

*Scheme 2.36 – Harada's catalytic enantioselective vinylation of aldeydes*

In 2012, our research group developed a catalytic enantioselective addition of organoaluminium reagents to aldehydes catalysed by the Ar-BINMOL ligand (*$S_a$,R*)-**$L_{14}$**.[89] The addition of $Me_3Al$ to several aldehydes in the presence of $Ti(O^iPr)_4$ affords a wide range of methyl carbinol units in excellent yields (80-99%) and moderate to excellent enantioselectivities (62-98%) (*Scheme 2.37*). The reaction with *o*-methylbenzaldehyde provides low selectivity together with 4% of the reduced product, probably due to the increased steric hindrance close to the carbonyl group. It is worth mentioning, that the bulky pivaldehyde affords the highest enantioselectivity of the series.




*Scheme 2.37 – Maciá and Yus' catalytic enantioselective addition of trimethylaluminium to aldehydes*

Furthermore, our research group tested the reactivity of different organoaluminium reagents using this methodology.[89] The reaction provides good yields (65-77%) and excellent enantioselectivities (87-92%) when $Et_3Al$ is used an electrophile (*Scheme 2.38*). Unfortunately, the reaction with $(^nPr)_3Al$, although providing excellent enantioselectivities (92-94%), leads to high amounts of the reduced aldehyde, affording low yields (26-35%) of the desired addition product. No product was observed from the reaction with $^iBu_3Al$ as a nucleophile.




*Scheme 2.38 – Maciá and Yus' catalytic enantioselective addition of organoaluminium reagents to aldehydes*

## 2.1.5. Hydrozirconation reaction for the use of alkenes as nucleophiles.

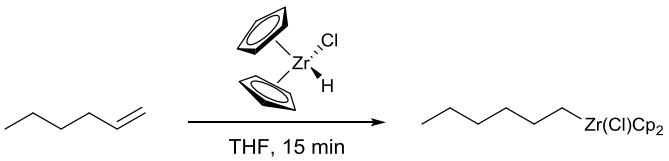
As it has been shown in the previous sections of this thesis, the catalytic enantioselective 1,2-addition reaction to carbonyl compounds with organometallic reagents is a powerful method in synthetic chemistry. However, the developed methodologies for this 1,2-addition reaction, that normally use non-stabilized carbanions (i.e. organomagnesium, organolithium, organotitanium and organoaluminium reagents), suffer from a number of limitations that prevent their use in many situations. For example, reactions with organometallic reagents typically require the use of cryogenic temperatures to restrain their high reactivity and achieve high levels of enantioselectivity. A principle of green chemistry states that synthetic methods should be conducted at ambient temperature.[90] Therefore, the development of new methods for 1,2-addition reactions to carbonyl compounds that are effective at room temperature would be highly recognized.

Additionally, the reactivity of organometallic reagents presents challenges in the use of functionalized reagents[50, 91] and it is associated with safety

issues that can restrict implementation in industrial processes and large scale reactions.[14] For example, most of the reactions involving premade organometallic reagents require the use of inert gas (nitrogen or argon) and moisture-free reaction conditions.[92]

Using alkenes as nucleophilic partners in enantioselective 1,2-addition reactions to carbonyl compounds would be very advantageous and highly desirable. Alkenes are among the most readily available organic molecules, and are feedstocks for the preparation of many commodity chemicals.[93] In addition, alkenes are inexpensive and have favourable properties when compared to pre-made organometallics; for example, they are easy to handle.[94, 95]

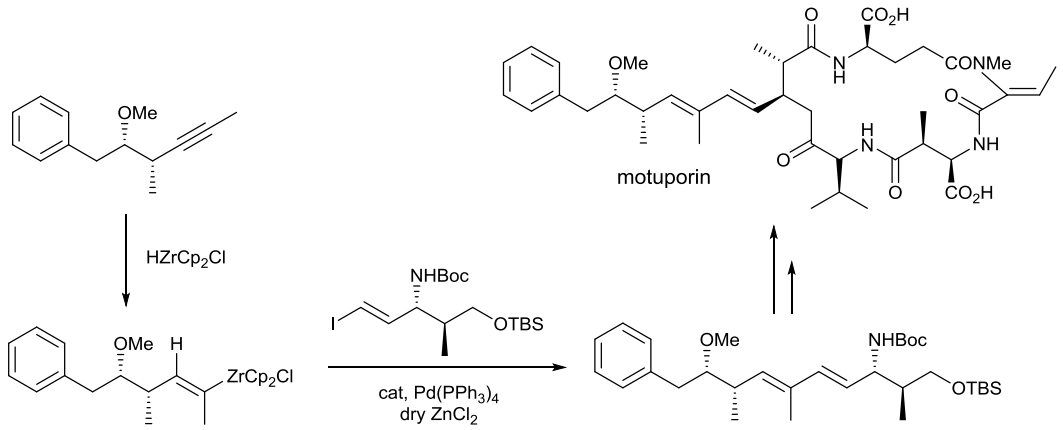
Alkylmetal species, such as organozirconium reagents,[96-98] can be easily generated from cheap and readily available alkenes *via* hydrometalation, using the Schwartz reagent ($Cp_2ZrHCl$, *Scheme 2.39*).[96, 99-101] Many functional groups are compatible with the hydrozirconation reaction conditions[102, 103] and both alkyl- or alkenylzirconocene chlorides prepared with this method are stable complexes at ambient temperature.




*Scheme 2.39 – Preparation of organozirconium reagents with the Schwartz reagent*

Organozirconium compounds are gaining an increasing importance in organic synthesis.[104, 105] Zirconium occurs in the lithosphere to the extent of 0.022%.[106] It is therefore roughly as abundant as C. It is also one of the several least expensive transition metals along with Ti, Mn, Fe and Cu and probably the least expensive second transition series element. Although due precautions must always be taken, Zr does not appear to have been associated with acute and/or severe toxicity.

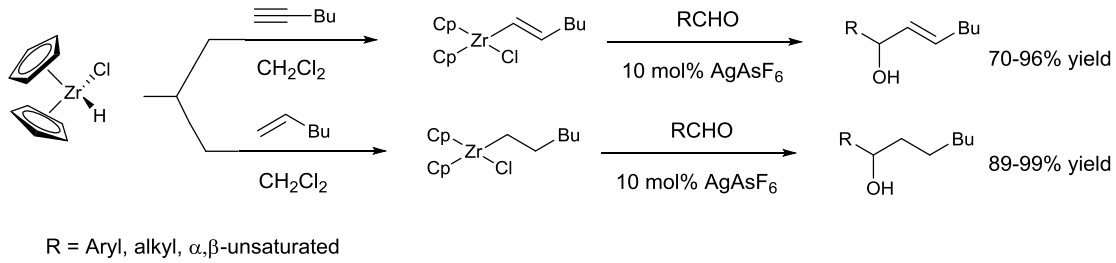
Organozirconium reagents can undergo C–C bond-forming processes, a fruitful area of research pioneered by and extensively developed by Wipf and others.[96, 103, 107-112] One major area of applicability is the use of organozirconium derivatives in transition-metal-catalyzed cross-couplings, such as Negishi couplings with palladium and nickel catalysts.[113] These cross-coupling reactions have proved to be an excellent tool for the formation of conjugated dienes, and have been successfully applied to synthesis of natural products such as motuporin,[114, 115] reveromycin B[116] and xerulin[117] (see example in *Scheme 2.40*).




*Scheme 2.40 – Palladium catalysed cross-coupling with an organozirconium reagent for the synthesis of motuporin*

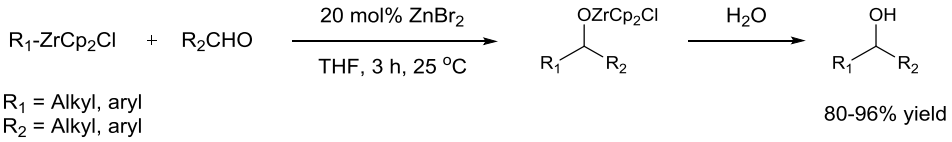
The inherently low reactivity of the organozirconocene chloride compounds (produced after hydrometalation with Schwartz reagent) to electrophilic reagents, such as carbonyl groups, restrains their use as synthetic reagents. The electronegativity value for Zr is 1.4; roughly comparable to Ti (1.5), Al (1.5) and Zn (1.6). This suggests that the low reactivity of $RZrCp_2Cl$ is due to the large steric impediment or to specific electronic interactions of C–C and C–H bonds of alkyl groups with low-lying empty d-orbitals.[118] While these facts limit the scope of electrophiles that organozirconocenes may engage directly, transmetalation enables a broad variety of transformations. Thus, the use of a catalyst or a stoichiometric mediator for the reaction of organozirconocene chlorides is essential to promote a carbon-carbon bond formation (including in the racemic form).[119] It has been reported that Ag(I)[120-123] and $ZnBr_2$[124] are

efficient catalysts for the addition of alkyl- and alkenylzirconocene chloride to aldehydes. K. Suzuki et al. described, in 1995, the use of $AgAsF_6$ as a catalyst for the addition of organozirconocene chlorides to aldehydes in excellent yields (*Scheme 2.41*).[122]



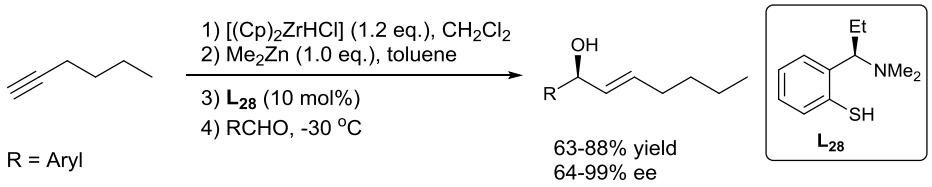

*Scheme 2.41 – Addition of organozirconocene chlorides to aldehydes catalysed by $AgAsF_6$*

Alternatively, M. Srebnik reported the use of $ZnBr_2$ as an efficient catalyst for this chemical transformation, achieving excellent yields for both aromatic and aliphatic aldehydes (*Scheme 2.42*).[124]

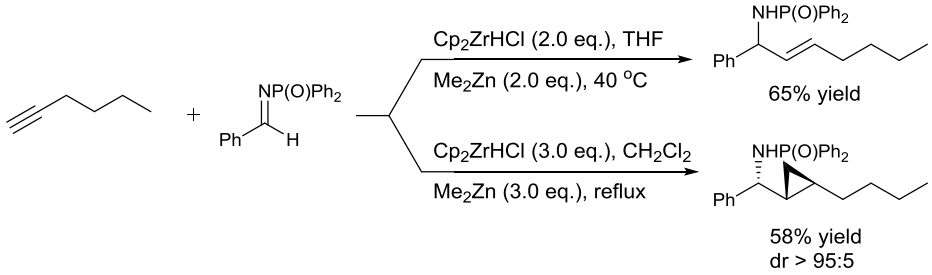



*Scheme 2.42 – Addition of organozirconium reagents to aldehydes catalysed by $ZnBr_2$*

It has also been reported that the $Me_2Zn$-mediated addition of alkenylzirconocene chloride to aldehydes[107, 125, 126] or aldimines[125, 127-129] yields allylic alcohols or amines, respectively. In both methodologies, described by P. Wipf et al., the alkenyl zirconocene is prepared by reacting an alkyne with the Schwartz reagent, followed by reaction with an aldehyde (*Scheme 2.43*) or with an aldimine (*Scheme 2.44*) in the presence of $Me_2Zn$.[125] In case of the reaction with aldimines, the allylic amine or the cyclopropyl amine can be obtained depending on the solvent used and the reaction temperature.



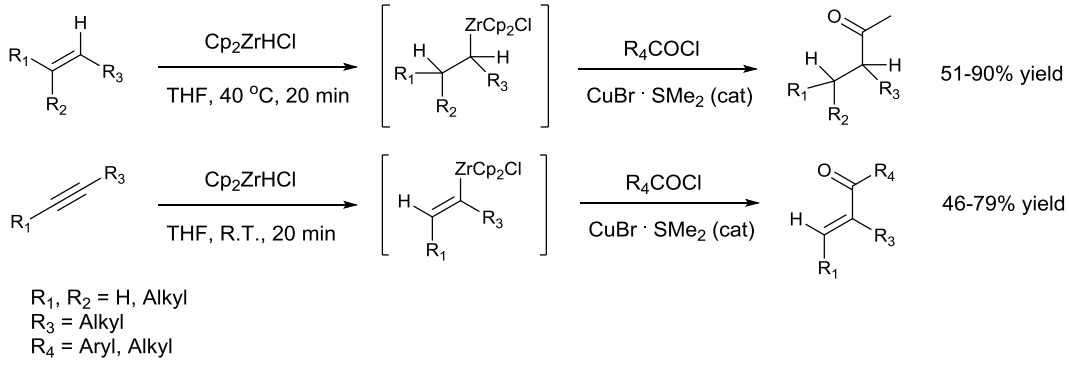

*Scheme 2.43 – Asymmetric addition of alkenyl zirconocenes to aldehydes in the presence of $Me_2Zn$*




*Scheme 2.44 – Solvent dependent addition of alkenyl zirconocenes to aldimines in the presence of $Me_2Zn$.*

A Rh(I) catalyst for the addition of alkenylzirconocene chlorides to aldimine derivatives has also been reported.[130] The transmetalation of organozirconocenes to aluminum,[131] boron, copper,[112, 132-135] mercury, nickel, palladium, tin, and zinc metals[107, 125, 126, 136-139] is also known.

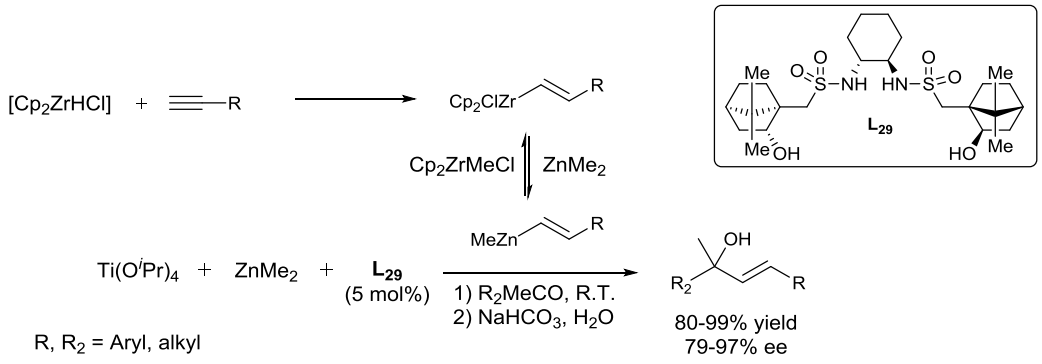
By way of example, the hydrozirconation of alkenes and alkynes and their addition to acyl chlorides in the presence of catalytic amounts of copper (I) has been summarised in *Scheme 2.45*. This methodology, developed by Wipf in 1992,[135] provides the corresponding ketones in moderate to high yields.




*Scheme 2.45 – Transmetalations of organozirconocenes to copper (I) by Wipf*

Although it is not within the scope of this thesis, it should be briefly mentioned that, while alkyl and alkenylzirconocene[54, 123, 140, 141] derivatives are quite inert toward carbonyl compounds, alkyl, aryl and alkenylzirconium trialkoxides such as $MeZr(O^nBu)_3$ readily add to aldehydes and ketones,[142, 143] although enolizable substrates are often problematic and the rate of reduction *via* a Meerwein-Ponndorf-Verley reaction is quite high, since they react slowly.[144] Also, allylzirconocenes, such as chloroallylzirconocene, are more reactive than alkyl and alkenylzirconocene derivatives and react with aldehydes.[145-148]

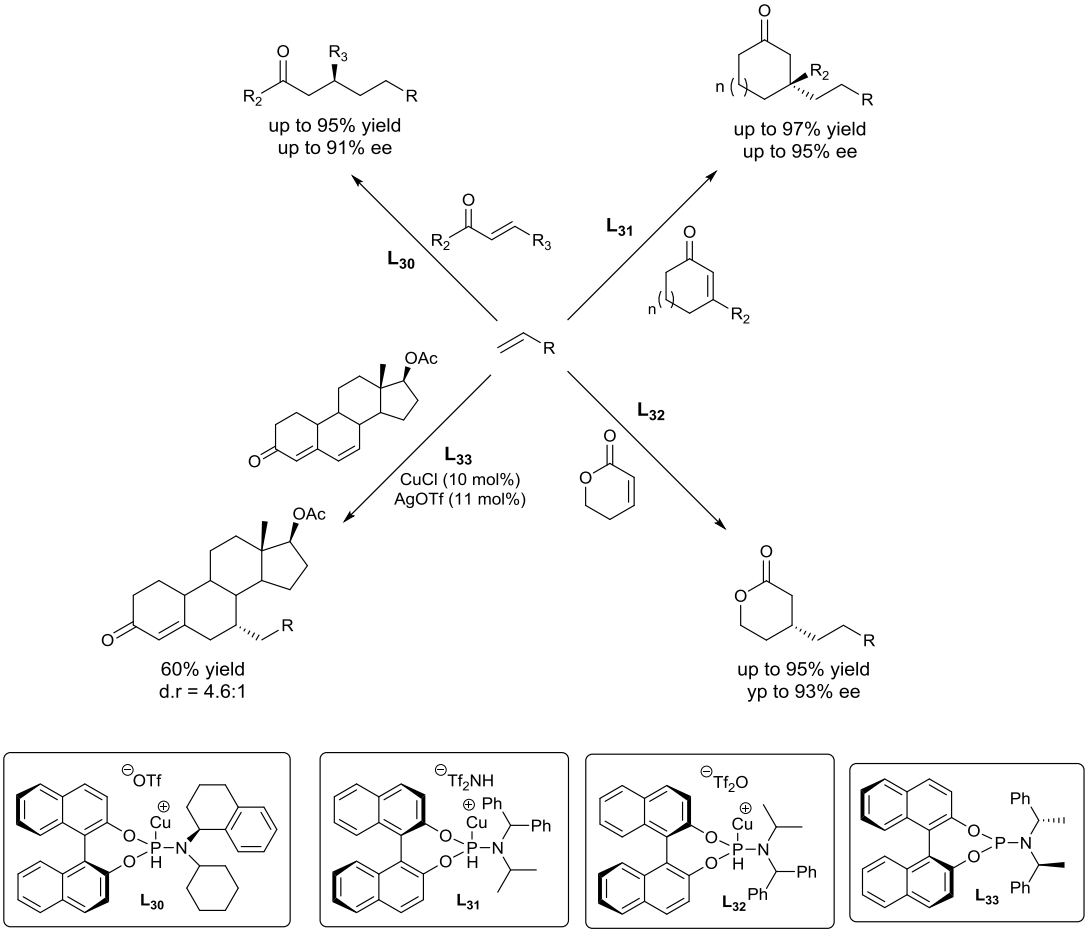
In general, organozirconium reagents have been rarely used in enantioselective reactions, especially those involving catalytic processes.[149] In 1994, Wipf reported[107, 127] a high-yielding protocol for the catalytic asymmetric addition of alkenylzirconocenes to aldehydes, based on an *in situ* transmetalation of the zirconium reagents to alkylzinc species using stoichiometric amounts of $Me_2Zn$.[126, 150, 151] On similar lines, the catalytic asymmetric addition of alkenylzirconium reagents $Cp_2ZrCH{=}CHR$ to ketones has been carried out in the presence of a bis-(sulphonamide) diol ligand (**$L_{29}$**) in the presence of 1.2 eq of $Ti(O^iPr)_4$. In this last procedure, the alkenylzirconium reagent prior to being transmetallated to Ti needs to be treated with 1 eq of $Me_2Zn$ and transmetallated to the corresponding $MeZnCH{=}CHR$.[137] The corresponding allylic alcohols are obtained in excellent yields and enantioselectivities (*Scheme 2.46*).



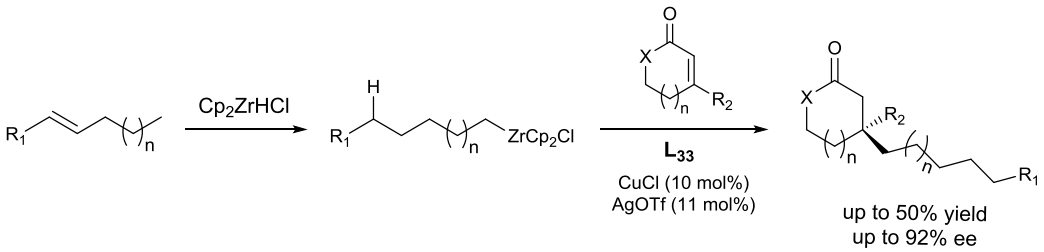

*Scheme 2.46 – Catalytic asymmetric vinylation and of ketones in the presence of the ligand* ***$L_{29}$***

Only recently, other enantioselective catalytic methodologies involving organozirconium reagents have been developed. These include:

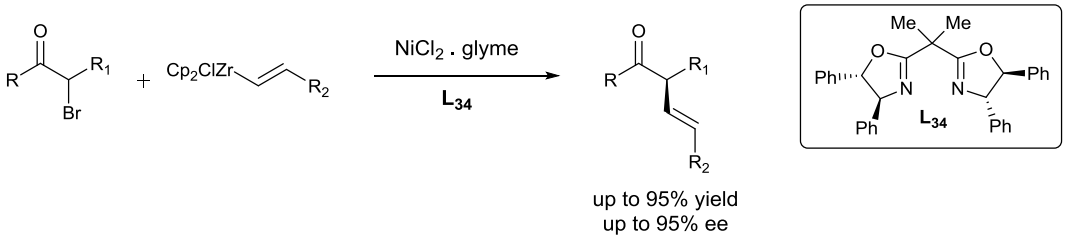
- enantioselective copper-catalysed asymmetric conjugate addition reactions[103, 111, 152, 153] to acyclic[154] and cyclic[94, 155-158] enones, lactones,[159] 1,4- and 1,6-additions to functionalised steroid derivatives (*Scheme 2.47)*,[95, 160] remote asymmetric C–H activations sequences initiated by alkene isomerization 9 *(Scheme 2.48)*.[161]
- enantioselective alkenylation of α-bromoketones *via* nickel-catalyzed cross-coupling (*Scheme 2.49)*.[162]




*Scheme 2.47 – Copper-catalysed asymmetric conjugate addition to acyclic[154] and cyclic[155] enones, lactones[159] and 1,6-addition to functionalised steroid derivatives[160]*




*Scheme 2.48 – Remote asymmetric C-H activation*[161]




*Scheme 2.49 – enantioselective alkenylation of $\alpha$-bromoketones via nickel-catalyzed cross-coupling*[162]

## 2.2. Aims and objectives

Extensive research has been done during the last 20 years for the asymmetric formation of carbinol motifs. In particular, the presence of chiral methyl carbinol units in a large number of natural products and biologically active compounds, has turned them into especially attractive synthetic targets for both academia and industry.[66, 163-167]

The anticancer drug Cruzotinib, developed by Pfizer,[168] and the natural products (*E*)-15,16-dihydrominquartynoic acid[164] and tarchonanthuslactone[165] (*Figure 2.3*) are some examples, amongst many others, of relevant chemicals containing methyl carbinol units.

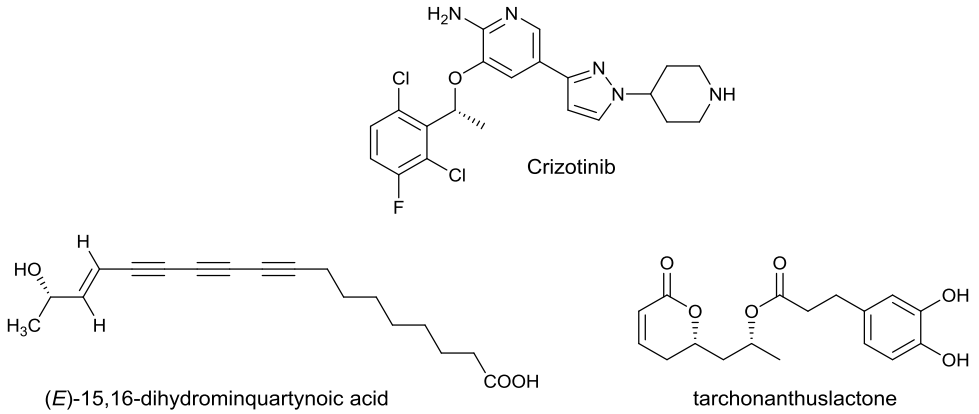



*Figure 2.3 – Chiral methyl carbinols in natural products and biologically active compounds*

Amongst all the approaches to access this structural fragment, the enantioselective addition of organometallic reagents to carbonyl compounds stands out for its simplicity to form a C-C bond and an asymmetric centre at the same time.[1, 2, 8-14]

As discussed in the introductory section of this chapter, enantioselective catalysed versions of this transformation have been extensively studied with organozinc and organoaluminium compounds, and fairly studied with organomagnesium and organolithium reagents. However, there are still some limitations that need to be overcome. For example, in many cases, the required super stoichiometric amounts of $Ti(O^iPr)_4$ make the process

inefficient on an industrial production scale. Furthermore, the need of stoichiometric amounts of Lewis acid additives and/or the low temperatures are, in most cases, industrially impractical.

Additionally, the currently available methodologies to perform this transformation involve the use of non-stabilised organometallic reagents as nucleophiles, which are frequently unstable, too reactive, sometimes pyrophoric and, therefore unsafe on industrial scale.

Being aware of the limitations of the currently available methodologies, the particular aims of the work discussed in this chapter can be summarised as follows:

(i) Development of an alternative methodology for the addition of organometallic reagents to carbonyl compounds that allows a reduction in the titanium content and allows milder reaction conditions, compared to currently existing procedures.

(ii) Expand the use of Ar-BINMOL ligands to other organometallic reagents such as organotitanium and organozirconium compounds. These nucleophiles, although less reactive, are considered safer than the corresponding organomagnesium, organolithium and organozinc reagents.

# 2.3. Results and discussion

## 2.3.1. Catalytic asymmetric addition of organolithium reagents to aldehydes

Our studies on alternative methodologies for the catalytic enantioselective addition of organometallic reagents to carbonyl compounds that allow a reduction in the titanium content, started with the addition of organolithium reagents to aldehydes.

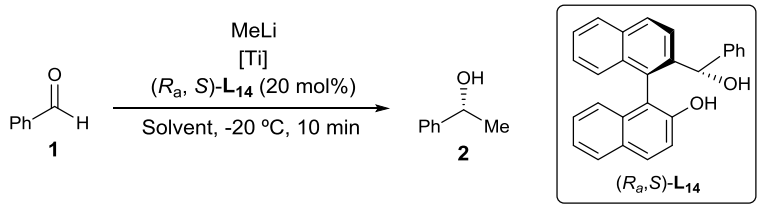
Due to the relevance of methyl carbinol motifs, we decided to start our research by testing the enantioselective addition of methyllithium to different aldehydes.

Our group had previously reported[79] that the addition of MeLi to benzaldehyde (**1**), to provide 1-phenylethanol (**2**), proceeds in 87% yield and 90% ee when Ph-BINMOL ligand (*S*$_a$,*R*)-**L$_{14}$** is used as catalyst, at –40 °C in toluene and in the presence of 6 eq. of Ti(O$^i$Pr)$_4$.

Assuming that the first step of this chemical transformation is a transmetallation of the methyl group from the MeLi to the Ti(O$^i$Pr)$_4$, we envisioned that a more labile chloride ligand in the titanium source would facilitate the process and allow both a reduction of the titanium loading and an increase of the reaction temperature. For this reason, we decided to explore TiCl(O$^i$Pr)$_3$ as an alternative titanium source.

The optimisation of the reaction conditions was carried out on the addition of methyllithium to benzaldehyde, which was chosen as model reaction. Results are shown in the *Table 2.1* below.

*Table 2.1 – Optimisation of reaction conditions for the addition of MeLi to benzaldehyde*




| Entry | [Ti] source (eq.) | Solvent | MeLi (eq.) | Conv.[b] (%) | *ee*[b] (%) |
|---|---|---|---|---|---|
| 1[c] | $TiCl(^{i}PrO)_3$ (6.0) | Toluene | 3.2 | 72 | 22 (*R*) |
| 2[c] | $TiCl(^{i}PrO)_3$ (3.2) | Toluene | 3.2 | 98 | 92 (*R*) |
| 3[c] | $TiCl(^{i}PrO)_3$ (2.5) | Toluene | 3.2 | 92 | 92 (*R*) |
| 4[d] | $TiCl(^{i}PrO)_3$ (2.5) | THF | 3.2 | 0 | n.d. |
| 5 | $TiCl(^{i}PrO)_3$ (2.5) | $Et_2O$ | 3.2 | 99 | 70 (*R*) |
| 6 | $TiCl(^{i}PrO)_3$ (2.0) | $Et_2O$ | 3.2 | 89 | 30 (*R*) |
| 7 | $TiCl(^{i}PrO)_3$ (2.0) | $Et_2O$ | 2.0 | 99 | 78 (*R*) |
| 8 | $TiBr_2(^{i}PrO)_2$ (2.5) | $Et_2O$ | 3.2 | 99 | 0 |
| 9 | $TiF_4$ (2.5) | $Et_2O$ | 3.2 | 98 | 0 |
| 10 | $TiCl(^{i}PrO)_3$ (2.5) | $Et_2O$ | 2.0 | 99 | 86 (*R*) |
| 11 | $TiCl(^{i}PrO)_3$ (2.6) | $Et_2O$ | 2.0 | 98 | 84 (*R*) |
| **12** | **$TiCl(^{i}PrO)_3$ (2.8)** | $Et_2O$ | **2.0** | **99 (90)[e]** | **93 (*R*)** |
| 13 | $TiCl(^{i}PrO)_3$ (2.8) | $Et_2O$ | 1.7 | 92 | 78 (*R*) |

[a] Reaction conditions: **1** (0.1 mmol, 1 eq.), MeLi (1.6 M in $Et_2O$), [Ti], ($R_a$,*S*)-**$L_{14}$** (0.2 eq.), $Et_2O$ (C = 0.067 M), −20 °C, 10 min. [b] Determined by Chiral GC (see Experimental Part for details). [c] Performed at −40 °C, 1 h. [d] Reaction time 1 h. [e] Isolated yield after flash chromatography.

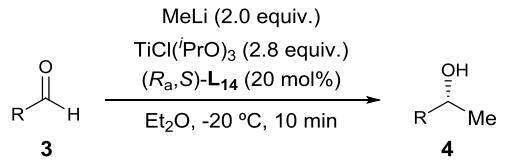
The addition of MeLi (3.2 eq.) to benzaldehyde (**1**) in the presence of $TiCl(O^{i}Pr)_3$ (6.0 eq.) in toluene at –40 °C, using Ph-BINMOL ($R_a$,*S*)-**$L_{14}$** (20 mol%) as ligand, afforded 1-phenylethanol (**2**) in moderate yield (72%) and low enantioselectivity (22% ee, *entry 1*, *Table 2.1*). Fortunately, a reduction in the amount of $TiCl(O^{i}Pr)_3$ down to 3.2 eq., provided the desired alcohol **2** in excellent conversion (98%) and enantioselectivity (92% ee, *entry 2*). Further reductions in the titanium content (down to 2.5 eq.) could be performed without having an effect in the enantioselectivity of the reaction (*entry 3*).

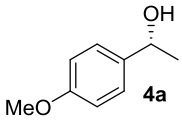
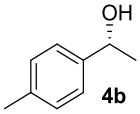
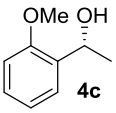
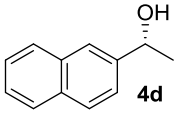
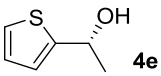
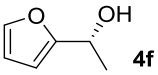
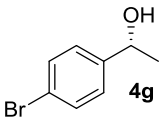
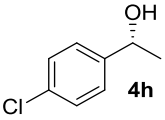
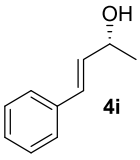
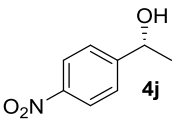
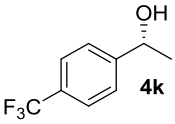
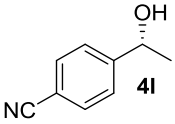
The model reaction was also tested using different solvents and temperatures. No product was observed when the reaction was carried out in THF at higher temperatures (–20 °C, *entry 4*), and when $Et_2O$ was used as a solvent at the same temperature, the product **2** was obtained in 99% conversion and 70% ee (*entry 5*). When the amount of $TiCl(O^iPr)_3$ was reduced to 2.0 eq. the enantioselectivity decreased drastically (30% ee, *entry 6*). Fortunately, full conversion and 78% ee was achieved by adjusting the amount of MeLi to 2.0 eq (*entry 7*).

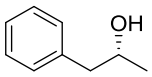
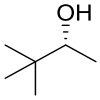
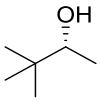
Other titanium sources like $TiBr_2(O^iPr)_2$ and $TiF_4$ were also examined, but both of them led to the alcohol **2** as a racemic mixture (*entries 8 and 9*). Next, we kept the loading of MeLi at 2.0 eq. and we gradually increased the amount of $TiCl(O^iPr)_3$ (*entries 10–12*). The optimal amount of $TiCl(O^iPr)_3$ proved to be 2.8 eq., providing full conversion and 93% ee (*entry 12*). Other attempts to lower the amount of methyllithium were unsuccessful, affording lower conversions and enantioselectivities (*entry 13*).

With the optimised conditions in hand, we proceeded to test the scope of the reaction with a wide range of aldehydes, with different substitution patterns and electronic properties (*Table 2.2*). Gratifyingly, full conversion was obtained after only 10 min of reaction, achieving high enantioselectivities in most of the cases. The stereochemistry of the products obtained was determined by comparing the optical rotation values with the data previously reported in the literature.

*Table 2.2 – Asymmetric addition of MeLi to aldehydes catalysed by ($S_a$,R)-**$L_{29}$***




| Entry | Product | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|
| 1 |  **4a** | 93 | 92 (*R*) |
| 2 |  **4b** | 94 | 90 (*R*) |
| 3 |  **4c** | 92 | 44 (*R*) |
| 4 |  **4d** | 85 | 89.5 (*R*) |
| 5 |  **4e** | 95 | 93 (*R*) |
| 6 |  **4f** | (98)[d] | 84 (*R*) |
| 7 |  **4g** | 90 | 87 (*R*) |
| 8 |  **4h** | 89 | 86 (*R*) |
| 9 |  **4i** | 92 | 80 (*R*) |
| 10 |  **4j** | 15 (97)[e] | 80 (*R*) |
| 11 |  **4k** | 92 | 94 (*R*) |
| 12 |  **4l** | 93 | 91 (*R*) |

| | | | |
|---|---|---|---|
| 13 |  **4m** | 80 | 73 (*R*) |
| 14 |  **4n** | 94 | 63 (*R*)[f] |
| 15 |  **4o** | (15)[d] | 95 (*R*) |
| 16[g] |  **4o** | (20)[d] | 89 (*R*) |

[a] Reaction conditions: aldehyde (0.1 mmol, 1.0 eq.), MeLi (1.6 M in $Et_2O$, 2.0 eq.), ($R_a$,*S*)-**$L_{14}$** (0.2 eq.), $TiCl(^iPrO)_3$ (1.0 M in hexane, 2.8 eq.), $Et_2O$, −20 °C, 10 min. [b] Isolated yield after flash chromatography. [c] Determined by Chiral GC. Configuration based on literature data (see Experimental Part for details). [d] Conversion determined by Chiral GC due to the high volatility of the product. [e] Conversion determined by GC due to the product being inseparable from the ligand by flash chromatography. [f] Determined on the corresponding acetate derivative (see Experimental Part for details). [g] Performed at 0 °C.

The addition of methyllithium to electron-rich aromatic aldehydes such as *p*-anisaldehyde and *p*-tolylaldehyde led to high yields and enantioselectivities (*entries 1 and 2*, *Table 2.2*). Unfortunately, only a 44% ee was obtained in the reaction with *o*-anisaldehyde (*entry 3*), probably due to the increased steric hindrance close to the carbonyl group. The reaction with other aromatics like 2-naphthaldehyde and the heteroaromatics 2-thiophen-2-carbaldehyde and furfural provided high yields (85-98%) and enantioselectivities (84-93%, *entries 4–6*). *p*-Bromo and *p*-chlorobenzaldehyde were compatible with the reaction conditions and afforded the corresponding secondary alcohols in excellent yields (89-90%) and enantioselectivities (86-87%, *entries 7 and 8*). The reaction with (*E*)-cinnamaldehyde provided high yield (92%) but only moderate enantiocontrol (80%, *entry 9*).

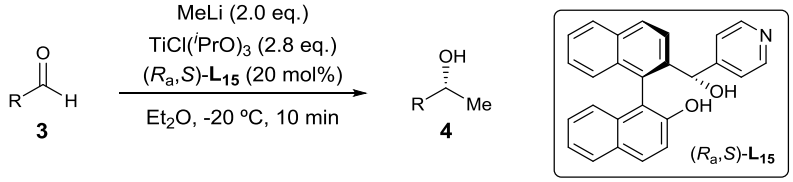
When the reaction was attempted with aromatic aldehydes with electron-withdrawing substituents (*entries 10–12*), high yields (93-97%) and moderate to high enantioselectivities (80-91%) were obtained. It is worth

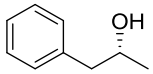
mentioning that the reaction conditions are compatible with a cyano group in the substrate (*entry 12*).

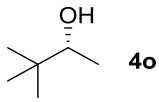
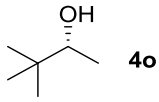
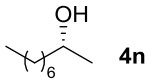
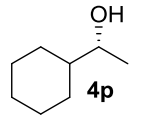
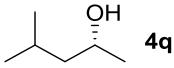
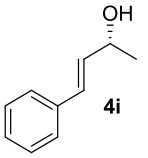
The scope of the reaction was also expanded to the more challenging aliphatic aldehydes. Promising results were obtained for the addition of MeLi to aliphatic aldehydes with an enolizable position (*entries 13 and 14*). For instance, 2-phenylacetaldehyde provided the corresponding carbinol in 80% yield and 73% ee (*entry 13*), whilst 1-octanal achieved higher yield (94%) but a lower enantiocontrol (63% ee, *entry 14*). On the other hand, the non-enolizable but bulky pivaldehyde led to the formation of the corresponding product in excellent enantioselectivity (95%) but really low conversion (15%, *entry 15*). However, the low conversion could be improved by performing the reaction at higher temperatures (0 °C), which caused a slightly drop in the enantioselectivity (89% ee, *entry 16*).

It had been previously demonstrated in our research group that the use of the 4-Py-BINMOL furnished higher enantiocontrol than Ph-BINMOL in the addition of Grignard reagents to aliphatic aldehydes.[60] With this in mind, we tested the new titanium source with aliphatic aldehydes, using (*R*$_a$,*S*)-**L$_{15}$** as catalyst. To our delight, the addition of MeLi in the presence of TiCl(O$^i$Pr)$_3$, catalysed by the ligand (*R*$_a$,*S*)-**L$_{15}$**, provided higher enantioselectivities in the addition to aliphatic aldehydes than (*R*$_a$,*S*)-**L$_{14}$** (*Table 2.3*).

*Table 2.3 – Asymmetric addition of MeLi to aliphatic aldehydes catalysed by* (*R*$_a$,*S*)-***L$_{15}$***




| Entry | RCHO | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|
| 1 |  **4m** | 93 | 91 (*R*) |

| | | | |
|---|---|---|---|
| 2 |  **4o** | (28)[d] | 97 (*R*) |
| 3[e] |  **4o** | (30)[d] | 83 (*R*) |
| 4 |  **4n** | 84 | 89 (*R*)[f] |
| 5 |  **4p** | (98)[d] | 92 (*R*)[f] |
| 6 |  **4q** | (87)[d] | 94 (*R*)[f] |
| 7 |  **4i** | 94 | 90 (*R*) |

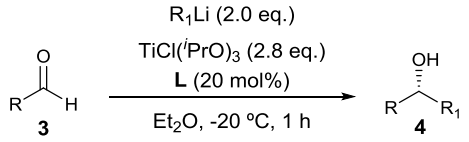
[a] Reaction conditions: aldehyde (0.1 mmol, 1.0 eq.), MeLi (1.6 M in $Et_2O$, 2.0 eq.), ($R_a$,*S*)-**L$_{15}$** (0.2 eq.), Ti(O$^i$Pr)$_3$Cl (1.0 M in hexane, 2.8 eq.) $Et_2O$, −20 °C, 10 min. [b] Isolated yield by flash chromatography. [c] Determined by chiral GC. Configuration based on literature data (see Experimental Part for details). [d] Conversion determined by chiral GC due to the high volatility of the product. [e] Performed at 0 °C. [f] Determined on the corresponding acetate derivative (see Experimental Part).

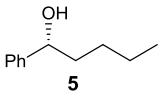
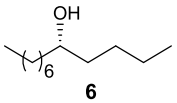
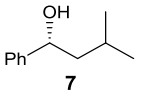
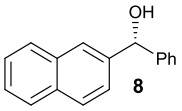
The addition of methyllithium to 2-phenylacetaldehyde catalysed by ($R_a$,*S*)-**L$_{30}$** exhibited excellent yield (93%) and enantioselectivity (91% ee, *Table 2.3*, *entry 1*), providing a significant improvement compared with the result obtained with the previous Ph-BINMOL ligand ($R_a$,*S*)-**L$_{14}$** (*Table 2.2*, *entry 13*). The reaction with pivaldehyde afforded a low conversion (28%) but an excellent enantioselectivity (97% ee, *entry 2*). Unfortunately, increasing the reaction temperature to 0 °C did not improve the conversion, and decreased the enantioselectivity to 83% ee (*entry 3*). The addition of MeLi to octanal (*entry 4*), provided the corresponding product **4n** in high yield and enantioselectivity (84% yield, 89% ee). The α- and β-branched aliphatic aldehydes such as cyclohexylcarbaldehyde and isopentanal led to the corresponding alcohols **4p** and **4q** in high conversions and enantioselectivities (*entries 5 and 6*). Finally, the addition of MeLi to the α,β-unsaturated cinnamaldehyde proceeded with excellent yield (94%) and remarkably improved

enantiocontrol (*90%, entry 7*) compared to the use of the ligand ($R_a$,*S*)-**$L_{14}$** (80% ee, *entry 9*, *Table 2.2*).

To finish the study of the scope of the reaction, different organolithium reagents were tested (*Table 2.4*).

*Table 2.4 – Asymmetric addition of organolithium reagents to aldehydes*




| Entry | Product | L | Yield[b] (%) | *ee*[c] (%) |
|---|---|---|---|---|
| 1[d] |  **5** | **$L_{15}$** | 87 | 97 (*R*) |
| 2 |  **6** | **$L_{15}$** | 78 | 91 (*R*)[e] |
| 3[f] |  **7** | **$L_{14}$** | 91 | 60 (*R*) |
| 4 |  **8** | **$L_{14}$** | 91 | 13 (*R*) |

[a] Reaction conditions: aldehyde (0.1 mmol, 1.0 eq.), $R_1Li$ (2.0 eq.), ($R_a$,*S*)-**L** (0.2 eq.), $TiCl(^iPrO)_3$ (1.0 M in hexane, 2.8 eq.) $Et_2O$, −20 °C, 10 min. [b] Isolated yield by flash chromatography. [c] Determined by chiral GC or HPLC. Configuration based on literature data (see Experimental part for details). [d] Reaction conditions: aldehyde (0.1 mmol, 1.0 eq.), $TiCl(^iPrO)_3$ (1 M in hexane, 3.2 eq.), $^n$BuLi (1.6 M in hexane, 2.5 eq.), $Et_2O$, −20 °C. [e] Determined on the corresponding acetate derivative (see Experimental part for details). [f] Reaction conditions: aldehyde (0.1 mmol, 1.0 eq.), $TiCl(^iPrO)_3$ (1 M in hexane, 5.0 eq.), $^i$BuLi (1.7 M in heptane, 2.5 eq.), $Et_2O$, −20 °C.

The addition of $^n$BuLi to both the aromatic benzaldehyde and the aliphatic octanal, provided good yields and excellent enantioselectivities (*entries 1 and 1*, *Table 2.4*). However, when the reaction was attempted with the sterically more demanding $^i$BuLi, high yield (91%) but only moderate enantioselectivity (60% ee, *entry 3*) was obtained. Finally, the reaction of PhLi with naphthaldehyde provided a good yield but low enantioselectivity (13% ee, *entry 4*).

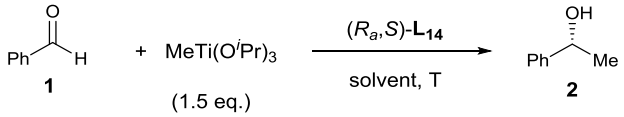
To summarize, a new catalytic system for the addition of alkylithium reagents to aldehydes has been developed using Ar-BINMOL ligands in the presence of $TiCl(O^iPr)_3$. This methodology allows the preparation of methyl carbinol units in good yields and high levels of enantiocontrol. The reaction takes place under milder conditions compared to the methodologies previously described in the literature, employing lower titanium loadings and allowing more practical reaction temperatures and shorter reaction times. All those characteristics make the methodology more suitable for both academic and industrial applications.

## 2.3.2. Catalytic enantioselective addition of methyltriisopropoxititanium to aldehydes

As previously mentioned in the introduction of this chapter, although an exact mechanism for the enantioselective addition of organozinc, organomagnesium or organolitium reagents to carbonyl compounds in the presence of a titanium salt such as $Ti(O^iPr)_4$ is not fully known, the general belief is that a transmetallation of the corresponding R group from the Zn, Mg or Li atom to a Ti center must take place at some stage in the catalytic cycle.[56]

For this reason, we decided to test our very versatile Ar-BINMOL ligands as catalysts for the direct enantioselective addition of organotitanium reagents to carbonyl compounds. Our studies focused on the use of the commercially available $MeTi(O^iPr)_3$. We rationalised that the direct use of this nucleophile would allow the avoidance of an excess of a titanium source (e.g. $Ti(O^iPr)_4$) because no transmetallation would be in this case needed. In addition, since the $MeTi(O^iPr)_3$ is not a very reactive nucleophile, we also speculated that milder conditions and more practical temperatures would be probably allowed in the process, compared to the previously used more reactive organomagnesium and organolithium reagents.

*Table 2.5 – Optimisation of reaction conditions for the addition of MeTi(O$^i$Pr$_3$) to benzaldehyde*




| Entry | Solvent | T (°C) | $L_{14}$ (mol%) | Conv. (%)[b] | *ee* (%)[b] |
|---|---|---|---|---|---|
| 1 | Toluene | –40 | 20 | 78 | 94 (*R*) |
| 2 | $Et_2O$ | 0 | 20 | >99 | 97 (*R*) |
| **3** | **$Et_2O$** | **0** | **10** | **99** | **96 (*R*)** |
| 4 | $Et_2O$ | 0 | 5 | 99 | 78 (*R*) |
| 5 | $Et_2O$ | RT | 10 | >99 | 94 (*R*) |
| 6 | $Et_2O$ | 0 | 10[c] | 11 | 24 (*R*) |

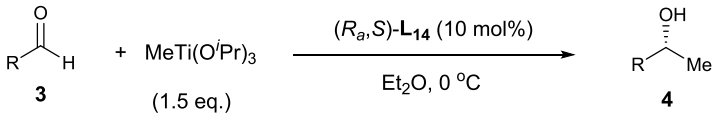
[a] Reaction conditions: **1** (1 eq., 0.07 M), MeTi(O$^i$Pr)$_3$ (1 M in THF, 1.5 eq.), ($R_a$,*S*)-$\mathbf{L_{14}}$, 1.5 h. [b] Determined by chiral GC. [c] (*R*)-BINOL was used as ligand.

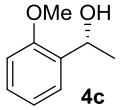
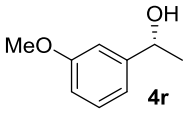
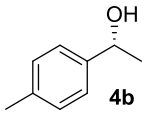
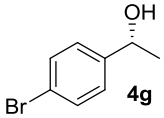
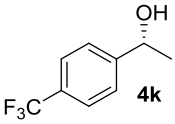
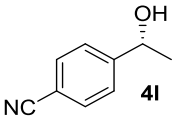
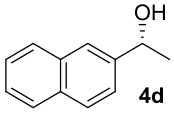
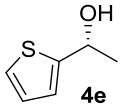
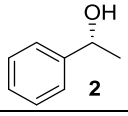
The optimisation of the reaction conditions was carried out using benzaldehyde (**1**) as the model substrate. Our studies started with the testing of the optimal solvent and temperature conditions previously found in our research group for the addition of Grignard reagents to aldehydes using $\mathbf{L_{14}}$ as a ligand. Very promising results were obtained using 20 mol% of $\mathbf{L_{14}}$ and 1.5 eq. of MeTi(O$^i$Pr)$_3$; the reaction afforded 78% conversion and 94% *ee* after 1 h (*Table 2.5*, *entry 1*). The use of $Et_2O$ as a solvent allowed the increase of the reaction temperature to 0 °C, reaching full conversion and excellent enantioselectivity (97% *ee*, *entry 2*). Under these conditions, the catalyst loading could be reduced to 10 mol% without observing any significant loss of conversion and enantiocontrol (*entry 3*). Lower catalyst loadings provided full conversion but lower enantioselectivity (78% ee, *entry 4*).

The reaction could be carried at room temperature in the presence of 10 mol% of $\mathbf{L_{14}}$ and only a small decrease in enantioselectivity was observed (compare *entries 3 and 5*). As a mode of camparison, we performed the reaction using (*R*)-BINOL as chiral ligand (*entry 6*) in $Et_2O$ at 0 °C, leading to a very low conversion (11%) and enantioselectivity (24% ee).

With the optimised conditions in hand, we examined the scope of the reaction with different aldehydes (*Table 2.6*). The system proved to be efficient, providing good yields (84-96%) and enantioselectivities (56 to >99%).

*Table 2.6 – Asymmetric addition of MeTi(O$^i$Pr)$_3$ to aromatic aldehydes catalysed by ($S_a$,R)-**L$_{14}$***




| Entry | Product | Conv. (%)[b] | Yield (%)[c] | ee (%)[b] |
|---|---|---|---|---|
| 1 |  **4c** | 90 | n.d. | 55 (*R*) |
| 2[d] | | >99 | 96 | 56 (*R*) |
| 3 |  **4r** | 82 | n.d. | >99 (*R*) |
| 4[d] | | 99 | 92 | >99 (*R*) |
| 5[d] |  **4b** | 99 | 96 | 93 (*R*) |
| 6 |  **4g** | 97 | 90 | 97 (*R*) |
| 7 |  **4k** | 99 | 89 | 95 (*R*) |
| 8 |  **4l** | 97 | 94 | 96 (*R*) |
| 9[d] |  **4d** | 58 | n.d. | 86 (*R*) |
| 10[e] | | 89 | 84 | 87 (*R*) |
| 11 |  **4e** | 67 | n.d. | 90 (*R*) |
| 12[e] | | 98 | 95 | 94 (*R*) |
| 13[f] |  **2** | 97 | 95 | 95 (*R*) |

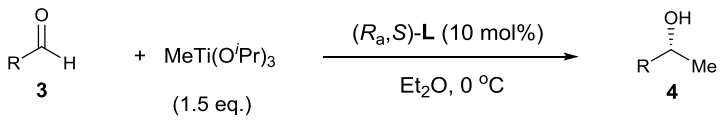
[a] Reaction conditions: **3** (1 eq., 0.07 M), MeTi(O$^i$Pr)$_3$ (1 M in THF, 1.5 eq.), ($R_a$,*S*)-**L$_{14}$** (10 mol%), 1.5 h. [b] Determined by chiral GC or HPLC. [c] Isolated yield after flash chromatography. [d] Reaction performed with 1.7 eq. of MeTi(O$^i$Pr)$_3$. [e] Reaction performed with 2.0 eq. of MeTi(O$^i$Pr)$_3$. [f] Reaction performed using 0.5 g of **1**.

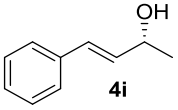
A wide variety of (hetero)aromatic aldehydes, containing both electron donating and withdrawing groups, were tested. In some cases, the loading of $MeTi(O^iPr)_3$ was increased up to 1.7 eq. (*Table 2.6*, *entries 2, 4, 5 and 9*) or 2.0 eq. (*entries 10 and 12*) in order for the reaction to reach full conversion. In those cases, a small increase of the enantioselectivity was also observed.

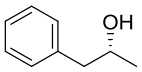
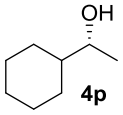
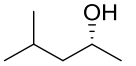
The reaction with *o*-methoxybenzaldehyde provided the lowest enantioselectivity (56%, *entry 2*) probably due to the high steric hindrance close to the reactive site. Remarkably, the methodology proved to be compatible with functionalised substrates, such as **4g** and **4l** (*entries 6 and 8*). To our delight, all the reactions reached full conversion in less than 1.5 h and no by-product was observed in any case. Additionally, the unreacted starting material and the ligand could be both recovered from the reaction crude. The recovered ligand could be recycled and reused without any loss of activity. Furthermore, in order to test the robustness of the methodology, a larger scale reaction was performed with benzaldehyde **1** (47 mmol, 0.5 g, *entry 13*) and no erosion of conversion or enantioselectivity was observed compared to the lower scale reaction (compare *entry 3*, *Table 2.5* with *entry 13*, *Table 2.6*).

Next, the reaction was tested with some aliphatic and α,β-unsaturated aldehydes (*Table 2.7*). In some of the reactions, the ligand $\mathbf{L_{15}}$ showed a higher efficiency than the ligand $\mathbf{L_{14}}$.

*Table 2.7 – Asymmetric addition of $MeTi(O^iPr)_3$ to aliphatic and α,β-unsaturated aldehydes*




| Entry | Product | L | Conv. (%)[b] | Yield (%)[c] | ee (%)[b] |
|---|---|---|---|---|---|
| 1[d] |  **4i** | $\mathbf{L_{14}}$ | 65 | n.d. | 80 (*R*) |
| 2 | | $\mathbf{L_{15}}$ | 90 | 88 | 82 (*R*) |

| | | | | | |
|---|---|---|---|---|---|
| 3 |  **4m** | **$L_{14}$** | 99 | n.d. | 81 (*R*) |
| 4 | | **$L_{15}$** | 99 | 93 | 85 (*R*) |
| 5 |  **4n** | **$L_{15}$** | 99 | 95 | 90[e] (*R*) |
| 6 |  **4p** | **$L_{15}$** | 99 | | 94[e] (*R*) |
| 7 |  **4q** | **$L_{15}$** | 77[f] | | 90[e] (*R*) |
| 8[d] |  **4o** | **$L_{15}$** | 20 | n.d. | 94 (*R*) |
| 9[g] | | **$L_{14}$** | 78 | n.d. | 93 (*R*) |

[a] Reaction conditions: **3** (1 eq., 0.07 M), MeTi($O^iPr$)$_3$ (0.5 M in THF, 1.5 eq.), ($R_a$,*S*)-**L** (10 mol%), 1 h. [b] Determined by chiral GC or HPLC. [c] Isolated yield after flash chromatography. [d] Reaction performed with 1.7 eq. of MeTi($O^iPr$)$_3$. [e] Determined by chiral GC on the acetate derivative. [f] 7% of $(CH_3)_2CHCH_2CH_2OH$ was detected. [g] Reaction performed with 2.0 eq. of MeTi($O^iPr$)$_3$.

The addition of MeTi($O^iPr$)$_3$ to cinnamaldehyde catalysed by **$L_{14}$** afforded a low conversion (65%) and enantioselectivity (80%) even when 1.7 eq. of the nucleophile were used (*Table 2.7*, *entry 1*). However, the use of the ligand **$L_{15}$** provided a higher conversion (90%) and enantioselectivity (82% ee, *entry 2*). A similar effect was observed with the addition to phenylacetaldehyde, increasing the selectivity from 81% to 85% when **$L_{15}$** was used (compare *entries 3 and 4*). The addition to the linear octanal and the α-branched cyclohexanal afforded full conversion and high enantioselectivities (90% and 94% ee, respectively, *entries 5 and 6*). The reaction with the β-branched isovaleraldehyde led to a high enantioselectivity (90% *ee*) but moderate conversion (77%, *entry 7*). Finally, the bulkier pivaldehyde provided an excellent enantiocontrol (94% *ee*) but very low conversion (20%, *entry 8*). The result could be improved by switching to the ligand **$L_{14}$** and using 2 eq. MeTi($O^iPr$)$_3$, which increased the conversion to 78% (*entry 9*).

In conclusion, the use of MeTi($O^iPr$)$_3$ allowed a decrease in the catalyst loading to 10 mol% and an increase of the reaction temperature to 0 °C, compared to the more reactive organolithium and organomagnesium reagents, which require higher catalysts loadings (20 mol%) and usually

lower and more impractical temperatures (down to –40 °C). This one pot methodology, allows the preparation of the very versatile methyl carbinol units using readily available reagents. The shorter reaction times and the higher temperatures make this process more attractive for both academia and industry.

## 2.3.3. Catalytic enantioselective 1,2-addition of alkenes to aldehydes

In the search of new synthetic strategies for the catalytic enantioselective addition of easy-to-handle and readily available nucleophiles to carbonyl compounds, we decided to evaluate the use of alkenes as alkylmetal equivalents in the asymmetric 1,2-addition to aldehydes. This reaction would be synthetically relevant as it would accomplish a transformation that is not currently possible.

Our investigations started[2] by evaluating the use of the very versatile Ar-BINMOLs[38-40, 169] as ligands in the addition of 1-hexene to benzaldehyde (*Table 2.8*). We envisioned that the hydrozirconation of 1-hexene with Schwartz reagent would generate the corresponding organozirconium reagent, which could act as the nucleophile in the addition to the carbonyl.

Following known procedures,[96, 99-101] 2 eq. of 1-hexene were treated with 2 eq. of $Cp_2ZrHCl$; a change from a white suspension to a yellow solution indicated the successful formation of the corresponding organozirconium compound, which was then added to a solution of benzaldehyde (1 eq., 0.125 M) and Ph-BINMOL (20 mol%) in THF or DCM at RT. As expected, very low conversion of the desired alcohol **6** was observed in both cases (9 and 13%, respectively, *Table 2.8*, *entries 1 and 2*). Under similar conditions (0.125 M in benzaldehyde), the reaction was attempted in the presence of 2.5 – 2.8 eq. of different additives (AgOTs, $TiCl(O^iPr)_3$, CuI and $Et_2Zn$) in both THF and DCM at RT. Unfortunately, no conversion was

[2] The optimisation of the reaction conditions was carried out by Dr Marcos Veguillas at Manchester Metropolitan University during the spring of 2016.

observed in any case; only the presence of 2 eq. of $Et_2Zn$ provided 19% conversion of racemic product **6** (*entry 3*). We observed that when the reaction was carried out under more concentrated conditions (0.5 M in benzaldehyde) and using DCM as solvent, the conversion towards the desired product **6** could be increased up to 44%, although the enantioselectivity of the process remained zero (*entry 4*).

Next, we decided to evaluate the use of different zinc sources as additives for the reaction. After an extensive screening, we observed that the use of $ZnBr_2$ (0.5 eq.) in combination with $Ti(O^iPr)_4$ (1.5 eq.) provided the desired alcohol **6** in 83% isolated yield and a promising 80% *ee*, using only 1.4 eq. of the alkene and 1.2 eq. of the Schwartz reagent, in DCM (0.5 M in benzaldehyde) at RT (*entry 5*). It is important to mention that the reaction proved to be very sensitive to the concentration and no conversion was observed under more diluted conditions (0.11 M of **1** in DCM, *entry 6*).

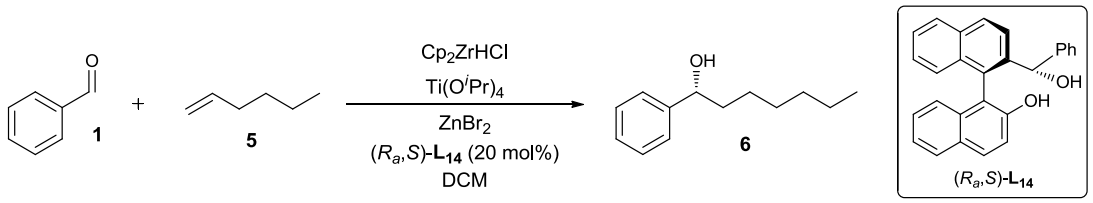
Working at the optimal 0.5 M concentration of substrate in DCM, we trialled a different titanium source ($TiCl(O^iPr)_3$ instead of $Ti(O^iPr)_4$), however, an increased reduction of the starting material to phenylmethanol was observed, whilst the desired product **6** was obtained in a racemic form (*entry 7*). It is worth mentioning that the use of $TiCl(O^iPr)_3$ in combination with $Et_2Zn$ or AgOTs did not provide any conversion either in DCM or THF, at 0.125 M or at 0.5 M.

Changing the titanium loading (*entries 8 and 9*) or the amount of $ZnBr_2$ used in the reaction (*entries 10 and 11*), also afforded increased amounts of the undesired reduced product and lower enantioselectivities. To our surprise, when the reaction was carried out at lower temperature (0 °C, overnight) lower enantioselectivity was observed (35% ee, *entry 12*). Higher temperatures (35 °C), provided slightly higher enantioselectivity to the value obtained at RT. (82% *ee*, compare *entries 13 and 5*), but lower conversion (51%).

By way of comparison, the reaction was assayed using (*R*)-BINOL (20 mol%) as ligand; 9% conversion to the desired product **6** was obtained in 56% *ee* (*entry 14*). Different solvent systems – *tert*-butylmethyl ether, toluene and diethyl ether (*entries 15 to 17*) – were assayed for the reaction, in combination with DCM, which is the optimal solvent for the hydrozirconation step; unfortunately, all of them provided lower conversions and enantioselectivities than the exclusive use of DCM.

Lowering the amounts of the Schwartz reagent and the alkene provided higher enantioselectivity (90%) but lower conversion towards the desired **6**, due to a substantial increase of reduction byproduct (*entry 18*). Fortunately, improved results were obtained with increased amounts of Schwartz reagent and the alkene, and, after fine adjustments, 99% conversion and 91% ee could be reached in 5 h when 2 eq. of Schwartz reagent were used in combination with 2.2 eq. of alkene in DCM at slightly higher temperature (35 °C, *entry 19*).

*Table 2.8 – Optimisation of reaction conditions for the addition of 1-hexene to benzaldehyde*[a]




| Entry | $Cp_2ZrHCl$ (eq.) | 1-hexene (eq.) | T (°C) | $Ti(O^iPr)_4$ (eq.) | $ZnBr_2$ (eq.) | 1/reduced/6[b] | ee[c] |
|---|---|---|---|---|---|---|---|
| 1[d,e] | 2 | 2 | RT | - | - | 91/0/9 | 0 |
| 2[e] | 2 | 2 | RT | - | - | 87/0/13 | 0 |
| 3[e] | 2 | 2 | RT | - | 2.0[f] | 81/0/19 | 0 |
| 4 | 2 | 2 | RT | - | 2.0[f] | 56/0/44 | 0 |
| 5 | 1.2 | 1.4 | RT | 1.5 | 0.5 | n.d. (83)[g] | 80 (*R*) |
| 6[h] | 1.2 | 1.4 | RT | 1.5 | 0.5 | 99/0/1 | 0 |
| 7 | 1.2 | 1.4 | RT | 1.5[i] | 0.5 | 0/78/22 | 0 |

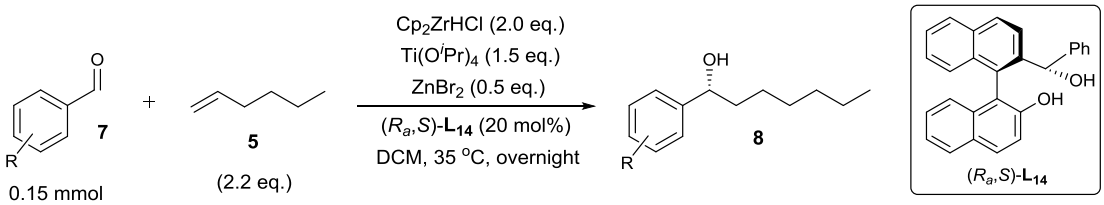
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 | 1.2 | 1.4 | RT | 1.0 | 0.5 | 0/57/43 | 35 (*R*) |
| 9 | 1.2 | 1.4 | RT | 2.0 | 0.5 | 5/89/5 | 62 (*R*) |
| 10 | 1.2 | 1.4 | RT | 1.5 | 0.2 | 9/73/18 | 80 (*R*) |
| 11 | 1.2 | 1.4 | RT | 1.5 | 0.7 | 5/74/20 | 66 (*R*) |
| 12 | 1.2 | 1.4 | 0 | 1.5 | 0.5 | 25/67/6 | 35 (*R*) |
| 13 | 1.2 | 1.4 | 35 | 1.5 | 0.5 | 13/36/51 | 82 (*R*) |
| 14[j] | 1.2 | 1.4 | RT | 1.5 | 0.5 | 8/83/9 | 56 (*R*) |
| 15[k] | 1.2 | 1.4 | RT | 1.5 | 0.5 | 9.6/74/15.4 | 79 (*R*) |
| 16[l] | 1.2 | 1.4 | RT | 1.5 | 0.5 | 6.4/93/1.2 | n.d. |
| 17[m] | 1.2 | 1.4 | RT | 1.5 | 0.5 | 4.5/89/6.5 | 59 (*R*) |
| 18 | 1.0 | 1.2 | RT | 1.5 | 0.5 | 30/59/11 | 90 (*R*) |
| **19** | **2.0** | **2.2** | **35** | **1.5** | **0.5** | **0/0/99 (87)[g]** | **91 (*R*)** |

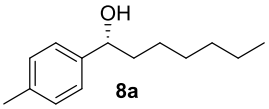
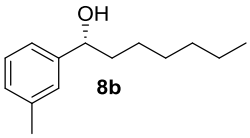
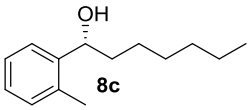
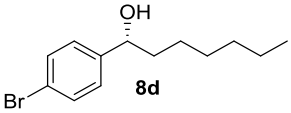
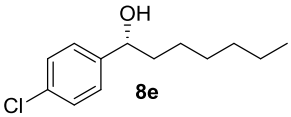
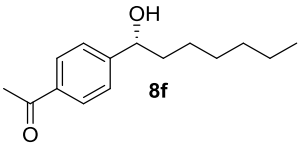
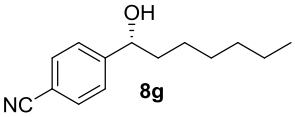
[a] Reaction conditions: **1** (0.15 mmol, 1.0 eq.), ($R_a$,*S*)-**L$_{14}$** (0.2 eq.), Ti(O$^i$Pr)$_4$ (1.5 eq.), DCM (0.5 M), room temperature, overnight. [b] Determined by CG-MS; reduced = phenyl methanol. [c] Determined by Chiral GC (see Experimental Part for further details). [d] Reaction carried out in THF. [e] 0.125 M in benzaldehyde. [f] Reaction carried out with $Et_2Zn$ instead of $ZnBr_2$. [g] Isolated yield after flash chromatography. [h] Concentration of **1** was 0.11 M in DCM. [i] Reaction carried out with TiCl(O$^i$Pr)$_3$ instead of Ti(O$^i$Pr)$_4$. [j] (*R*)-BINOL (20 mol%) used as a ligand. [k] TBDME/DCM were used as a solvent [l] Toluene/DCM were used as a solvent. [m] $Et_2O$/DCM were used as a solvent.

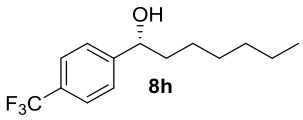
With the optimised conditions in hand, we tested the scope of the reaction with different aromatic aldehydes (*Table 2.9*). Thus, the reaction of 1-hexene with *p*-tolualdehyde afforded product **8a** with good yield (74%) and excellent enantioselectivity (94%, *Table 2.9*, *entry 1*). In the case of *m*- and *o*-tolualdehyde (*entries 2 and 3*), where the methyl substituent in the aromatic ring is closer to the reactive site, higher percentages of reduced and dehydration product **8'** (*Figure 2.4*) were obtained, as well as lower enantioselectivity (85% and 75% respectively), probably due to increased steric hindrance close to the carbonyl group. The reaction with *p*-bromo and *p*-chlorobenzaldehyde afforded moderated yields (56% and 59%) and excellent enantioselectivities (91% and 90%, *entries 4 and 5*, respectively). The use of *p*-acetylbenzaldehyde as starting material (*entry 6*), provided the corresponding alcohol **8f** in excellent enantioselectivity (91%) but low yield (32%). This is due to the reduction of the acetyl

group by β-hydride transference from the organometallic reagent, by-product that could be detected by GC-MS (**8f''**, *Figure 2.4*). Gratifyingly, the methodology proved to be compatible with other functional groups like *p*-CN (*entry 7*) and *p*-$CF_3$ (*entry 8*), leading to good yields (55-58%) and high enantioselectivities (87% *ee*).

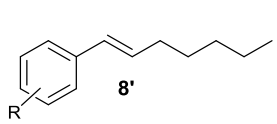
*Table 2.9 – Enantioselective catalysed addition of 1-hexene to aromatic aldehydes - Scope of the reaction*[a]




| Entry | Product | 7/reduced/8[b] | Yield (%)[c] | *ee* (%)[d] |
|---|---|---|---|---|
| 1 |  **8a** | 0/6/94 | 74 | 91 (*R*) |
| 2 |  **8b** | 0/15/77[e] | 54 | 85 (*R*) |
| 3 |  **8c** | 0/28/54[f] | 49 | 75 (*R*) |
| 4 |  **8d** | 3/10/87 | 56 | 91 (*R*) |
| 5[g] |  **8e** | 2/6/92 | 59 | 90 (*R*) |
| 6 |  **8f** | 1/4/76[h] | 32 | 91 (*R*) |
| 7[g] |  **8g** | 0/19/81 | 58 | 87 (*R*) |

| | | | | |
|---|---|---|---|---|
| 8 |  **8h** | 3/28/69 | 55 | 87[i] (*R*) |

[a] Reaction conditions: **7** (0.15 mmol, 1.0 eq.), ($R_a$,*S*)-**$L_{14}$** (0.2 eq.), Ti(O$^i$Pr)$_4$ (1.5 eq.), 1-hexene (2.2 eq.), $Cp_2ZrHCl$ (2.0 eq.), $ZnBr_2$ (0.5 eq.), DCM (0.375 M), 35 °C, overnight. [b] Determined by GC-MS. [c] Isolated yield after flash chromatography. [d] Determined by Chiral GC. Configuration based on literature data (see Experimental Part for details). [e] 8% of dehydration product **8'** was observed by GC-MS. [f] 18% of dehydration product was observed by GC-MS. [g] The reaction was carried out in DCM (0.3 M). [h] 19% of **8f'** was observed by GC-MS. [i] Determined on the corresponding acetate derivative (see Experimental part for further details).


**8'**

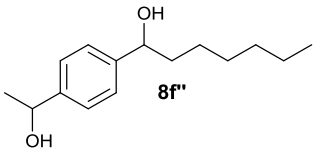
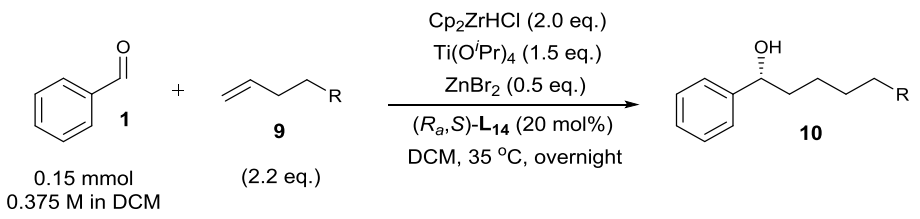
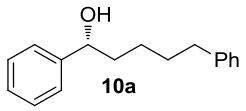
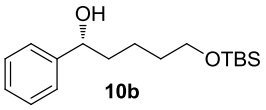
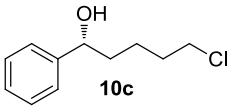

**8f''**

*Figure 2.4 – By-products of the reaction detected by GC-MS*

Next, we tested the scope of the reaction with different alkenes (*Table 2.10*). Thus, the reaction of 4-phenyl-1-butene with benzaldehyde (*entry 1*), provided excellent yield (93%) and good enantioselectivity (77% *ee*). To our delight, the methodology is also compatible with functionalised alkenes. The reaction of benzaldehyde with 4-[(tert-butyldimethylsilyl)oxy]-1-butene led to the desired alcohol **10b** in moderate yield (42%) but good enantioselectivity (88% *ee*, *entry 2*). Similar results were obtained when 4-chlorobut-1-ene was used as nucleophile (*entry 3*), providing 40% yield and 86% *ee*.

*Table 2.10 – Enantioselective catalysed addition of alkenes to benzaldehyde - Scope of the reaction*[a]



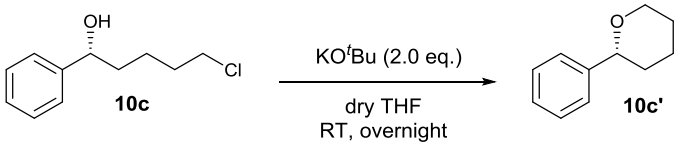

| Entry | Product | 1/reduced/10[b] | Yield (%)[c] | *ee* (%)[d] |
|---|---|---|---|---|
| 1[e] |  **10a** | 0/0/>99 | 93 | 77 (*R*) |
| 2 |  **10b** | n.d. | 42 | 88 (*R*) |
| 3 |  **10c** | 0/10/75[f] | 40 | 86[g] (*R*) |

[a] Reaction conditions: **1** (0.15 mmol, 1.0 eq.), (*R*$_a$,*S*)-**L$_{14}$** (0.2 eq.), Ti(O$^i$Pr)$_4$ (1.5 eq.), **9** (2.2 eq.), $Cp_2ZrHCl$ (2.0 eq.), $ZnBr_2$ (0.5 eq.), DCM (0.375 M), 35 °C, overnight. [b] Determined by GC-MS. [c] Isolated yield after flash chromatography. [d] Determined by Chiral GC. Configuration based on literature data (see Experimental Part for details). [e] Reaction carried out with **9** (3.0 eq.) and $Cp_2ZrHCl$ (2.8 eq.). [f] 15% of dehydration product was observed by GC-MS. [g] Determined on the corresponding cyclised derivative **10c'** (see Experimental part for details).

As an application of this methodology, product **10c** was transformed into its corresponding tetrahydropyran adduct **10c'**. Tetrahydropyran rings are very important structural moieties, which are present in a large variety of natural products such as polyether antibiotics and marine macrocycles.[170-174] Additionally, they are also employed in the perfume industry or as flavouring ingredients in the food industry.[175]

Thus, following a common and straightforward procedure,[176] alcohol **10c** was dissolved in dry THF and treated with 2 eq. of KO$^t$Bu at RT. Tetrahydropyran **10c'** was obtained in 84% yield after purification by column chromatography (*Scheme 2.50*). It is worth pointing out that no racemization occurs during the cyclisation,[177] both **10c** and **10c'** were

obtained in 86% ee. This strategy constitutes a novel and straight forward method for the synthesis of chiral tetrahydropyran derivatives *via* an enantioselective 1,2-addition of an alkene to a carbonyl followed by an intramolecular $SN_2$ reaction.




*Scheme 2.50 – Formation of the tetrahydropyran ring from product* ***10c***

In conclusion, we have developed a new and efficient procedure for the catalytic asymmetric addition reaction of alkylzirconium species to aromatic aldehydes, based on the use of a readily available non-racemic diol ligand and Ti(O$^i$Pr)$_4$. The alkylzirconium nucleophiles are generated *in situ* by hydrozirconation of alkenes with Schwartz reagent; thus avoiding the use of premade organometallic reagents. The reaction proceeds under mild conditions and it allows the synthesis of the corresponding chiral secondary alcohols in moderated to good yields (32-93%) and good to excellent enantioselectivities (75-91% *ee*). It is worth mentioning that the reaction is compatible with the presence of functional groups in both the aldehyde and the alkene. Furthermore, the methodology allows the enantioselective synthesis of chiral tetrahydropyrans by a subsequent $SN_2$ reaction on the addition product obtained. These tetrahydropyrans are important motifs from a pharmaceutical and an agricultural point of view.

## 2.3.4. Attempted enantioselective synthesis of fluoxetine

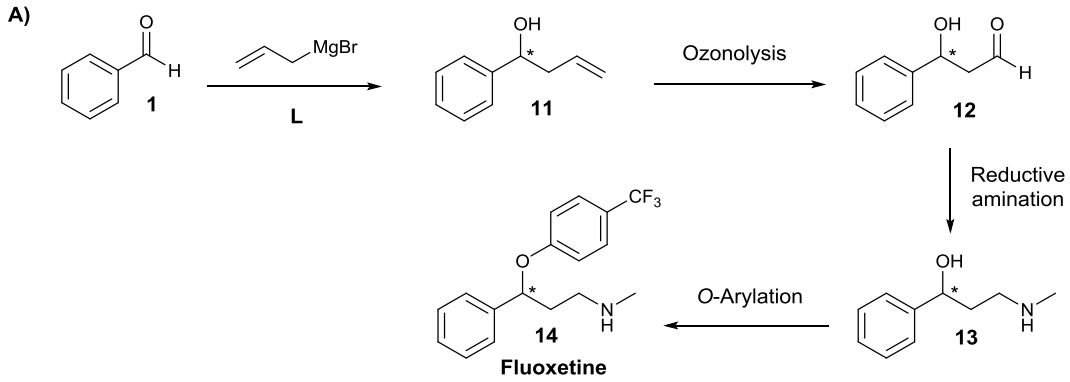
Being aware of the potential of all the catalytic asymmetric methodologies developed in our group during the last years,[59, 60, 62, 79, 89, 178, 179] we envisioned their application to the enantioselective synthesis of the antidepressant fluoxetine, whose racemic synthesis has been studied in the first chapter of this thesis.

As stated by the 9th principle of Green Chemistry,[90] "Catalytic reagents are superior to stoichiometric reagents"; therefore, a synthetic pathway for the preparation of fluoxetine, that involves catalytic methods, would constitute a greener and highly desirable strategy (see *Chapter 1, section 1.3.2*).

As previously mentioned in Chapter 1, section 1.3.1; even though Prozac is sold as a racemate, the different activities and metabolic rates between both enantiomers have generated a growing interest in the synthesis of both isomers in an optically pure way. Ideally, once the catalytic asymmetric step has been developed, it could be attempted using ball milling or microwave assisted heating in order to make the process even more sustainable.

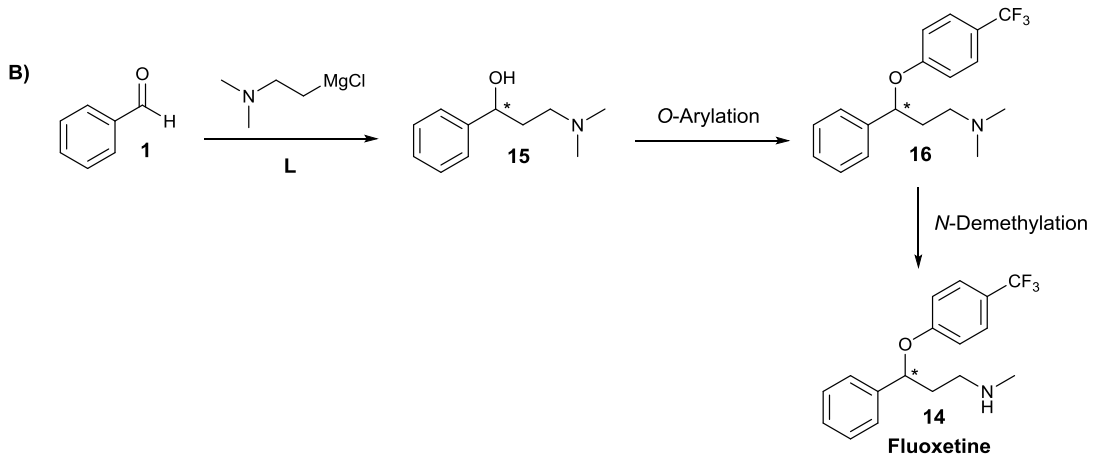
Thus, three different strategies for the asymmetric synthesis of fluoxetine were proposed and evaluated (*Schemes 2.51–2.53*); all of them based on the enantioselective addition of a Grignard reagent to the cheap and commercially available benzaldehyde.

Route A consists on the catalytic asymmetric addition of allylmagnesium bromide to benzaldehyde, which would provide enantiopure **11**. Next, an ozonolysis reaction would afford the aldol **12**, that could be transformed to the hydroxylamine **13** *via* a reductive amination process. Last, the *O*-arylation methodology developed in the first chapter of this thesis would lead to enantiopure fluoxetine (**14**) (*Scheme 2.51*).



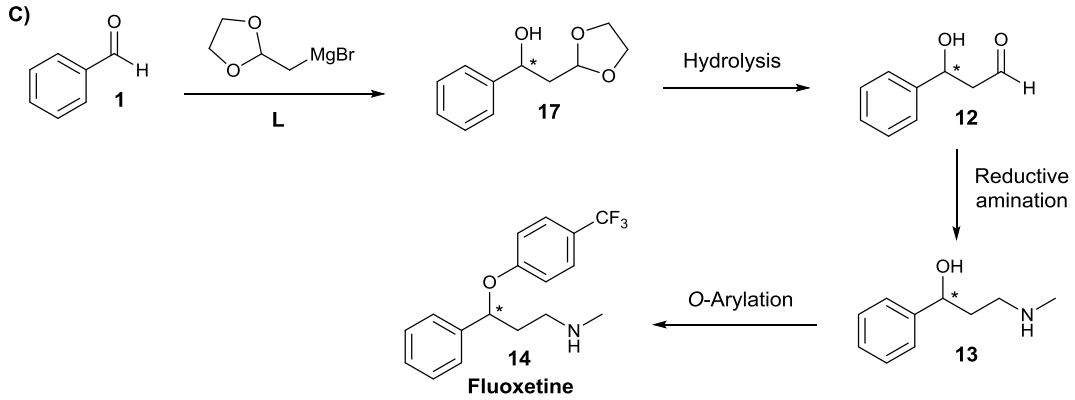

*Scheme 2.51 – Proposed asymmetric synthesis of fluoxetine – Route A, 4 steps*

Route B starts with the asymmetric addition of 3-dimethylaminopropylmagnesium chloride to benzaldehyde, which would provide enantiopure hydroxyamine **15**. Next, the *O*-arylation and *N*-demethylation steps previously studied would afford fluoxetine (**14**) (*Scheme 2.52*).




*Scheme 2.52 – Proposed asymmetric synthesis of fluoxetine – Route B, 3 steps*

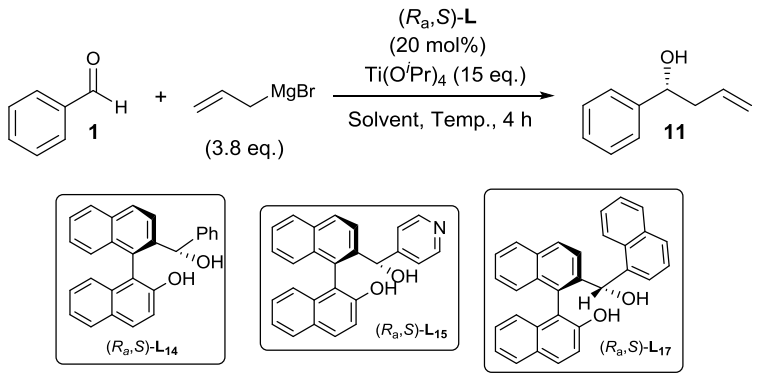
Finally, route C consists of the asymmetric addition of (1,3-dioxolan-2-ylmethyl)magnesium bromide to benzaldehyde, which would provide the acetal **17**. Next, a simple hydrolysis would allow the synthesis of **12**, common intermediate with route A (*Scheme 2.53*).




*Scheme 2.53 – Proposed asymmetric synthesis of fluoxetine – Route C, 4 steps*

Route A was firstly attempted, due to the commercial availability of allylmagnesium bromide. The results obtained are summarised on the *Table 2.11* below.

*Table 2.11 – Attempted catalytic enantioselective addition of allylmagnesium bromide to benzaldehyde*




| Entry | ($R_a$,*S*)-**L** | Solvent | Temperature (°C) | Conv. (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|
| 1 | $\mathbf{L_{14}}$ | Toluene | −40 | 58 | 0 |
| 2 | $\mathbf{L_{17}}$ | Toluene | −40 | >99 | 0 |
| 3 | $\mathbf{L_{15}}$ | Toluene | −40 | >99 | 0 |
| 4 | $\mathbf{L_{17}}$ | $Et_2O$ | −20 | 50 | 0 |
| 5[d] | $\mathbf{L_{17}}$ | $Et_2O$ | −20 | 25 | 0 |

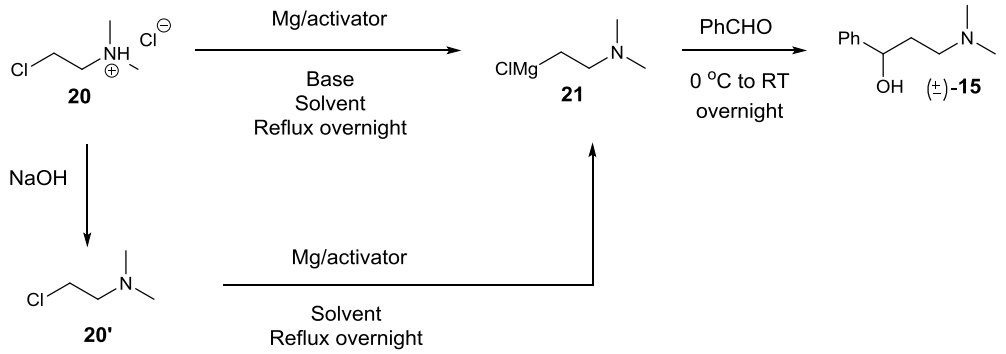
[a] Reaction conditions: **1** (0.3 mmol, 1.0 eq.), allylmagnesium bromide (1 M in $Et_2O$, 3.8 eq.) ($R_a$,*S*)-**L** (0.2 eq.), $Ti(O^iPr)_4$ (1.5 eq.), toluene or $Et_2O$ (2.5 mL), −20 or −40 °C, 4 h. [b] Determined by GC-MS. [c] Determined by Chiral GC on the corresponding acetate derivative (see Experimental Part for details). [d] The reaction was carried out with $Ti(O^iPr)_4$ (10 eq.) and allylmagnesium bromide (2.5 eq.).

We started our investigations by using the optimised conditions for the addition of Grignard reagents to aldehydes catalysed by Ar-BINMOLs ligands developed by our group in 2011.[59] Unfortunately, the reaction of benzaldehyde with allylmagnesium bromide (3.8 eq.) in the presence of $Ti(O^iPr)_4$ (15 eq.) and catalysed by ($R_a$,*S*)-$\mathbf{L_{14}}$ afforded racemic alcohol **11** in 58% conversion (*Table 2.11*, *entry 1*). Under the same reaction conditions, the Ar-BINMOL ligands $\mathbf{L_{15}}$ and $\mathbf{L_{17}}$ provided full conversion,

but no enantioselectivity (*entries 2 and 3*, respectively). When the reaction was carried out in $Et_2O$ at –20 °C (optimal temperature and solvent for the addition of Grignard reagents to aliphatic aldehydes, developed in our group in 2013),[60] 50% conversion to the racemic alcohol **11** (entry 4) was obtained. Variations in the equivalents of $Ti(O^iPr)_4$ and/or allylmagnesium bromide did not result in any improvement (see, for example, *entry 5*).

Our investigations on the proposed Route B started with the attempt to prepare 3-dimethylaminopropylmagnesium chloride from the commercially available 2-chloro-*N*,*N*-dimethylethylamine hydrochloride salt **20** (*Table 2.12*). To test if the Grignard reagent **21** was successfully formed, the solution was reacted with benzaldehyde at 0 °C, allowing the resulting mixture to reach room temperature overnight. The reaction was analysed by GC-MS to determine the conversion of racemic product **15**.

*Table 2.12 – Attempted formation of the Grignard reagent **21** and reaction with benzaldehyde*




| Entry | Starting material | Mg (eq.) | Activator | Base (eq.) | Solvent | Conversion to (±)-15 (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **20** | 3.0 | $I_2$ | - | $Et_2O$ | 0 |
| 2 | **20'** | 1.0 | $I_2$ | - | $Et_2O$ | 0 |
| 3 | **20'** | 3.0 | $I_2$ | - | $Et_2O$ | 0 |
| 4 | **20'** | 1.0 | $I_2$ | - | THF | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 | **20'** | 1.0 | $I_2$ | - | $^{t}$BuOMe | 0 |
| 6 | **20** | 1.5 | - | BuLi (1 eq.) | THF | 0 |
| 7 | **20** | 1.5 | - | BuLi (1 eq.) | $Et_2O$ | 0 |
| 8 | **20** | 1.5 | - | NaH (1 eq.) | $Et_2O$ | 0 |

[a] Reaction conditions: **20** or **20'** (12.5 mmol, 1.0 eq.), Mg powder (1.0, 1.5 or 3.0 eq.), base (1.0 eq.), solvent (1 M) [b] Determined by GC-MS after overnight reaction with benzaldehyde (see Experimental Part for details).

Our investigations started with the reaction of the hydrochloride salt **20** with 3 eq. of magnesium powder in diethyl ether using catalytic amounts of $I_2$ to activate the surface of the magnesium powder (*Table 2.12*, *entry 1*), the mixture was heated to reflux overnight. The resulting solution was cooled down to room temperature and added to benzaldehyde but no product **15** was detected by GC-MS (*entry 1*). We assumed that the hydrochloride salt was not reactive enough to form the Grignard reagent or the solubility was too low in $Et_2O$, for these reasons, we attempted to make the Grignard reagent **21** from the free amine **20'**.

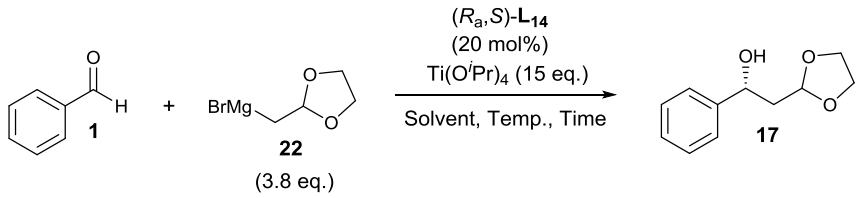
The free amine **20'** is, however, too volatile to be isolated using common work-up techniques, therefore, we opted for dissolving the hydrochloride salt **20** in aqueous 2 M NaOH. After stirring at RT for 30 min, an organic layer (free amine **20'**) was formed on top of the solution. The free amine was taken with a syringe, and subsequently added to a suspension of Mg turnings (preactivated with $I_2$) in different solvents. Using this experimental procedure, we attempted the formation of the Grignard reagent **21** in diethyl ether – using 1 or 3 eq. of magnesium powder (*entries 2 and 3*) – in THF (*entry 4*) and in $^{t}$BuOMe (*entry 5*) as solvents. Unfortunately, no product **15** was observed by GC-MS in any case.

Next, we envisioned that the free amine could be generated *in situ* by the reaction with a strong base like $^{n}$BuLi or NaH, and that the Grignard reagent **21** could be subsequently formed by the reaction with the Mg turnings under reflux conditions. Thus, to a suspension of **20** in dry THF

and Mg (1.5 eq.), $^{n}$BuLi (1 eq.) was added was added dropwise at 0 °C and the reaction was heated to reflux overnight (*entry 6*). After the addition of benzaldehyde, no conversion to **15** was observed. The same strategy was attempted using $Et_2O$ as a solvent and $^{n}$BuLi (1 eq., *entry 7*) or NaH 60% dispersion in mineral oil (1 eq., *entry 8*) as base; unfortunately, no product was formed in either case.

Last, we attempted the synthesis of fluoxetine through Route C (*Scheme 2.53*), which begins with the asymmetric addition of (1,3-dioxolan-2-ylmethyl)magnesium bromide (commercially available as a 0.5 M solution in THF) to benzaldehyde. Our attempts at this reaction are summarized in the table below.

*Table 2.13 – Attempted enantioselective addition of (1,3-dioxolan-2-ylmethyl)magnesium bromide to benzaldehyde catalysed by Ph-BINMOL* ***L*****$_{14}$**[a]




| Entry | Solvent | Temperature (°C) | Time (h) | Conversion (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|
| 1[d] | THF | Reflux | 18 | 36[e] | 0 |
| 2[f] | Toluene | –40 | 3 | 0 | - |
| 3[f] | Toluene | 0 | 2 | 0 | - |
| 4[f] | Toluene | RT | 18 | n.d.[e] | - |
| 5[f] | $Et_2O$ | –20 | 4 | 0 | - |
| 6[f] | $Et_2O$ | RT | 18 | n.d.[e] | - |
| 7 | THF | –40 | 4 | 0 | - |
| 8 | THF | RT | 18 | n.d.[e] | - |

| | | | | | |
|---|---|---|---|---|---|
| 9 | THF | Reflux | 18 | n.d.[g] | - |
| 10 | Toluene | –40 | 4 | 0 | - |
| 11 | Toluene | RT | 18 | n.d.[e] | - |
| 12 | $Et_2O$ | –20 | 4 | 0 | - |
| 13 | $Et_2O$ | RT | 18 | n.d.[e] | - |

[a] Reaction conditions: **1** (0.1 mmol, 1.0 eq.), Ti($O^iPr$)$_4$ (15 eq.), ($R_a$,*S*)-**L$_{14}$** (0.20 eq.), **22** (0.5 M in THF, 3.8 eq.), dry THF (0.06 M). [b] Determined by GC-MS. [c] Determined by chiral GC. [d] Reaction performed in the absence of ligand and Ti($O^iPr$)$_4$. [e] The formation of reduced product (phenylmethanol) was observed by GC-MS. [f] The THF present in the Grignard reagent was removed under vacuum (see Experimental Part for details).

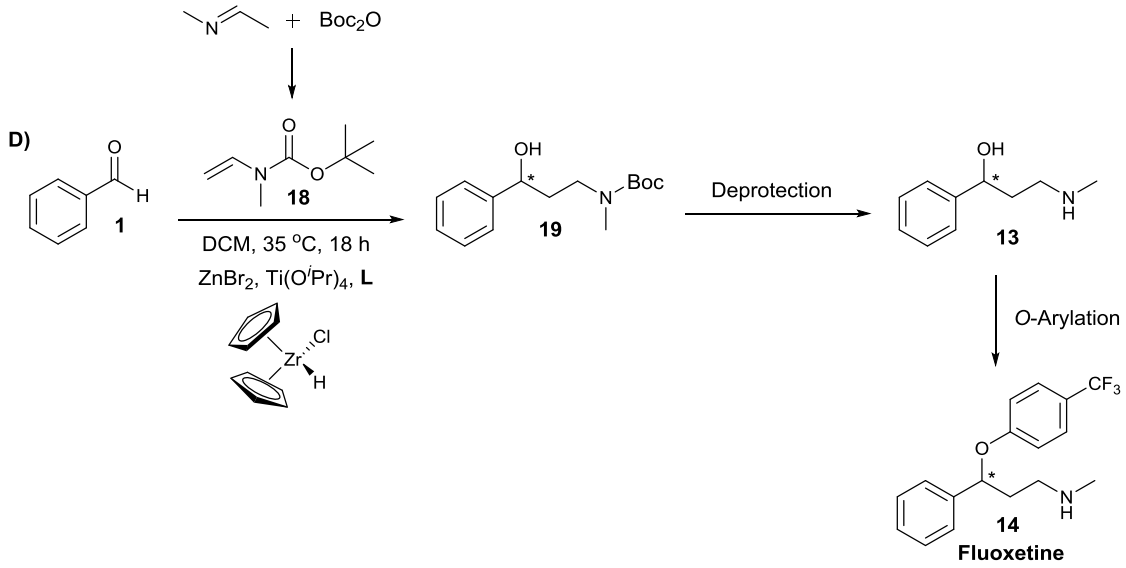
The reaction of **22** with benzaldehyde in THF, in the absence of chiral ligand and Ti($O^iPr$)$_4$, provided 36% of conversion to the corresponding racemic product **17** together with 64% of conversion to the reduced product phenylmethanol (*entry 1*).

Our investigations started by exploring the use of the optimal conditions for the addition of Grignard reagents to aldehydes developed by our group[59] (*entry 2*). Our previous studies have shown that THF is not compatible with our methodology,[59] for this reason, the THF of the Grignard solution was removed under vacuum before use. Thus, a solution of ($R_a$,*S*)-**L$_{14}$** and Ti($O^iPr$)$_4$ in toluene was transferred into a Schlenk flask containing **22** (the THF of which had been previously removed under vacuum), followed by the addition of benzaldehyde. The reaction was attempted at –40°C, 0 °C and RT (*entries 2-4*). Analysis by GC-MS confirmed that no reaction took place at –40°C or 0 °C (*Table 2.13*, *entries 2 and 3*), while room temperature provided full conversion to the reduced product phenylmethanol (*entry 4*). The same outcome was observed when the reaction was carried out in $Et_2O$ as solvent (*entries 5 and 6*); no conversion was obtained at –20°C and full conversion to the reduced product was achieved when working at RT.

The same reaction conditions were tested using dry THF as solvent, without removing the solvent of the Grignard reagent. Unfortunately, no reaction took place at –40 °C (*entry 7*) and room temperature and reflux conditions provided exclusively reduced product phenylmethanol (*entry 8 and 9*). Next, we attempted the reaction using in toluene (*entries 10 and 11*) and diethyl ether (*entry 12 and 13*) as solvent, but without removing the THF from the Grignard reagent. In all cases, no reaction was observed at low temperature while RT led to full conversion to the reduced product.

In conclusion, our preliminary research on the Ar-BINMOL catalysed enantioselective synthesis of fluoxetine by addition of a Grignard reagent to benzaldehyde have been unsuccessful.

Different reaction conditions and titanium sources remain to be studied. In addition, other synthetic routes could be also explored. For example, the proposed route D (*Scheme 2.54*) constitutes a promising approach, based on the high enantioselectivities achieved through the addition of organozirconium reagents to aldehydes described in the previous section.




*Scheme 2.54 – Proposed asymmetric synthesis fluoxetine – Route D, 3 steps*

This strategy, route D, begins with the formation of the alkylzirconium reagent obtained from the reaction between **18** and Schwartz reagent. The alkene **18** could be easily prepared by the acylation of *N*-

ethylidenemethylamine with Boc anhydride, as previously described by Breederveld.[180, 181] Next, the addition of the corresponding alkylzirconium reagent to benzaldehyde in the presence of a chiral ligand would provide enantiomerically pure **19**. A subsequent deprotection of the Boc group and an *O*-arylation reaction would finally provide our target fluoxetine (*Scheme 2.54*).

# 2.4. Experimental Part

## 2.4.1. General instrumentation

**TLC:** Thin layer chromatography (TLC) was run on silica gel 60 aluminium sheets, 0.25 mm thick ($F_{254}$ *Merck KGaA*®). The components were visualized by UV light (254 nm), phosphomolybdic acid or $KMnO_4$ staining solutions.

**IR:** IR spectra were recorded on *Nicolet*® 380 FT/IR – Fourier Transform Infrared Spectrometer. Only the most significant frequencies have been considered for the characterisation, and have been reported in $cm^{-1}$.

**NMR:** $^{1}H$ NMR, $^{13}C$ NMR and $^{19}F$ NMR were recorded on a *JEOL*® ECS-400 (400, 100.6 and 376.5 MHz, respectively) using $CDCl_3$ or $CD_3OD$ as solvent. Chemical shift values are reported in ppm with TMS as internal standard ($CDCl_3$: δ 7.26 for $^{1}H$-NMR, δ 77.0 for $^{13}C$-NMR). Data are reported as follows: chemical shifts, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, quint = quintet, m= multiplet, br= broad), coupling constants (Hz), and integration.

**Flash chromatography:** Column chromatography was carried out using *Geduran*® Silica gel 60, 40-63 microns RE. The eluent used is mentioned in each particular case.

**Melting points:** Melting points were measured in a *Stuart*® SMP10 melting point apparatus and are not corrected.

**GC:** Chromatograms (for both conversion and enantioselectivity determination) have been recorded using an Agilent Technologies® 7890A GC System and a Hewlett Packard® 5890 Series II GC System, with a CycloSil-β (Agilent Technologies, 30 m x 0.25 mm) and a CP-Chirasil-DEX CB (Varian, 25 m x 0.25 mm) column, respectively; injector and detector temperatures: 250 °C.

**HPLC:** Analysis (for enantioselectivity determination) was carried out on a Agilent 1100 Series HPLC equipped with a G1315B diode array detector and a Quat. Pump G1311A, using the columns Lux 5µ Cellulose-1 and Lux 5µ Cellulose-3 (Phenomenex®, 250 mm x 4.60 mm).

**Optical rotations:** Were measured on a Bellingham + Stanley® ADP 440+ Polarimeter with a 0.5 cm cell (*c* given in g/100 mL).

**GCMS:** Low resolution mass spectra were recorded on a GC-MS spectrometer (*Hewlett Packard*® HP 5890 Series II GC System) equipped with a DB-5 column (*J&W Scientific*®, 30 m × 0.32 mm), connected to a *Hewlett Packard*® HP 5972 Series Mass Selective Detector. Helium was used as carrier gas at 10 psi, and the samples were ionized by an electronic impact (EI) source at 70 eV.

**HRMS:** High resolution mass spectra were obtained on a *Agilent Technologies*® 6540 Ultra-High-Definition (UHD) Accurate-Mass equipped with a time of flight (Q-TOF) analyser and the samples were ionized by ESI techniques and introduced through a high pressure liquid chromatography (HPLC) model *Agilent Technologies*® 1260 Infinity Quaternary LC system. Samples were eluted with mixture of MeOH and 0.1% formic acid, with a flow of 0.2 ml/min.

## 2.4.2. General methods and considerations

All glassware employed during inert atmosphere experiments was flame-dried under vacuum. Dry argon was used as inert gas for reactions that required inert atmosphere. All liquid aldehydes were freshly distilled before use. Organolithium reagents were purchased from Sigma-Aldrich and used without further purification. Anhydrous THF, DCM, toluene and $Et_2O$ were obtained from a Pure Solv™ Solvent Purification Systems.

The rest of the commercially available reagents were purchased from Aldrich, Acros, Alfa Aesar, Manchester Organics, Fisher and Maybridge and used without further purification, unless stated otherwise.

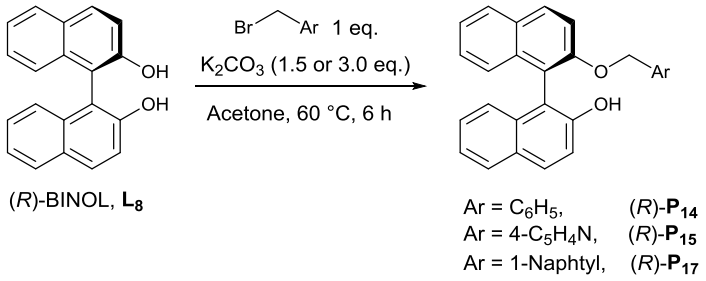
Ligands ($R_a$,*S*)-**L14**, ($R_a$,*S*)-**L15** and ($R_a$,*S*)-**L17** were prepared according to literature procedures[60] from (*R*)-BINOL, purchased from Manchester Organics.

## 2.4.3. Experimental procedure and data of compounds

### 2.4.3.1. Synthesis of Ar-BINMOL ligands

#### 2.4.3.1.1. Synthesis of monobenzylated (*R*)-BINOL derivatives (*R*)-**P14**, **P15** and **P17**

The intermediates (*R*)-**P14**, **P15** and **P17** were prepared starting from commercially available (*R*)-BINOL according to two different procedures:




*Scheme 2.55 – Synthesis of Ar-BINMOL ligands, first step*

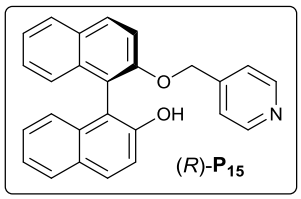
**Procedure A:**[182] Synthesis of (*R*)-**P14** and (*R*)-**P17**.

(*R*)-BINOL (2.0 g, 7.0 mmol) was dissolved in 50 mL of acetone in a round bottom flask, then $K_2CO_3$ (1.5 g, 10.5 mmol, 1.5 eq.) and the corresponding benzyl bromide derivative ($ArCH_2Br$, 7.0 mmol, 1.0 eq) were added and the mixture was heated at 60 °C during 6 h. The reaction crude was concentrated under vacuum and was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated under vacuum. Synthetic intermediates **P** were used in the next step without further purification, Data of the products were in accordance with the previously reported in literature.[40, 59]

**Procedure B:** Synthesis of (*R*)-**P15**.

(*R*)-BINOL (2.0 g, 7.0 mmol) was dissolved in 40 mL of acetone in a round bottom flask and a solution of $K_2CO_3$ (2.9 g, 21.0 mmol, 3.0 eq.) in 4 mL

of water was added. Next, 4-(bromomethyl)pyridine (7.0 mmol, 1.0 eq.) was added and the mixture was heated at 65 °C during 12 h. The reaction crude was filtered under vacuum over Celite®, washing the cake with EtOAc (3 × 50 mL) and solvent was evaporated under vacuum. The hydroxyether (*R*)-**P$_{15}$** was purified by flash silica gel chromatography. Data of the product in accordance with the previously reported in literature.[60]




**(*R*)-2'-(pyridin-4-ylmethoxy)-(1,1'-binaphthalen)-2-ol ((*R*)-P$_{15}$):**[60] Obtained as a white solid after column chromatography (Hex/EtOAc 100:0 to 0:100) and recrystallisation in Hex/EtOAc. **Yield:** 66%. **M$_p$** = 182–184 °C. **IR** (ATR) 3064, 1610, 1504, 1325, 1264, 1044, 798. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.5 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.91 (d, *J* = 8.9 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.42–7.34 (m, 3H), 7.34–7.26 (m, 3H), 7.21 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 5.2 Hz, 2H), 5.08 (d, *J* = 13.9 Hz, 1H), 5.03 (d, *J* = 13.8 Hz, 1H), 3.18 (br s, 1H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 154.3, 151.6, 148.9, 146.9, 134.0, 133.8, 130.9, 129.9, 129.1, 128.2, 127.5, 126.5, 125.2, 124.7, 123.3, 121.2, 117.7, 115.4, 114.8, 69.4.

2.4.3.1.2. Synthesis of Ar-BINMOLs derivatives (*R$_a$*,*S*)-**L$_{14}$**, **L$_{15}$** and **L$_{17}$**

Two different procedures were used to synthesize the ligands **L$_{14}$**, **L$_{15}$** and **L$_{17}$** through a [1,2]-Wittig rearrangement from the corresponding hydroxyethers (*R*)-**P$_{14}$**, **P$_{15}$** and **P$_{17}$**.

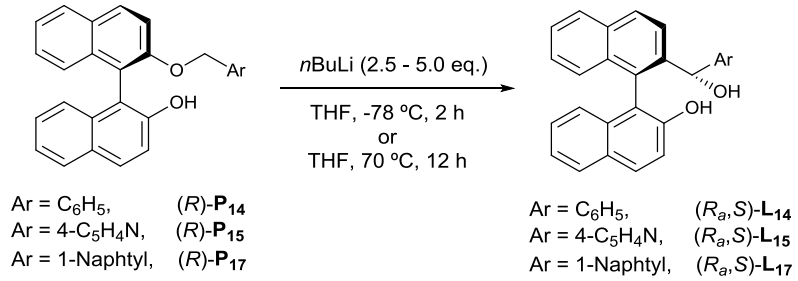
**Procedure A**: Synthesis of (*R$_a$*,*S*)-**L$_{14}$** and (*R$_a$*,*S*)-**L$_{17}$**

*n*-BuLi (2.5 M in hexane, 2.5 eq) was slowly added to a solution of the corresponding precursor (*R*)-**P$_{14}$** or (*R*)-**P$_{17}$** (4.0 mmol) in dry THF (30 mL) at –78 °C. The mixture was stirred for 2 h at –78 °C and then quenched with water at 0 °C. The resulting mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by chromatography on flash silica gel to give the

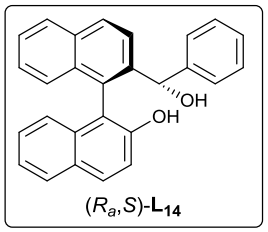
desired products. Data of the products was in accordance with the previously reported in the literature.

**Procedure B**: Synthesis of ($R_a$,*S*)-**$L_{15}$**

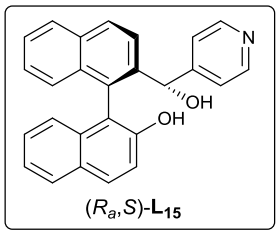
*n*-BuLi (2.5 M in hexane, 5.0 eq) was slowly added to a solution of (*R*)-**$P_{15}$** (4.0 mmol) in dry THF (40 mL) at room temperature. The mixture was stirred for 12 h at 70 °C and then the reaction was quenched with water at 0 °C. The resulting mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by chromatography on flash silica gel to give the desired product ($R_a$,*S*)-**$L_{15}$**.




*Scheme 2.56 – Synthesis of Ar-BINMOL ligands, second step*

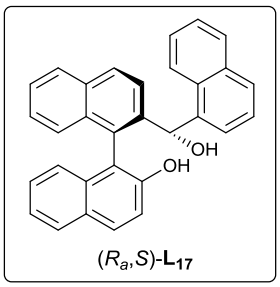



**($R_a$)-2'-[(*S*)-hydroxy(phenyl)methyl]-(1,1'-binaphthalen)-2-ol (($R_a$,*S*)-$L_{14}$):**[40] Obtained as a white solid after column chromatography (Hex/EtOAc 100:0 to 85:15). **Yield:** 85%. **$M_p$** = 72–75 °C. **IR** (ATR) 3276, 3058, 2926, 2850, 1620, 1595, 1341, 1268, 1027, 1012. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.90 (ddd, *J* = 21.8, 13.0, 8.5 Hz, 4H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.47 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.27–7.24 (m, 1H), 7.20–7.08 (m, 5H), 7.06–6.98 (m, 2H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.69 (s, 1H), 5.61 (br s, 1H), 2.64 (br s, 1H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 151.2, 142.5, 141.4, 134.0, 133.4, 132.9, 130.2, 129.9, 129.7, 129.1, 128.1, 127.1, 126.8, 126.7, 126.5, 126.0, 125.1, 125.0, 123.6, 117.9, 117.2, 73.4.



($R_a$,*S*)-**L15**

**(*Ra*)-2'-[(*S*)-hydroxy(pyridin-4-yl)methyl]-(1,1'-binaphthalen)-2-ol ((*Ra*,*S*)-L15):**[60] Obtained as a yellow solid after column chromatography (Hex/EtOAc 100:0 to 20:80). **Yield:** 33% (two steps). **$M_p$**: 100–103 °C. **IR** (ATR) 3297, 3055, 1606, 1506, 1342, 813, 747. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 6.2 Hz, 2H), 7.95–7.73 (m, 4H), 7.42 (ddd, *J* = 8.1, 6.5, 1.6 Hz, 1H), 7.36–7.26 (m, 3H), 7.25–7.13 (m, 3H), 6.97 (d, *J* = 5.8 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 5.64 (s, 1H), 3.56 (br s, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 152.8, 152.0, 148.3, 139.8, 134.2, 133.4, 132.9, 131.8, 130.2, 129.4, 128.9, 128.2, 128.1, 126.8, 126.8, 126.5, 125.0, 124.8, 123.6, 121.5, 118.3, 117.3, 72.1.



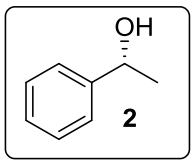
($R_a$,*S*)-**L17**

**(*Ra*)-2'-[(*S*)-hydroxy(naphthalen-1-yl)methyl]-(1,1'-binaphthalen)-2-ol ((*Ra*,*S*)-L17):**[60] Obtained as a yellow solid after column chromatography (Hex/EtOAc 100:0 to 80:20). **Yield:** 72%. **$M_p$** = 105–108 °C. **IR** (ATR) 3227, 3051, 1621, 1508, 1268, 783, 748. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.87 (t, *J* = 6.8 Hz, 2H), 7.81 (t, *J* = 6.9 Hz, 2H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.48–7.41 (m, 2H), 7.37 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.34–7.27 (m, 3H), 7.27–7.21 (m, 4H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.91 (ddd, *J* = 8.3, 6.9, 1.1 Hz, 1H), 6.40 (s, 1H), 3.45 (br s, 1H), 1.60 (br s, 1H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 151.9, 140.1, 137.5, 133.8, 133.6, 133.4, 133.2, 131.4, 130.4, 129.8, 129.4, 128.4, 128.3, 128.1, 127.9, 126.8, 126.7, 126.5, 126.4, 125.6, 125.4, 125.3, 125.2, 124.9, 123.8, 123.7, 123.4, 118.6, 118.1, 71.6.

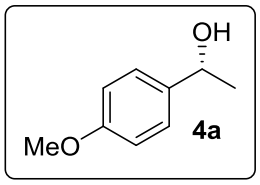
## 2.4.3.2. Catalytic asymmetric addition of organolithium reagents to aldehydes

**General procedure for the addition of organolithium reagents to aldehydes:** To a stirred solution of (*Ra*,*S*)-**L14** or **L15** (0.20 eq.) in $Et_2O$ (1.60 mL, 0.06 M), $TiCl(O^iPr)_3$ (0.28 mL, 2.80 eq., 1 M in hexane) was

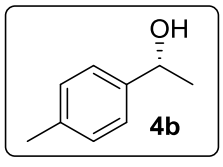
added at room temperature. The solution was stirred for 5 min and then cooled to –20 °C. Next, the organolithium reagent was added (2.00 eq., unless stated differently in the corresponding table) followed by immediate addition of the aldehyde (0.1 mmol). The reaction mixture was stirred for 10 min and the reaction was then quenched by the addition of water. The layers were separated, and the aqueous layer was extracted three times with $Et_2O$. The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated. The crude reaction product was purified by flash silica gel chromatography.




**(*R*)-1-Phenylethanol (2):**[183] Obtained as a colorless oil after column chromatography (Hex/EtOAc 5:1). **Yield:** 90%. ***ee*:** 93%. $[\alpha]_D^{24}$ = +40 (*c* 1.0, $CHCl_3$) [Lit.[183] $[\alpha]_D^{26}$ = +97 (*c* 0.28, $CHCl_3$) for 95% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.21 (m, 5H), 4.86 (q, *J* = 6.5 Hz, 1H), 2.10 (br s, 1H), 1.47 (d, *J* = 6.5 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 145.8, 128.4, 127.4, 125.3, 70.3, 25.1. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 125 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 11.3 min (major enantiomer), $t_r$(*S*) = 12.2 min.

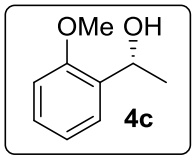



**(*R*)-1-(4-Methoxyphenyl)ethanol (4a):**[60] Obtained as a colorless oil after column chromatography (Hex/EtOAc 7:1). **Yield:** 93%. ***ee*:** 92%. $[\alpha]_D^{24}$ = +26 (*c* 1.5, $CHCl_3$) [Lit.[184] $[\alpha]_D^{20}$ = +16.5 (*c* 1.1, $CHCl_3$) for 95.5% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.85 (q, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 1.85 (br s, 1H), 1.47 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 159.0, 138.0, 126.6, 113.8, 70.0, 55.3, 25.0. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 125 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 19.8 min (major enantiomer), $t_r$(*S*) = 20.5 min.

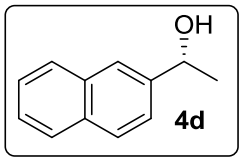



**(*R*)-1-(*4*-Methylphenyl)ethanol (4b)**:[185] Obtained as a colourless oil after column chromatography (eluent

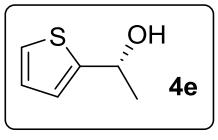
Hex/EtOAc 9:1). **Yield:** 94%. ***ee*:** 90%. **[α]$_D^{25}$** = +35 (*c* 4.0, $CHCl_3$) [Lit.[186] **[α]$_D^{26}$** = +56 (*c* 1.0, $CHCl_3$) for 96% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 4.86 (q, *J* = 6.4 Hz, 1H), 2.34 (s, 3H), 2.03 (br s, 1H), 1.48 (d, *J* = 6.5 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 142.8, 137.1, 129.1, 125.3, 70.2, 25.0, 21.1. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 125 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 13.1 min (major enantiomer), $t_r$(*S*) = 14.3 min.




**(*R*)-1-(2-Methoxyphenyl)ethanol (4c):**[183] Obtained as a colorless oil after column chromatography (Hex/EtOAc 6:1). **Yield:** 92%. ***ee*:** 44%. **[α]$_D^{24}$** = +1.7 (*c* 1, $CHCl_3$) [Lit.[183] **[α]$_D^{26}$** = +24 (*c* 0.98, $CHCl_3$) for 99% *ee*]. **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.35–7.25 (m, 2H), 6.98–6.88 (m, 2H), 5.12–5.06 (m, 1H), 3.87 (s, 3H), 2.68 (d, *J* = 5.1 Hz, 1H), 1.51 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ 156.4, 133.3, 128.2, 126.0, 120.7, 110.3, 66.4, 55.2, 22.8. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 150 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 10.6 min, $t_r$(*S*) = 12.3 min (major enantiomer).

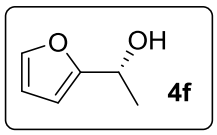



**(*R*)-1-(Naphthalen-2-yl)ethanol (4d):**[183] Obtained as a white solid after column chromatography (eluent Hex/EtOAc 8:1). **Yield:** 85%. ***ee*:** 90%. **[α]$_D^{24}$** = +27 (*c* 3.7, $CHCl_3$) [Lit.[183] **[α]$_D^{28}$** = +30 (*c* 0.97, $CHCl_3$) for 87% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.84–7.70 (m, 4H), 7.50–7.39 (m, 3H), 4.98 (q, *J* = 6.4 Hz, 1H), 2.39 (br s, 1H), 1.52 (d, *J* = 6.5 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 143.1, 133.2, 132.8, 128.2, 127.9, 127.6, 126.0, 125.7, 123.8, 123.7, 70.4, 25.0. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 150 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 55.7 min (major enantiomer), $t_r$(*S*) = 58.5 min.

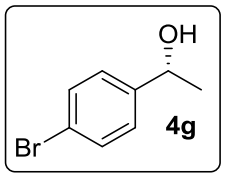



**(*R*)-1-(Thiophen-2-yl)ethanol (4e):**[183] Obtained as a volatile yellow oil after column chromatography

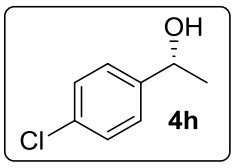
(Hex/EtOAc 6:1). **Yield:** 86%. ***ee*:** 93%. **[α]$_D^{24}$** = +6 (*c* 3.2, $CHCl_3$) [Lit.[183] **[α]$_D^{25}$** = +20 (*c* 1.04, $CHCl_3$) for 96% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.00–6.94 (m, 2H), 5.13 (q, *J* = 6.4 Hz, 1H), 2.09 (br s, 1H), 1.60 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 149.8, 126.6, 124.4, 123.2, 66.2, 25.2. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 125 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 12.1 min (major enantiomer), $t_r$(*S*) = 13.2 min.




**(*R*)-1-(Furan-2-yl)ethanol (4f):**[183] This product was volatile and could not be isolated. **Conversion:** 98%. ***ee*:** 84%. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 4.89 (q, *J* = 6.6 Hz, 1H), 1.55 (d, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 157.5, 141.9, 110.1, 105.1, 63.6, 21.2. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 100 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 10.6 min (major enantiomer), $t_r$(*S*) = 11.2 min.

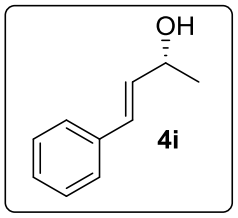



**(*R*)-1-(4-Bromophenyl)ethanol (4g):**[183] Obtained as a white solid after column chromatography (Hex/EtOAc 6:1). **Yield:** 90%. ***ee*:** 87%. **[α]$_D^{25}$** = +36 (*c* 3.3, $CHCl_3$) [Lit.[183] **[α]$_D^{20}$** = +34.6 (*c* 1.7, $CHCl_3$) for 94% *ee*]. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.42–7.40 (m, 2H), 7.15–7.12 (m, 2H), 4.73 (q, *J* = 6.3 Hz, 1H), 3.10 (br s, 1H), 1.37 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz): δ 144.6, 131.3, 127.0, 120.9, 69.4, 25.0. *ee* determination by chiral **GC** analysis, Cyclosil β 125 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 68.2 min (major enantiomer), $t_r$(*S*) = 76.3 min.

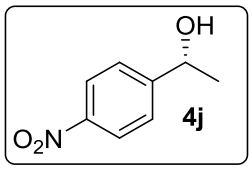



**(*R*)-1-(4-Chlorophenyl)ethanol (4h):**[183] Obtained as a yellow oil after column chromatography (Hex/EtOAc 5:1). **Yield:** 89%. ***ee*:** 86%. **[α]$_D^{25}$** = +23 (*c* 4.3, $CHCl_3$) [Lit.[183] **[α]$_D^{26}$** = +39 (*c* 1.1, $CHCl_3$) for 97% *ee*]. **$^1$H NMR** (400MHz, $CDCl_3$) δ 7.31 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 8.9 Hz, 2H), 4.86 (q, *J* = 6.5 Hz, 1H), 2.40 (br s, 1H), 1.46 (d, *J* = 6.5 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 144.2, 133.0, 128.5, 126.8, 69.7, 25.2. *ee*

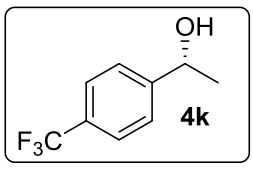
determination by chiral **GC** analysis, Cyclosil β column, T = 115 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 65.1 min (major enantiomer), $t_r$(*S*) = 72.5 min.




**(*R*,*E*)-4-Phenylbut-3-en-2-ol (4i):**[60] Obtained as a white solid after column chromatography (Hex/EtOAc 5:1). **Yield:** 94%. ***ee*:** 90%. **[α]$_D^{24}$** = +18 (*c* 1.0, $CHCl_3$) [Lit.[187] **[α]$_D^{20}$** = +23 (*c* 1.0, $CH_2Cl_2$) for 99% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 5.3, 3.2 Hz, 2H), 7.34–7.27 (m, 2H), 7.27–7.20 (m, 1H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.25 (dd, *J* = 15.9, 6.4 Hz, 1H), 4.47 (p, *J* = 6.3 Hz, 1H), 1.99 (br s, 1H), 1.36 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 136.6, 133.5, 129.3, 128.5, 127.6, 126.4, 68.8, 23.3. ee determination by chiral **HPLC** analysis, Lux 5u Cellulose 3 column, Hex/*i*-PrOH 97:2 flow = 1 mL/min, retention times: $t_r$(*S*) = 15.8 min, $t_r$(*R*) = 16.9 min (major enantiomer).

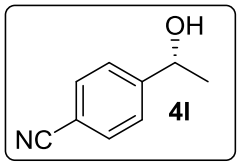



**(*R*)-1-(4-Nitrophenyl)ethanol (4j):**[188] Obtained as a colourless oil after column chromatography (Hex/EtOAc 9:1 to 7:3). Only 5 mg of **4j** were isolated pure, the rest of the product was obtained together with the ligand as they have the same retention time. **Yield:** 97%. ***ee*:** 80%. **[α]$_D^{25}$** = +12 (*c* 1.67, $CHCl_3$) [Lit.[189] **[α]$_D^{23}$** = +32.3 (*c* 1.03, $CHCl_3$) for 99% *ee*]. **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.12 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 5.00 (q, *J* = 6.9 Hz, 1H), 3.85 (br s, 1H), 1.49 (d, *J* = 6.9 Hz, 3H). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ 153.3, 146.6, 125.9, 123.4, 69.0, 25.0. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 170 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 30.2 min (major enantiomer), $t_r$(*S*) = 31.3 min.

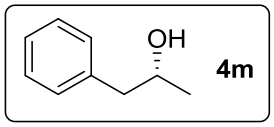



**(*R*)-1-[*4*-(Trifluoromethyl)phenyl]ethanol (4k):**[76] Obtained as a yellow oil after column chromatography (Hex/EtOAc 9:1). **Yield:** 92%. ***ee*:** 94%. **[α]$_D^{25}$** = +18 (*c 6.7*, $CHCl_3$) [Lit.[190] **[α]$_D^{20}$** = +35.3 (*c 1.56*, $CHCl_3$) for 99% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J*

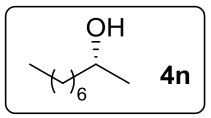
= 8.2 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 4.95 (q, *J* = 6.5 Hz, 1H), 2.16 (br s, 1H), 1.49 (d, *J* = 6.5 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 149.7, 129.8, 129.4, 125.6, 125.4, 125.4, 122.3, 69.8, 25.3. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 125 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 16.9 min (major enantiomer), $t_r$(*S*) = 18.1 min.




**(*R*)-4-(1-Hydroxyethyl)benzonitrile (4l):**[191] Obtained as a yellow oil after column chromatography (Hex/EtOAc 8:2). **Yield:** 93%. ***ee*:** 91%. **[α]$_D^{25}$** = +27.69 (*c 4.3*, $CHCl_3$) [Lit.[189] **[α]$_D^{25}$** = +43.1 (*c* 1.02, $CHCl_3$) for 96% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 4.96 (q, *J* = 6.5 Hz, 1H), 2.22 (br s, 1H), 1.49 (d, *J* = 6.5 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 151.1, 132.3, 126.0, 118.8, 111.0, 69.6, 25.4. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 200 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 38.7 min (major enantiomer), $t_r$(*S*) = 39.4 min.

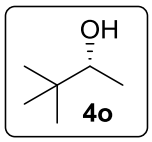



**(*R*)-1-Phenylpropan-2-ol (4m):**[192] Obtained as a colourless oil after column chromatography (Hex/EtOAc 9:1). **Yield:** 80%. ***ee*:** 73%. **[α]$_D^{25}$** = –23 (*c 4.3*, $CHCl_3$) [Lit.[193] **[α]$_D^{28}$** = –35.4 (*c 0.75*, $CHCl_3$) for 99% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 2H), 7.26–7.16 (m, 3H), 4.08–3.90 (m, 1H), 2.75 (dd, *J* = 28.1, 6.4 Hz, 1H), 2.70 (dd, *J* = 28.1, 6.4 Hz, 1H), 1.66 (br s, 1H), 1.23 (d, *J* = 6.2 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 138.5, 129.4, 128.5, 126.4, 68.8, 45.8, 22.7. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 140 °C, P = 15.9 psi, retention times: $t_r$(*S*) = 40.4 min, $t_r$(*R*) = 41.7 min (major enantiomer).

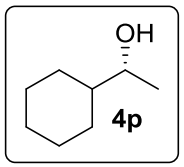



**(*R*)-2-Nonanol (4n):**[194] Obtained as a colourless oil. **Conversion:** 84%. ***ee*:** 89.5%. **IR** (ATR) 3340, 2924, 2855, 1464, 1375, 1114. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.82–3.75 (m, 1H), 1.62 (br s, 1H), 1.54–1.20 (m, 12H), 1.19 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 68.2,

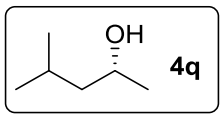
39.3, 31.8, 29.7, 29.3, 25.8, 23.5, 22.6, 14.1. *ee* was determined by chiral **GC** analysis on derivative **23**.



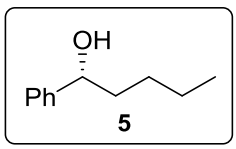

**(*R*)-3,3-Dimethylbutan-2-ol (4o):**[195] This product was volatile and could not be isolated. **Conversion:** 28%. ***ee*:** 97%. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 3.47 (q, *J* = 6.4 Hz, 1H), 1.76 (br s, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 75.6, 34.8, 25.4, 17.8. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 35 °C, P = 6 psi, retention times: $t_r$(*R*) = 95.9 min (major enantiomer), $t_r$(*S*) = 96.7 min.




**(*R*)-1-Cyclohexylethan-1-ol (4p)**:[196] This product was volatile and could not be isolated. **Conversion:** 98%. ***ee*:** 93%. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 3.54 (quint, *J* = 6.2 Hz, 1H), 1.92–1.59 (m, 6H), 1.34–1.09 (m, 7H), 1.09–0.87 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 72.2, 45.1, 28.6, 28.3, 26.5, 26.2, 26.1, 20.3. *ee* was determined by chiral **GC** analysis on derivative **24**.

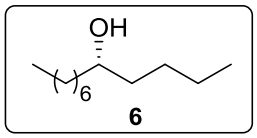



**(*R*)-4-Methylpentan-2-ol (4q)**:[83, 197] This product was volatile and could not be isolated. **Conversion:** 87%. ***ee*:** 94%. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 3.98–3.75 (m, 1H), 1.85–1.60 (m, 2H), 1.57 (br s, 1H), 1.50–1.35 (m, 1H), 1.20 (d, *J* = 3.2 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 66.1, 48.6, 24.8, 23.9, 23.1, 22.3. *ee* was determined by chiral **GC** analysis on derivative **25**.



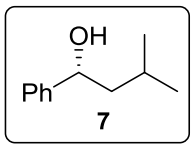

**(*R*)-1-Phenylpentan-1-ol (5):**[198] Obtained as a white solid after column chromatography (Hex/EtOAc 8:1). **Yield:** 83%. ***ee*:** 96%. **$[\alpha]_D^{24}$** = +12 (*c* 3.3, $CHCl_3$) [Lit.[198] **$[\alpha]_D^{31}$** = +39 (*c* 0.53, $CHCl_3$) for 95% *ee*]. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.43–7.21 (m, 5H), 4.64 (t, *J* = 6.6 Hz, 1H), 1.99 (br s, 1H), 1.87–1.61 (m, 2H), 1.48–1.16 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 144.9, 128.4, 127.4, 125.9, 74.6, 38.8, 28.0, 22.6, 14.0. *ee* determination by chiral **GC** analysis, Cyclosil β column, T =

125 °C, P = 15.9 psi, retention times: $t_r(S)$ = 13.5 min, $t_r(R)$ = 13.8 min (major enantiomer).



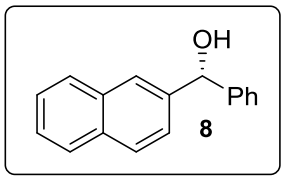
6

**(*R*)-5-Dodecanol (6):**[199] Obtained as a colourless oil. **Conversion:** 78%. ***ee*:** 91%. **IR** (ATR) 3370, 2925, 2855, 1466, 1278. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.68–3.54 (m, 1H), 1.63 (br s, 1H), 1.65–1.20 (m, 18H), 0.96–0.84 (m, 6H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 72.0, 37.5, 37.1, 31.8, 29.7, 29.3, 27.8, 25.6, 22.7, 22.6, 14.1, 14.0. *ee* was determined by chiral **GC** analysis on derivative **26**.



7

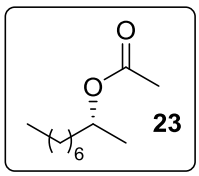
**(*R*)-3-Methyl-1-phenylbutan-1-ol (7)**:[200] Obtained as a white solid after column chromatography (Hex/EtOAc 10:1). **Yield:** 91%. ***ee*:** 60%. **$[\alpha]_D^{24}$** = +17 (*c* 2.3, $CHCl_3$) [Lit.[200] **$[\alpha]_D^{25}$** = +45 (*c* 1, $CH_2Cl_2$) for 94% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.79–4.70 (m, 1H), 1.85 (br s, 1H), 1.78–1.63 (m, 2H), 1.57–1.44 (m, 1H), 0.96 (d, *J* = 1.4 Hz, 3H), 0.94 (d, *J* = 1.5 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 145.2, 128.5, 127.5, 125.8, 72.8, 48.3, 24.8, 23.1, 22.2. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 125 °C, P = 6 psi, retention times: $t_r(S)$ = 40.7 min, $t_r(R)$ = 41.9 min (major enantiomer).



8

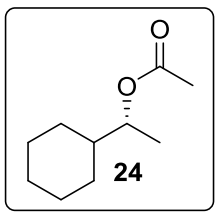
**(*R*)-Naphthalen-2-yl(phenyl)methanol (8):**[201] Obtained as a white solid after column chromatography (Hex/EtOAc 95:5). **Yield:** 91%. ***ee*:** 13%. **$[\alpha]_D^{25}$** = −1.40 (*c* 14.3, $CHCl_3$) [Lit.[202] **$[\alpha]_D^{20}$** = −5.99 (*c* 1.5, $CHCl_3$) for 92% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.83–7.61 (m, 4H), 7.47–7.36 (m, 2H), 7.36–7.15 (m, 6H), 5.81 (s, 1H), 2.87 (br s, 1H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 143.5, 141.0, 133.1, 132.8, 128.4, 128.2, 128.0, 127.6, 127.5, 126.6, 126.1, 125.9, 125.0, 124.7, 76.2. ee determination by chiral **HPLC** analysis, Lux 5u Cellulose-1 column, Hex/$^i$PrOH 95:5 flow = 1 mL/min, retention times: $t_r(S)$ = 27.0 min, $t_r(R)$ = 33.7 min (major enantiomer).

**General procedure for the synthesis of acetates derivatives 23-26:** In a flame dried Schlenk tube, the corresponding aliphatic alcohol [**4n**, **4p**, **4q**, or **6**] (0.10 mmol) was dissolved in anhydrous DCM (1 mL, 0.1 M) at 0 °C and $Et_3N$ (28 µL, 0.20 mmol, 2.0 eq.), DMAP (1.3 mg, 0.01 mmol, 0.1 eq.) and acetic anhydride (22 µL, 0.20 mmol, 2.0 eq.) were added sequentially. The reaction mixture was stirred at RT for 12 h. The reaction was quenched with water (1 mL), extracted with $Et_2O$ (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by chromatographic column to provide the desired products **23-26**.



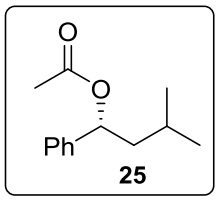
**23**

**(*R*)-Nonan-2-yl acetate (23):**[203] Obtained as a colourless oil after purification by column chromatography (eluent Hex/EtOAc 97:3) as colorless oil. **Yield**: 84%. ***ee*:** 91%. **$[\alpha]_D^{25}$** = –3.75 (*c* 5.3, $CHCl_3$). **IR** (ATR) 2926, 2856, 1736, 1371, 1239. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.94–4.82 (m, 1H), 2.03 (s, 3H), 1.64–1.40 (m, 2H), 1.38–1.14 (m, 10H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 170.8, 71.1, 35.9, 31.8, 29.4, 29.2, 25.4, 22.6, 21.4, 19.9, 14.1. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 125 °C, P = 15.9 psi, retention time: $t_r$(*S*) = 9.3 min, $t_r$(*R*) = 10.0 min (major enantiomer).



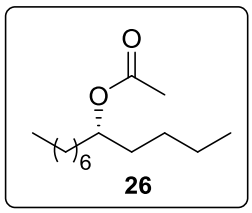
**24**

**(*R*)-1-Cyclohexylethyl acetate (24):**[204] This product was volatile and could not be isolated. ***ee*:** 93%. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.72 (quint, *J* = 6.4 Hz, 1H), 2.04 (s, 3H), 1.80–1.61 (m, 5H), 1.43 (m, 1H), 1.27–1.09 (m, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.07–0.90 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 171.0, 74.7, 42.5, 28.4, 26.3, 26.0, 25.9, 20.92, 17.0. *ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 100 °C, P = 6 psi, retention time: $t_r$(*S*) = 27.3 min, $t_r$(*R*) = 35.6 min (major enantiomer).



25

**(*R*)-4-Methylpentan-2-yl acetate (25):**[205] The product was volatile and could not be isolated. *ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 100 °C, P = 6 psi, retention time: $t_r$(*S*) = 4.9 min, $t_r$(*R*) = 5.3 min (major enantiomer).

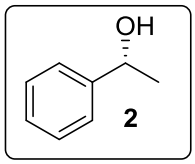


26

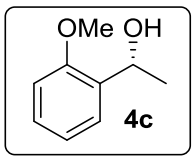
**(*R*)-Dodecan-5-yl acetate (26):** Obtained as a yellow oil after purification by column chromatography (Hex/EtOAc 97:3). **Yield:** 78%. ***ee*:** 91%. **[α]$_D^{25}$** = –2.4 (*c* 8.3, $CHCl_3$). **IR** (ATR) 2955, 2926, 2858, 1737, 1236, 1019. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.86 (quint, *J* = 6.4 Hz, 1H), 2.04 (s, 3H), 1.57–1.44 (m, 4H), 1.38–1.18 (m, 14H), 0.94–0.82 (m, 6H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 171.0, 74.4, 34.1, 33.8, 31.8, 29.5, 29.2, 27.5, 25.3, 22.6, 22.6, 21.3, 14.1, 14.0. **HRMS** (+ESI): m/z calculated for $C_{14}H_{28}O_2Na$ $[M+Na]^+$: 251.1987. Found: 251.1975. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 115 °C, P = 6 psi, retention time: $t_r$(*S*) = 51.4 min, $t_r$(*R*) = 52.2 min (major enantiomer).

### 2.4.3.3. Catalytic enantioselective addition of methyltriisopropoxititanium to aldehydes

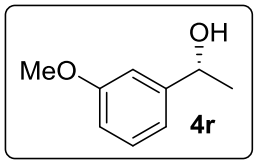
**General procedure for the addition of methyltriisopropoxititanium to aldehydes:** To a stirred solution of (*R*$_a$,*S*)-**L$_{14}$** or **L$_{15}$** (0.2 eq.) in $Et_2O$ (3.0 mL, 0.07 M) at 0 °C, MeTi(O$^i$Pr)$_3$ (0.3 mL, 1.5 eq. 0.5 M in THF, unless stated differently in the corresponding table) was added. The solution was stirred for 1 min and then the aldehyde (0.10 mmol) was added. The reaction was stirred for 10 min and then quenched with water. The layers were separated and the aqueous layer was extracted three times with $Et_2O$. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The reaction crude was purified by flash silica gel chromatography.



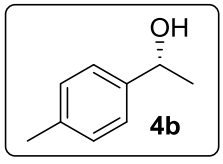

**(*R*)-1-Phenylethanol (2):**[183] Obtained as a colorless oil after column chromatography (Hex/EtOAc 6:1). **Yield:** 96%. ***ee*:** 96%. $[\alpha]_D^{24}$ = +47 (*c* 0.7, $CHCl_3$) [Lit.[183] $[\alpha]_D^{26}$ = +97 (*c* 0.3, $CHCl_3$) for 95% *ee*]. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 100 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 30.9 min (major enantiomer), $t_r$(*S*) = 34.8 min.



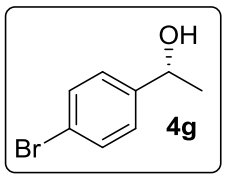

**(*R*)-1-(2-Methoxyphenyl)ethanol (4c):**[183] Obtained as a colorless oil after column chromatography (Hex/EtOAc 7:1). **Yield:** 95%. ***ee*:** 56%. $[\alpha]_D^{24}$ = +33 (*c* 0.3, $CHCl_3$) [Lit.[183] $[\alpha]_D^{26}$ = +24 (*c* 1.0, $CHCl_3$) for 99% *ee*]. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 150 °C, P = 15.9 psi, retention times: $t_r$(*R*) = 9.1 min, $t_r$(*S*) = 10.4 min (major enantiomer).



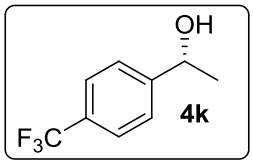

**(*R*)-1-(3-Methoxyphenyl)ethanol (4r):**[206] Obtained as a colorless oil after column chromatography (Hex/EtOAc 7:1). **Yield:** 92%. ***ee*:** 99.5%. $[\alpha]_D^{24}$ = +28 (*c* 1.0, $CHCl_3$) [Lit.[206] $[\alpha]_D^{20}$ = +51.2 (*c* 1.0, $CHCl_3$) for 96% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8.0 Hz, 1H), 6.94 (m, 2H), 6.98–6.75 (m, 1H), 4.86 (q, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 1.99 (s, 1H), 1.48 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 159.8, 147.6, 129.6, 117.7, 112.9, 110.9, 70.3, 55.2, 25.2. *ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 125 °C, P = 6 psi, retention times: $t_r$(*R*) = 45.1 min (major enantiomer), $t_r$(*S*) = 49.4 min.



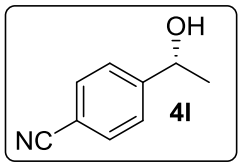

**(*R*)-1-(*4*-Methylphenyl)ethanol (4b)**:[185] Obtained as a colourless oil after column chromatography (eluent Hex/EtOAc 9:1). **Yield:** 96%. ***ee*:** 93%. $[\alpha]_D^{25}$ = +39.4 (*c* 0.7, $CHCl_3$) [Lit.[186] $[\alpha]_D^{26}$ = +56 (*c* 1.0, $CHCl_3$) for 96% *ee*]. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 130 °C, P = 6 psi, retention times: $t_r$(*R*) = 14.7 min (major enantiomer), $t_r$(*S*) = 16.4 min.



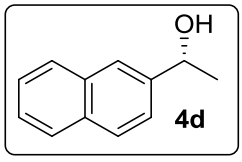

**(*R*)-1-(4-Bromophenyl)ethanol (4g):**[183] Obtained as a white solid after column chromatography (Hex/EtOAc 6:1). **Yield:** 90%. ***ee*:** 97%. $[\alpha]_D^{25}$ = +28 (*c* 0.4, $CHCl_3$) [Lit.[183] $[\alpha]_D^{20}$ = +34.6 (*c* 1.7, $CHCl_3$) for 94% *ee*]. *ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, 140 °C, P = 6 psi, retention times: $t_r$(*R*) = 34.3 min (major enantiomer), $t_r$(*S*) = 39.3 min.



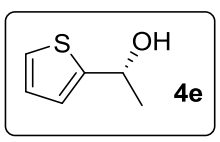

**(*R*)-1-[*4*-(Trifluoromethyl)phenyl]ethanol (4k):**[76] Obtained as a yellow oil after column chromatography (Hex/EtOAc 9:1). **Yield:** 89%. ***ee*:** 95%. $[\alpha]_D^{25}$ = +28.9 (*c 0.9*, $CHCl_3$) [Lit.[190] $[\alpha]_D^{20}$ = +35.3 (*c 1.6*, $CHCl_3$) for 99% *ee*]. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 140 °C, P = 6 psi, retention times: $t_r$(*R*) = 10.9 min (major enantiomer), $t_r$(*S*) = 12.5 min.




**(*R*)-4-(1-Hydroxyethyl)benzonitrile (4l):**[191] Obtained as a yellow oil after column chromatography (Hex/EtOAc 8:2). **Yield:** 94%. ***ee*:** 96%. $[\alpha]_D^{25}$ = +35.3 (*c 0.9*, $CHCl_3$) [Lit.[189] $[\alpha]_D^{25}$ = +43.1 (*c 1.02*, $CHCl_3$) for 96% *ee*]. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 170 °C, P = 6 psi, retention times: $t_r$(*R*) = 18.8 min (major enantiomer), $t_r$(*S*) = 21.0 min.

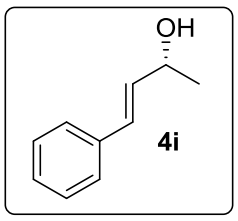



**(*R*)-1-(Naphthalen-2-yl)ethanol (4d):**[183] Obtained as a white solid after column chromatography (eluent Hex/EtOAc 8:1). **Yield:** 92%. ***ee*:** 84%. $[\alpha]_D^{24}$ = +31 (*c* 0.4, $CHCl_3$) [Lit.[183] $[\alpha]_D^{28}$ = +30 (*c* 0.97, $CHCl_3$) for 87% *ee*]. *ee* determination by chiral **HPLC** analysis, Lux 5u Cellulose 3 column, Hex/*i*-PrOH 97:3 flow = 1 mL/min, retention times: $t_r$(*S*) = 29.7 min, $t_r$(*R*) = 38.7 min (major enantiomer).

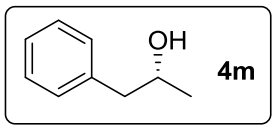



**(*R*)-1-(Thiophen-2-yl)ethanol (4e):**[183] Obtained as a volatile colorless oil after column chromatography

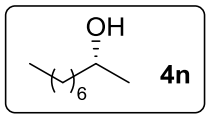
(Hex/EtOAc 6:1). **Yield:** 95%. ***ee*:** 94%. **[α]$_D^{24}$** = +12.5 (*c* 0.8, $CHCl_3$) [Lit.[183] **[α]$_D^{25}$** = +20 (*c* 1.04, $CHCl_3$) for 96% *ee*]. *ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 125 °C, P = 6 psi, retention times: $t_r$(*R*) = 14.5 min (major enantiomer), $t_r$(*S*) = 15.9 min.



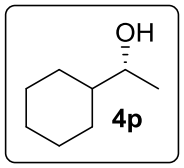

**(*R*,*E*)-4-Phenylbut-3-en-2-ol (4i):**[207] Obtained as a white solid after column chromatography (Hex/EtOAc 5:1). **Yield:** 88%. ***ee*:** 82%. **[α]$_D^{24}$** = +35 (*c* 0.6, $CHCl_3$) [Lit.[187] **[α]$_D^{20}$** = +23 (*c* 1.0, $CH_2Cl_2$) for 99% *ee*]. *ee* determination by chiral **HPLC** analysis, Lux 5u Cellulose 3 column, Hex/$^i$PrOH 97:3 flow = 1 mL/min, retention times: $t_r$(*S*) = 14.2 min, $t_r$(*R*) = 15.3 min (major enantiomer).



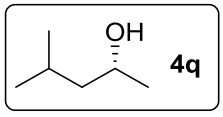

**(*R*)-1-Phenylpropan-2-ol (4m):**[192] Obtained as a colourless oil after column chromatography (Hex/EtOAc 9:1). **Yield:** 93%. ***ee*:** 85%. **[α]$_D^{25}$** = −35.4 (*c 0.7*, $CHCl_3$) [Lit.[193] **[α]$_D^{28}$** = −35.4 (*c 0.8*, $CHCl_3$) for 99% *ee*]. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 85 °C, P = 15.9 psi, retention times: $t_r$(*S*) = 76.0 min, $t_r$(*R*) = 78.2 min (major enantiomer).



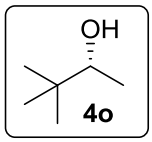

**(*R*)-2-Nonanol (4n):**[194] Obtained as a colourless oil. **Conversion:** 99%. ***ee*:** 90%. **IR** (ATR) 3340, 2924, 2855, 1464, 1375, 1114. *ee* was determined by chiral **GC** analysis on derivative **23**.




**(*R*)-1-Cyclohexylethan-1-ol (4p)**:[196] This product was volatile and could not be isolated. **Conversion:** 99%. ***ee*:** 94%. *ee* was determined by chiral **GC** analysis on derivative **24**.

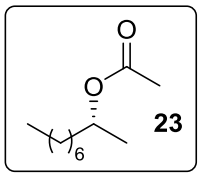



**(*R*)-4-Methylpentan-2-ol (4q)**:[83, 197] This product was volatile and could not be isolated. **Conversion:** 77%. ***ee*:** 90%. *ee* was determined by chiral **GC** analysis on derivative **25**.

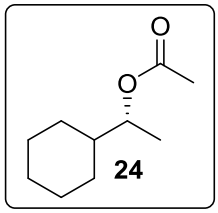



**(*R*)-3,3-Dimethylbutan-2-ol (4o):**[195] This product was volatile and could not be isolated. **Conversion:** 78%. ***ee*:** 93%. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 35 °C, P = 6 psi, retention times: $t_r$(*R*) = 96.3 min (major enantiomer), $t_r$(*S*) = 97.0 min.

**General procedure for the synthesis of acetates derivatives:** In a flame dried Schlenk tube, the corresponding aliphatic alcohol [**4n**, **4p**, or **4q**] (0.20 mmol) was dissolved in anhydrous DCM (2 mL, 0.1 M) at 0 °C and $Et_3N$ (56 µL, 0.40 mmol, 2.0 eq.), DMAP (2.6 mg, 0.02 mmol, 0.1 eq.) and acetic anhydride (44 µL, 0.40 mmol, 2.0 eq.) were added sequentially. The reaction mixture was stirred at RT for 12 h. The reaction was quenched with water (2 mL), extracted with $Et_2O$ (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by chromatographic column to provide the desired products **23-25**.

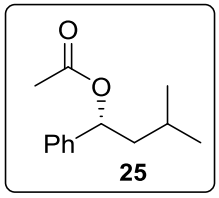



**(*R*)-Nonan-2-yl acetate (23):**[203] Obtained as a colourless oil after purification by column chromatography (eluent Hex/EtOAc 97:3). **Yield**: 95%. ***ee*:** 90%. **$[\alpha]_D^{25}$** = –5.6 (*c* 0.9, $CHCl_3$). [Lit.[178] **$[\alpha]_D^{25}$** = –3.8 (*c 5.3*, $CHCl_3$) for 91% *ee*]. **IR** (ATR) 2926, 2856, 1736, 1371, 1239. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.94–4.82 (m, 1H), 2.03 (s, 3H), 1.64–1.40 (m, 2H), 1.38–1.14 (m, 10H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 170.8, 71.1, 35.9, 31.8, 29.4, 29.2, 25.4, 22.6, 21.4, 19.9, 14.1. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 125 °C, P = 6 psi, retention times: $t_r$(*S*) = 10.6 min, $t_r$(*R*) = 11.9 min (major enantiomer).




**(*R*)-1-Cyclohexylethyl acetate (24):**[204] This product was volatile and could not be isolated. ***ee*:** 94%. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.72 (quint, *J* = 6.4 Hz, 1H), 2.04 (s, 3H), 1.80–1.61 (m, 5H), 1.43 (m, 1H), 1.27–1.09 (m, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.07–0.90 (m, 2H). **$^{13}$C NMR**

(100.6 MHz, $CDCl_3$) δ 171.0, 74.7, 42.5, 28.4, 26.3, 26.0, 25.9, 20.92, 17.0. *ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 100 °C, P = 6 psi, retention time: $t_r(S)$ = 27.7 min, $t_r(R)$ = 34.3 min (major enantiomer).



25

**(*R*)-4-Methylpentan-2-yl acetate (25):**[205] This product was volatile and could not be isolated. *ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 100 °C, P = 6 psi, retention time: $t_r(S)$ = 4.9 min, $t_r(R)$ = 5.3 min (major enantiomer).

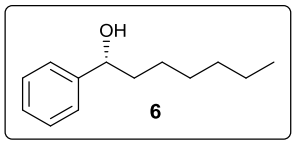
### 2.4.3.4. Catalytic enantioselective 1,2-addition of alkenes to aldehydes

**General procedure for the catalytic enantioselective 1,2-addition of alkenes to aldehydes:** To a stirred suspension of $Cp_2ZrHCl$ (77 mg, 0.30 mmol, 2.0 eq.) in dry DCM (0.3 mL) at RT, the corresponding alkene (0.33 mmol, 2.2 eq.) was added dropwise and the solution was stirred at RT for 30 min. The mixture turned into a clear yellow solution, which indicates the successful formation of the organozirconium reagent. Next, flame dried $ZnBr_2$ (0.08 mmol, 0.5 eq.) was added into the solution and the mixture was stirred at RT for 2 min. Subsequently, a solution of $Ti(O^iPr)_4$ (0.23 mmol, 1.5 eq.) and ($R_a$,*S*)-**$L_{14}$** (20 mol%) in dry DCM (0.1 mL) was added into the schlenk flask and stirred for further 2 min at RT. Finally, the aldehyde (0.15 mmol) was added and the solution was stirred at 35 °C for 18 h.

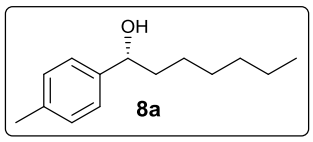
In cases where the aldehyde was a liquid, this was previously distilled before its addition. Whereas with the solid ones, the aldehyde was dissolved in dry DCM (0.1 or 0.2 mL depending on its solubility) and added to the solution.

The reaction was quenched by the addition of water (1 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$,

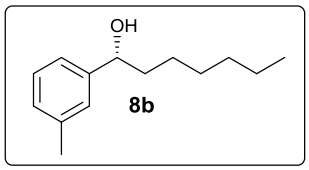
filtered and concentrated under vacuum. The crude reaction product was purified by flash silica gel chromatography.




**(*R*)-1-phenylheptanol (6):**[208, 209] Obtained as a colourless oil after purification by column chromatography (Hex/EtOAc 95:5). **Yield:** 87%. ***ee*:** 91%. **$[\alpha]_D^{25}$** = +16.7 (*c* 8.4, $CHCl_3$). [lit.[212] **$[\alpha]_D^{25}$** = +31.8 (*c* 1.1, $CHCl_3$) for 99% *ee*]. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.24 (m, 5H), 4.68–4.55 (m, 1H), 2.76 (s, 1H), 1.95–1.65 (m, 2H), 1.48–1.25 (m, 8H), 0.95 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 145.1, 128.4, 127.4, 126.0, 74.6, 39.2, 31.9, 29.3, 25.8, 22.7, 14.1. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 150 °C, P = 15.9 psi, retention times: $t_r$(*S*) = 28.7 min, $t_r$(*R*) = 31.2 min (major enantiomer).

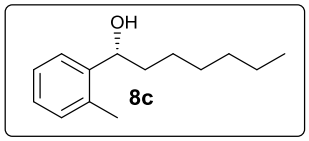



**(*R*)-1-p-tolylheptan-1-ol (8a):**[210] Obtained as a white solid after purification by column chromatography (Hex/EtOAc 95:5). **Yield:** 74%. ***ee*:** 91%. **$M_p$** = 34–37 °C. **$[\alpha]_D^{25}$** = +18.7 (*c* 7.5, $CHCl_3$). [lit.[210] **$[\alpha]_D^{26}$** = +27.7 (*c* 1.1, $CHCl_3$) for 89% *ee*]. **IR** (ATR) 3344, 2924, 2855, 1456, 1041, 816. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.25–7.10 (m, 4H), 4.65–4.58 (m, 1H), 2.34 (s, 3H), 1.80–1.60 (m, 2H), 1.45–1.28 (m, 8H), 0.86 (t, *J* = 7.6 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 142.0, 137.1, 129.1, 125.8, 74.5, 39.0, 31.7, 29.2, 25.8, 22.6, 21.1, 14.1. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 140 °C, P = 6 psi, retention times: $t_r$(*R*) = 73.3 min (major enantiomer), $t_r$(*S*) = 75.7 min.

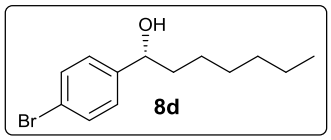



**(*R*)-1-m-tolylheptan-1-ol (8b):** Obtained as a yellowish oil after purification by column chromatography (Hex/EtOAc 95:5). **Yield:** 34%. ***ee*:** 88%. **$[\alpha]_D^{25}$** = +19.3 (*c* 5.7, $CHCl_3$). **IR** (ATR) 3348, 2925, 2856, 1457, 784, 702. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.05 (m, 4H), 4.65–4.57 (m, 1H), 2.35 (s, 3H), 1.85 (s broad, 1H), 1.83–1.60 (m, 2H), 1.45–1.20 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 145.1, 138.2, 128.4, 128.3, 126.7, 123.1, 74.9,

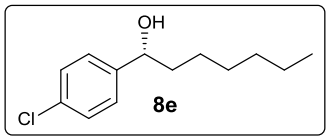
39.2, 31.9, 29.3, 26.0, 22.7, 21.6, 14.2. **HRMS** (+ESI): m/z calculated for $C_{14}H_{22}ONa$ $[M+Na]^+$: 229.1563. Found: 229.1562. *ee* determination by chiral **HPLC** analysis, Phenomenex® Lux Cellulose-1, Hex/*i*-PrOH 95:5 flow = 1 mL/min, retention times: $t_r(R)$ = 7.9 min (major enantiomer), $t_r(S)$ = 8.9 min.




**(*R*)-1-o-tolylheptan-1-ol (8c):**[211] Obtained as a yellowish oil after purification by column chromatography (Hex/EtOAc 95:5). **Yield:** 49%. ***ee*:** 75%. **$[\alpha]_D^{25}$** = +28.6 (*c* 4.9, $CHCl_3$). **IR** (ATR) 3347, 2925, 2855, 1459, 1043, 754. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.50–7.10 (m, 4H), 4.95–4.88 (m, 1H), 2.33 (s, 3H), 1.78 (s broad, 1H), 1.75–1.60 (m, 2H), 1.55–1.22 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 143.2, 134.6, 130.5, 127.2, 126.4, 125.2, 70.9, 38.3, 31.9, 29.4, 26.2, 22.8, 19.2, 14.2. *ee* determination by chiral **HPLC** analysis, Phenomenex® Lux Cellulose-1, Hex/*i*-PrOH 95:5 flow = 1 mL/min, retention times: $t_r(R)$ = 8.9 min (major enantiomer), $t_r(S)$ = 9.5 min.

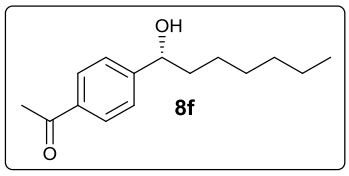



**(*R*)-1-(4-bromophenyl)heptan-1-ol (8d):**[211] Obtained as a white solid after purification by column chromatography (Hex/EtOAc 95:5). **Yield:** 56%. ***ee*:** 91%. **$M_p$** = 35–37 °C. **$[\alpha]_D^{25}$** = +18.6 (*c* 7.5, $CHCl_3$). [lit.[212] **$[\alpha]_D^{25}$** = +23.3 (*c* 0.6, $CHCl_3$) for 99% *ee*]. **IR** (ATR) 3299, 2920, 2851, 1483, 1404, 1007. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.50–7.16 (m, 4H), 4.66–4.58 (m, 1H), 1.91 (s broad, 1H), 1.82–1.58 (m, 2H), 1.45–1.15 (m, 8H), 0.87 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 144.0, 131.6, 127.8, 121.3, 74.2, 39.2, 31.9, 29.3, 25.8, 22.7, 14.2. *ee* determination by chiral **HPLC** analysis, Phenomenex® Lux Cellulose-1, Hex/*i*-PrOH 95:5 flow = 1 mL/min, retention times: $t_r(R)$ = 8.9 min (major enantiomer), $t_r(S)$ = 9.5 min.

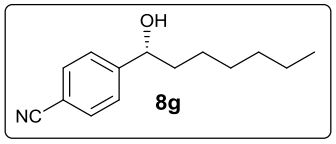



**(*R*)-1-(4-chlorophenyl)heptan-1-ol (8e):**[210] Obtained as a white solid after purification by

column chromatography (Hex/EtOAc 95:5 to 90:10). **Yield:** 59%. ***ee*:** 90%. **$M_p$** = 33–35 °C. **$[\alpha]_D^{25}$** = +18.1 (*c* 6.6, $CHCl_3$). [lit.[212] **$[\alpha]_D^{25}$** = +26.1 (*c* 0.3, $CHCl_3$) for 99% *ee*]. **IR** (ATR) 3280, 2923, 2854, 1466, 1089, 827. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.22 (m, 4H), 4.68–4.60 (m, 1H), 1.89 (s broad, 1H), 1.82–1.58 (m, 2H), 1.44–1.18 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 143.5, 133.2, 128.7, 127.4, 74.1, 39.3, 31.9, 29.3, 25.8, 22.7, 14.2. *ee* determination by chiral **HPLC** analysis, Phenomenex® Lux Cellulose-1, Hex/*i*-PrOH 95:5 flow = 1 mL/min, retention times: $t_r$(*R*) = 7.3 min (major enantiomer), $t_r$(*S*) = 7.8 min.

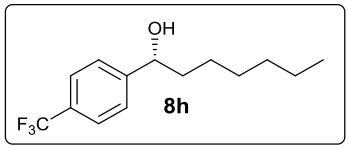



**(*R*)-1-[4-(1-oxidanylheptyl)phenyl]ethanone (8f):** Obtained as a white solid after purification by column chromatography (Hex/EtOAc 80:20). **Yield:** 32%. ***ee*:** 91%. **$M_p$** = 37–39 °C. **$[\alpha]_D^{25}$** = +15.8 (*c* 3.8, $CHCl_3$). **IR** (ATR) 3283, 2925, 2854, 1678, 1606, 1266. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 4.78–4.70 (m, 1H), 2.60 (s, 3H), 1.98 (s broad, 1H), 1.85–1.64 (m, 2H), 1.46–1.18 (m, 8H), 0.87 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 198.0, 150.4, 136.5, 128.7, 126.1, 74.3, 39.4, 31.9, 29.3, 26.8, 25.7, 22.7, 14.2. **HRMS** (+ESI): m/z calculated for $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1693. Found: 235.1693. *ee* determination by chiral **HPLC** analysis, Phenomenex® Lux Cellulose-1, Hex/*i*-PrOH 95:5 flow = 1 mL/min, retention times: $t_r$(*R*) = 18.4 min (major enantiomer), $t_r$(*S*) = 19.5 min.

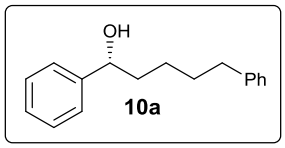



**(*R*)-4-(hydroxyheptyl)-benzonitrile (8g):**[213] Obtained as a colourless oil after purification by column chromatography (Hex/EtOAc 95:5 to 80:20). **Yield:** 58%. ***ee*:** 87%. **$[\alpha]_D^{25}$** = +17.5 (*c* 6.3, $CHCl_3$). **IR** (ATR) 3433, 2927, 2856, 2228, 1609, 839, 732. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 4.78–4.70 (m, 1H), 2.07 (s broad, 1H), 1.82–1.58 (m, 2H), 1.46–1.18 (m, 8H),

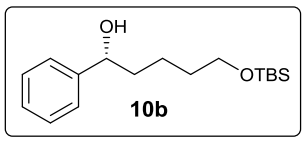
0.87 (t, *J* = 6.8 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 150.3, 132.3, 126.5, 118.9, 111.1, 73.8, 39.3, 31.7, 29.1, 25.5, 25.6, 14.0. *ee* determination by chiral **HPLC** analysis, Phenomenex® Lux Cellulose-1, Hex/*i*-PrOH 95:5 flow = 0.5 mL/min, retention times: $t_r$(*R*) = 30.9 min (major enantiomer), $t_r$(*S*) = 32.8 min.




**(*R*)-1-[4-(trifluoromethyl)phenyl]heptan-1-ol (8h):**[214] Obtained as a yellowish oil after purification by column chromatography (Hex/EtOAc 95:5). **Conversion:** 69%. ***ee*:** 87%. *ee* was determined by chiral **HPLC** analysis on derivative **27**. **IR** (ATR) 3336, 2929, 2858, 1620, 1323, 1122. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 4.78–4.70 (m, 1H), 1.95 (s broad, 1H), 1.84–1.64 (m, 2H), 1.48–1.20 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 148.9, 129.6 (q, *J* = 128.8 Hz), 126.1, 125.4 (q, *J* = 14.8 Hz), 122.8, 74.0, 39.3, 31.7, 29.1, 25.6, 22.6, 14.1.

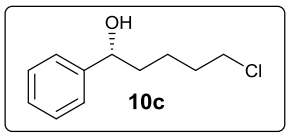



**(*R*)-1,5-Diphenyl-pentan-1-ol (10a):**[215] Obtained as a colourless oil after purification by column chromatography (Hex/EtOAc 90:10). **Yield:** 93%. ***ee*:** 77%. **$[\alpha]_D^{25}$** = +5.4 (*c* 11.2, $CHCl_3$). **IR** (ATR) 3381, 2931, 2856, 1494, 1452, 696. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.13 (m, 10H), 4.72–4.62 (m, 1H), 2.59 (t, *J* = 8.0 Hz, 2H), 1.89–1.60 (m, 4H), 1.53–1.43 (m, 1H), 1.40–1.25 (m, 1H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 144.8, 142.6, 128.5, 128.4, 128.3, 127.5, 125.9, 125.6, 74.6, 38.9, 35.8, 31.4, 25.5. *ee* determination by chiral **GC** analysis, Cyclosil β column, T = 180 °C, P = 15.9 psi, retention times: $t_r$(*S*) = 20.0 min, $t_r$(*R*) = 20.5 min (major enantiomer).



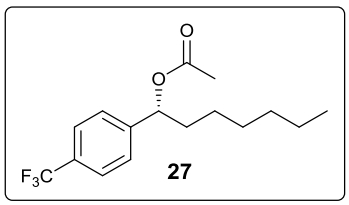

**(*R*)-5-(tert-butyl-dimethyl-silanyloxy)-1-phenyl-pentan-1-ol (10b):**[216, 217] Obtained as a yellowish oil after purification by column chromatography (Hex/EtOAc 95:5). **Yield:** 42%. ***ee*:** 88%. **$[\alpha]_D^{25}$** = +13.3 (*c* 6.0, $CHCl_3$). **IR** (ATR) 3376, 2927, 2856, 1253, 1096, 833. **$^{1}$H**

**NMR** (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5H), 4.70–4.64 (m, 1H), 3.59 (t, *J* = 6.4 Hz, 2H), 1.95 (s broad, 1H), 1.88–1.26 (m, 6H), 0.87 (s, 9H), 0.03 (s, 6H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 145.0, 128.6, 127.6, 126.0, 74.8, 63.2, 39.0, 32.7, 29.8, 26.1, 22.3, 18.5, –5.1. *ee* determination by chiral **HPLC** analysis, Phenomenex® Lux Cellulose-1, Hex/*i*-PrOH 95:5 flow = 0.5 mL/min, retention times: $t_r$(*R*) = 13.3 min (major enantiomer), $t_r$(*S*) = 15.0 min.




**(*R*)-5-chloro-1-phenylpentanol (10c):**[218] Obtained as a colourless oil after purification by column chromatography (Hex/EtOAc 95:5 to 90:10). **Conversion:** 75%. ***ee*:** 86%. *ee* was determined by chiral **HPLC** analysis on derivative **10c'**. **IR** (ATR) 3355, 2918, 2863, 1453, 1027, 699. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 4.68 (dd, *J* = 5.6, 7.6 Hz, 1H), 3.52 (t, *J* = 6.4 Hz, 2H), 1.89 (s broad, 1H), 1.88–1.36 (m, 6H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 144.6, 128.5, 127.7, 125.8, 74.4, 44.9, 38.2, 32.5, 23.2.

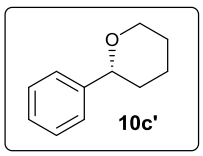
**General procedure for the synthesis of acetates derivatives:** In a flame dried Schlenk tube, the aliphatic alcohol **8h** (0.20 mmol) was dissolved in anhydrous DCM (2 mL, 0.1 M) at 0 °C and $Et_3N$ (56 µL, 0.40 mmol, 2.0 eq.), DMAP (2.6 mg, 0.02 mmol, 0.1 eq.) and acetic anhydride (44 µL, 0.40 mmol, 2.0 eq.) were added sequentially. The reaction mixture was stirred at RT for 12 h. The reaction was quenched with water (2 mL), extracted with $Et_2O$ (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by chromatographic column to provide **27**.




**(*R*)-1-[4-(trifluoromethyl)phenyl]heptan-1-yl acetate (27):** Obtained as a yellowish oil after purification by column chromatography (Hex/EtOAc 98:2). **Yield**: 55%. ***ee*:** 87%. **$[\alpha]_D^{25}$** = +29.5 (*c* 8.1, $CHCl_3$). **IR** (ATR) 2930, 2859, 1739, 1622, 1323, 1123. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* =

8.0 Hz, 2H), 5.78–5.70 (m, 1H), 2.08 (s, 3H), 1.98–1.66 (m, 2H), 1.40–1.16 (m, 8H), 0.87 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 170.3, 144.9, 130.0 (q, *J* = 129.2 Hz), 126.7, 125.4 (q, *J* = 14.8 Hz), 122.7, 75.5, 36.3, 31.6, 28.9, 25.3, 22.5, 21.2, 14.0. **HRMS** (+ESI): m/z calculated for $C_{16}H_{25}NO_2F_3$ $[M+NH_4]^+$: 320.1839. Found: 320.1837. *ee* determination by chiral **HPLC** analysis, Phenomenex® Lux Cellulose-1, Hexane 100 flow = 0.5 mL/min, retention times: $t_r$(*R*) = 21.4 min (major enantiomer), $t_r$(*S*) = 22.5 min.

**General procedure for the synthesis of 2-substituted chiral tetrahydropyrans:** In a flame dried Schlenk tube, the corresponding chiral 4-chlorobutyl alcohol **10c** (0.15 mmol) was dissolved in anhydrous THF (1.5 mL). Then, KO$^t$Bu (50 mg, 0.45 mmol, 3 eq.) was added to the previous solution and the resulting suspension was stirred at RT for 18 h. The reaction was quenched with water (2 mL) and the crude was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by chromatographic column to provide **10c'**.

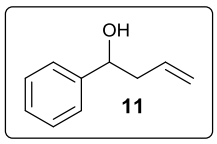



**(*R*)-2-Phenyltetrahydro-2*H*-pyran (10c'):**[219, 220] Obtained as a yellowish oil after purification by column chromatography (Hex/EtOAc 95:5). **Yield**: 84%. ***ee*:** 86%. **$[\alpha]_D^{25}$** = +21.4 (*c* 1.4, $CHCl_3$). **IR** (ATR) 2934, 2844, 1604, 1451, 1087, 697. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5H), 4.32 (dd, *J* = 11.2, 2.2 Hz, 1H), 4.18–3.58 (m, 1H), 3.62 (td, *J* = 11.6, 2.4 Hz, 1H), 1.98–1.89 (m, 1H), 1.87–1.78 (m, 1H), 1.76–1.52 (m, 4H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 143.3, 128.2, 127.2, 125.8, 80.1, 69.0, 34.0, 25.9, 24.0. *ee* determination by chiral **HPLC** analysis, Chiralcel® OJ-H, Hex/$^i$PrOH 95:5 flow = 0.5 mL/min, retention times: $t_r$(*R*) = 16.4 min (major enantiomer), $t_r$(*S*) = 17.7 min.

## 2.4.3.5. Attempted enantioselective synthesis of fluoxetine

**General procedure for the catalytic addition of allylmagnesium bromide to benzaldehyde:** In a flame dried Schlenk tube, ($R_{ar}$,*S*)-**$L_{14}$**, **$L_{15}$** or **$L_{17}$** (7.5 mg, 0.02 mmol, 0.2 eq.) were dissolved in dry toluene or $Et_2O$ (1.6 mL, 0.06 M). The solution was then cooled down to the corresponding temperature (–40 or –20 °C) and $Ti(O^iPr)_4$ (0.44 mL, 1.50 mmol, 15.0 eq., unless stated differently in the corresponding table) was added into the mixture. Five minutes later, allylmagnesium bromide (0.38 mL, 0.38 mmol, 3.8 eq. 1 M in $Et_2O$, unless stated differently in the corresponding table) was added. After stirring the mixture for additional 10 min, benzaldehyde (**1**) (10 µL, 0.10 mmol) was added and the reaction mixture was stirred for 4 h at the same temperature.

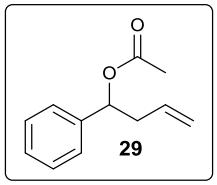
The reaction was quenched by the addition of water (1 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were neutralised with aq. saturated $NaHCO_3$ solution (5 mL), dried with anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude reaction product was purified by flash silica gel chromatography to provide **11**.




**1-Phenyl-3-buten-1-ol (11):**[221] Obtained as a colourless oil after purification by column chromatography (Hex/EtOAc 90:10). **IR** (ATR) 3371, 3064, 2906, 1604, 913, 698. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.20 (m, 5H), 5.88–5.72 (m, 1H), 5.20–5.07 (m, 2H), 4.72 (t, *J* = 6.4 Hz, 1H), 2.58–2.42 (m, 2H), 2.18 (s, 1H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 143.8, 134.4, 128.4, 127.5, 125.8, 118.4, 73.2, 43.8. *ee* was determined by chiral **GC** analysis on derivative **28**.

**General procedure for the synthesis of acetates derivatives:** In a flame dried Schlenk tube, the aliphatic alcohol **11** (0.36 mmol) was dissolved in anhydrous DCM (3.6 mL, 0.1 M) at 0 °C and $Et_3N$ (101 µL, 0.73 mmol, 2.0 eq.), DMAP (4.5 mg, 0.04 mmol, 0.1 eq.) and acetic

anhydride (68 µL, 0.73 mmol, 2.0 eq.) were added sequentially. The reaction mixture was stirred at RT for 12 h. The reaction was quenched with water (4 mL), extracted with $Et_2O$ (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography to provide **29**.




**1-phenylbut-3-enyl acetate (29):**[222] Obtained as a colourless oil after purification by column chromatography (Hexane 100% to Hex/EtOAc 90:10). **IR** (ATR) 3081, 2919, 1733, 1643, 1229, 1020. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 5.80 (dd, *J* = 6.0, 7.2 Hz, 1H), 5.78–6.62 (m, 1H), 5.12–5.02 (m, 2H), 2.72–2.50 (m, 2H), 2.07 (s, 3H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 170.3, 140.0, 133.3, 128.4, 127.9, 126.5, 118.0, 75.1, 40.7, 21.2. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 100 °C, P = 6 psi, retention times: $t_r$ = 56.9 and 58.9 min.

**General procedure for the attempted preparation of the Grignard reagent 3-dimethylaminopropylmagnesium chloride (21) and its addition to benzaldehyde (1):**

- Preparation of the free amine (**20'**): A solution of NaOH (14.8 g, 370 mmol, 7.4 eq.) in $H_2O$ (25 mL) was cooled down to 0 °C and was added to a stirred solution of the hydrochloride salt **20** (7.2 g, 50 mmol) in $H_2O$ at 0 °C. The resulting mixture was stirred for 15 min at 0 °C. The formation of the free amine (**20'**) was easily appreciated on top the aqueous solution.

- Preparation of the Grignard reagent **21** from **20'**: In a triple-neck round-bottom flask, magnesium powder (1.0 or 3.0 eq.) was activated with $I_2$ (tip of a spatula) by the use of a heat gun. Next, the corresponding dry solvent ($Et_2O$, THF or $^t$BuOMe) was added and the suspension was heated to reflux. The free amine **20'** was added dropwise to the stirred solution and the mixture was heated

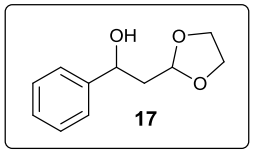
to reflux overnight. The suspension was allowed to cool down before its addition to a solution of benzaldehyde (**1,** see below).

- Preparation of the Grignard reagent **21** from **20**: The hydrochloride salt **20** (1.5 mmol) was dissolved in dry $Et_2O$ or THF (12.5 mL, 1 M) in a triple-neck round-bottom flask and the mixture was cooled down to 0 °C. Next, $^{n}$BuLi or NaH (1.0 eq.) were added at 0 °C, followed by magnesium turnings (1.5 eq.). The suspension was stirred for 2 h at room temperature and heated to reflux overnight. The suspension was allowed to cool down before its addition to benzaldehyde (**1,** see below).

- Addition of the attempted Grignard reagent **21** to benzaldehyde (**1**): In a flame dried Schlenk tube, benzaldehyde (0.5 mmol) was dissolved in dry $Et_2O$ (7.5 mL, 0.07 M) and the solution was cooled down to 0 °C. The attempted Grignard reagent (2.5 mmol, 5 eq.) was added dropwise and the mixture was stirred at room temperature overnight. The reaction was quenched with water (1 mL) and the organic layer analysed by GC-MS to determine the formation of the product **15**.

**General procedure for the addition of (1,3-dioxolan-2-ylmethyl)magnesium bromide to benzaldehyde:** In a flame dried Schlenk tube, ($R_a$,*S*)-**$L_{14}$** (7.5 mg, 0.02 mmol, 0.2 eq.) was dissolved in dry THF, toluene or $Et_2O$ (1.6 mL, 0.06 M). The solution was then cooled down to the corresponding temperature (–40 or –20 °C) and $Ti(O^{i}Pr)_4$ (0.44 mL, 1.50 mmol, 15.0 eq.) was added into the mixture. Five minutes later, 1,3-dioxolan-2-ylmethyl)magnesium bromide (0.38 mL, 0.38 mmol, 3.8 eq. 0.5 M in THF) was added. After stirring the mixture for an additional 10 min, benzaldehyde (**1**) (10 µL, 0.10 mmol) was added and the reaction mixture was stirred overnight at the corresponding temperature. The reaction was quenched with water (1 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were neutralised with aq. saturated

$NaHCO_3$ solution, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude reaction product was purified by flash silica gel chromatography to provide **17**.



17

**2-(2'-hydroxy-2'-phenyl)ethyl-1,3-dioxolane (17):**[223] Was obtained as a yellowish oil after purification by column chromatography (Hex/EtOAc 80:20 to 60:40). **IR** (ATR) 3443, 2957, 2886, 1603, 1411, 1023, 699. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.22 (m, 5H), 5.10–4.98 (m, 2H), 4.12–4.00 (m, 2H), 4.00–3.85 (m, 2H), 3.33 (s, 1H), 2.20–2.04 (m, 2H). **$^{13}$C NMR** (100.6 MHz, $CDCl_3$) δ 143.8, 128.4, 127.4, 125.7, 103.2, 70.3, 65.0, 64.8, 42.3. *ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 150 °C, P = 6 psi, retention times: $t_r$ = 54.5 and 56.9 min.

## 2.5. References


1. Noyori, R.; Kitamura, M., *Angew. Chem.* **1991**, *103*, 34-55.

2. Noyori, R.; Kitamura, M., *Angew. Chem. Int. Ed. (English)* **1991**, *30* (1), 49-69.

3. Soai, K.; Niwa, S., *Chem. Rev.* **1992**, *92* (5), 833-856.

4. Pu, L.; Yu, H. B., *Chem. Rev.* **2001**, *101* (3), 757-824.

5. Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N., *Angew. Chem.* **2001**, *113*, 3382-3407.

6. Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N., *Angew. Chem. Int. Ed.* **2001**, *40* (18), 3285-3308.

7. Pu, L., *Tetrahedron* **2003,** *59* (50), 9873-9886.

8. Luderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Sommer, M. B., *Tetrahedron:Asymmetry* **2009,** *20* (9), 981-998.

9. Hatano, M.; Miyamoto, T.; Ishihara, K., *Curr. Org. Chem.* **2007**, *11* (2), 127-157.

10. Zhu, H. J.; Jiang, J. X.; Ren, J.; Yan, Y. M.; Pittman, C. U., *Curr. Org. Synth.* **2005**, *2* (4), 547-587.

11. Hodgson, D. M., *Organolithiums in Enantioselective Chemistry*. Springer: Berlin, **2003**.

12. Wu, G.; Huang, M. S., *Chem. Rev.* **2006**, *106* (7), 2596-2616.

13. Wu, G. G.; Huang, M., *Top. Organomet. Chem.* **2004,** *6*, 1-35.

14. Howell, G. P., *Org. Process Res. Dev.* **2012**, *16* (7), 1258-1272.

15. Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A., *Chem. Lett.* **1983**, (6), 841-842.

16. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R., *J. Am. Chem. Soc.* **1986**, *108* (19), 6071-6072.

17. Dosa, P. I.; Fu, G. C., *J. Am. Chem. Soc.* **1998**, *120* (2), 445-446.

18. Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S., *Tetrahedron* **1995**, *51* (44), 12013-12026.

19. Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P. Y.; Knochel, P., *J. Org. Chem.* **1996**, *61* (23), 8229-8243.

20. Knochel, P.; Jones, P., *Organozinc Reagents*. Oxford University Press: Oxford, **1999**.

21. Garcia, C.; LaRochelle, L. K.; Walsh, P. J., *J. Am. Chem. Soc.* **2002**, *124* (37), 10970-10971.

22. Jeon, S. J.; Li, H. M.; Garcia, C.; LaRochelle, L. K.; Walsh, P. J., *J. Org. Chem.* **2005**, *70* (2), 448-455.

23. Jeon, S. J.; Li, H. M.; Walsh, P. J., *J. Am. Chem. Soc.* **2005**, *127* (47), 16416-16425.

24. Binder, C. M.; Singaram, B., *Org. Prep. Proc. Int.* **2011**, *43* (2), 139-208.

25. Lemiere, A.; Cote, A.; Janes, M. K.; Charette, A. B., *Aldrichimica Acta* **2009**, *42*, 71-83.

26. Yus, M.; Ramon, D. J., *Recent Res. Dev. Org. Chem.* **2002**, *6*, 297-378.

27. Ramon, D. J.; Yus, M., *Chem. Rev.* **2006**, *106* (6), 2126-2208.

28. Yus, M.; Ramon, D. J., *Pure Appl. Chem.* **2005**, *77* (12), 2111-2119.

29. Noyori, R., *Asymmetric Catalysis in Organic Synthesis.* Wiley: New York, **1994**, Chapter 5.

30. Caprio, V.; Williams, J. J. M., *Catalysis in Asymmetric Synthesis.* 2nd ed.; Wiley-Blackwell: Chichester, **2009**.

31. Nugent, W. A., *Org. Lett.* **2002,** *4* (13), 2133-2136.

32. Shen, B.; Huang, H. Y.; Bian, G. L.; Zong, H.; Song, L., *Chirality* **2013**, *25* (9), 561-566.

33. Nugent, W. A., *Chem. Commun.* **1999**, (15), 1369-1370.

34. Sun, J. T.; Pan, X.; Dai, Z. Y.; Zhu, C. J., *Tetrahedron:Asymmetry* **2008**, *19* (21), 2451-2457.

35. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P., *Tetrahedron* **1999**, *55* (51), 14685-14692.

36. Hsieh, S. S.; Gau, H. M., *Chirality* **2006**, *18* (8), 569-574.

37. Zhang, F. Y.; Yip, C. W.; Cao, R.; Chan, A. S. C., *Tetrahedron:Asymmetry* **1997**, *8* (4), 585-589.

38. Gao, G.; Bai, X. F.; Yang, H. M.; Jiang, J. X.; Lai, G. Q.; Xu, L. W., *Eur. J. Org. Chem.* **2011**, (26), 5039-5046.

39. Kiyooka, S.; Tsutsui, T.; Kira, T., *Tetrahedron Lett.* **1996**, *37* (49), 8903-8904.

40. Gao, G. A.; Gu, F. L.; Jiang, J. X.; Jiang, K. Z.; Sheng, C. Q.; Lai, G. Q.; Xu, L. W., *Chem. Eur. J.* **2011**, *17* (9), 2698-2703.

41. Grignard, V., *Compt. Rend.* **1900,** *130*, 1322-1325.

42. Richey, H. G., *New Developments: Girgnard Reagents*. Wiley: Chichester, **2000**.

43. Wakefield, B. J., *Organomagnesium Methods in Organic Synthesis*. Academic Press: San Diego, CA, **1995**.

44. Osakama, K.; Nakajima, M., *Org. Lett.* **2016**, *18* (2), 236-239.

45. Muramatsu, Y.; Harada, T., *Angew. Chem. Int. Ed.* **2008**, *47* (6), 1088-1090.

46. Muramatsu, Y.; Harada, T., *Chem. Eur. J.* **2008**, *14* (34), 10560-10563.

47. Muramatsu, Y.; Kanehira, S.; Tanigawa, M.; Miyawaki, Y.; Harada, T., *Bull. Chem. Soc. Jpn* **2010**, *83* (1), 19-32.

48. Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P., *Angew. Chem. Int. Ed.* **1998**, *37* (12), 1701-1703.

49. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A., *Angew. Chem.* **2003**, *115*, 4438-4456.

50. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A., *Angew. Chem. Int. Ed.* **2003**, *42* (36), 4302-4320.

51. Krasovskiy, A.; Knochel, P., *Angew. Chem. Int. Ed.* **2004**, *43* (25), 3333-3336.

52. Shi, L.; Chu, Y. Y.; Knochel, P.; Mayr, H., *J. Org. Chem.* **2009**, *74* (7), 2760-2764.

53. Itakura, D.; Harada, T., *Synlett.* **2011**, (19), 2875-2879.

54. Da, C. S.; Wang, J. R.; Yin, X. G.; Fan, X. Y.; Liu, Y.; Yu, S. L., *Org. Lett.* **2009**, *11* (24), 5578-5581.

55. Liu, Y.; Da, C. S.; Yu, S. L.; Yin, X. G.; Wang, L. R.; Fan, X. Y.; Li, W. P.; Wang, R., *J. Org. Chem.* **2010**, *75* (20), 6869-6878.

56. Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J., *J. Am. Chem. Soc.* **2002**, *124* (35), 10336-10348.

57. Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C., *Chem. Soc. Rev.* **2006**, *35* (5), 454-470.

58. Fan, X. Y.; Yang, Y. X.; Zhuo, F. F.; Yu, S. L.; Li, X. A.; Guo, Q. P.; Du, Z. X.; Da, C. S., *Chem. Eur. J.* **2010**, *16* (27), 7988-7991.

59. Fernandez-Mateos, E.; Macia, B.; Ramon, D. J.; Yus, M., *Eur. J. Org. Chem.* **2011**, (34), 6851-6855.

60. Fernandez-Mateos, E.; Macia, B.; Yus, M., *Adv. Synth. Catal.* **2013**, *355* (7), 1249-1254.

61. Zheng, L. S.; Jiang, K. Z.; Deng, Y.; Bai, X. F.; Gao, G.; Gu, F. L.; Xu, L. W., *Eur. J. Org. Chem.* **2013**, (4), 748-755.

62. Fernandez-Mateos, E.; Macia, B.; Yus, M., *Eur. J. Org. Chem.* **2014**, (29), 6519-6526.

63. Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R., *Chem. Commun.* **2012**, *48* (10), 1478-1480.

64. Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J., *Angew. Chem. Int. Ed.* **2012**, *51* (13), 3164-3167.

65. Ortiz, P.; del Hoyo, A. M.; Harutyunyan, S. R., *Eur. J. Org. Chem.* **2015**, (1), 72-76.

66. Hanessian, S., *Total Synthesis of Natural Products: The Chiron Approach*. Pergamon: Oxford, **1983**.

67. Franz, A. K.; Wilson, S. O., *J. Med. Chem.* **2013**, *56* (2), 388-405.

68. Mortensen, M.; Husmann, R.; Veri, E.; Bolm, C., *Chem. Soc. Rev.* **2009**, *38* (4), 1002-1010.

69. Rong, J. W.; Oost, R.; Desmarchelier, A.; Minnaard, A. J.; Harutyunyan, S. R., *Angew. Chem.* **2015**, *127*, 3081-3085.

70. Rong, J. W.; Oost, R.; Desmarchelier, A.; Minnaard, A. J.; Harutyunyan, S. R., *Angew. Chem. Int. Ed.* **2015**, *54* (10), 3038-3042.

71. Tidwell, T. T., *Angew. Chem. Int. Ed.* **2001**, *40* (2), 331-337.

72. Rappoport, Z.; Marek, I., *The Chemistry of Organolithium Compounds*. Wiley-VCH: Weinheim, **2004**.

73. Najera, C.; Yus, M., *Curr. Org. Chem.* **2003**, *7* (9), 867-926.

74. Weber, B.; Seebach, D., *Tetrahedron* **1994**, *50* (25), 7473-7484.

75. Salvi, L.; Kim, J. G.; Walsh, P. J., *J. Am. Chem. Soc.* **2009**, *131* (34), 12483-12493.

76. Nakagawa, Y.; Muramatsu, Y.; Harada, T., *Eur. J. Org. Chem.* **2010**, (34), 6535-6538.

77. Yang, Y. X.; Liu, Y.; Zhang, L.; Jia, Y. E.; Wang, P.; Zhuo, F. F.; An, X. T.; Da, C. S., *J. Org. Chem.* **2014**, *79* (21), 10696-10702.

78. Lecachey, B.; Fressigne, C.; Oulyadi, H.; Harrison-Marchand, A.; Maddaluno, J., *Chem. Commun.* **2011**, *47* (35), 9915-9917.

79. Fernandez-Mateos, E.; Macia, B.; Yus, M., *Eur. J. Org. Chem.* **2012**, (20), 3732-3736.

80. Hallwachs, W.; Schafarik, A., *Liebigs Ann. Chem.* **1859,** *109*, 206-209.

81. Mukaiyama, T.; Minowa, N.; Oriyama, T.; Narasaka, K., *Chem. Lett.* **1986**, (1), 97-100.

82. Chan, A. S. C.; Zhang, F. Y.; Yip, C. W., *J. Am. Chem. Soc.* **1997**, *119* (17), 4080-4081.

83. Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S., *Angew. Chem. Int. Ed.* **2005**, *44* (15), 2232-2234.

84. Mata, Y.; Dieguez, M.; Pamies, O.; Woodward, S., *Inorg. Chim. Acta* **2008**, *361* (5), 1381-1384.

85. Alegre, S.; Dieguez, M.; Pamies, O., *Tetrahedron:Asymmetry* **2011**, *22* (8), 834-839.

86. Wu, K. H.; Gau, H. M., *J. Am. Chem. Soc.* **2006**, *128* (46), 14808-14809.

87. Zhou, S. L.; Wu, K. H.; Chen, C. A.; Gau, H. M., *J. Org. Chem.* **2009**, *74* (9), 3500-3505.

88. Kumar, R.; Kawasaki, H.; Harada, T., *Chem. Eur. J.* **2013**, *19* (52), 17707-17710.

89. Fernandez-Mateos, E.; Macia, B.; Yus, M., *Tetrahedron:Asymmetry* **2012,** *23* (10), 789-794.

90. Anastas, P. T.; Warner, J., *Green Chemistry Theory and Practice*. Oxford Univ. Press: Oxford, **1998**.

91. Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L., *Chem. Rev.* **2008**, *108* (8), 2824-2852.

92. Bower, J. F.; Krische, M. J., Handbook of Green Chemistry Vol. 1. Wiley-VCH: **2009**.

93. Patai, S., *The Chemistry of the Double Bonded Functional Groups*. Wiley: Chichester, UK, **1997**.

94. Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P., *Nat. Chem.* **2012**, *4* (8), 649-654.

95. Maksymowicz, R. M.; Roth, P. M. C.; Thompson, A. L.; Fletcher, S. P., *Chem. Commun.* **2013**, *49* (39), 4211-4213.

96. Wipf, P.; Jahn, H., *Tetrahedron* **1996**, *52* (40), 12853-12910.

97. Negishi, E.-I., *Organometallics in Synthesis: A Manual*. John Wiley & Sons: Hoboken, NJ, USA, **2001**.

98. Negishi, E.; Takahashi, T., *Synthesis (Stuttg.)* **1988**, (1), 1-19.

99. Schwartz, J.; Labinger, J. A., *Angew. Chem.* **1976**, *88*, 402-409.

100. Schwartz, J.; Labinger, J. A., *Angew. Chem. Int. Ed. (English)* **1976**, *15* (6), 333-340.

101. Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B., *Org. Synth.* **1993**, *71*, 77-82.

102. Uhlig, E.; Burglen, B.; Kruger, C.; Betz, P., *J. Organomet. Chem.* **1990**, *382* (1-2), 77-88.

103. Wipf, P.; Xu, W. J.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M., *Tetrahedron* **1994**, *50* (7), 1935-1954.

104. Marek, I., *Titanium and Zirconium in Organic Synthesis*. Wiley-VCH: Weinheim, Germany, **2002**.

105. Buchwald, S. L.; Nielsen, R. B., *Chem. Rev.* **1988**, *88* (7), 1047-1058.

106. Wailes, P. C.; Coutts, R. S. P.; Weigold, H., *Organometallic Chemistry of Titanium, Zirconium, and Hafnium*. Academic Press: New York, **1974**.

107. Wipf, P.; Xu, W. J., *Tetrahedron Lett.* **1994**, *35* (29), 5197-5200.

108. Negishi, E. I., *Angew. Chem. Int. Ed.* **2011**, *50* (30), 6738-6764.

109. Lipshutz, B. H.; Ellsworth, E. L., *J. Am. Chem. Soc.* **1990**, *112* (20), 7440-7441.

110. Corey, E. J.; Carpino, P., *Tetrahedron Lett.* **1990**, *31* (52), 7555-7558.

111. Wipf, P.; Smitrovich, J. H., *J. Org. Chem.* **1991**, *56* (23), 6494-6496.

112. Venanzi, L. M.; Lehmann, R.; Keil, R.; Lipshutz, B. H., *Tetrahedron Lett.* **1992**, *33* (40), 5857-5860.

113. Negishi, E., *Dalton Trans.* **2005**, (5), 827-848.

114. Panek, J. S.; Hu, T., *J. Org. Chem.* **1997**, *62* (15), 4914-4915.

115. Hu, T.; Panek, J. S., *J. Org. Chem.* **1999**, *64* (9), 3000-3001.

116. Drouet, K. E.; Theodorakis, E. A., *J. Am. Chem. Soc.* **1999**, *121* (2), 456-457.

117. Negishi, E.; Alimardanov, A.; Xu, C. D., *Org. Lett.* **2000**, *2* (1), 65-67.

118. Kulinkovich, O., Organotitanium and Organozirconium Reagents. In *Comprehensive Organic Synthesis, Additions to C –X pi-Bonds*, Elsevier: Oxford, **2014**.

119. Ferreri, C.; Palumbo, G.; Caputo, R., *Organotitanium and Organozirconium Reagents in Comprehensive Organic Synthesis, Additions to C – X pi-Bonds*. Elsevier Ltd: Oxford, **1991**.

120. Suzuki, K.; Hitermann, L.; Yamanoi, S., *Titanium and Zirconium in Organic Synthesis*. Wiley-VCH: Weinheim: Germany, **2002**.

121. Suzuki, K., *Pure Appl. Chem.* **1994**, *66* (7), 1557-1564.

122. Suzuki, K.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohba, S., *Tetrahedron* **1995**, *51* (15), 4483-4494.

123. Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K., *Tetrahedron Lett.* **1992**, *33* (40), 5965-5968.

124. Zheng, B.; Srebnik, M., *J. Org. Chem.* **1995**, *60* (11), 3278-3279.

125. Wipf, P.; Kendall, C., *Chem. Eur. J.* **2002**, *8* (8), 1778-1784.

126. Wipf, P.; Ribe, S., *J. Org. Chem.* **1998**, *63* (19), 6454-6455.

127. Wipf, P.; Xu, W., *Org. Synth.* **1996**, *74*, 205.

128. Wipf, P.; Kendall, C., *Org. Lett.* **2001**, *3* (17), 2773-2776.

129. Wipf, P.; Kendall, C.; Stephenson, C. R. J., *J. Am. Chem. Soc.* **2001**, *123* (21), 5122-5123.

130. Kakuuchi, A.; Taguchi, T.; Hanzawa, Y., *Tetrahedron Lett.* **2003**, *44* (5), 923-926.

131. Carr, D. B.; Schwartz, J., *J. Am. Chem. Soc.* **1979**, *101* (13), 3521-3531.

132. Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L., *J. Am. Chem. Soc.* **1990**, *112* (20), 7441-7442.

133. Deloux, L.; Skrzypczakjankun, E.; Cheesman, B. V.; Srebnik, M.; Sabat, M., *J. Am. Chem. Soc.* **1994**, *116* (22), 10302-10303.

134. Sun, A. M.; Huang, X., *Synthesis (Stuttg.)* **2000**, (6), 775-777.

135. Wipf, P.; Xu, W. J., *Synlett.* **1992**, (9), 718-721.

136. Chavez, D. E.; Jacobsen, E. N., *Angew. Chem. Int. Ed.* **2001**, *40* (19), 3667-3670.

137. Li, H. M.; Walsh, P. J., *J. Am. Chem. Soc.* **2005**, *127* (23), 8355-8361.

138. Negishi, E.; Okukado, N.; King, A. O.; Vanhorn, D. E.; Spiegel, B. I., *J. Am. Chem. Soc.* **1978**, *100* (7), 2254-2256.

139. Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2001**, *123* (41), 9974-9983.

140. Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K., Tetrahedron Lett. **1992**, 33 (40), 5965-5968.

141. Wipf, P.; Xu, W. J., *J. Org. Chem.* **1993**, *58* (4), 825-826.

142. Weidmann, B.; Maycock, C. D.; Seebach, D., *Helv. Chim. Acta* **1981**, *64* (5), 1552-1557.

143. Weidmann, B.; Seebach, D., *Angew. Chem. Int. Ed.* **1983**, *22* (1), 31-45.

144. Meerwein, H.; Bock, B. V.; Kirschnick, B.; Lenz, W.; Miggie, A., *Adv. Synth. Catal.* **1936**, *147*, 211-225.

145. Yamamoto, Y.; Maruyama, K., *Tetrahedron Lett.* **1981**, *22* (30), 2895-2898.

146. Mashima, K.; Yasuda, H.; Asami, K.; Nakamura, A., *Chem. Lett.* **1983**, (2), 219-222.

147. Yamamoto, Y.; Saito, Y.; Maruyama, K., *J. Organomet. Chem.* **1985**, *292* (3), 311-318.

148. Fan, G. Q.; Xie, X.; Liu, Y. H.; Li, Y. X., *Organometallics* **2013**, *32* (6), 1636-1642.

149. Wipf, P.; Takahashi, H., *Chem. Commun.* **1996**, (23), 2675-2676.

150. Wipf, P.; Jayasuriya, N.; Ribe, S., *Chirality* **2003**, *15* (3), 208-212.

151. Bauer, T., *Coord. Chem. Rev.* **2015**, *299*, 83-150.

152. Lipshutz, B. H.; Wood, M. R., *J. Am. Chem. Soc.* **1994**, *116* (26), 11689-11702.

153. Westmeier, J.; Pfaff, C.; Siewert, J.; von Zezschwitz, P., *Adv. Synth. Catal.* **2013**, *355* (13), 2651-2658.

154. Roth, P. M. C.; Fletcher, S. P., *Org. Lett.* **2015**, *17* (4), 912-915.

155. Sidera, M.; Roth, P. M. C.; Maksymowicz, R. M.; Fletcher, S. P., *Angew. Chem. Int. Ed.* **2013**, *52* (31), 7995-7999.

156. Roth, P. M. C.; Sidera, M.; Maksymowicz, R. M.; Fletcher, S. P., *Nat. Protoc.* **2014**, *9* (1), 104-111.

157. Rideau, E.; Masing, F.; Fletcher, S. P., *Synthesis (Stuttg.)* **2015**, *47* (15), 2217-2222.

158. Maksymowicz, R. M.; Sidera, M.; Roth, P. M. C.; Fletcher, S. P., *Synthesis (Stuttg.)* **2013**, *45* (19), 2662-2668.

159. Maciver, E. E.; Maksymowicz, R. M.; Wilkinson, N.; Roth, P. M. C.; Fletcher, S. P., *Org. Lett.* **2014**, *16* (12), 3288-3291.

160. Caprioglio, D.; Fletcher, S. P., *Chem. Commun.* **2015**, *51* (80), 14866-14868.

161. Mola, L.; Sidera, M.; Fletcher, S. P., *Aust. J. Chem.* **2015**, *68* (3), 401-403.

162. Lou, S.; Fu, G. C., *J. Am. Chem. Soc.* **2010**, *132* (14), 5010-5011.

163. Cohen, F.; Overman, L. E., *J. Am. Chem. Soc.* **2006**, *128* (8), 2604-2608.

164. Sabitha, G.; Reddy, C. S.; Yadav, J. S., *Tetrahedron Lett.* **2006**, *47* (26), 4513-4516.

165. Scott, M. S.; Luckhurst, C. A.; Dixon, D. J., *Org. Lett.* **2005**, *7* (26), 5813-5816.

166. Pattenden, G.; Critcher, D. J.; Remuinan, M., *Can. J. Chem.* **2004**, *82* (2), 353-365.

167. Jones, G. B.; Guzel, M.; Chapman, B. J., *Tetrahedron:Asymmetry* **1998,** *9* (6), 901-905.

168. Ding, H. X.; Liu, K. K. C.; Sakya, S. M.; Flick, A. C.; O'Donnell, C. J., *Bioorg. Med. Chem.* **2013**, *21* (11), 2795-2825.

169. Xu, Z.; Xu, L. W., *Chem. Rec.* **2015**, *15* (5), 925-948.

170. Boivin, T. L. B., *Tetrahedron* **1987**, *43* (15), 3309-3362.

171. Cardillo, G.; Orena, M., *Tetrahedron* **1990**, *46* (10), 3321-3408.

172. Kotsuki, H., *Synlett.* **1992**, (2), 97-106.

173. Bartlett, P. A., *Tetrahedron* **1980**, *36* (1), 3-72.

174. Elliott, M. C.; Williams, E., *J. Chem. Soc. Perkin. Trans. 1* **2001**, (19), 2303-2340.

175. Narula, A. P. S., In *International Conference on Essential Oil and Aroma, IFEAT 2002*, Perfum. Flavor.: Warsaw, Poland, **2003**; Vol. 28, p 62.

176. Loman, J. J.; Carnaghan, E. R.; Hamlin, T. A.; Ovian, J. M.; Kelly, C. B.; Mercadante, M. A.; Leadbeater, N. E., *Org. Biomol. Chem.* **2016**, *14* (16), 3883-3888.

177. Chan, T. H.; Pellon, P., *J. Am. Chem. Soc.* **1989**, *111* (23), 8737-8738.

178. Veguillas, M.; Sola, R.; Shaw, L.; Macia, B., *Eur. J. Org. Chem.* **2016**, (9), 1788-1794.

179. Veguillas, M.; Sola, R.; Fernandez-Ibanez, M. A.; Macia, B., *Tetrahedron:Asymmetry* **2016**, *27* (14-15), 643-648.

180. Bach, T.; Schroder, J., *J. Org. Chem.* **1999**, *64* (4), 1265-1273.

181. Breederveld, H., *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 401-407.

182. Bremner, J. B.; Keller, P. A.; Pyne, S. G.; Boyle, T. P.; Brkic, Z.; Morgan, J.; Somphol, K.; Coates, J. A.; Deadman, J.; Rhodes, D. I., *Bioorg. Med. Chem.* **2010**, *18* (13), 4793-4800.

183. Ren, X. Y.; Li, G.; Wei, S. M.; Du, H. F., *Org. Lett.* **2015**, *17* (4), 990-993.

184. Guo, J.; Chen, J. H.; Lu, Z., *Chem. Commun.* **2015**, *51* (26), 5725-5727.

185. Zhu, Q. M.; Shi, D. J.; Xia, C. G.; Huang, H. M., *Chem. Eur. J.* **2011**, *17* (28), 7760-7763.

186. Li, F.; Wang, N. N.; Lu, L.; Zhu, G. J., *J. Org. Chem.* **2015**, *80* (7), 3538-3546.

187. Gladkowski, W.; Skrobiszewski, A.; Mazur, M.; Siepka, M.; Bialonska, A., *Eur. J. Org. Chem.* **2015**, (3), 605-615.

188. Lowicki, D.; Bezlada, A.; Mlynarski, J., *Adv. Synth. Catal.* **2014**, *356* (2-3), 591-595.

189. Thvedt, T. H. K.; Kristensen, T. E.; Sundby, E.; Hansen, T.; Hoff, B. H., *Tetrahedron:Asymmetry* **2011**, *22* (24), 2172-2178.

190. Tang, T. X.; Liu, Y.; Wu, Z. L., *J. Mol. Catal. B:Enzym.* **2014**, *105*, 82-88.

191. Kantam, M. L.; Yadav, J.; Laha, S.; Srinivas, P.; Sreedhar, B.; Figueras, F., *J. Org. Chem.* **2009**, *74* (12), 4608-4611.

192. Erdelyi, B.; Szabo, A.; Seres, G.; Birincsik, L.; Ivanics, J.; Szatzker, G.; Poppe, L., *Tetrahedron:Asymmetry* **2006,** *17* (2), 268-274.

193. Kataoka, N.; Okudomi, M.; Chihara, N.; Matsumoto, K., *Lett. Org. Chem.* **2012**, *9* (9), 615-621.

194. Yadav, J. S.; Reddy, B. V. S.; Sreelakshmi, C.; Rao, A. B., *Synthesis (Stuttg.)* **2009**, (11), 1881-1885.

195. Gilmore, N. J.; Jones, S.; Muldowney, M. P., *Org. Lett.* **2004**, *6* (16), 2805-2808.

196. Mizoguchi, H.; Uchida, T.; Katsuki, T., *Angew. Chem. Int. Ed.* **2014**, *53* (12), 3178-3182.

197. Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S., *Angew. Chem.* **2005**, 2272-2274.

198. Ema, T.; Ura, N.; Yoshii, M.; Korenaga, T.; Sakai, T., *Tetrahedron* **2009**, *65* (46), 9583-9591.

199. Suzuki, N.; Rousset, C. J.; Aoyagi, K.; Kotora, M.; Takahashi, T.; Hasegawa, M.; Nitto, Y.; Saburi, M., *J. Org. Chem.* **1994**, *473* (1-2), 117-128.

200. Li, Q. H.; Gau, H. M., *Chirality* **2011,** *23* (10), 929-939.

201. Tjosas, F., *Arkivoc* **2008**, 81-90.

202. Li, K.; Hu, N. F.; Luo, R. S.; Yuan, W. C.; Tang, W. J., *J. Org. Chem.* **2013**, *78* (12), 6350-6355.

203. Hellner, G.; Boros, Z.; Tomin, A.; Poppe, L., *Adv. Synth. Catal.* **2011**, *353* (13), 2481-2491.

204. Konrad, T. M.; Schmitz, P.; Leitner, W.; Francio, G., *Chem. Eur. J.* **2013**, *19* (40), 13299-13303.

205. Kamijo, T.; Yamamoto, R.; Harada, H.; Iizuka, K., *Chem. Pharm. Bull.* **1983**, *31* (10), 3724-3727.

206. Inagaki, T.; Phong, L. T.; Furuta, A.; Ito, J.; Nishiyama, H., *Chem. Eur. J.* **2010**, *16* (10), 3090-3096.

207. Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kuhnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D., *Helv. Chim. Acta* **1994**, *77* (8), 2071-2110.

208. Salvi, N. A.; Chattopadhyay, S., *Tetrahedron* **2001,** *57* (14), 2833-2839.

209. Zong, H.; Huang, H. Y.; Song, L., *Tetrahedron:Asymmetry* **2016,** *27* (20-21), 1069-1074.

210. Kumar, R.; Kawasaki, H.; Harada, T., *Org. Lett.* **2013**, *15* (16), 4198-4201.

211. Kabalka, G. W.; Wu, Z. Z.; Ju, Y. H., *Tetrahedron* **2001,** *57* (9), 1663-1670.

212. Cho, J.; Lee, J.; Park, J.; Kim, M. J., *Tetrahedron:Asymmetry* **2015**, *26* (15-16), 840-845.

213. Keh, C. C. K.; Wei, C. M.; Li, C. J., *J. Am. Chem. Soc.* **2003**, *125* (14), 4062-4063.

214. Hamada, S.; Furuta, T.; Wada, Y.; Kawabata, T., *Angew. Chem. Int. Ed.* **2013**, *52* (31), 8093-8097.

215. Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T., *J. Am. Chem. Soc.* **2010**, *132* (32), 11033-11035.

216. Zlotorzynska, M.; Zhai, H. M.; Sammis, G. M., *J. Org. Chem.* **2010**, *75* (3), 864-872.

217. Zhai, H. M.; Wickenden, J. G.; Sammis, G. M., *Synlett.* **2010**, (20), 3035-3038.

218. Foubelo, F.; Abou, A.; Yus, M., *Eur. J. Org. Chem.* **2005**, (23), 5089-5093.

219. Zhu, Q. L.; Gentry, E. C.; Knowles, R. R., *Angew. Chem. Int. Ed.* **2016**, *55* (34), 9969-9973.

220. Zhu, Q. L.; Gentry, E. C.; Knowles, R. R., *Angew. Chem.* **2016**, *128*, 10123-10127.

221. Das, M.; O'Shea, D. F., *J. Org. Chem.* **2014**, *79* (12), 5595-5607.

222. Murugan, K.; Srimurugan, S.; Chen, C. P., *Tetrahedron* **2011**, *67* (31), 5621-5629.

223. Eid, C. N.; Konopelski, J. P., *Tetrahedron* **1991**, *47* (6), 975-992.