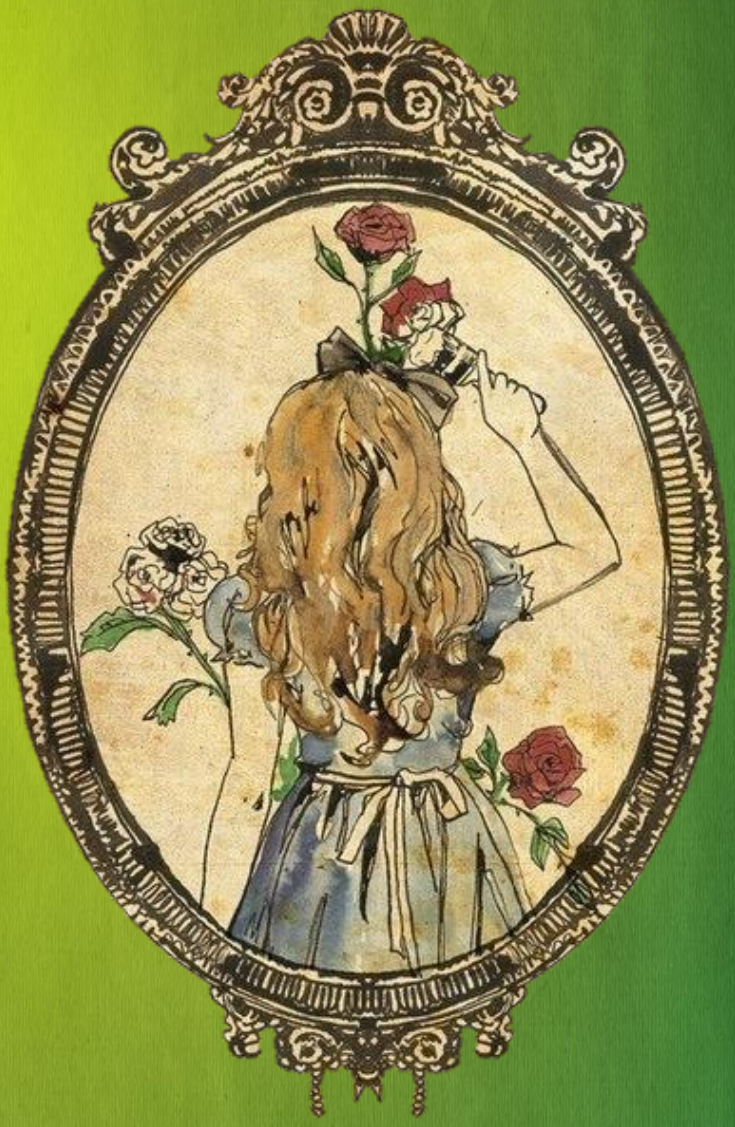
# The Study of the Catalytic Asymmetric Addition of Alkylzinc to form Fluorinated Tertiary Alcohols



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**Universidad de Valladolid**

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# The Study of the Asymmetric Addition of Alkylzinc to form Fluorinated Tertiary Alcohols

**Tomaz Neves Garcia**

**Master~~'s~~ thesis**

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**“How do you run from what’s inside your head?”**

**- Lewis Carroll**

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# Abstract:

Chiral fluorinated products have a huge importance in the fine chemical synthesis, and their synthesis is one of the most important challenges nowadays, due to its outstanding bioactive properties: they are widely used in numerous agrochemicals and pharmaceuticals, product classes that move trillion dollars, save lives and help in the humanity progress. Our group has a much interest in this kind of compound, and uses our expertise in $^{19}F$ NMR to study them. This work is focused on the alkylation of fluorinated ketones using alkylzincs to generate fluorinated chiral tertiary alcohols as a building block to be used to synthetize other molecules with different bioactive properties; for example, the chiral molecule p-$(HO_2C)$-$C_6H_4$-$C(CF_3)(CH_3)OH$, which is a precursor of a product's family that is being really effective in the obesity and type II diabetes treatment.

We have studied the addition reaction with different ligands and ketones and figured out some tendencies. For instance, the difference in reaction of different ketones is a relation between the steric hindrance and the LUMO orbital's energy of the ketones. When diethylzinc was used, the more hindered the ligand more important the steric hindrance of the ketone and with the more hindered ketones the steric hindrance of the ligand gains more importance in the reaction's rate.

After this study, which took most of the time due to the labour to synthetize the ligands, came the more exciting part of the project. Dimethylzinc is more interesting than diethylzinc, due to its lack of β-elimination and to the fact the precursor target be methylated and not ethylated. For that reasons, and the modest results in the literature (up to 83% of e.e.) we decided to study the methylation using L* and, to our surprise, it behave differently than with diethylzinc. It led us to find an outstanding condition, which gives one virtually enantiomeric pure addition product and a great reaction scope. Gratifyingly, three out of four ketones tested in this work; presented more the 95% of enantiomeric excesses.

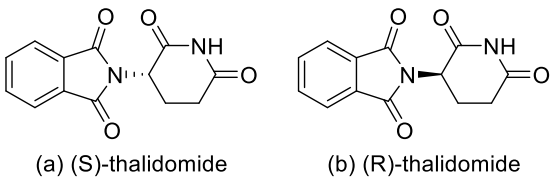
In addition, at the same time we were doing this study, we tried to synthetize a stable $Zn(CF_3)_2$, and we have done it successfully by stabilizing it with a ligand. This

compound was stable enough to be characterized by crystallography x-ray diffraction and its reactivity will be tested in the next future.

Nowadays one of the most important fields in the industry and humanity's progress is the fine chemical synthesis, above all, the research and development (R&D) of pharmaceuticals. The global pharmaceutical market, in 2018, is expected to reach about 1,3 trillion dollars[1]. Pharmaceuticals are traditionally a highly R&D intensive sector, and much of its profit is reinvested in research and development of new drugs[2].

In the pharmaceuticals development, the highly enantiomeric purity synthesis is quite desirable: in 2001, 72% of the pharmaceuticals in the market are enantiomeric pure, compared to 28% of achiral products[3]. Such importance is due to our enantiomeric nature, generally the proteins that will receive the pharmaceutical is enantiomeric, and has a specific interaction in a molecular level.

Generally, one enantiomer has the desired chemical property and the other has not, or has it worsened, or has a completely different reactivity towards other chiral reagents. The classic and unforgettable example is the Thalidomide, figure 1, an example of the worse way to discover a problem.




(a) (S)-thalidomide (b) (R)-thalidomide

**Figure 1: Thalidomide**

In 1957 thalidomide was first marketed in West Germany under the trade name Contergan, primarily prescribed as a sedative, thalidomide also claimed to cure anxiety, insomnia, gastritis, and tension[4]. Afterwards, it was used against nausea and to alleviate morning sickness in pregnant women. The birth of approximately 10,000 teratogenic babies was reported in 46 nations called Thalidomide Tragedy[5].

It turns out that the (R) isomer, figure 1(b), has the sedative effect and the (S) isomer, figure 1(a) has the teratogenic effect. To make it worse, the individual enantiomers can racemize due to the acidic hydrogen at the chiral center and the process can occur *in vivo*[6–8]. After that tragedy the legislation of pharmaceuticals is very restricted and rarely the racemic mixture is approved[3]. It makes no sense to administer a new-found drug in its racemic mixture, which contains the isomer with different reactivity and the threat of holding an unknown effect.

Summing up, there are two reasons to desire a highly enantiomeric reaction: (1) In a reaction that leads to a racemic product or with a poor enantiomeric excess (e.e.) much of the reagents are forming an undesirable product, and are a waste (against at least four out of the twelve green chemistry principles[9]). (2) The desired isomer must be isolated from the other, which is quite hard, since the isomers have the same physical properties. i.e. synthetize a racemic product wastes both resources and time, furthermore, breaking principles of the green chemistry, which gains importance day by day.

Besides the enantiomeric excess, fluorinated compounds are highly desirable as well, even there are few fluorinated natural products in the nature, the presence of fluorinated moieties in active molecules has been proving to be very efficient as pharmaceuticals and crop protection products[10], in medicinal chemistry it is said that the presence of fluorine in the molecule can improve ten times[11].

What makes the fluorine so special chemically is shown in Table 1, fluorine being at the far end of the first row of the periodic table, is small, of low atomic weight and the most electronegative element. This lead to the high polarization of the carbon-fluorine bond, this makes the C-F bond very strong, a property widely exploited by medicinal chemists in attempts to block the metabolism of drug candidates. Introduction of a fluorine atom typically leads to an increase in lipophilicity despite the C-F bond's high polarity, and its introduction is associated with the term 'polar hydrophobicity' to describe its influence on properties. However, it should be noted that decreases in lipophilicity can be observed in certain situations.

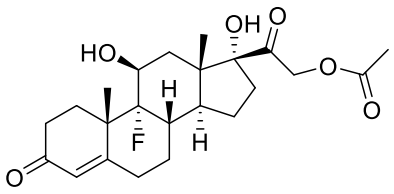
As a result of these influences, the introduction of a single fluorine atom can have a significant impact on many properties of interest to a medicinal chemist while effecting only small or modest changes in molecular size and shape. Impacts on lipophilicity, pKa, conformation, molecular recognition and metabolic oxidation potential have all been exploited to improve potency, selectivity, absorption and metabolism— often at the same time.[12]

**Table 1: Properties of fluorine and the C-F bond compared with other commonly used elements.**

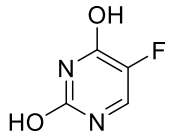
| | H | C | N | O | F | Cl | Br |
|---|---|---|---|---|---|---|---|
| **Van de Waals Radius** | 1.2 | 1.7 | 1.55 | 1.52 | 1.47 | 1,75 | 1.85 |
| **Electronegativity** | 2.1 | 2.5 | 3 | 3.5 | 4 | 3.2 | 2.8 |
| **Bond Strength to C** | 98 | 83 | 70 | 84 | 105 | 77 | 66 |

Consequently, there is a growing demand on organic fluorinated structures, being probably, one of the most important synthetic challenge nowadays. In figure 2 is shown different fluorinated products with biological activity. Fludrocortisone, an anti-inflammatory [Figure 2 (a)] and 5-fluorouracil, an anticarcinogenic [Figure (b)] are two notable examples of the fifties, that the introduction of a single fluorine atom in the molecule greatly enhances its pharmacological properties[13–15], the last one it is still produced in large scale by Clariant®[10].

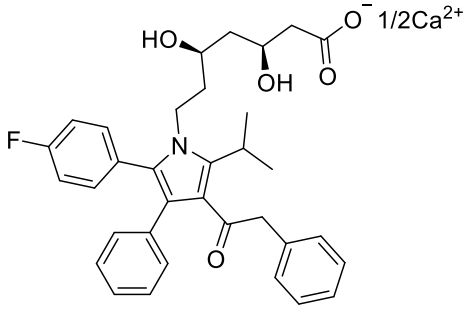
Since then the introduction of fluorine in active principles is a standard procedure in the research and development of pharmaceuticals. In 2006 the bestselling dugs was Lipitor® [Figure (c)], 14,4 billion dollars a year and Advair® [Figure (d)], 6 billion dollars a year, with one and three fluorine atoms respectively[12]. Some another examples are Efavirenz [Figure (e)], 6,6-difluoroshikimic acid [Figure (f)] and pyrazole derivative fungicide [Figure (g)]. It is noteworthy that six out of the seven fluorinated molecules examples have one or more chiral centres emphasizing the importance of the chirality in pharmaceuticals.



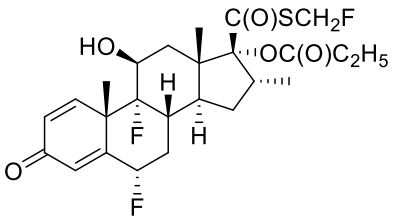
(a) Fludrocortisone



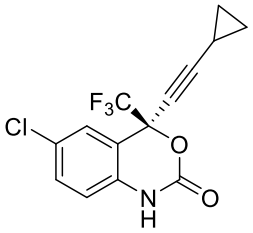
(b) 5-fluorouracil



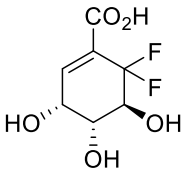
(c) Liptor®



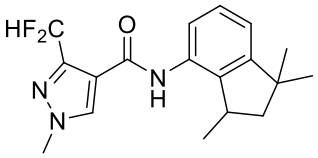
(d) Advair®



(e) Efavirenz



(f) 6,6-difluoroshikimic acid



(g) pyrazole derivative fungicide

**Figure 2: Examples of fluorinated compounds with biological activity**

With all this in mind, it is not surprising the huge interest on fine synthesis of molecules with fluorinated moieties and chiral centre with a good e.e. as a building block. To elucidate what is a building block in chemistry you can think it as a Lego®, there are predefined pieces (molecules), that contains contactable parts (functional groups) that it is assemble to give different complex structures with the desired function.

Building blocks containing chiral tertiary alcohol with fluorinated group is present in various biologically active compounds behaving as anticancer drugs[16], anticonvulsants[17], protease inhibitors[18], (11β-HSD1) enzyme inhibitors[19], anti-HIV agents[20–22], and others.

For example, the chiral molecule p-($HO_2C$)-$C_6H_4$-$C(CF_3)(CH_3)OH$ is a precursor of a family of products (Figure 3) which is being investigated as inhibitors of the 11β-HSD1 enzyme that catalyses the transformation of cortisone to cortisol[19], consequently it can be really effective in the obesity and type II diabetes treatment.

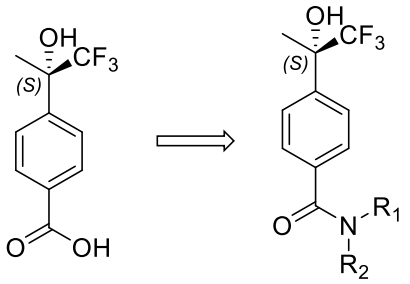



**Figure 3: Optically active p-substituted arylic derivatives**

Two possible strategies to synthetize this kind of compound is the asymmetric trifluoromethylation of regular ketones[23], and the asymmetric alkylation of fluorinated ketones[24–30].

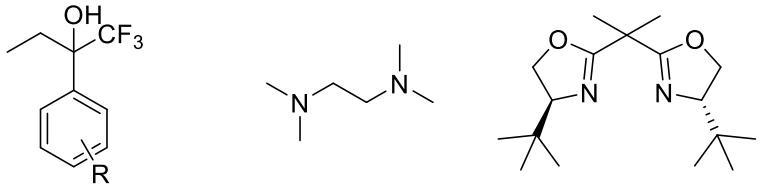
To carry out the asymmetric addition of organometallics to carbonylic compounds is necessary introduce a chiral environment in the organometallic specie, which can be done with a chiral ligand coordination in the metal centre or through the modification of the organometallic by a chiral auxiliary[31–33].

Organolithium reactive and Grignard derivative as the asymmetric C-C bond formation source, due its high reactivity, it requires at least stoichiometric amount of chiral ligand (Expensive and, as it is shown hereafter, quite difficult to prepare) and very low temperatures to reach acceptable enantiomeric excesses (e.e.).

On the other hand, the organozinc compounds are quite less reactive asymmetric C-C bond formation source, nevertheless in the presence of a chiral ligand, it can behave as excellent asymmetric nucleophiles[34]. This allows use the ligand in catalytic amount and carry out the reaction at higher temperatures. Moreover, the organozincs possess a great tolerance to different functional groups, for example, esters, amides, nitriles and nitro group. With all these advantages and versatility, it is not that hard to figure out why organozinc is the best organometallic to form

secondary and tertiary alcohols by the alkylation of ketones and aldehydes, and it is widely used for this purpose.

The reactivity of fluorinated ketones is quite different from aldehydes and non-fluorinated ketones. Until the publication, in Organic Letters - 2008, of Kimberly Yearick and Christian Wolf, the numerous examples of asymmetric additions of alkylzincs to ketones and aldehydes has not been successfully applied to fluorinated ketones[24]. In this paper, they had developed the first procedure for ligand-catalysed nucleophilic addition of diethylzinc to trifluoromethyl ketones. After test 22 different ligands, they concluded that tertiary diamines give the best result and, as final result, they manage to get a range of 2-aryl-1,1,1-trifluorobutan-2-ols (Figure 4(a)) from 81 to 99% of yield using TMEDA (Figure 4(b)) and from 71 to 99% with e.e. from 0 to 63% using TBOX (Figure 4 (c)).




(a)Addition Products (b)TMEDA (c) TBOX

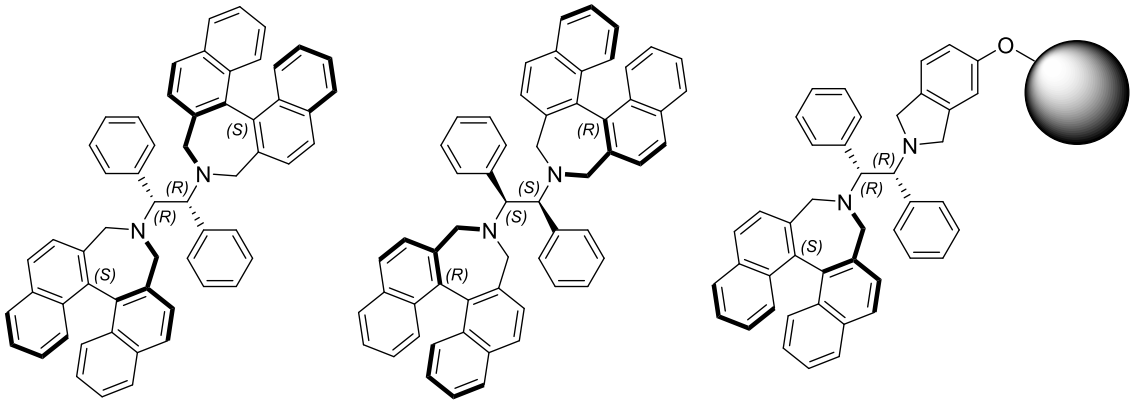
**Figure 4: Compounds of Kimberly Yearick and Christian Wolf paper: (a) the products of addition, (b) and (c) the catalysts which gave the best results.**

The publication of this paper gave our group interest about the matter. Mercedes Calvillo Barahona has your PhD thesis in our group about the study of this system, and it has result in three papers[27–29].

Summing up her work, it was done a thorough study of this matter, and after test numerous different ligands the first conclusion is that the best kind of ligand is 1,2 diamines, TMEDA's offspring, and it was found that the ligand, which we call in the laboratory L* (Figure 5 (a)), gives an incredible, at that time, 92% of e.e. of the (S) tertiary alcohol in the ethylation of 2,2,2-Trifluoroacetophenone with 97% of yield without detectable reduction product. It is noteworthy that it was tested the

enantiomer of L*, we call it ent-L* (Figure 5 (b)), and gives, as expected, the exactly inversed reaction, 97% of yield and e.e. of 92% of the (R) tertiary alcohol[27]

After that, our group started studying Merrifield supported chiral diamines for the enantioselective addition of alkylzincs (methylzinc or ethylzinc) to fluorinated ketones. And as a conclusion the immobilized tail-tied $PL^4$ (Figure 5 (c)) affords moderated e.e.(up to 58%) but allows a much easier handling and recycling.[28]




(a) (b) (c)

**Figure 5: Main Ligands of our group: (a) L*; (b) ent-L* and (c) $PL^4$.**

Finally, after this early results, our group has done a mechanistic study of the addition of diethylzinc in 2,2,2-Trifluoroacetophenone with the ligands: TMEDA, L* and tBuBOX (TBOX) using $^{19}$F-NMR spectroscopy[29].

The figure 6 shows the spectrums of the reactions for each ligand. As it is shown, the reactions with TMEDA and TBOX (Figure 6 (a) and (b) respectively) originate the same species, therefore goes through the same reaction path, but when it was used L* the specie of the zinc alkoxide with the ligand do not appear (Figure 6 (c)), it has been noticed, by spectroscopy, that the dissociation rate of $ZnEt_2$ with L* is very high and is more likely to be coordinated by just one nitrogen.

It is noteworthy highlight the possibility of calculate the enantiomeric excess integrating the peaks of the diastereomers in figure 6 (b) and (c). The result coincide with the results of the chiral column chromatography.

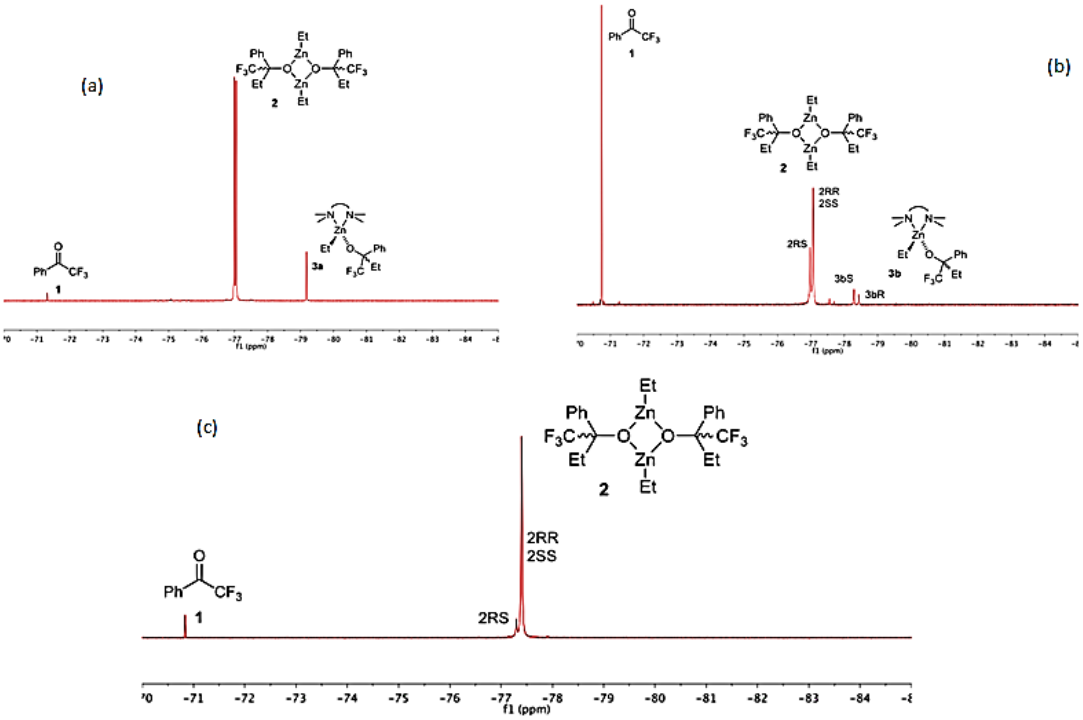
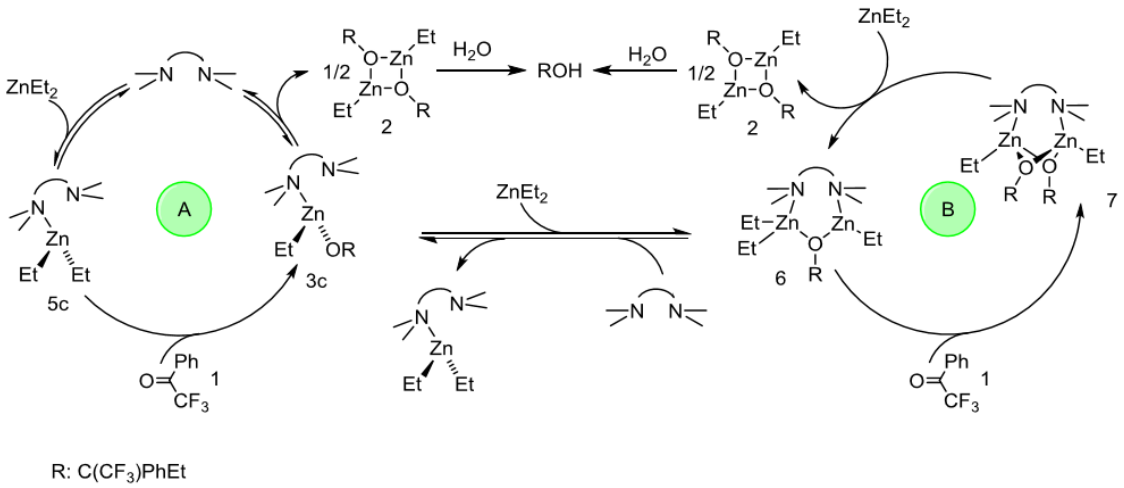



**Figure 6: $^{19}$F NMR of the reactions: (a) with TMEDA; (b) with TBOX and (c) with L***

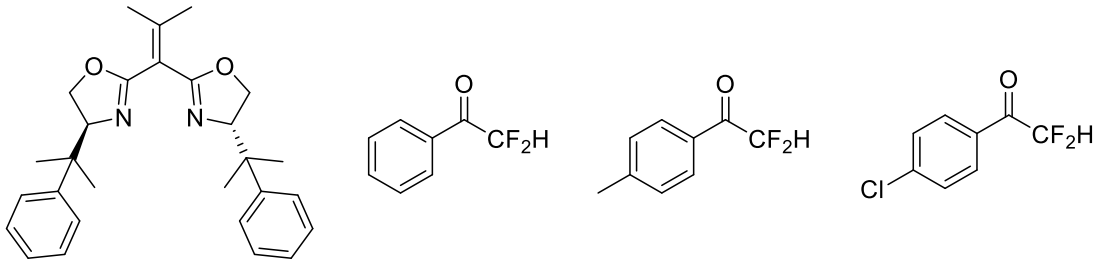
To make the L* more different than the others, it was discovered that the relation of the L* concentration and the reaction rate is inversed, that is, the more ligand concentration lower is the reaction rate, and the enantiomeric excess increase with the reaction progress. After study the elementary parts it was propose the following mechanism in the scheme 1:




**Scheme 1: Mechanism proposed by our group.**

Where the A cycle is slower and poor enantiomerically, because the amine is coordinated by just one nitrogen, after the specie 3c is formed the reactions is displaced to the cycle B, fast and rich enantiomerically. As is shown in the mechanism high concentration of L* can displace the reaction to the A cycle worsening the reaction.

After that it was issued a paper of Sasaki, et al.[30], where they intent to improve the enantioselectivity of ethylzinc using BOX catalysts with a variety of substituents at the oxazoline ring, different length of carbon spacer between the two groups and different conditions of reactions. They find out the best solvent for this reaction are dichloromethane and after test 22 ligands with 24 fluorinated ketones the only interesting results are with the ligand 25 (Figure 7 (a)) with the phenyl with three ketones (Figure 7 (b), (c) and (d)) giving yields of 93% ketone (b), 92% ketone (c) and 99% ketone (d) with e.e. of the (R) isomer respectively, 95, 91 and 90%, they omitted how much of reduction this reaction gives and if the ligand's enantiomer gives the inverted reaction. To finalize they test another alkylzincs, methylzinc, isopropylzinc and n-butylzinc giving really bad results.

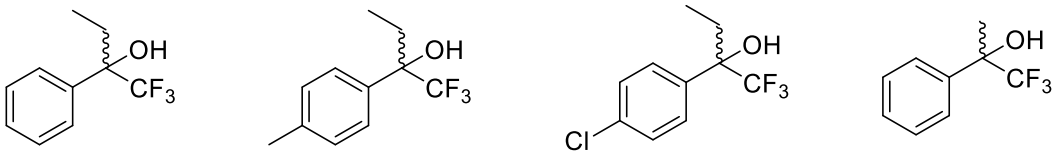



(a) (b) (c) (d)

**Figure 7: Compounds of Sasaki et al. work:**
**(a) The best Ligand, (b), (c) and (d) the best ketones**

It's noteworthy pointing out that there is no chiral ligand, so far, that is capable to provide greats both enantioselectivity and yields with a good scope of fluorinated ketones and alkylzincs. This big difference of reactivity to different ketones and alkylzincs is not well understood, being one of the objectives of the present study.

Summing up the figure 8 shows all the results with enantiomeric excess higher than 90%, all with diethylzinc, and the best result obtained of dimethylzinc published so far.




| (a) | (b) | (c) | (d) |
|---|---|---|---|
| Yield:93%<br>e.e.:95% | Yield:92%<br>e.e.:91% | Yield:99%<br>e.e.:90% | Yield:98%<br>e.e.:83% |

**Figure 8: All significant results published so far**

As shown therefore, the formation of the fluorinated chiral tertiary alcohol is one of the most important synthesis in the fine chemistry. The lack of scope presented by the ligands/conditions so far shows the great necessity to study further this topic.

# Objectives:

The general objective is the study of the asymmetric alkylation of fluorinated aryl ketones with organozincs using chiral diamines as catalysts. As the study progressed another questions and opportunities was raised, the mainly objectives of the present work are:

- Have a better understanding of the addition of alkylzincs to fluorinated ketones, more specific dimethylzinc, which is less understood and is more interesting than diethylzinc whose reaction can lead to reduction products by having a β-hydrogen.

- Optimize the conditions to have the methylation with great yield and better enantiomeric excess.

- Find a stable compound of trifluoromethylzinc to form the chiral alcohol at the same time is forming the precious C-$CF_3$ bound. This can lead to a secondary or tertiary fluorinated alcohol starting from an aldehyde or a ketone, and there is possibility of the resulting alcohol having two fluorinated group, if the starting ketone is fluorinated.

# Conclusions:

- The difference in the reaction to different ketones is relation with the difference in the steric hindrance and the LUMO orbital's energy. To diethylzinc the more hindered the ligand more important the steric hindrance of the ketone. And for diethylzinc with the more hindered ketones the steric hindrance of the ligand gains more importance in the reaction rate.

- The dimethylzinc with L* has a completely different behaviour than dimethylzinc with L*. With dimethylzinc the reaction's rate increases with the concentration of L*.

- A new stable $Zn(CF_3)_2$ specie has been synthetized and Its reactivity will be test in the next steps.

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