**UNIVERSITE CATHOLIQUE DE LOUVAIN**

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# New Catalysts for the Enantioselective Addition of Diorganozinc Compounds to Aldehydes and Imines

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par **Jérôme HOET**

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# Résumé

Cette dissertation traite de l'activation de composés diorganozinciques par des catalyseurs asymétriques dans le cadre de leur addition énantiosélective sur des doubles liaisons carbone-oxygène et carbone-azote. Les propriétes de divers catalyseurs originaux ont été investiguées.

Plusieurs sulfonamidoalcools chiraux dérivés du (*S*)-leucinol et du (1*S*)-3-aminoisoborneol ont été synthétisés pour couvrir un domaine de propriétés électroniques et stériques. Ceux-ci ont été testés lors l'addition du $Et_2Zn$ sur les *N*-phosphinoyl et *N*-sulfonyl-imines, mais ils n'ont pas fourni de rendements et excès énantiomériques intéressants malgré leur utilisation en quantité stoechiométrique. Leurs propriétés catalytiques ont également été examinées dans le cadre de l'addition de $Et_2Zn$ au benzaldéhyde. Malheureusement, un faible contrôle de l'énantiosélectivité (max. 47% ee) est obtenu en présence de 10mol% de ligand chiral.

Une autre approche abordée concerne l'influence de l'anion fluorure sur la nucléophilie des composés dialkylzincs envers le benzaldehyde. La combinaison de quantités stoechiométriques d'un sel fluoré inorganique et d'une quantités sub-stoechiométrique d'un agent de transfert de phase (10mol% éther couronne 18-C-6) conduit à un accroissement non négligeable de la vitesse de réaction. Toutefois, le développement d'une version asymétrique de ce système n'a pas été considéré.

A la suite de notre découverte de l'activation due à l'anion fluorure, les complexes métalliques fluorés ont été examinés en tant que catalyseurs potentiels. En particulier, le complexe du cuivre, $(Ph_3P)_3CuF$, accélère la réaction d'addition du $Et_2Zn$ sur le benzaldéhyde. Après un criblage de divers ligands, la combinaison de $(Ph_3P)_3CuF$ et de la diphosphine chirale BINAP en quantité catalytique (1mol%) conduit à une catalyse efficace de l'addition du $Et_2Zn$ sur des aldéhydes aromatiques. Les rendements obtenus sont bons, par contre l'énantiosélectivité est modeste (49-63% ee).

Une version améliorée de catalyseurs cuivre-fluorure a été obtenue en combinant un sel de cuivre, une source de fluorure et une diphosphine chirale. L'optimisation de divers paramètres de réaction a été effectuée (source de cuivre, origine de l'anion fluorure, ligand chiral, stoechiométries relatives des précurseurs du catalyseur, charge de catalyseur, solvant et température). Le catalyseur optimisé a été appliqué à divers aldéhydes (jusqu'à 87% ee). Un mécanisme réactionnel a été proposé sur la base d'arguments de la littérature et d'observations expérimentales.

Le rôle du contre-ion a été exploré par un examen attentif de divers complexes du cuivre en combinaison avec la BINAP chirale en tant que catalyseurs de l'addition du $Et_2Zn$ sur le benzaldehyde. Les dicétonates du cuivre(II) ont conduit à une bonne énantiosélectivité (jusqu'à 88% ee) qui a pu être améliorée en utilisant des dicétonates du cuivre(II) optiquement actifs assortis avec le bon énantiomère de la BINAP (jusqu'à 91% ee). Ce nouveau système a été appliqué pour l'addition du $Et_2Zn$ sur divers aldéhydes avec une charge réduite en catalyseur (0.5mol%). Un mécanisme a été proposé afin de supporter les observations expérimentales.

**Mots-clés** : diorganozincique, aldéhyde, cuivre, fluorure, 1,3-dicétonate, énantiosélectivité

# Abstract

This PhD thesis deals with the activation of diorganozinc compounds by asymmetric catalysts in the framework of their enantioselective addition on carbon-oxygen and carbon-nitrogen double bonds. The properties of several new catalysts systems were investigated.

Several chiral sulfonamido alcohols derived from (*S*)-leucinol and (1*S*)-3-aminoisoborneol were synthesized to cover a range of electronic and steric properties. These were evaluated in the addition of $Et_2Zn$ to *N*-phosphinoyl and *N*-sulfonyl-imines, but they did not provide any acceptable yields or enantioselectivities while used in stoichiometric quantities. Their catalytic properties were also investigated for the addition of $Et_2Zn$ to benzaldehyde. Unfortunately, only modest enantiocontrol (max. 47% ee) could be obtained with 10mol% of chiral ligand.

We investigated another approach based on the possible activation of the nucleophilicity of dialkylzinc compounds towards benzaldehyde by fluoride anion. The combination of stoichiometric amount of an inorganic fluoride salt and a substoichiometric amount of a phase transfer catalyst (10mol% of crown ether 18-C-6) provided non-negligible rate acceleration. However, an asymmetric version of this catalytic system was not considered.

Following our discovery of the activation provided by the fluoride anion, metal fluoride complexes were tapped as potential catalysts. In particular, copper(I) fluoride complex, $(Ph_3P)_3CuF$, was shown to accelerate the reaction on benzaldehyde. After screening a range of ligands, the combination of $(Ph_3P)_3CuF$ and chiral BINAP in catalytic amounts (1mol%) was found to catalyze efficiently the $Et_2Zn$ addition on aromatic aldehydes. Yields were good but enantiocontrol was modest (49-63% ee).

An improved copper fluoride-based catalyst was developed by combining a copper salt, a fluoride source and a chiral diphosphine ligand. Optimization of this second generation catalyst was carried out (copper source, fluoride source, chiral ligand, relative stoichiometries of catalyst's precursors, catalyst's loading, solvent, temperature) and applied to a range of aldehydes (upto 87% ee). A mechanism was proposed based on literature data and experimental observations.

The influence of the counterion was then thoroughly explored by assessing the catalytic potential of various copper complexes in combination with chiral BINAP in the $Et_2Zn$ addition to benzaldehyde. Copper(II) diketonates provided good enantiocontrol (upto 88% ee) which could be improved even further by using optically active copper diketonates in a matched combination with chiral BINAP (upto 91% ee). This new system was applied to control the addition of $Et_2Zn$ to a range of aldehydes with a low catalyst loading (0.5mol%). A mechanism was proposed to explain a series of experimental observations.

**Keywords** : diorganozinc, aldehyde, copper, fluoride, 1,3-diketonate, enantioselectivity

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# Chapter 1

# Introduction

## 1.1. The Generation of Chirality

"Carbon", the main component of organic molecules, can bear four substituents placed at the summits of a tetrahedron. Four different substituents can be arranged in two different dispositions in space around the carbon center. These two forms are mirror images of each other and cannot be superposed. The interconversion between the two forms is not possible by a simple rotation operation, only breaking a covalent bond will allow it. These two forms are called enantiomers (Figure 1).

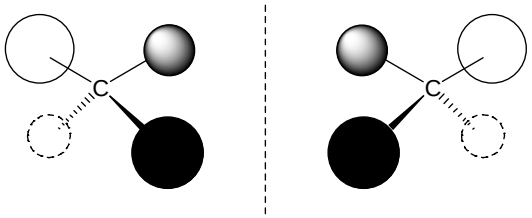



**Figure 1**

Even though enantiomers are distinguishable in three dimensions, they have some common physical properties ( *i.e.*: melting point, boiling point, color, NMR & IR spectra). These identical properties relate to molecular interactions in a symmetrical world. In a non-symmetric environment, enantiomers can behave differently*.

The real world is asymmetric for the most part. In particular, the molecular environment defined by living things whose main molecular building blocks are optically active amino-acids and chiral sugars. In the following scheme, a few pairs of enantiomers which have different tastes, flavors and other biological properties when they interact with taste and odor receptors and other asymmetric binding sites (Figure 2)[1].

* The most representative example of enantiomer properties differentiation is directly related to the term "chirality" or "handedness" in Greek. When one looks at their hands, they are not superposable to each other, yet they are mirror-images of one another. When trying a mitt, both hands will fit the same mitt. However, when we only have one glove, it will either fit the right or the left hand. Left and right hand possess similar properties when confronted to the symmetric mitt but different properties in face of a non-symmetric glove. Left and right hands are chiral or, in chemical terminology, enantiomers of each other.

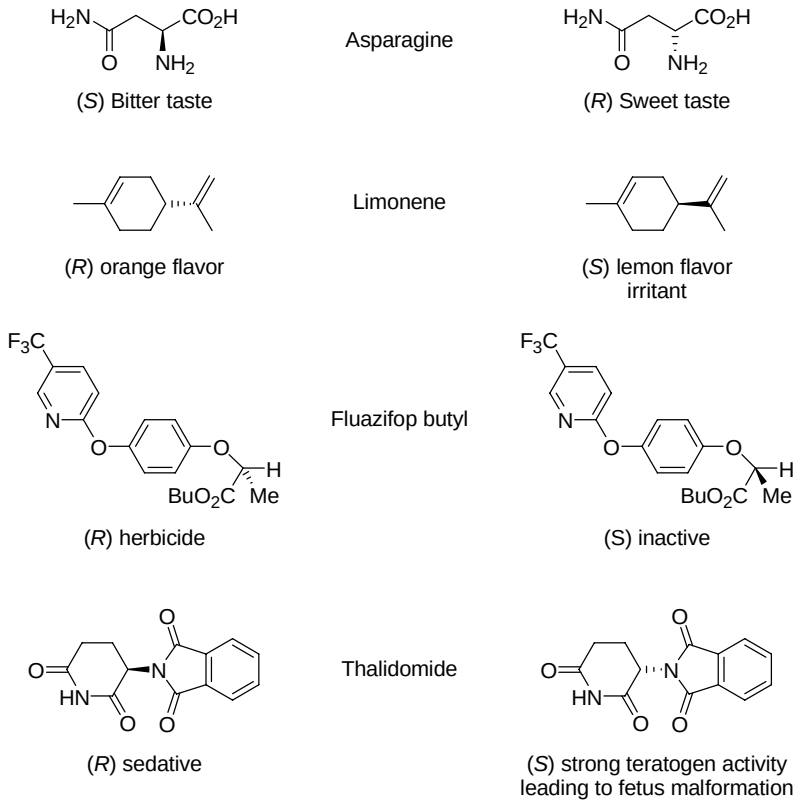



**Figure 2**

Since a given biologically activity is usually associated with only one enantiomer, there are evident reasons to produce enantiomerically pure materials :

- the undesirable effect of one enantiomer might be disastrous.
- the inactive enantiomer is ecologically wasteful.
- the inactive enantiomer is economically wasteful.

The need to control the absolute stereochemistry in a molecule has led chemists to devise several strategies to synthesize enantiopure compounds. Once a controlled chiral center has been introduced in a molecule, further chemical reactions will be affected by this stereo-information embodied in the reactive intermediate. Such a strategy to synthesize optically active molecules is called *diastereoselective* synthesis. Therefore, the problem for the chemist is the control of the first chiral stereocenter in a molecule. However one can also use the "chiral pool" of enantiopure natural or synthetic compounds which are now commercially available[2]. Yet the so-called chiral pool is limited from a structural point of view as well as by the absolute configuration of the enantiomer available (especially from natural sources) (Figure 3).

The introduction of a fragment possessing a chiral center in a non-chiral molecule for the sole purpose of directing a chemical transformation is a widely used technique. If both enantiomers of the chiral auxiliary are available, the two forms of the product can be obtained with a 100% theoretical yield. Another advantage of the technique is due to the diastereomeric nature of the products which allows for the increase of the optical purity by separation on an achiral phase. The disadvantages of the method are the supplementary steps to graft and

remove the auxiliary as well as the need for a stoichiometric amount of chiral auxiliary which cannot always be recovered easily (Figure 3).

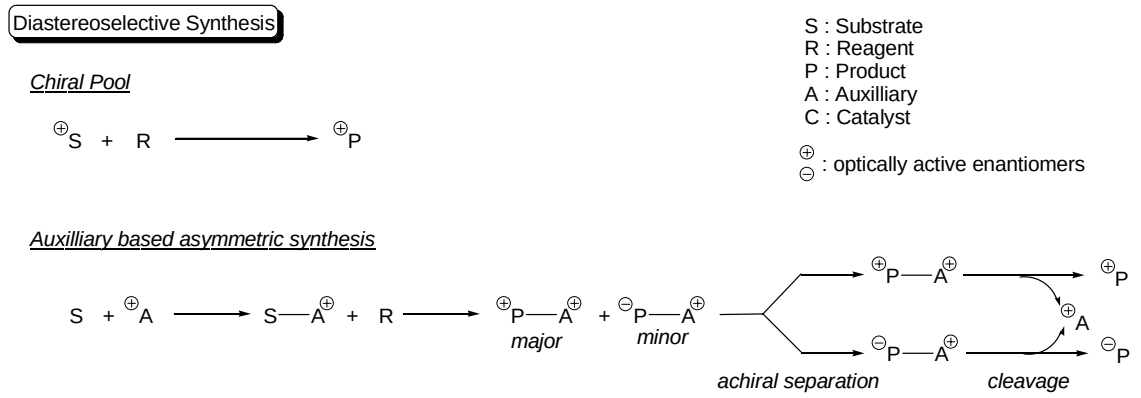



**Figure 3**

Producing a racemic mixture of a target molecule and then separating both enantiomers through some sort of chiral separation is often the method of choice. The chromatographic separation on a chiral stationary phase (which is to be made from some chiral staring material) is based through the preferential interaction of one enantiomer with the optically pure stationary phase. This technique is highly valuable for analytic purposes but more cumbersome for synthetic purposes. A more convenient technique from a synthetic point of view is the addition of a chiral resolving agent to the racemate which can lead to the diastereomeric salts or inclusion complexes separated by preferential crystallization. The recovery of the resolving agent increases the interest of the racemate separation. The production of an enantiopure compound starting from a racemic mixture can also be effected through the preferential consumption of one of the enantiomers in a reaction catalyzed by a chiral catalyst. In such a kinetic resolution, the enantiopure product and the remaining enantiomer from the starting racemic mixture are recovered (Figure 4).

In principle, the resolution of a racemate mixture can only yield a maximum yield of 50% of each enantiomer, the unwanted enantiomer being wasted. Yet, if possible, the racemization of the unwanted enantiomer can increase the atom economy of the process. Starting from a racemate, all the chiral separation processes can theoretically furnish both enantiomers in enantiopure form (Figure 4).

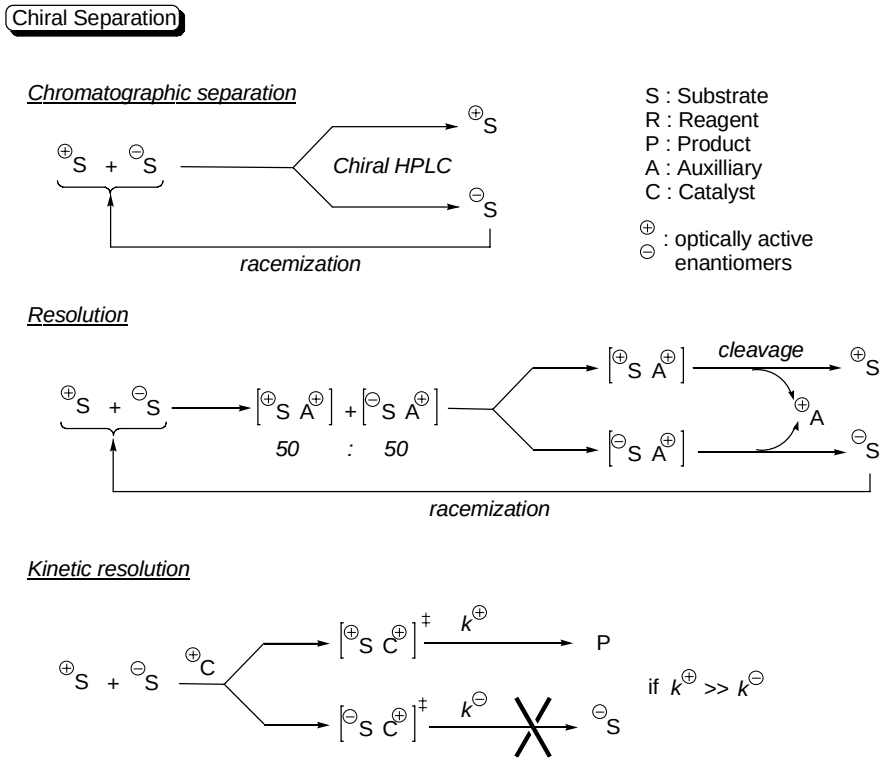



**Figure 4**

The introduction of chirality on a prochiral substrate can also be attained through binding to a chiral catalyst. By definition, a catalyst is involved in the reaction without being consumed. Therefore, the chiral information input is used several times to control the creation of chiral features during the course of the reaction. The quantity of chiral material needed to control such a reaction can be lowered to substoichiometric levels. If both isomers of the catalysts are available, access to the two enantiomers of the product is possible. The recovery of the chiral catalyst does not require any additional cleavage reaction. In conclusion, enantioselective catalysis has a number of advantages compared to other techniques to generate optically pure compounds (Figure 5).

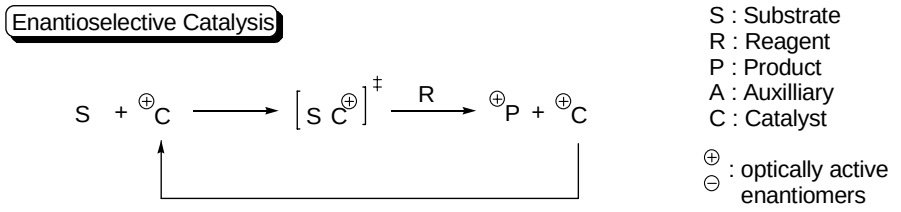



**Figure 5**

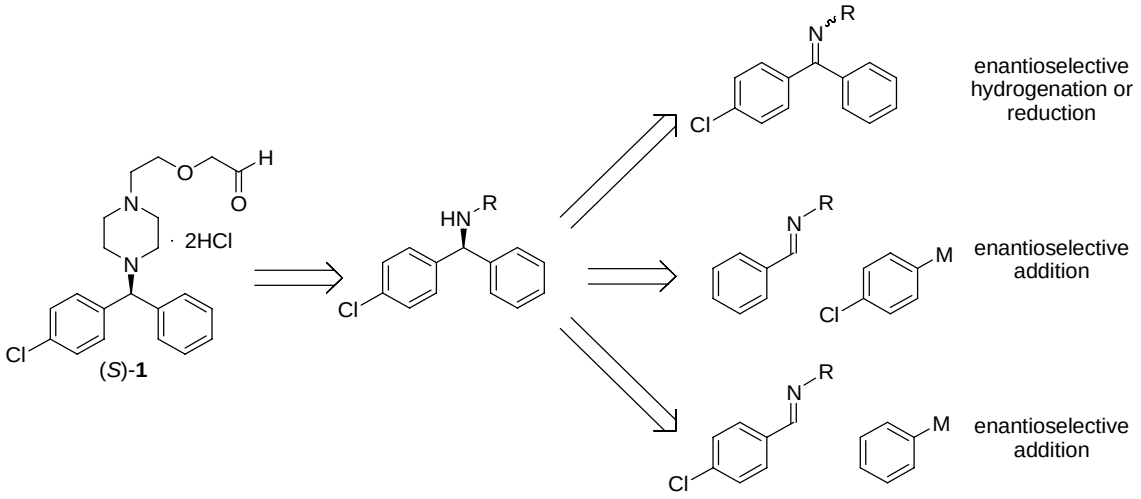
## 1.2. Background

During the last 15 years, much effort has been made in Ghosez's laboratory aiming at the introduction of chirality through enantioselective catalysis. Eric Jnoff, Deogratias Ntirampebura and Chloé Probst have explored the enantiocontrol provided by chiral copper(II)*bis*oxazoline complexes in the Diels-Alder reaction involving 2-azadienes[3-6]. A family of promising non-metallic chiral Lewis acid based on silicon have been designed and tested for the Diels-Alder reaction by Benoit

Mathieu and Zylong Tang[7-9]. Asymmetric epoxidation of olefins by persulfate salts in the presence of chiral iminium has been studied by Karima Cheboub[10]. Inroads towards cyclopentannulation catalyzed by chiral organocatalysts have been made by Patrick Schanen[11].

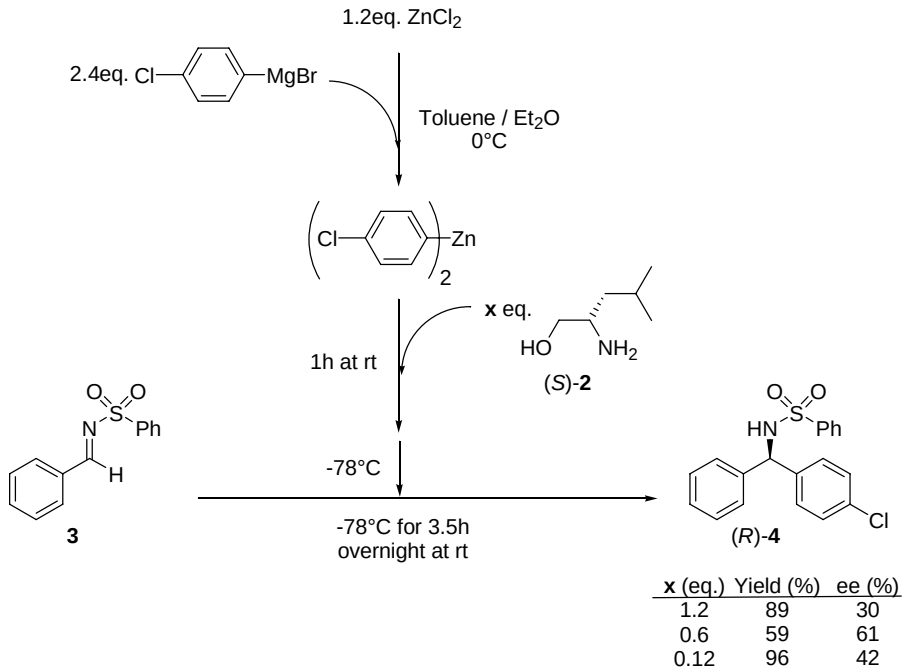
Delphine Renaut has investigated the enantioselective synthesis of diarylmethyleneamines[12]. The interest for this particular chiral fragment stemmed from the structure of a drug to treat allergies discovered by UCB (cetirizine dihydrochloride) **1**. Even though the molecule contains a chiral center, regulatory bodies have approved the use of the racemic mixture which was commercialized as such. Yet the (*S*)-enantiomer is a hundred times more active than the other enantiomer; thus finding a process to obtain only the (*S*)-enantiomer was highly desirable. More importantly, it could extend the patented-life of the molecule by introducing the single isomer as a new product[13].

Two enantioselective routes could be envisaged : the hydrogenation (or reduction) of a prochiral benzophenone-derived imine or the nucleophilic addition aryl moiety to an aromatic aldimine. The first approach was never considered since the enantiotopic face discrimination offered by the two aryl groups of the benzophenone was expected to be low. However, the enantiotopic face discrimination between the hydrogen and the aryl group of an aldimine is easier. Also, only the *syn* conformation is expected in the starting material. Moreover, by reversing the substitution of the imine/organometallic while keeping the same absolute configuration of the catalyst, the opposite enantiomer should be produced.




**Scheme 1**

Delphine Renaut probed different imine-organometallic systems in the presence of various ligands. The addition of a diarylzinc compound to a *N*-sulfonylimine in the presence of stoichiometric and substoichiometric quantities of chiral 1,2-amino-alcohol proved to be the most promising system. Yet, even with the best ligand - (*S*)-leucinol **2** - and under optimized conditions, the enantiomeric excess did not go over 61% in the best case[12] (Scheme 2).



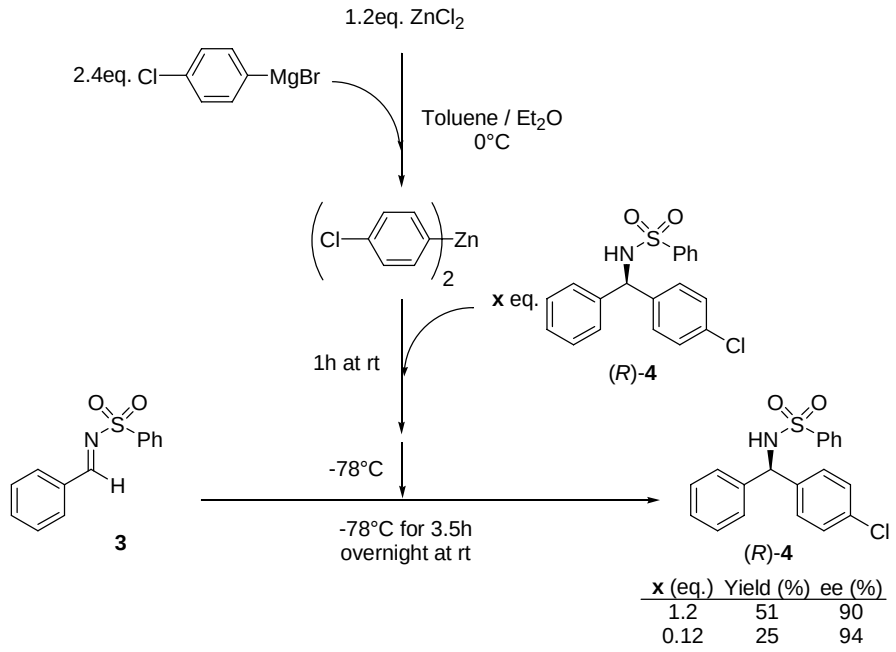

| **x** (eq.) | Yield (%) | ee (%) |
|---|---|---|
| 1.2 | 89 | 30 |
| 0.6 | 59 | 61 |
| 0.12 | 96 | 42 |

**Scheme 2**

Three hypothesis can be made to explain this upper limit of enantioselectivity:

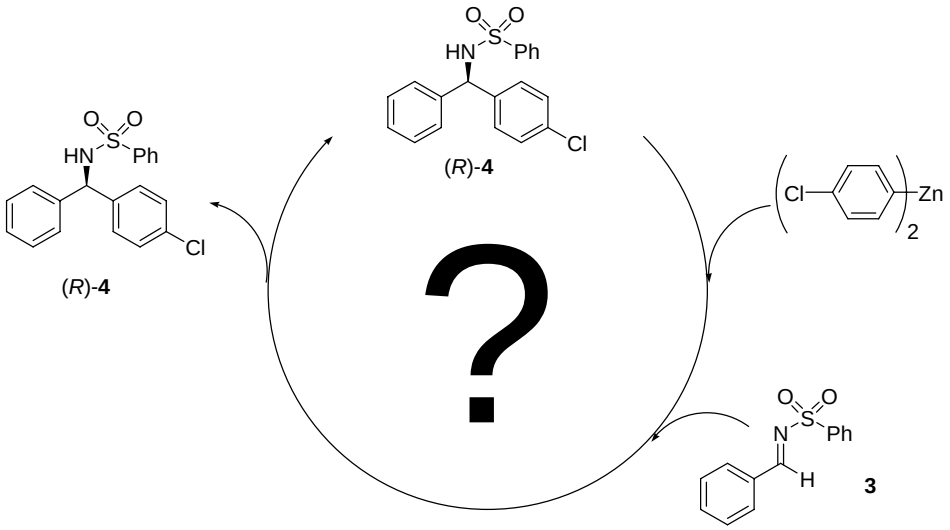
- The intrinsic facial discrimination of the amino-alcohols is reached
- Two reaction pathways compete. The chiral catalyst is deactivated during the course of the reaction and the uncatalyzed reaction overtakes the chiral pathway.
- Three reaction pathways compete: the uncatalyzed reaction, the 1,2-amino alcohol-directed addition and an addition pathway controlled by the adduct itself.

Could sulfonamide (*S*)-**4** be part of the chiral catalyst and control its own enantioselective production? Such a phenomenon of auto-induction of chirality had already been observed at the time in the case of the addition of organometallic compounds to aldehydes[14,15]. This hypothesis was verified by adding some product (*S*)-**4** from the beginning. It was calculated that the adduct was obtained with a very high enantiomeric excess (90-94% ee) depending on the amount of chiral ligand introduced.[12]




**Scheme 3**

The starting point of the present thesis was to study the inner workings of this autoinduction of chirality discovered in our laboratory by Delphine Renaut. Unfortunately, I was unable to reproduce these results over the course of the first year of the thesis even though numerous parameters were modified. Confirmation of this irreproducibility came when the reaction stopped working properly in the hands of Delphine Joseph who had been exploring the synthetic range of the autoinduction during her post-doctoral stay. After a year of unfruitful exploration and although no enantioselective generation of optically active diarylmethylamine was described at the time, it was decided to abandon this subject (Scheme 4).



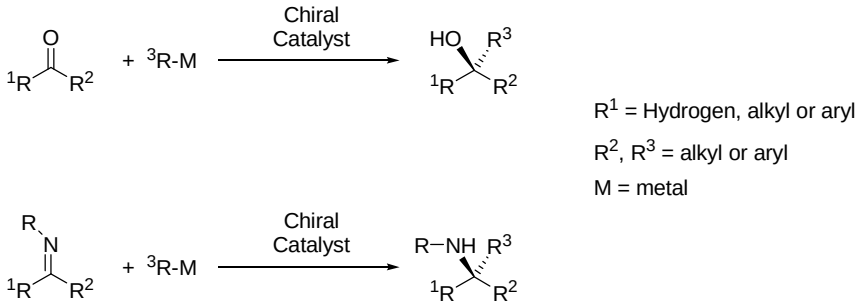

**Scheme 4**

In the meantime, these enantiopure diarylmethylamines have been obtained by chiral resolution in the presence of tartaric acid, by two different diastereoselective aryl addition to chiral sulfinyl aldimines[16-18] and by a

diastereoselective reduction of chiral benzophenone-$Cr(CO)_3$ complex followed by substitution[19]. It is only in 2002 that the first enantioselective route has been described by Bräse, Bolm *et al.* through a ligand-controlled addition of an arylzinc compound to a prochiral imine[20].

## 1.3. Objectives

When we started reorienting our research, reports of enantioselective additions of organometallics to aldehydes in the presence of a chiral catalyst were already quite numerous and some of them were highly successful[21,22]. However, enantioselective additions to imines were seldom and not very practical[23,24]. In the case of ketones, we were aware of only one report[25]. It seemed that the technology developed at the time in the case of aldehydes could not be directly transposed to imines and ketones. The search for new catalyst to control the enantioselective addition of organometallic compounds to carbonyls and imines was still relevant (Scheme 5).




**Scheme 5**

It seemed to us that we needed to look at new systems for the enantioselective addition of organometallic compounds to carbonyls and imines. This is the object of the present thesis.

# Chapter 2

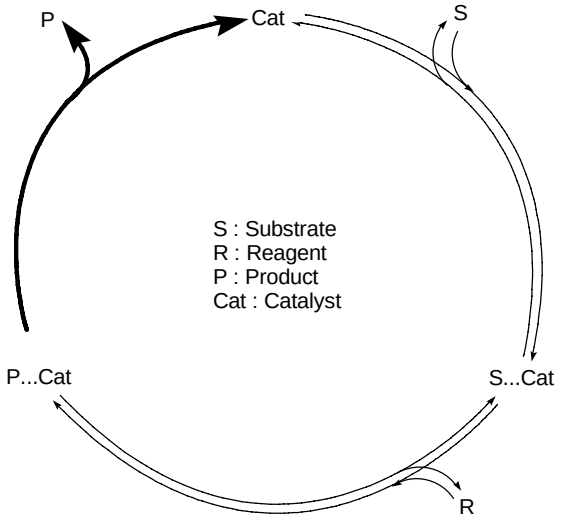
# Diorganozinc Activation

## 2.1. Introduction

In this chapter, we will first lay down the principles of enantioselective catalysis. We will then present selected results of the literature on the enantioselective addition of diorganozinc compounds to various substrates. The discussion will be centered on the mechanistic details of the activation of diorganozinc compounds by the various catalysts.

## 2.2. Asymmetric Catalysis

What are the requirements to implement a successful asymmetric catalysis? First of all, an achiral or chiral catalyst increases the rate of a given reaction without being consumed in the process. For a better understanding, the chemist dissects the catalyzed reaction in a series of reaction steps often arranged in a cycle. A crucial point to be made is that for the catalytic cycle to be complete the catalyst must be regenerated after the transformation of the reagents into the product. Very often, the steps involved are described as reversible reactions except one of them which makes the overall process irreversible. Very often, it is the cleavage of the product from the catalyst which drives forward the successful catalytic cycle (Scheme 6).




**Scheme 6**

From an asymmetric point of view, the chiral catalyst must lead to a differentiation of a reagent's approach towards the substrate. The ratio between the two enantiomers depends on the free energy difference ($\Delta\Delta G^{\ddagger}$) between the competing enantiotopic transition states (Figure 6).

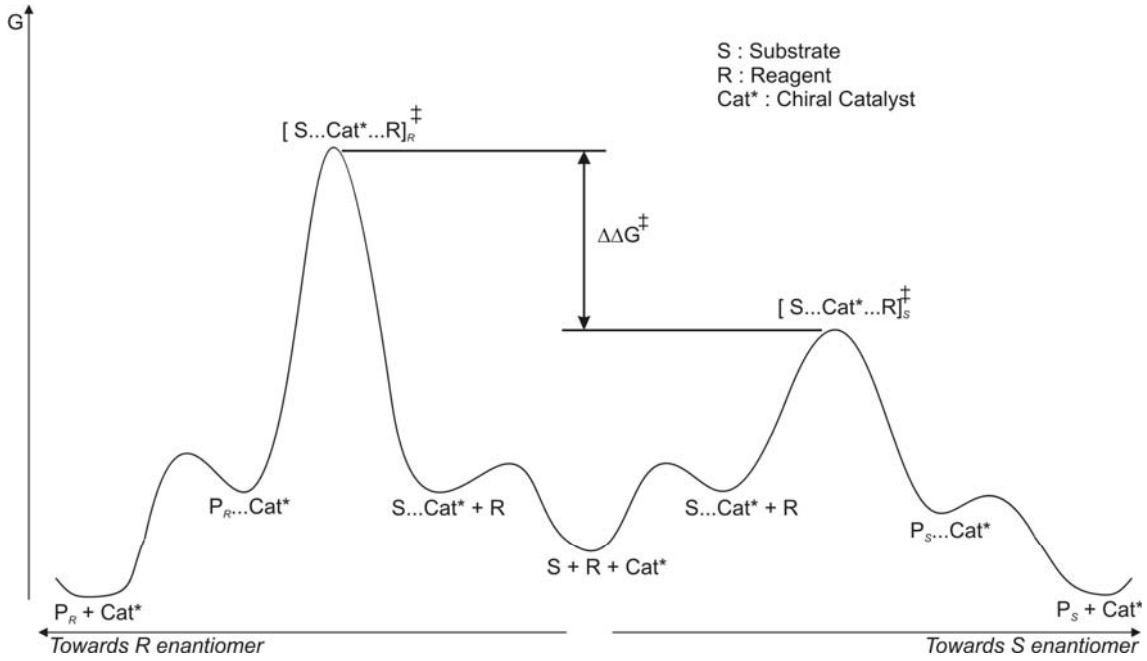
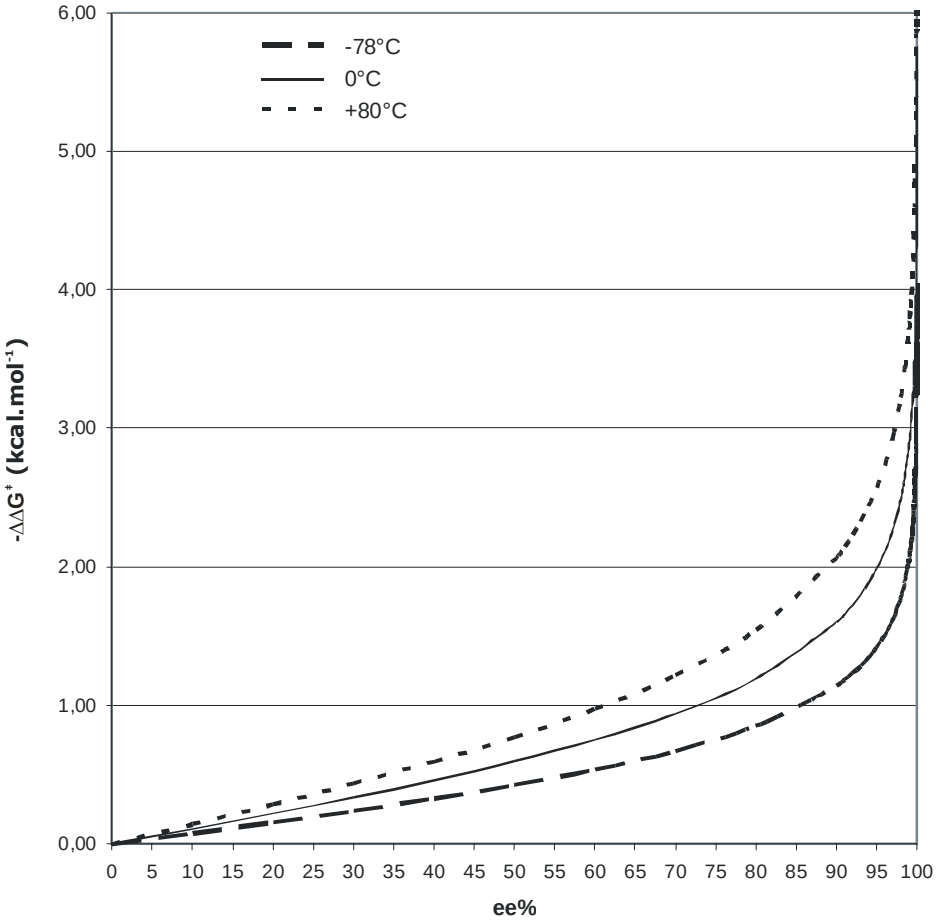



**Figure 6**

The relationship between the free energy difference of the two transition states ( $-\Delta\Delta G^{\ddagger}$) and the enantiomeric excess is exponential. Therefore, improving the enantioselectivity at higher ee's requires a larger energy difference between the two transition states. The energy difference ( $-\Delta\Delta G^{\ddagger}$) needed to achieve a constant level of enantioselectivity is reduced by lowering the reaction's temperature (Chart 1).

**Chart 1** : $-\Delta\Delta G^{\ddagger}$ *vs.* ee and temperature influence.

$$ee = \frac{[R]-[S]}{[R]+[S]} \qquad -\Delta\Delta G^{\ddagger} = RT \ln \frac{(1+ee)}{(1-ee)}$$




A large free energy difference between the two transition states leading to the two enantiomers is necessary to obtain high enantiomeric excesses, but it is not sufficient. Even a perfect transmission of the chiral information from the ligand does not insure a 100% enantiomeric excess. A competing uncatalyzed reaction producing the racemic product, the so-called "background reaction", will decrease the overall enantiomer excess of the reaction. The free energy difference between the transition states of the catalyzed $[S...Cat^{*}...R]_S^{\ddagger}$ and uncatalyzed $[S...R]^{\ddagger}$ reactions must be as high as possible (Figure 7).

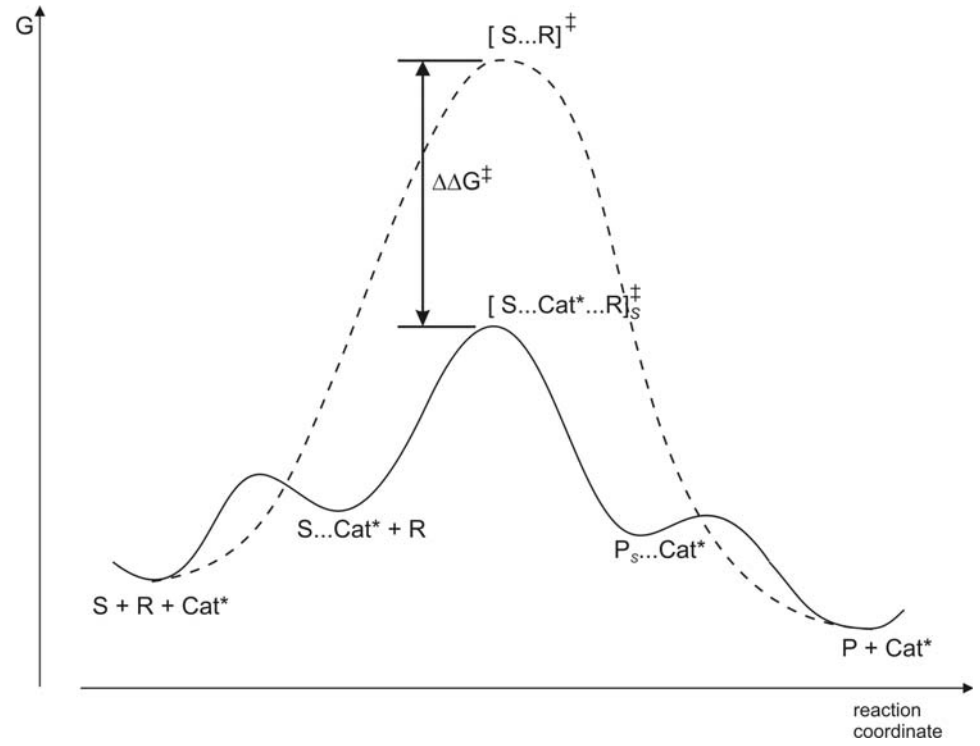



**Figure 7**

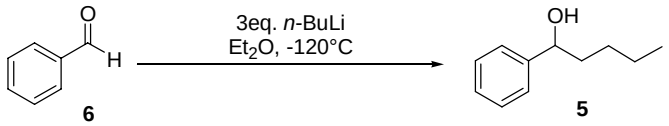
In conclusion, asymmetric catalysis is four-dimensional in nature. The three dimensional structure of the chiral catalyst is important for the chiral induction. Yet, the kinetic aspect is crucial to obtain a highly optically active compound.[26]

# 2.3. Activation of Diorganozinc Compounds by 1,2-Amino Alcohol and Related Ligands.

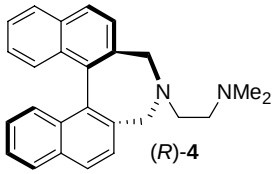
## 2.3.1. Asymmetric Catalysis In Practice

The first attempts in the asymmetric 1,2-addition of organometallic compounds to aldehydes in the presence of a chiral inducer illustrate the principles exposed above[27-34].

For example, Cram effected the addition of alkyllithium to aldehydes in the presence of chiral diamine (*R*)-**4** in different molar ratios of ligand / *n*-butyl lithium[29]. When a ratio of 1.1 was used, the adduct (*R*)-**5** was obtained with 54-55% ee. The ee dropped to 7% when the ratio was only 0.0077. In fact the poor enantioselectivity obtained in the presence of a catalytic amount of chiral diamine (*R*)-**4** is explained by a too small difference in the rates of the ligand controlled reaction and the uncatalyzed reaction since, in absence of ligand, the racemic adduct was obtained in 81% yield. With Grignard reagents[33], dialkylmagnesium[31] and organotitanium[32] reagents, stoichiometric amounts of the chiral ligand were also required (Scheme 7).




**6** **5**

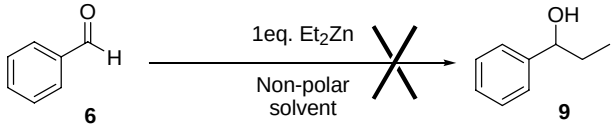



(*R*)-**4**

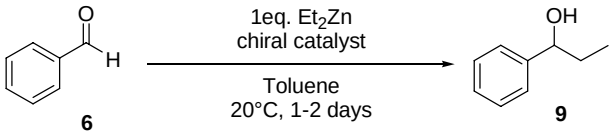
| (*R*)-**4** | *n*-BuLi (eq.) | yield (%) | ee (%) |
|---|---|---|---|
| 3.3 eq. | 3.0 | 71 | 55 |
| 0.023 eq. | 3.0 | n.r. | 7 |
| - | 3.0 | 81 | - |

**Scheme 7**

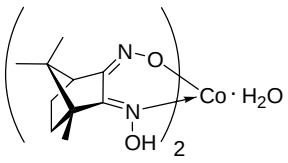
In 1983, a solution to this problem was reported by Oguni *et al.* who used diorganozinc reagents in the presence of a substoichiometric amount of chiral ligands[35]. In the presence of 1 mol% of *bis*((-)-camphorquinone-α-dioximato)cobalt(II) **7** and palladium(II) **8**, the addition of diethylzinc to benzaldehyde **6** yielded adduct **9** in respectively 43 and 58% ee's[35]. A year later, they showed that small quantities (2 mol%) of chiral 1,2-amino alcohols as ligands gave up to 49% ee in the same reaction[36] (Scheme 8, Table 1).



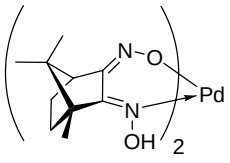

**6** **9**



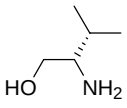

**6** **9**



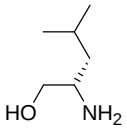

**7**



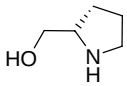

**8**




**10**




(*S*)-**2**




(*S*)-**11**

**Scheme 8**

**Table 1** : First attempts in the enantioselective catalytic addition of diethylzinc to benzaldehyde

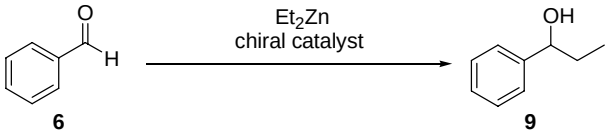
| Entry | Chiral Catalyst | Catalyst loading (mol%) | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | **7** | 1 | 88 | 43 |
| 2 | **8** | 1 | 98 | 58 |
| 3 | (*S*)-**10** | 2 | 95 | 47 |
| 4 | (*S*)-**2** | 2 | 96 | 49 |
| 5 | (*S*)-**11** | 2 | 100 | 28 |

In fact, the first organometallic compounds to be discovered (Frankland, 1849) were dimethylzinc and diethylzinc. At the time, the nucleophilicity of the diorganozinc compounds was recognized. Yet, diorganozinc compounds were overlooked, probably as a result of the discovery of the more nucleophilic organomagnesium compounds[37]. The breakthrough in the enantioselective catalytic addition of an organometallic compound to aldehydes was probably the recognition that dialkylzinc reagents were not reactive towards aldehydes in non-polar solvents. The "background" reaction yielding racemic adduct should not be a concern anymore since only the catalyst-controlled reaction could yield an adduct.

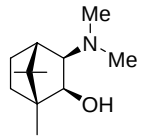
## 2.3.2. Ligands

Since these two seminal reports by Oguni, it has been recognized that diorganozinc compounds were very good nucleophiles for asymmetric catalyzed addition reactions. An incredible body of work has been published by laboratories all over the world on the enantioselective addition of diorganozinc compounds to aldehydes catalyzed by 1,2-amino-alcohols and related ligands[†]. To give the reader a sense of this diversity, we have listed some of the ligands that have been used to control the diorganozinc addition to aldehydes[39-46]. For comparison's purposes, results are shown for the often used model substrate, benzaldehyde, however some ligands also gave high enantiocontrol in the addition of aliphatic aldehydes[38,22] (Scheme 9).

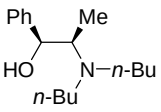
[†] Exhaustive reviews have been published on the enantioselective 1,2-addition of organometallics on aldehydes[38] Pu, L.; Yu, H.-J. *Chem. Rev.* **2001**, *101*, 757-824, [22] Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833-856.



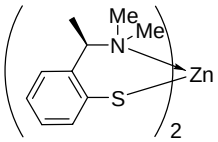

**6** **9**



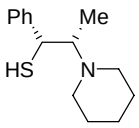

(-)-**12**, DAIB
Noyori, 1986
99%ee (*S*)



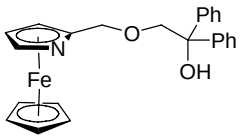

**13**, DBNE
Soai, 1987
90%ee (*S*)



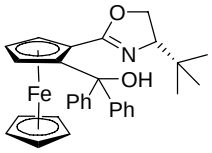

**14**
van Koten, 1994
94%ee (*S*)



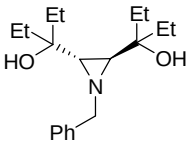

**15**
Kang, 1994
100%ee (*R*)



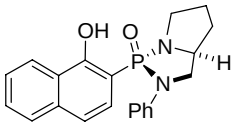

**16**
Fu, 1997
90%ee (*S*)




**17**
Bolm, 1997
93%ee, (*R*)




**18**
Tanner & Andersson, 1998
94%ee (*S*)



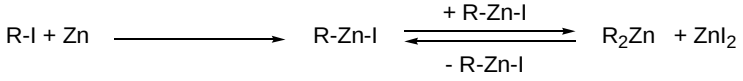

**19**
Buono, 1998
98%ee (*S*)

**Scheme 9**

In the following pages, we will only describe results which could help our understanding of these catalytic additions and highlight the problems faced in designing new catalysts.

## 2.3.3. Diorganozinc Compounds

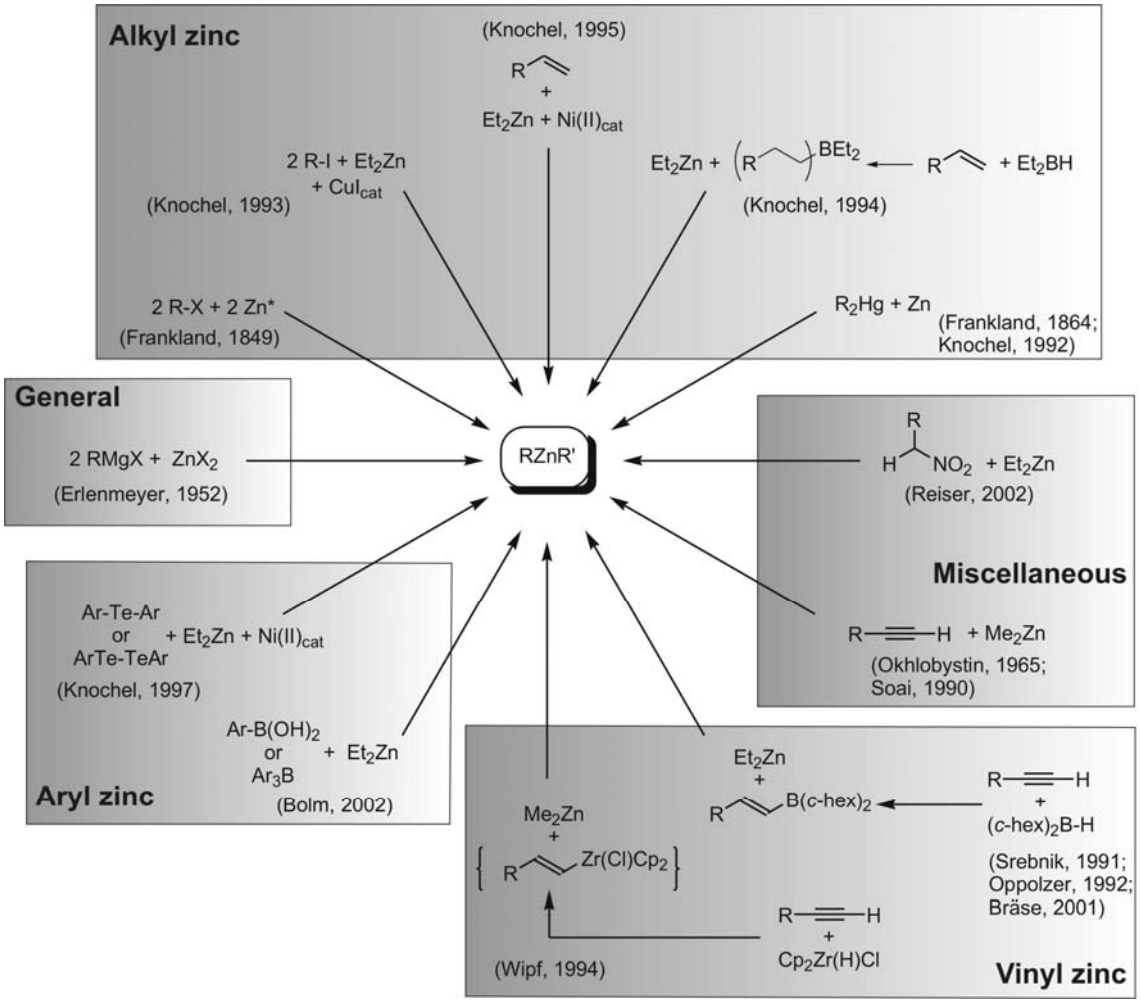
A large range of diorganozinc compounds is available. In 1849, Frankland obtained the first dialkylzinc compounds by heating an alkyliodide in the presence of zinc powder in a sealed flask[47,48]. An alkylzinc halide is generated in a first step. It can then disproportionate through a Schlenck-type equilibrium generating a zinc halide salt and a dialkylzinc compound. Yet, this method cannot be easily generalized since it only works for dialkylzincs and requires a distillation of the pyrophoric dialkylzinc compounds (Scheme 10).




**Scheme 10**

A more practical method consists in the transmetallation of the readily available Grignard reagents with a zinc salt. This is applicable to the synthesis of dialkyl-, diaryl- and dialkenylzinc compounds. However, the method also produces Lewis acidic magnesium salts which have to be eliminated to avoid achiral activation of the substrate[49,50]. An additional inconvenient is due to the reactivity of Grignard reagents with a large number of chemical functionalities which therefore cannot be present in the resulting diorganozinc compounds (Scheme 11).

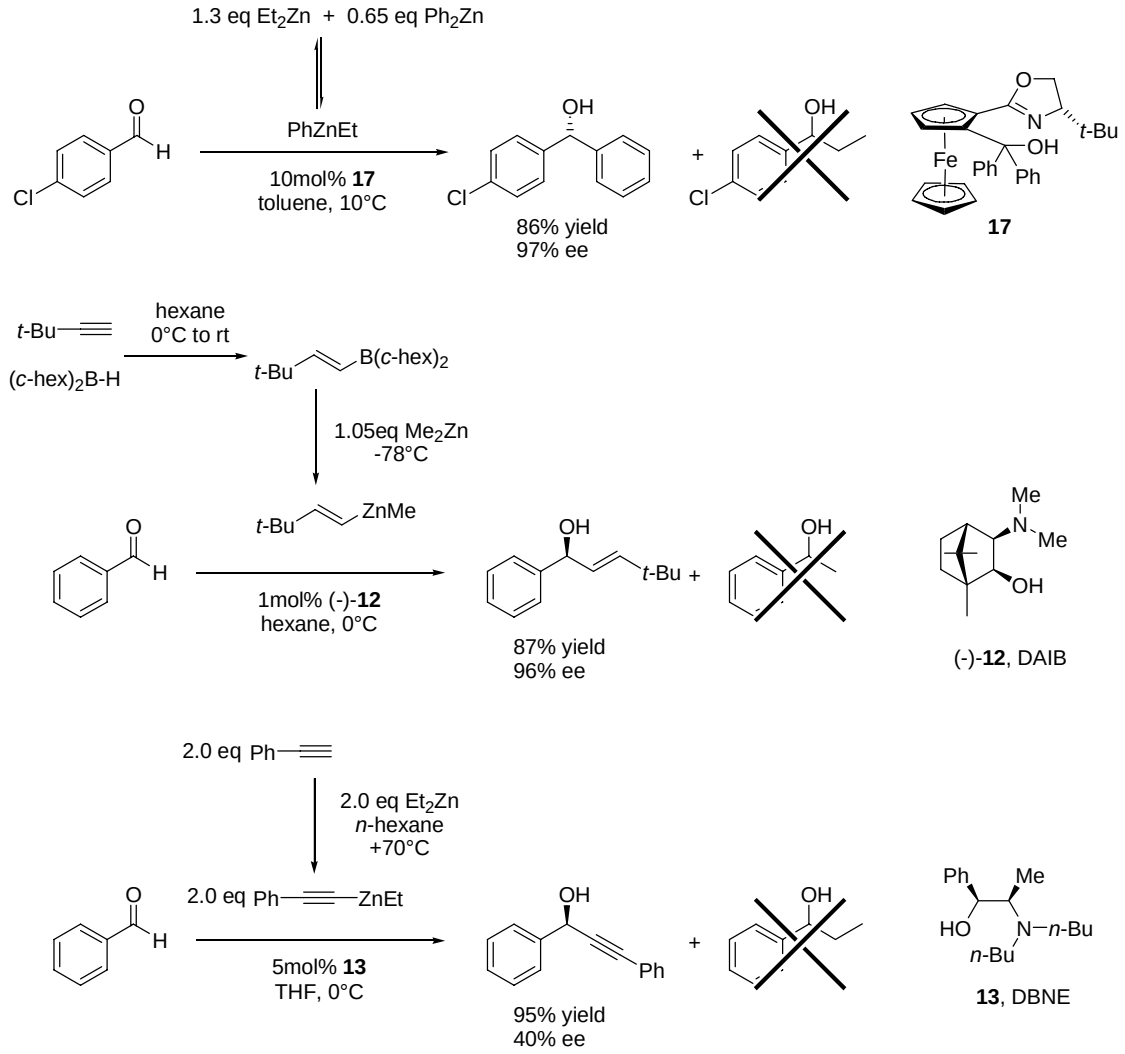
The production of functionalized diorganomercury compounds and their transmetallation with zinc powder leads to dialkylzinc compounds but is highly inconvenient due to the toxicity of organomercury compounds[51] and the produced mercury[52,47]. In the presence of a catalytic amount of a Ni(II) salt, the tellurium-zinc exchange has been used to generate arylzinc compounds[53]. Alkenylzirconium species produced by hydrozirconation of an alkyne can be transmetallated in the presence of dimethylzinc to produce alkenylzinc compounds[54]. More interestingly, the boron-zinc exchange by dialkylzinc generates alkyl[55], alkenyl[56-58] and arylzinc[59,60] compounds from easily available organoboron compounds. The weak reactivities of the primary organometallic compound and of the resulting organozinc product allowed a range of functionalities (ether, silylether, ester, nitrile, nitro) (Scheme 11).




**Scheme 11**

The use of an organometallic compound is not necessary: the exchange between a primary alkyliodide and diethylzinc mediated by a catalytic amount copper(I) iodide has been used for the preparation of functionalized dialkylzinc[61]. The hydrozincation of a terminal olefin by diethylzinc in the presence of Ni(II) catalyst provides another easy access to dialkylzinc compounds[62,63]. The generation of a stabilized carbanion by deprotonation of terminal alkynes or nitroalkanes with $Me_2Zn$ or $Et_2Zn$ is a strategy which has been used to generate alkynyl[64-66] and nitronate[67] nucleophiles (Scheme 11).

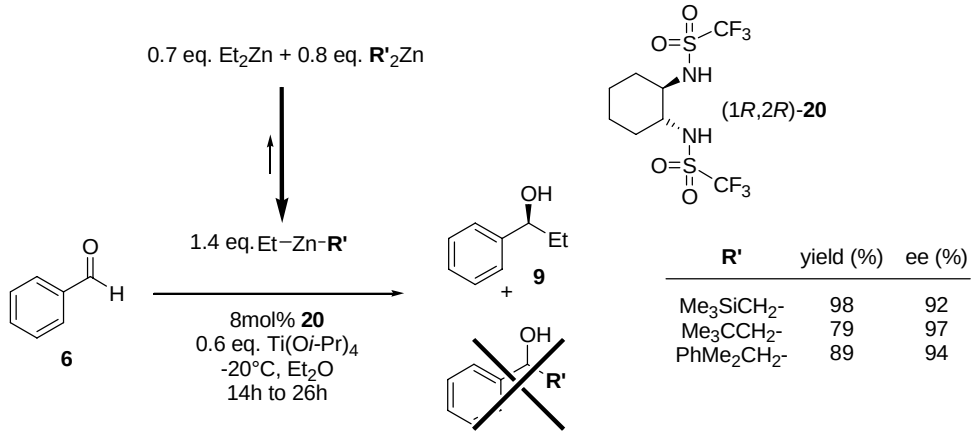
In the reaction of diorganozinc ($R_2Zn$) with an electrophile, only one R group can be transferred. The second organic fragment is thus wasted. This does not make sense if this organic fragment is valuable. A solution could be found by the use of mixed diorganozinc (R'ZnR) carrying the substituent to be transferred and a less reactive, less valuable substituent. Thus, when using a mixture of diphenyl- and diethylzinc in a 1:2 ratio in the presence of ligand **17**, Bolm *et al.* have only observed the transfer of the phenyl fragment onto aldehydes[68,69]. The methyl or ethyl fragments have also been used as non-transferable groups for the addition of alkenyl[54,57,56] and alkynyl[66,65] groups to aldehydes. It therefore seems that the unsaturated fragments are transferred in priority to alkyl groups in a mixed diorganozinc compound (Scheme 12).




**Scheme 12**

Mixed diorganozinc are involved in an equilibrium with the two symmetric diorganozinc compounds[47]. Knochel *et al.* have exploited such an equilibrium to generate mixed diorganozinc compounds starting from the two symmetric diorganozinc compounds. These mixed organozinc compounds have been used for the selective transfer of alkyl groups to Michael acceptors[70-73] and aldehydes[70,71,74]. It is believed that the position of the equilibrium as well as the selective transfer are due to the size of the non-transferable group (**R'**= $-CH_2SiMe_3$, $-CH_2CMe_3$,

$CH_2CMe_2Ph$)[71]. The role of the titanium catalytic complex in these reactions will be discussed later (see page 27) (Scheme 13).



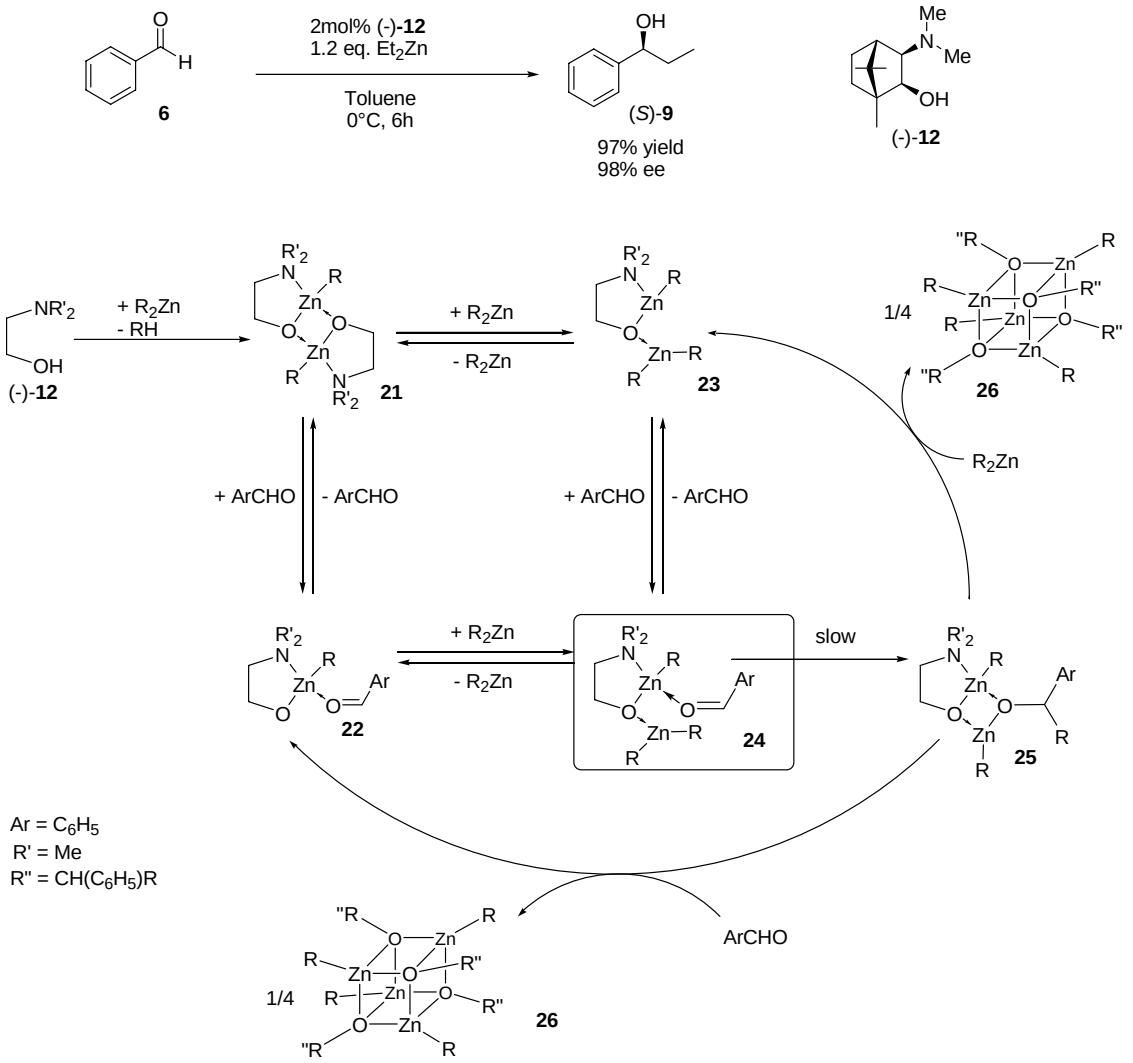

| R' | yield (%) | ee (%) |
|---|---|---|
| $Me_3SiCH_2$- | 98 | 92 |
| $Me_3CCH_2$- | 79 | 97 |
| $PhMe_2CH_2$- | 89 | 94 |

**Scheme 13**

## 2.3.4. Mechanism

In 1986, Noyori *et al.* discovered that 1,2-amino alcohol **12** provided high enantiocontrol in the dialkylzinc addition to aldehydes[40]. This discovery was followed by a thorough study that involved a range of techniques and observations such as kinetic experiments, non-linear effects, NMR and X-ray diffraction of various reaction intermediates, as well as their molecular mass determination by cryoscopy[75-79]. This enabled them to propose a detailed mechanism for the dialkylzinc addition to aldehydes controlled by chiral 1,2-amino alcohols (Scheme 14). This work can certainly be considered as a landmark in asymmetric catalysis.

In a first step, the dialkylzinc reagent acts as a Bronsted base and deprotonates the 1,2-amino alcohol **12** to generate the zinc dimer **21**. This dimer dissociates upon addition of aldehyde which is complexed by a zinc atom in species **22**. This species bears an alkyl fragment and an aldehyde in the same coordination sphere, but it is unable to undergo the intramolecular alkyl transfer reaction. The complexation of a dialkylzinc to an electron-pair of an oxygen atom of **22** leads to the reactive species **24**. This species can also be accessed through dissociation of **21** in the presence of dialkylzinc and then complexation of the aldehyde. In fact, the four species **21**, **22**, **23**, **24** exist as a rapidly equilibrating mixture. Bimetallic complex **24** undergoes an intramolecular alkyl transfer yielding the zinc alkoxide **25** which in the presence of aldehyde or dialkylzinc, decomposes to form a tetrameric zinc alkoxide **26** and regenerates chiral complexes **22** and **23**. The high stability of the tetrameric zinc alkoxide is the driving force of the reaction (Scheme 14).

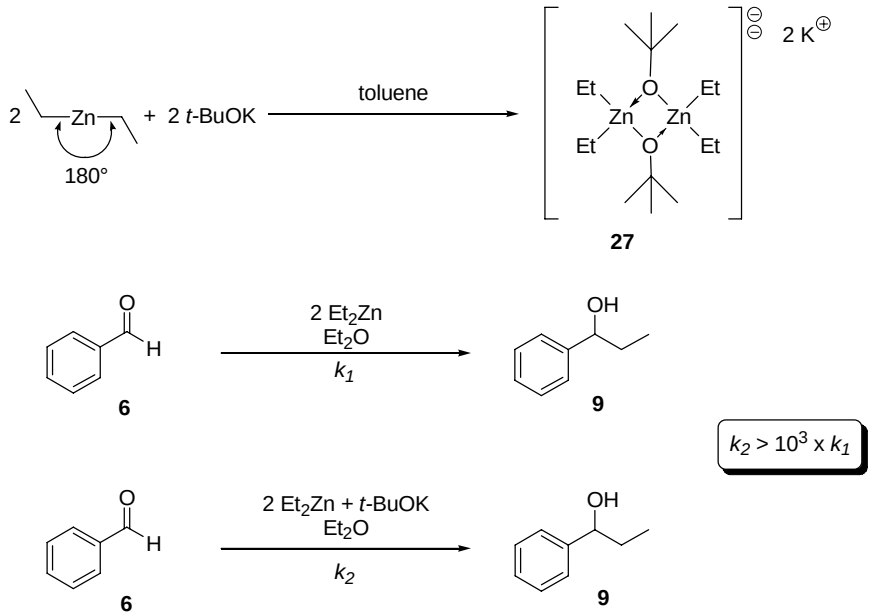



**Scheme 14**

A look at the electronic structure of diorganozinc reagents helps to understand their inherent inertness towards electrophiles such as aldehyde (Scheme 8). The dialkylzincs in non-polar solvents are linear and monomeric. Therefore, the molecule, as a whole, is characterized by a total dipole of zero and is non-polar. Following Pauling's definition of the ionic character between two unlike atoms based on their difference of electronegativities ( $\chi_P^b$(Zn)=2.55 and $\chi_P^b$(C)=1.6), the zinc-carbon bond exhibits only 21% of ionicity. Like most metal-carbon bonds that concern transition metal catalysis, the zinc-carbon bond is therefore best described as a polarized covalent bond[80]. The configuration of the outer electrons of the zinc atom in the ground state is $3d^{10}4s^2$. The zinc atom of a diorganozinc therefore lacks a partially-filled outer shell and only allows for electrostatic interactions with external ligands. The weak Lewis acidity of the zinc that ensues and the covalent nature of the organometallic bond explain the inertness of diorganozinc towards aldehydes in the absence of catalyst [48,81].

If we focus on the intermediate **24** which leads to the addition of the alkyl fragment to the aldehyde, it is clear that the carbonyl is activated through coordination with a zinc atom. In addition, both reaction partners are brought in close proximity which can only facilitate the addition step and help controlling the

face selectivity of the approach of the nucleophilic fragment towards the prochiral double bond. The binding of the diorganozinc to an electron pair from the oxygen in **24** has an added effect on the reactivity of the organozinc. It has been shown experimentally that potassium *tert*-butoxide adds to a linear dialkylzinc compound to form zincate complex **27**. In ether, these complexes exhibit higher reactivity in the addition to aldehydes than the parent diorganozinc[82,83](Scheme 15). Even though no charged alkoxide is involved in **24**, the oxygen chelation of the diorganozinc will bend the diorganozinc, increase the polarity of the C-Zn bonds and make the organic fragments more nucleophilic.




**Scheme 15**

The mechanism in Scheme 14 has been studied by Noyori through computer-assisted molecular modeling of a simplified model (formaldehyde, dimethylzinc and 2-aminoethanol). Elongation of the carbonyl bond confirmed the aldehyde's activation by complexation to the zinc atom (**23** to **24**). Upon complexation with the oxygen atom of **22**, the dimethylzinc bends and the carbon-zinc bond is stretched. From an electronic point-of-view, the formation of **24** is characterized by: (1) a lowering of the energy level of the LUMO of the formaldehyde leading to an enhancement of its electrophilicity; (2) an increase of the energy level of the HOMO of the dimethylzinc indicating an increase in nucleophilicity[77]. This confirms that in addition to a Lewis acidic activation of the aldehyde, the dialkylzinc is also activated by the Lewis base properties of the oxygen atom. This combination explains the success of 1,2-amino alcohols in catalyzing the addition of unreactive diorganozinc towards aldehydes

## 2.3.5. Scope and Limitations of 1,2-Amino Alcohols and Related Ligands

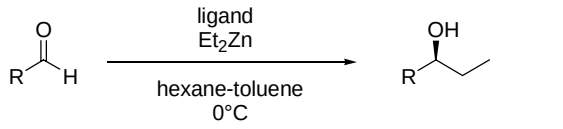
***Diorganozinc Addition to Various Aldehydes***

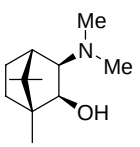
A large number *N,O*-ligands have been evaluated in the enantioselective dialkylzinc addition to aldehydes. In most cases, benzaldehyde and other aromatic aldehydes are tested with success. However this is not always the case with alkylaldehydes (if they are tested and the results published at all). For example,

Noyori's ligand, **12**, gives excellent enantioselectivities for the arylaldehydes, but the addition to alkylaldehydes is not as enantioselective[40]. However, ligand **28**, based on the same chiral backbone as **12**, provides excellent enantiocontrol with $\alpha$-branched alkylaldehydes as well as aromatic aldehydes[84]. There are also ligands, such as sulfonamide-oxazoline **29**, which work very well for a few alkylaldehydes but not as well for arylaldehydes[85]. Therefore, the appropriate chiral ligand has to be found for a particular substrate (Chart 2).

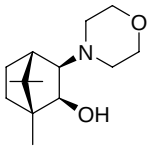
It is interesting to note that enolizable aldehydes undergo an addition reaction rather deprotonation leading to the formation of zinc enolates. Diorganozinc compounds seem less basic than their magnesium and lithium counterparts.

**Chart 2** : Enantioselective addition of $Et_2Zn$ to aldehydes catalyzed by various ligands

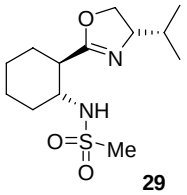


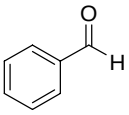
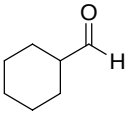
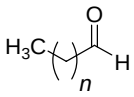

**12**, DAIB




**28**, MIB



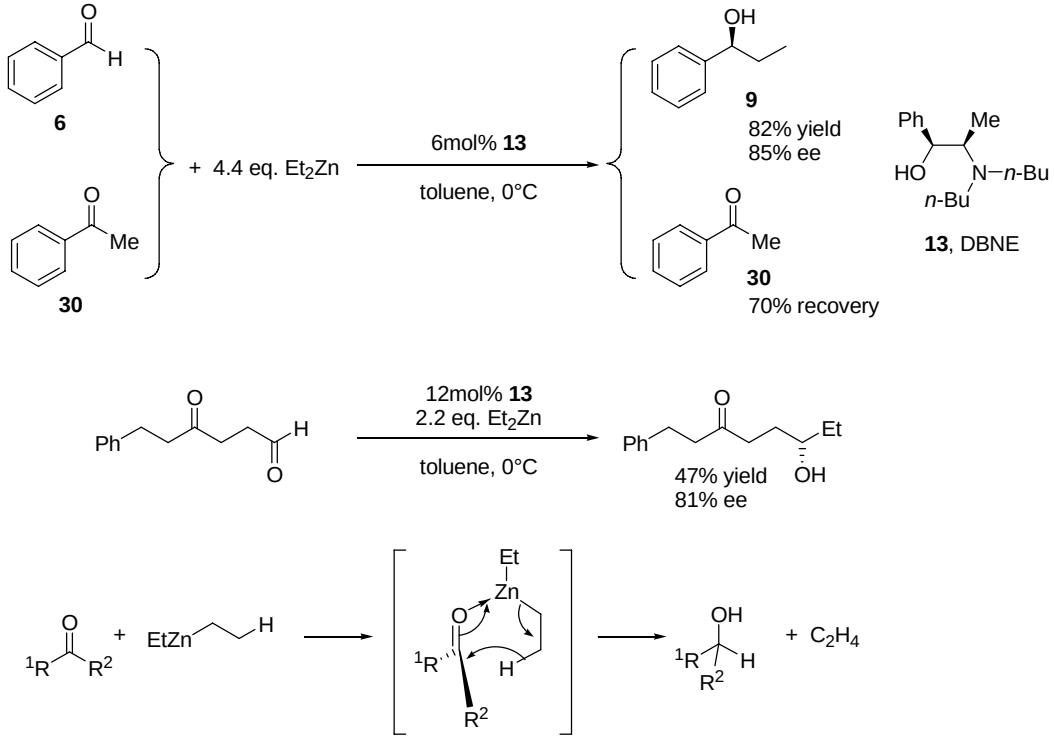

**29**

| Entry | Substrate | Ligand | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 |  | 2 mol% **12** | 97 | 98 |
| 2 | | 5 mol% **28** | 98 | 98 |
| 3 | | 5 mol% **29** | 91 | 86 |
| 4 |  | 2 mol% **12** | - | - |
| 5 | | 5 mol% **28** | 94 | 99 |
| 6 | | 5 mol% **29** | 68 | 98 |
| 7 |  | 2 mol% **12** (*n*=5) | 81 | 61 |
| 8 | | 5 mol% **28** (*n*=4) | 96 | 91 |
| 9 | | 5 mol% **29** (*n*=6) | 95 | 92 |

***Diorganozinc Addition to Ketones***

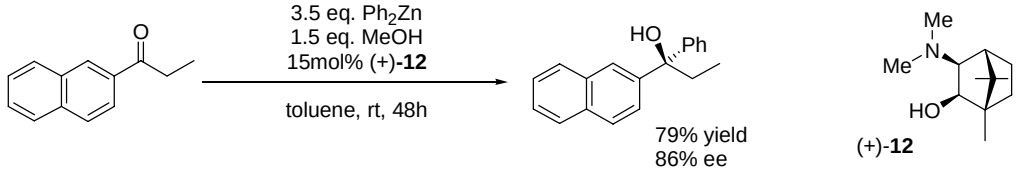
The generation of a chiral quaternary center is a synthetic challenge which could be addressed by the enantioselective addition of an organozinc nucleophile to a ketone. Here, however, the stereodifferenciation of the two electronic pairs of a

carbonyl by a chiral Lewis acid will be less obvious than in the case of an aldehyde. In addition, the carbonyl group of a ketone is less electrophilic than that of an aldehyde. Thus, Soai *et al.* showed that, in the presence of DBNE **13**, diethylzinc selectively reacts with the aldehyde function in a benzaldehyde **6**-acetophenone **30** mixture or in the presence of a keto-aldehyde[86]. Moreover, ketones tend to be reduced by dialkylzinc compounds bearing β-hydrogens. This reduction reaction also occurs with aldehydes but as a slow side-reaction compared to the addition reaction[48] (Scheme 16).




**Scheme 16**

One of the rare examples where an amino alcohol successfully activates the addition of an organozinc compound towards a ketone has been described by Fu. DAIB **12** was found to catalyze the addition of diphenylzinc to ketones[25]. However the addition of 1.5 eq. of methanol was needed in order to obtain good yield and enantioselectivity. A zinc methoxide is probably formed. Part of the success of this reaction could also be assigned to the use of a large excess of a more reactive unsaturated diorganozinc compound which lacks β-hydrogens thus avoiding the parasitic reduction reaction (Scheme 17).




**Scheme 17**

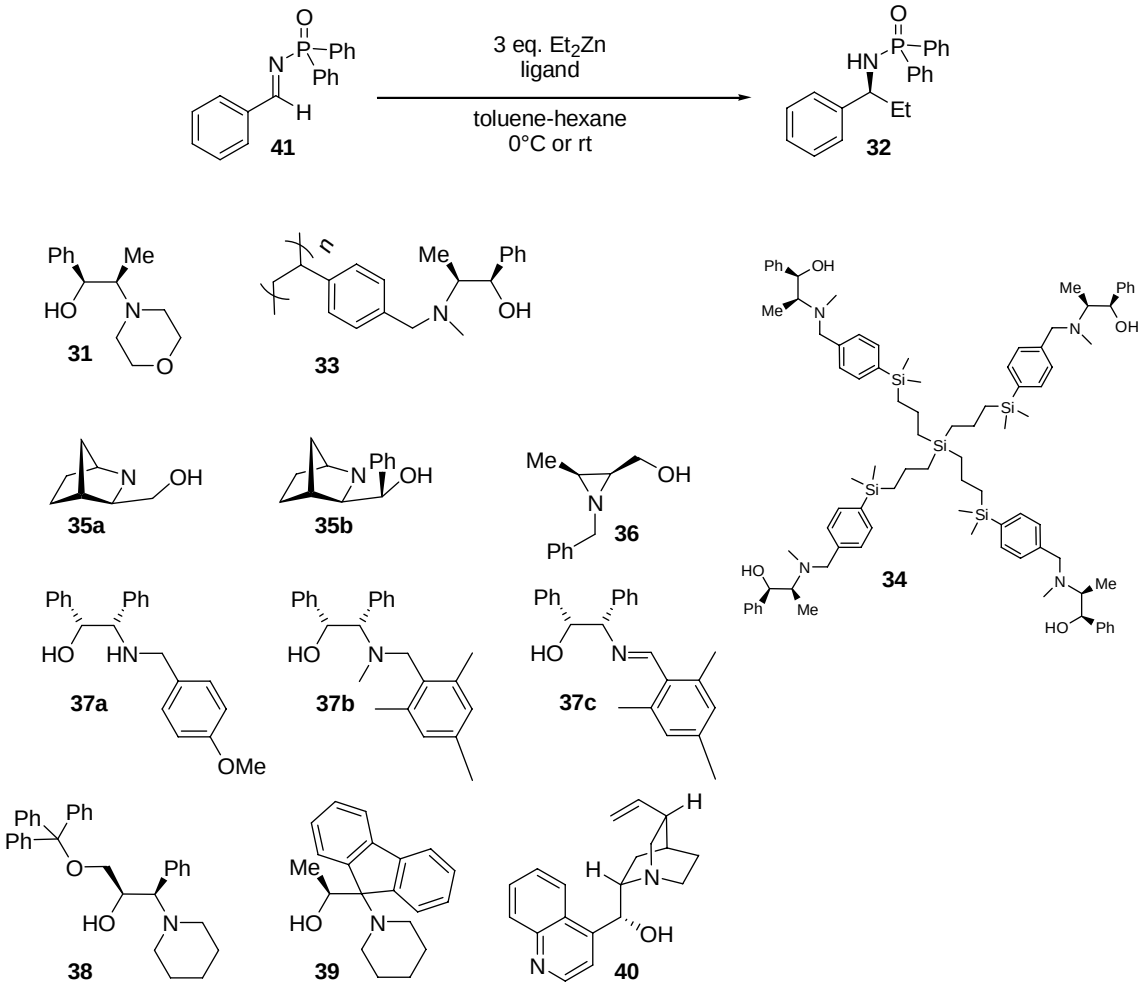
***Diorganozinc Addition to Imines***

The asymmetric addition of organometallic reagents to carbon-nitrogen double bonds in the presence of chiral *N,*O-ligands is underdeveloped compared to the addition to carbonyl groups[23,87,24]. A simple justification is that imines are weaker electrophiles than carbonyls. Moreover, the enolizable imines tend to undergo deprotonation rather than addition. Therefore, the enantioselective addition of an organometallic compound to an imine will require the use of a organometallic which is not a strong Bronsted base while still being nucleophilic enough[87].

It was observed that *N*-aryl and *N*-silyl imines did not react with diethylzinc in the presence of chiral amino alcohols and diols[88]. In 1992, Soai proposed to use imines activated by an electron-withdrawing diphenylphosphinoyl group on the nitrogen. These imines underwent the addition reaction with dialkylzinc compounds in the presence of chiral amino alcohols[89,90]. When a stoichiometric amount of **31** was used, the *N*-phosphinoylamide **32** was obtained in high yield and with good enantiomeric excess. When the ligand loading was brought down to substoichiometric levels, the reaction became slow, the yield decreases and the enantioselectivity slightly eroded. This group did not succeed in finding a true catalytic system. The use of a chiral amino alcohol supported on co-polymers such as **33**[91-94] and dendrimers such as **34**[95,96] also gave good results and allowed an easy recovery of the large amounts of chiral ligand (Scheme 18, entries 1-4 in Table 2).

Other groups have described stereocontrolled additions of dialkylzinc reagents to *N*-diphenylphosphinoyl imines in the presence of chiral 1,2-amino alcohols. Azanorbornyl-alcohols **35a**[97] and **35b**[98,99] and aziridino-alcohol **36**[100,101]described by Anderson *et al.* gave promising results. They provided good enantiocontrol even at substoichiometric loadings but yields were moderate (38 to 75%) and reactions needed 2-4 days (entries 5-9 in Table 2). Gong has developed a large library of successful *N,O*-ligands **37** based on a 1,2-diphenyl-2-aminoethanol skeleton. Stoichiometric amounts of *N*-monosubstituted amino alcohol **37a** provided slightly higher enantiomeric excesses than with their *N,N*-disubstituted counterparts **37b** and imino alcohols **37c** (entries 10-12)[102].

Péricas *et al.* discovered that a bulky silyl chloride in addition to the chiral amino alcohols **38** and **39** improved the enantiocontrol, but the ligand's loading could not be decreased (entries 13-15)[103,104]. In contrast, Beresford was able to lower the loading of cinchonidine alkaloids **40** by adding 2 equivalents of methanol. However an enormous excess of diethylzinc was then needed (entries 16-18)[105,106]. None of these tricks worked with the Andersson's ligand **35b**[99] (Scheme 18, Table 2).


3 eq. Et2Zn
ligand
toluene-hexane
0°C or rt
41
32
31
33
35a
35b
36
34
37a
37b
37c
38
39
40

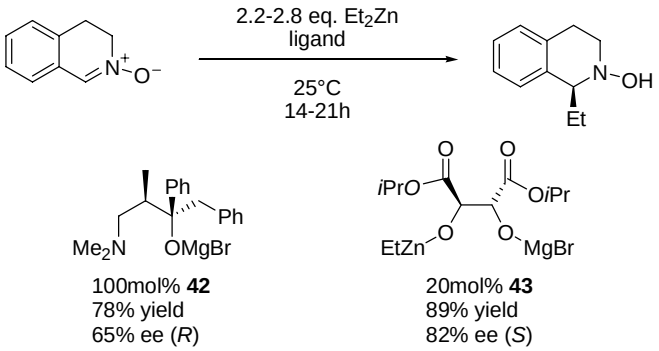
**Scheme 18**

**Table 2**: Addition of $Et_2Zn$ to *N*-diphenylphosphinoyl imine **41** in the presence of amino alcohols

| Entry | Ligand | Loading (mol%) | Additive | $Et_2Zn$ (eq.) | time | yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | **31** | 100 | - | 3 | 22h | 89 | 90 (*S*) |
| 2 | **31** | 50 | - | 3 | 99h | 69 | 85 (*S*) |
| 3[a] | **33** | 100 | - | 3 | 48h | 74 | 89 (*R*) |
| 4[a] | **34** | 100 | - | 3 | 48h | 81 | 82 (*R*) |
| 5 | **35a** | 100 | - | 3 | 48h | 63 | 91 (*S*) |
| 6 | **35a** | 25 | - | 3 | 48h | 46 | 85 (*S*) |
| 7 | **35a** | 10 | - | 3 | 48h | 38 | 68 (*S*) |
| 8 | **35b** | 100 | - | 3 | 48h | 75 | 97 (*S*) |
| 9 | **36** | 100 | - | 3 | 102h | 63 | 94 (*R*) |
| 10 | **37a** | 100 | - | 5 | 48h | 92 | 97 (*R*) |
| 11 | **37b** | 100 | - | 5 | 48h | 94 | 95 (*R*) |
| 12 | **37c** | 100 | - | 5 | 48h | 70 | 95 (*R*) |
| 13 | **38** | 50 | - | 3 | 96h | 82 | 78 (*S*) |
| 14 | **38** | 50 | 1 eq. $i$Pr$_3$SiCl | 3 | 24h | 75 | 79 (*S*) |
| 15 | **39** | 100 | 1 eq. $i$Pr$_3$SiCl | 3 | 24h | 75 | 92 (*S*) |
| 16 | **40** | 100 | | 12 | overnight | 76 | 93 (*R*) |
| 17 | **40** | 20 | | 12 | overnight | 52 | 80 (*R*) |
| 18 | **40** | 20 | 2 eq. MeOH | 12 | overnight | 70 | 93 (*R*) |

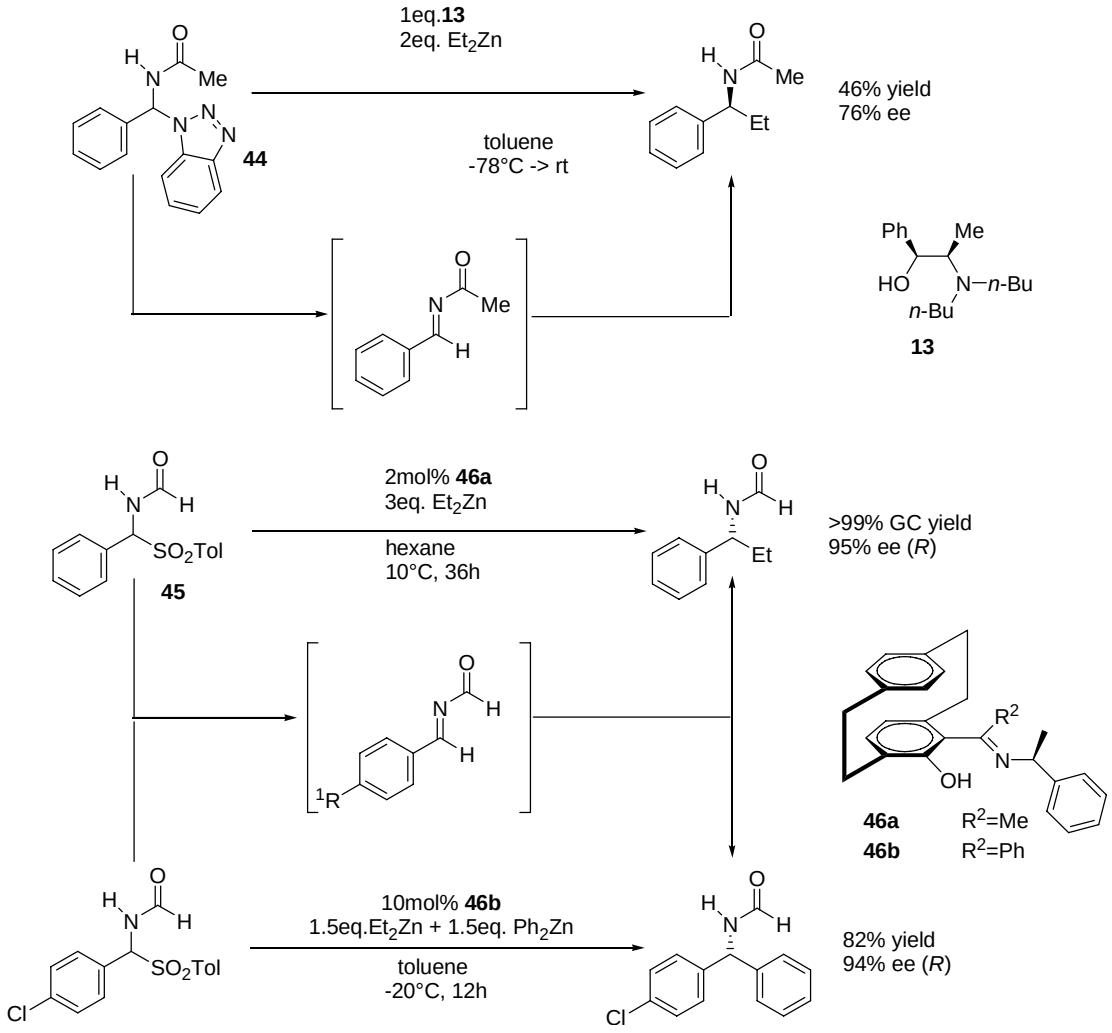
a: ligand loading based on number of chiral sites

The addition of diorganozinc compounds was also tested on other activated imines. *N*-sulfonylimine only gave the racemic adducts in the presence of amino alcohols **36**[100] or cinchonidine **40**[105]. In our laboratory, Delphine Renaut had shown that diarylzinc compounds produced *in situ* could add with some enantiocontrol in the presence of leucinol **2**. However the reaction product was also a catalyst of the reaction itself (Scheme 2, Scheme 3)[12]. Nitrones were tested in the presence of the magnesium salt of amino alcohol **42**[107,108] or the bimetallic salt **43**[109] of a tartaric acid ester which provided moderate to good enantiocontrol at least in the case of cyclic nitrones (Scheme 19).




**Scheme 19**

To our knowledge, *N*-acylimines have never been reported for this kind of reaction. The instability of such compounds towards hydrolysis is partly to blame[110,12]. This problem can be circumvented by using a masked-imine precursor which produces the *N*-acylimine *in situ* upon deprotonation by the diorganozinc nucleophile. In 1992, Katritsky obtained promising enantiomeric excess through such a strategy with *N*-(aminoalkyl)benzotriazoles **44** as imine precursors in the presence of a stoichiometric amount of Soai's DBNE ligand **13**[111]. In 2002, Bräse and Dahmen have used substrates **45** which upon deprotonation generate *N*-acylimines for the highly enantioselective addition of diethylzinc controlled by a catalytic quantity (2 mol%) of [2,2]-paracyclophane-based *N,O*-ligand **46a**[112]. The same system has been used with mixed diorganozinc compounds for the synthesis of chiral diarylmethylamines with catalytic amounts (5-10 mol%) of paracyclophane ligand **46b**. Up to now, all these systems have only been tested on aldimines and not on ketimines (Scheme 20).

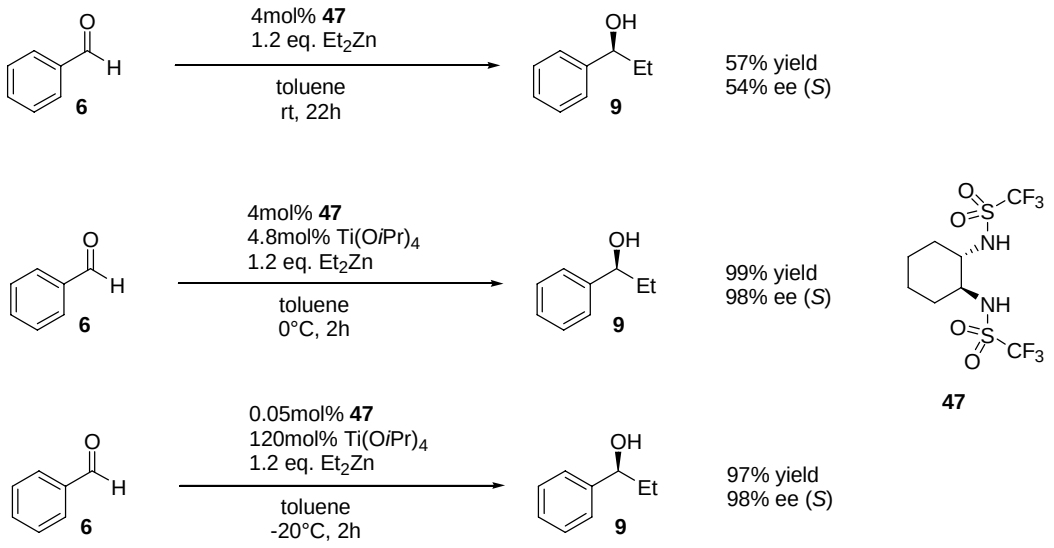



**Scheme 20**

# 2.4. Activation of Diorganozinc Compounds by Titanium Salts

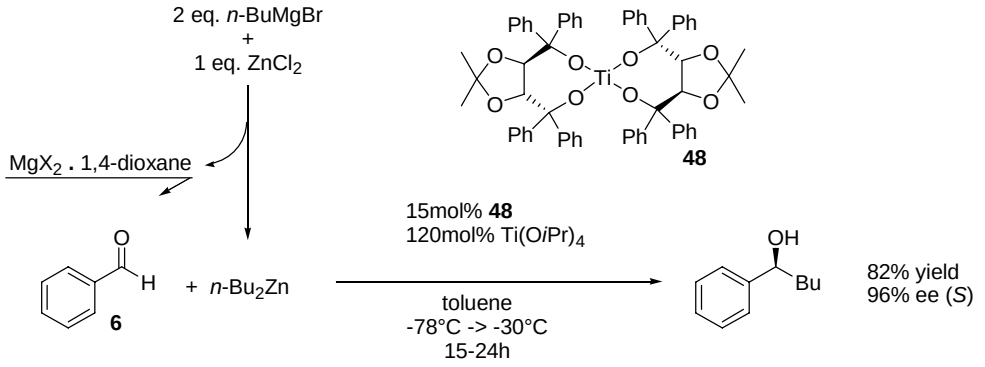
## 2.4.1. Addition to Aldehydes

In 1989, Ohno and Yoshioka described the asymmetric addition of diethylzinc to aldehydes in the presence of chiral *bis*sulfonamide **47** [113-115]. Reactions were found to proceed rather slowly (57% yield in 22 hours) and with moderate enantioselectivity (54% ee). Adding a catalytic amount of titanium *tetra*isopropoxide increased the reactivity of the organometallic complex which resulted in a faster addition and a better enantioselectivity. It was also discovered that the amount of chiral sulfonamide could be decreased to 0.05 mol% without affecting the reactivity and the enantioselectivity if an excess of $Ti(O\textit{i}\text{-}Pr)_4$ was used (Scheme 21). With this system, very high enantioselectivities could also be obtained with aliphatic aldehydes. Knochel's group used this procedure for the addition of highly functionalized diorganozinc compounds.[62,63,74,61,116-118]



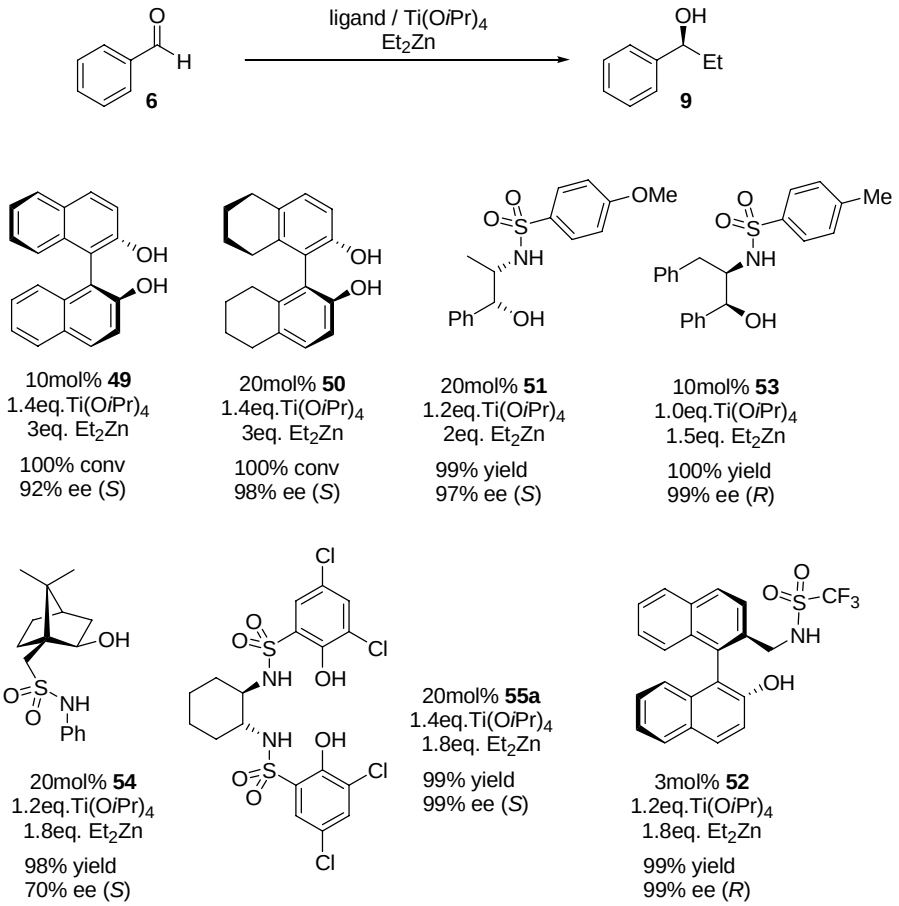

**Scheme 21**

Seebach has successfully replaced the *bis*sulfonamide by a TADDOL-titanium complex **48**[119,120]. The range of diorganozinc compounds used with this system has been widened by the possibility of generating the diorganozinc compounds from Grignard reagents and $ZnCl_2$ and removing the magnesium salts through precipitation with 1,4-dioxane or centrifugation[49,50](Scheme 22).




**Scheme 22**

It was later shown that BINOL **49**[121-124] and partially hydrogenated BINOL **50**[125] also led to a high enantiocontrol. In 1992, inspired by the pioneering work of Reetz[32], Katsuki found that sulfonamido alcohol **51** could induce high ee's for the titanium-catalyzed addition of dialkylzinc to aldehydes[126]. Since then, a range of chiral sulfonamido alcohols have been tested[127-129]. In 2003, Ha reported ligand **52** which gave excellent enantioselectivities (91%-99% ee with a 3mol% loading) for the reaction of diethylzinc with aromatic, aliphatic and conjugated aldehydes. The titanium-based catalysts provide yields and enantioselectivities comparable to that observed for the amino alcohol catalyzed reaction but at a generally faster rate for similar loadings. This higher activity requests however an excess of titanium tetraisopropoxide which makes the procedure less practical (Scheme 23).




**Scheme 23**

## 2.4.2. Mechanism

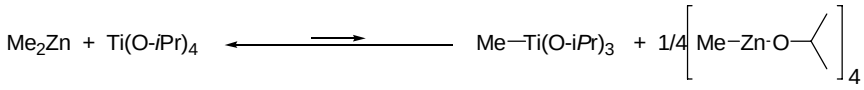
The mechanism of the titanium-catalyzed reaction has been difficult to investigate because of the kinetic lability of titanium alkoxides and their propensity to undergo oligomerization. At this stage, the entire catalytic cycle is uncertain, yet, meaningful pieces are known[‡, 130,131].

What is the role of the dialkylzinc reagent. Is this reagent involved directly in the C-C bond formation or is it only the primary source of the alkyl fragment? In 1986, Reetz had shown that chiral methyltitanium *bis*sulfonamide complexes did transfer their organic substituent to aldehydes in a diastereoselective fashion[32]. Seebach had proposed that the role of dialkylzinc reagents in the TADDOLate-titanium catalyzed reaction was to transfer the alkylgroup to a titanium center, the actual nucleophile being an alkyltitanium species R-Ti-(O-*i*Pr)$_3$[132].

Walsh was able to obtain almost identical enantioselectivities starting from a mixture of of dimethylzinc and Ti-(O-*i*Pr)$_4$ than with preformed Me-Ti-(O-*i*Pr)$_3$ with

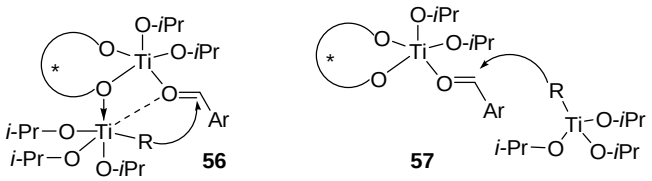
[‡] Unsubstantiated mechanistic hypothesis were made early on[114] Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657, [115] Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691.

BINOL as ligand. Additional proof of the intermediacy of organotitanium came with the observation (NMR) of very small quantities (2-3%) of Me-Ti-(O-*i*Pr)$_3$ and [Me-Zn(O-*i*Pr)]$_4$ upon mixing $Me_2Zn$ with Ti-(O-*i*Pr)$_4$[131]. However, this unfavorable transmetallation equilibrium is displaced towards the organotitanium under catalytic reaction conditions by adding an excess of Ti-(O-*i*Pr)$_4$ and also by the direct consumption of the organotitanium (Scheme 24).



**Scheme 24**

It has been proposed that the transition state for the addition step involves two titanium centers. It is reasonable to think that one titanium center activates the carbonyl through complexation and induces the facial discrimination through a complexed BINOL unit. The second titanium center delivers the nucleophilic fragment to the activated C=O bond. Because of the tendency of BINOLate-titanium complexes to associate[133], Walsh *et al.* are in favor of a binuclear species **56** with the two titanium centers bridged through an oxygen atom compared to two independent titanium moieties **57**[131] (Scheme 25).

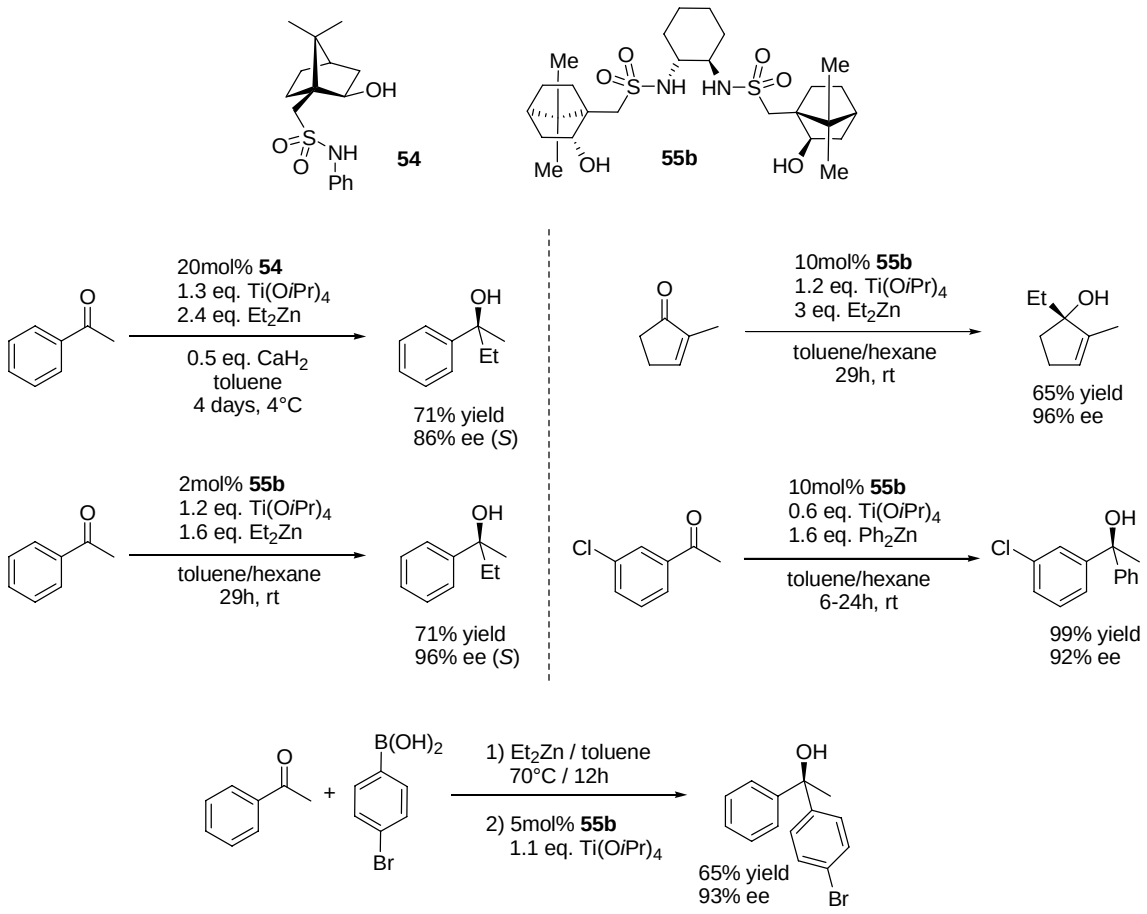


**Scheme 25**

## 2.4.3. Addition to Ketones

In 1998, Yus reported the first use of titanium catalysts for the enantioselective addition of diorganozinc to the less electrophilic ketones in the presence of sulfonamido alcohol **54** [134,135]. The reaction was much slower (1 hour for benzaldehyde *vs* 4 days for acetophenone) than the corresponding additions to aldehydes[128] (Scheme 23 & Scheme 26).

Independently both Walsh and Yus showed that the use of a *bis*(sulfonamido alcohol) **55b** improved the rate and increased the enantioselectivity of the alkylation of ketones[136,137]. The ligand was then applied to the enantioselective 1,2-addition to conjugated enones[138]. Under these conditions, diphenylzinc[139,140] or mixed diorganozinc obtained from arylboronic acids[139] reacted with ketones with good to excellent enantioselectivities (Scheme 26).

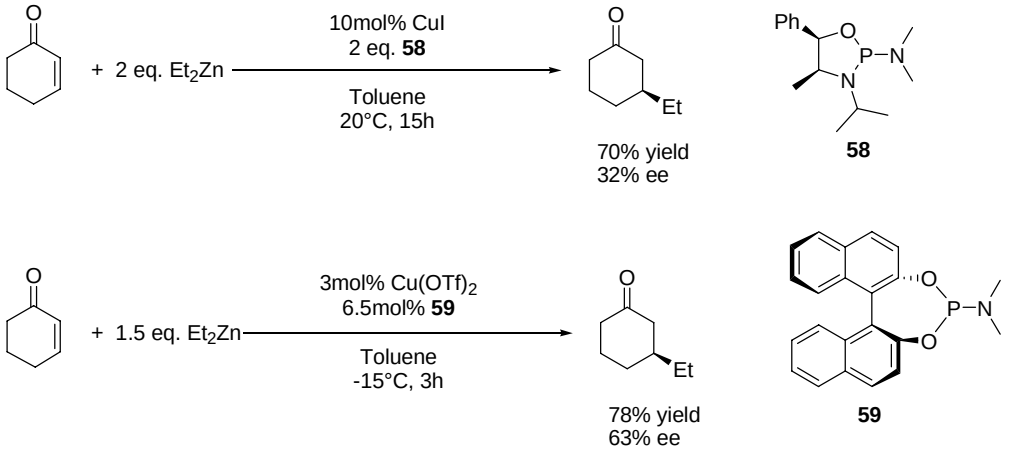



**Scheme 26**

# 2.5. Activation of Diorganozinc Compounds by Copper Salts

## 2.5.1. Michael Additions

Following the ground-breaking work of Lippard *et al.* in 1988[141], a large number of publications have been dedicated to the enantioselective Michael addition of organolithium, organomagnesium and organocopper reagents in the presence of chiral catalysts[142-145]. The addition of diorganozinc compounds to enones catalyzed by a chiral copper-phosphine **58**[146] catalyst was first described by Alexakis[147] in 1993. The major improvements were brought up by Feringa in 1996 who used copper(II) triflate in the presence of atropoisomeric phosphoramidite **59**[148] (Scheme 27).




**Scheme 27**

Since then a variety of phosphorus based ligands have been successfully used for these Michael additions : excellent yields and enantioselectivities have been observed for a large spectrum of activated olefins (cycloenones, chalcones, acyclic enones, nitroolefins). Feringa's $C_2$-symmetric phosphoramidite **60**[149], its simplified version **61** by Alexakis[150], the TADDOL derived phosphonamidite **62**[151] and the phosphonite **63**[152], the *P,N*-ligands developed by Pfaltz[153] **64** and Zhang[154] **65**, the three binaphtol units of Chan's ligand **66**[155] and Reetz's ferrocene-based diphosphonite **67**[156] are particularly interesting. The development of families of highly-modular amino acid-based ligands has been carried out by Hoveyda *et al.*. Two of these, **68** and **69**, have proved successful for the asymmetric conjugate addition of problematic substrates such as trisubstituted cyclic enones[157] and acyclic aliphatic enones[158]. Leighton's sulfonamido-phosphine **70** has been successfully used at loadings as low as 0.25 mol%[159] (Figure 8).

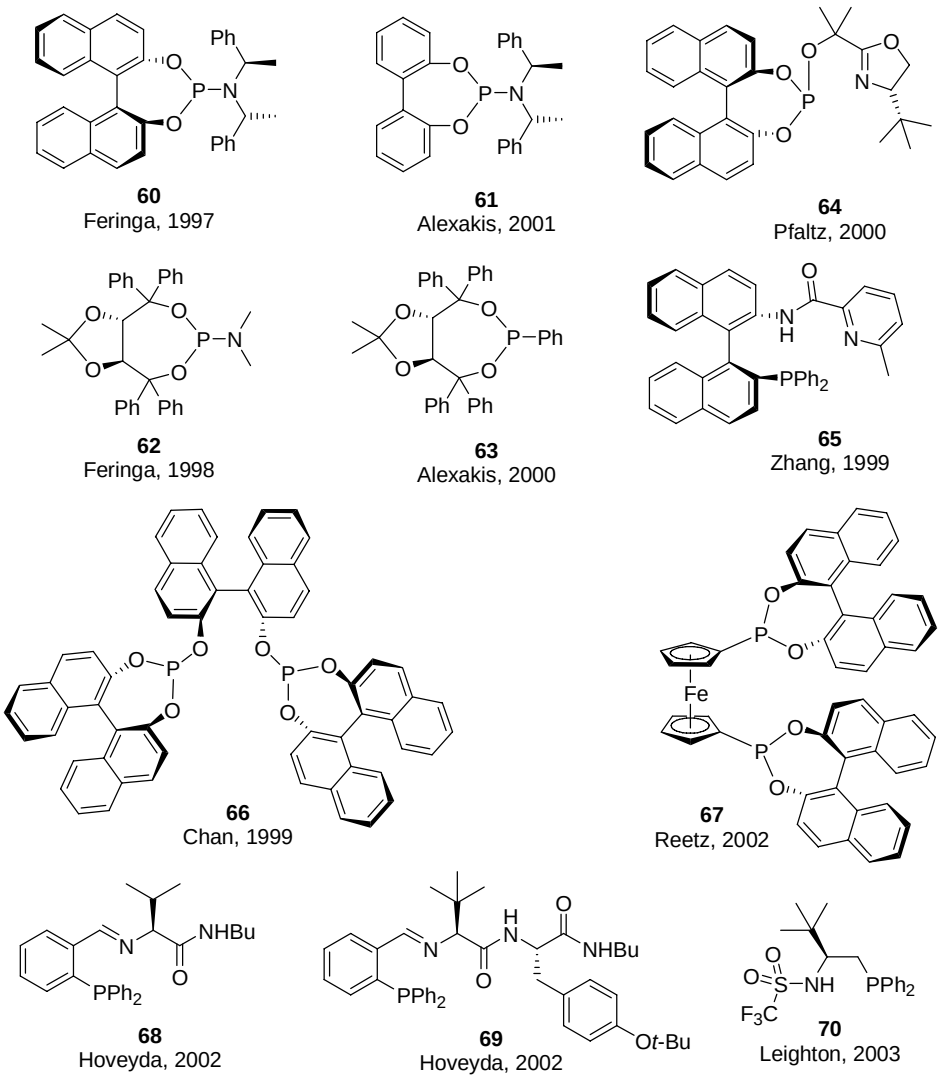
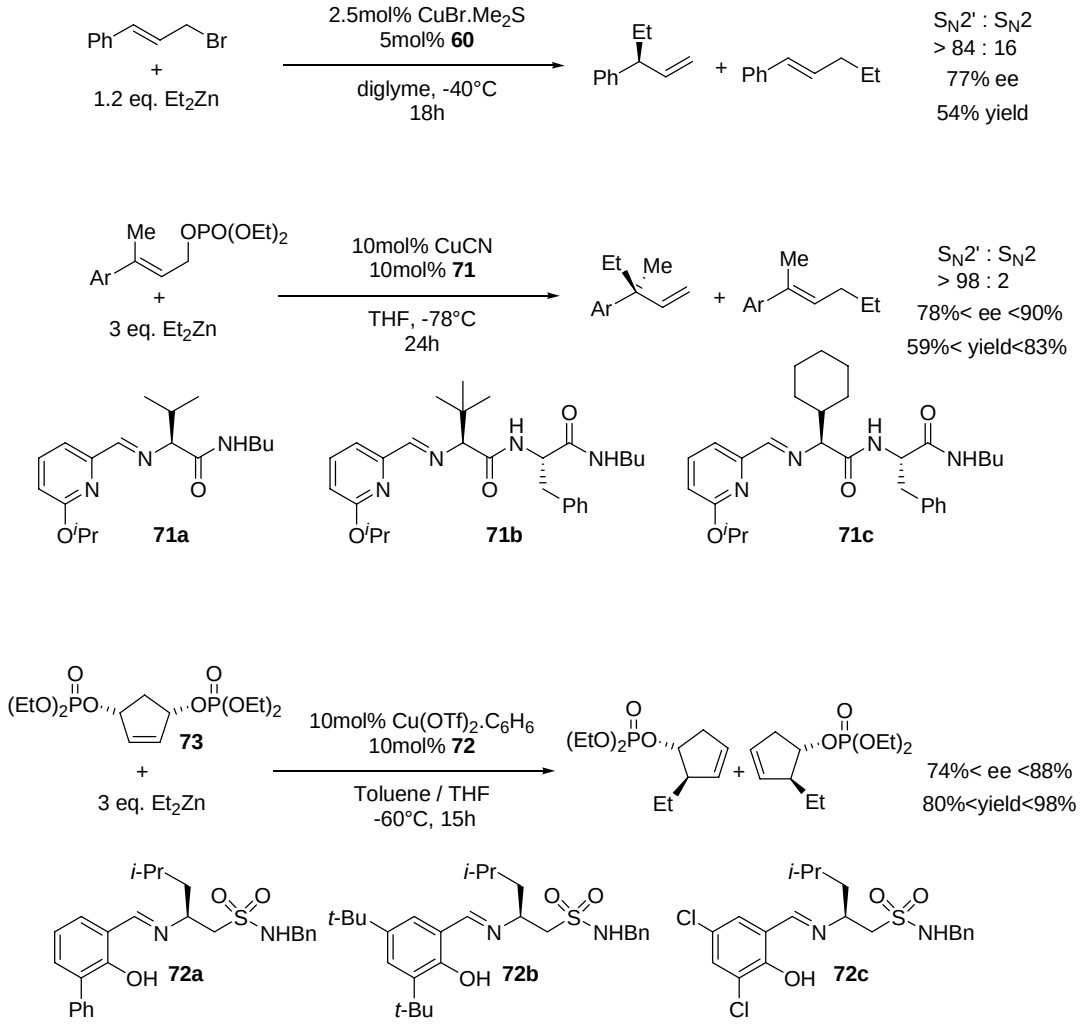



**Figure 8**

## 2.5.2. $S_N2'$ Substitution Reactions

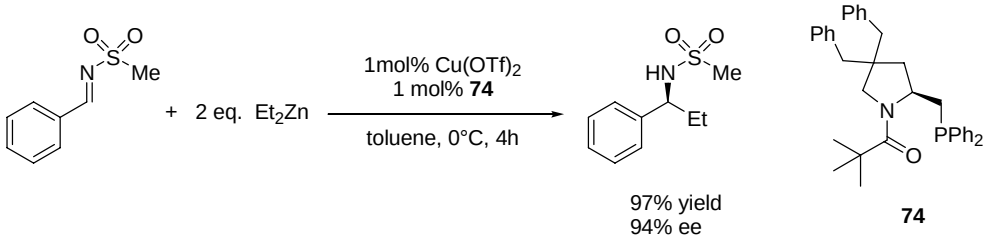
Asymmetric allylic substitution ($S_N2'$) can be readily effected with diorganozinc compounds in the presence of copper(I) catalysts and a phosphoramidite ligand such as **60**. This led to a good regioselectivity in favor of the $S_N2'$ product and encouraging enantioselectivity[160]. The development of new modular ligands **71** by Hoveyda *et al.* allowed the creation of chiral quaternary carbons through allylic substitution of allylic phosphates. The reactions proceeded with good to high enantioselectivity and excellent regiocontrol[161]. The use of combinatorial screening of ligands has led to the discovery of a series of ligands **72** for the desymmetrization of *meso*-cyclic allylic *bis*diethylphosphonate[162]. In this preliminary study, the product was obtained with excellent regio and diastereoselectivities, fair enantioselectivities and quantitative conversions for the cyclopentene derivative **73** (Scheme 28)




**Scheme 28**

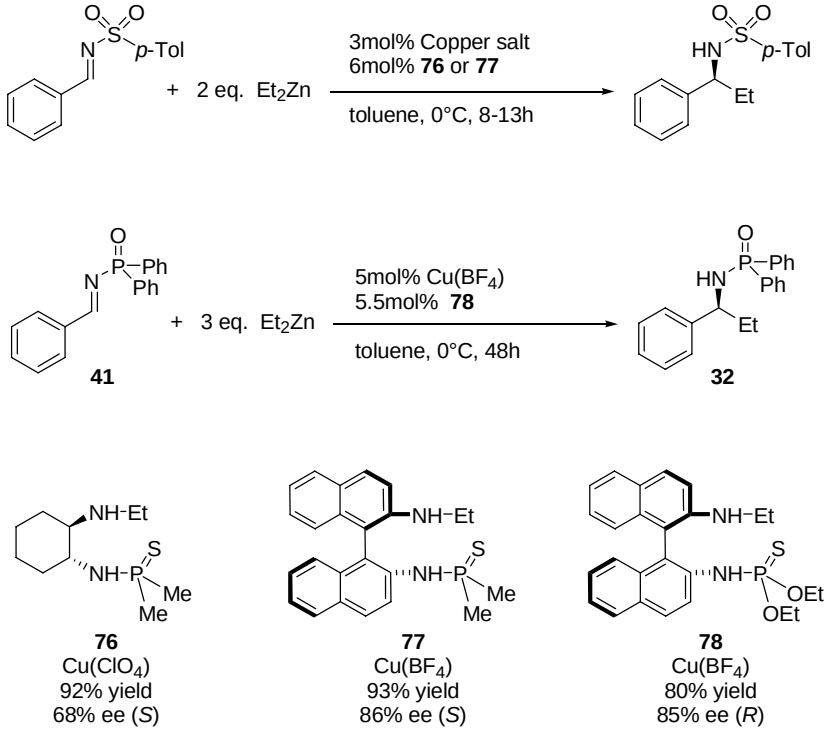
## 2.5.3. 1,2 Addition on Imines

A combination of copper(II) triflate-diethylzinc has been used for the asymmetric alkylation of imines in the presence of a chiral ligand. Amidophosphine **74**, reported by Tomioka *et al.*, was the first ligand giving a high enantioselectivity in the addition to *N*-sulfonylimines (up to 94% ee with only 1 mol% ligand). The use of a diphosphine such as (*R*)-BINAP **75** was not successful (only 2% ee with 20 mol% ligand)[163-165] (Scheme 29).



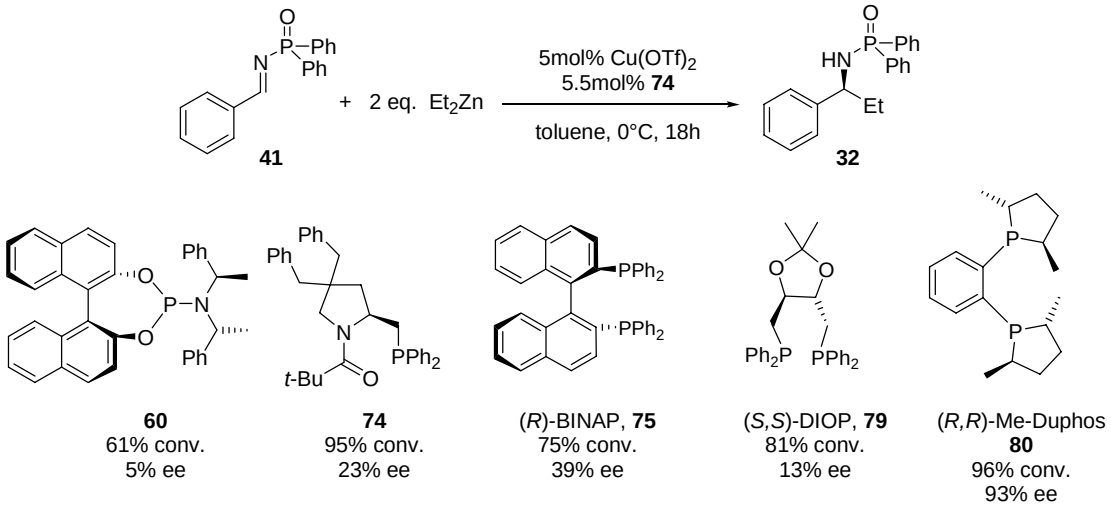

**Scheme 29**

Shi has developed a series of amino-thiophosphoramide ligands derived from chiral $C_2$-symmetric diamines. Ligand **76** has been used in conjunction with a copper salt to catalyze the addition of diethylzinc on *N*-sulfonylimines with ee's up to 74%[166]. With **77,** the enantioselectivity went up to 93% ee[167]. The highest enantioselectivities were observed when using ligand **78** and *N*-phosphinoylimines[168]. In all cases, the replacement of the sulfur atom by an oxygen decreased the catalytic activity showing that the sulfur atom is needed for complexation to the copper salt (Scheme 30).



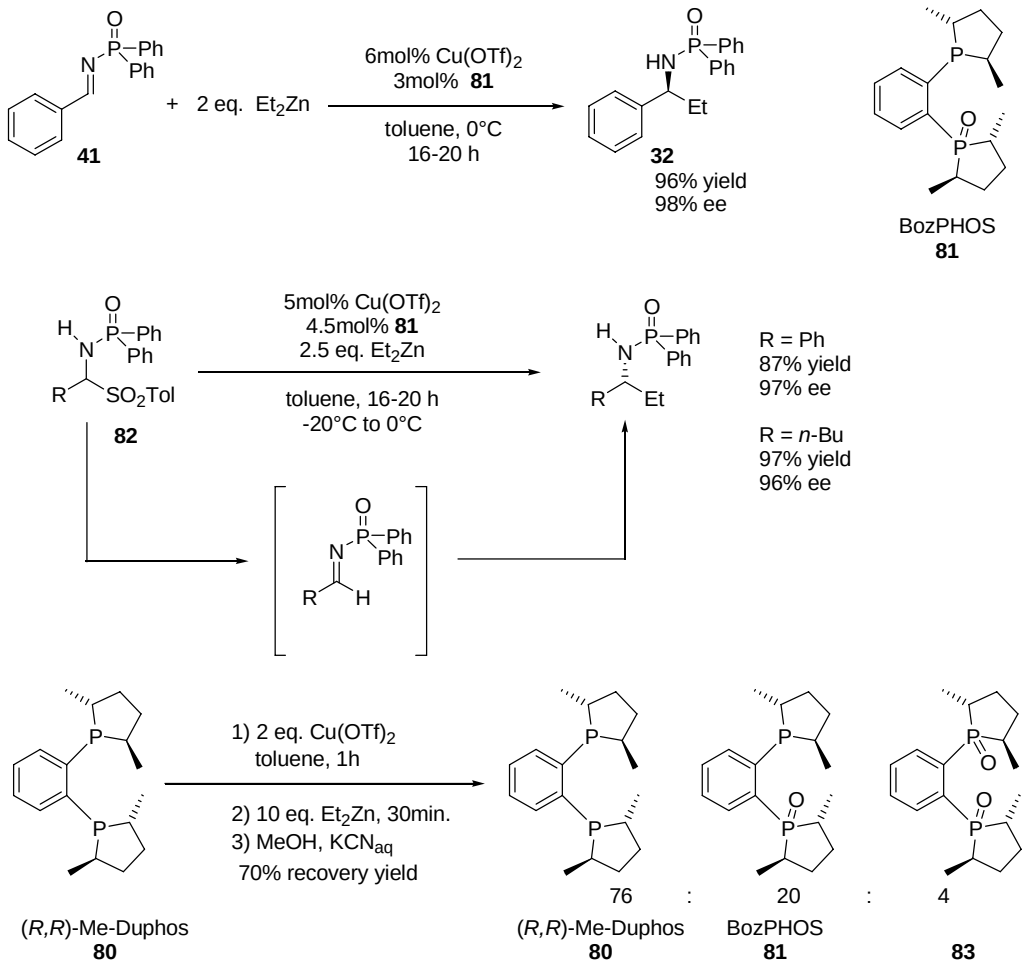

**Scheme 30**

In 2003, Charette reported on the addition of diethylzinc on *N*-phosphinoylimines in the presence of copper(II) triflate and chiral phosphorus ligands[169]. Phosphoramidite **60**, amidophosphine **74** as well as diphosphines BINAP **75** and DIOP **79** proved deceiving chiral inductors. However, the use of catalytic amounts of diphosphine (*R,R*)-Me-DuPHOS **80** provided excellent enantioselectivities (Scheme 31).




**Scheme 31**

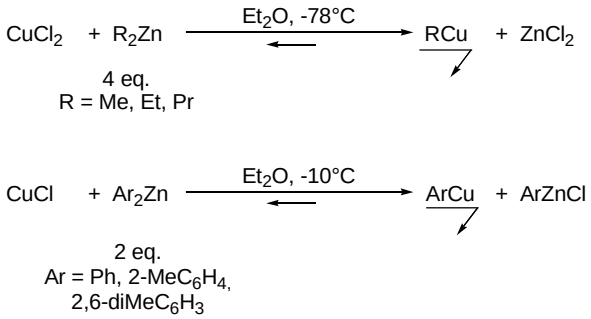
The use of diphosphine oxide ligand, BozPHOS **81**, further improved the enantioselectivity of the copper-catalyzed diethylzinc addition to *N*-phosphinoylimines[170] and to their masked analogs **82** [171]. It has been recently shown that the diphosphine **80** is oxidized by copper salts to the monoxide **81** and the *bis*oxide **83** under the catalytic conditions if traces of oxygen are not excluded[172] (Scheme 32).




**Scheme 32**

## 2.5.4. Mechanistic Considerations

The transmetallation reaction between diorganozinc compounds and copper salts was first used in 1859 by Buckton to access an organocopper reagent starting from copper(I) chloride and diethylzinc[173]. In 1968, Thiele and Köhler[174] obtained and properly characterized the first organocopper starting from a diorganozinc compound. Pure alkylcopper were prepared and isolated from anhydrous copper(II) chloride and dialkylzincs at low temperature. A large excess of dialkylzinc is used to first reduce the copper(II) chloride to a copper(I) species followed by the transmetallation step[174]. Arylcopper compounds have been prepared through transmetallation of copper(I) chloride with diarylzinc compounds[175]. Note that in both cases, the production of the organocopper compound is favored by the precipitation of the organocopper reagents under polymeric form (Scheme 33).



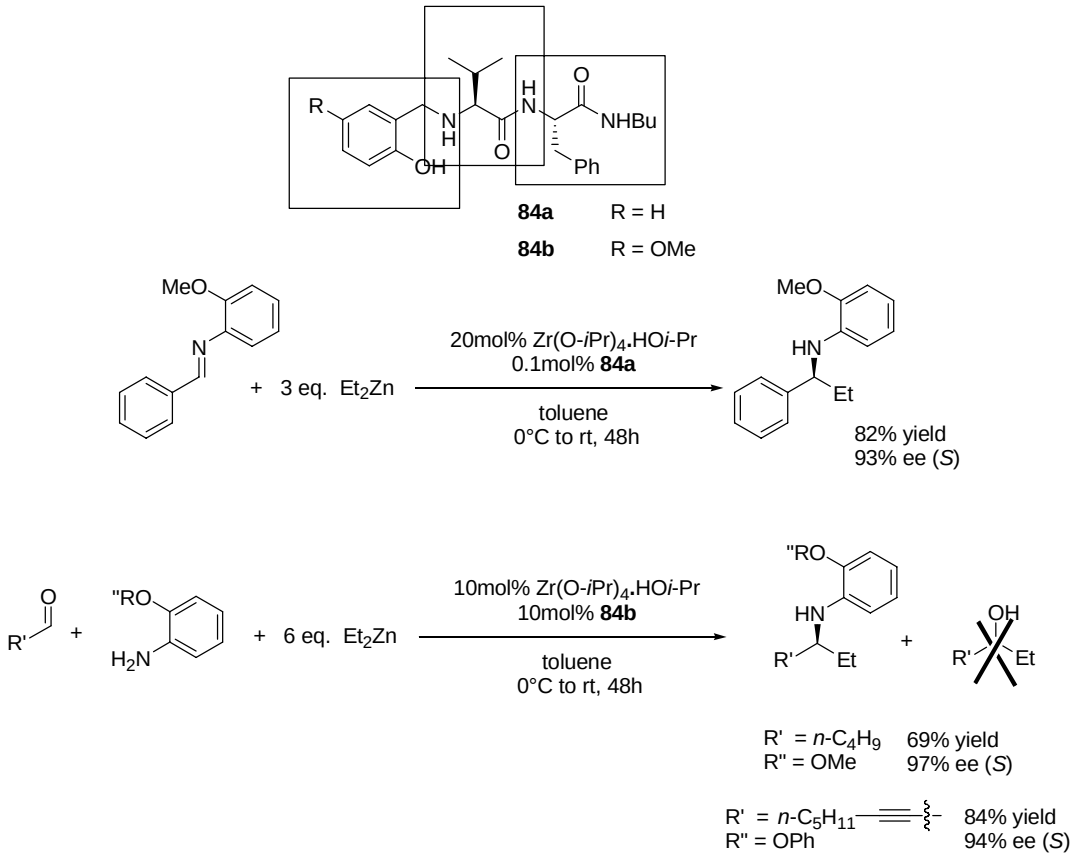

**Scheme 33**

Both copper(I) and copper(II) salts showed similar activity in the catalytic Michael addition[142]. The copper(II) precursors are reduced *in situ* by the diorganozinc compound yielding a copper(I) species[148,142]. This was confirmed by an EPR experiment showing that copper(II) triflate is reduced by an excess of diethylzinc[176].

It is expected that copper-catalyzed 1,2-addition of diorganozinc to imines also involves organocopper species. In the presence of catalytic amounts of the copper salts, the transmetallation equilibrium should be pushed towards the organocopper .

## 2.6. Activation of Diorganozinc Compounds by Zirconium Salts

Citing all the catalyzed reactions involving diorganozinc compounds would not be justified as most examples are of little interest to the subject of 1,2-addition to carbon-heteroatom double bonds which we are studying. Yet, we cannot do without mentioning the extraordinary results reported in 2001 by Hoveyda and Snapper in the enantioselective addition of diorganozinc to unactivated *N*-aryl imines[177]. The parallel screening of a family of ligands in conjunction with zirconium tetraalkoxide led to the identification of ligand **84** giving excellent enantioselectivities even at loading down to 0.1 mol%. This catalytic system was also effective with aliphatic imines[178] and alkynyl imines[179] generated by *in situ* condensation of the amine and the respective aldehyde. Quite extraordinarily, no addition to the more electrophilic aldehyde occurred. The low loading of chiral inductor, the yields and enantioselectivity together with the substrate specificity are remarkable features of this reaction (Scheme 34).




**Scheme 34**

## 2.7. Conclusions

In this chapter, we have reported on the use of diorganozinc compounds in enantioselective catalysis with a special interest towards 1,2-addition reactions to aldehydes, ketones and aldimines. The chapter covers the literature up to April 2005 and shows that several research groups have been very active and successful in finding solutions while we were working on the subject. Here are some of lessons from the literature that we could use at the start of our investigation :

- The weak reactivity compounds towards the electrophilic substrates inherent of diorganozinc warrants the absence of an uncatalyzed "background" reaction which would deplete the enantiomeric excess.

- Some form of activation was required for a successful addition of the diorganozinc: (1) the substrate can be activated through Lewis acid complexation, (2) the nucleophilicity of diorganozinc can be increased through coordination with a Lewis base forming an ate complex, (3) the nucleophilic fragment can be transferred from the diorganozinc to a suitable metal through transmetallation. When mechanisms were investigated, combination of the substrate's activation and the organometallic activation have been found.

- The catalytic systems based on 1,2-amino alcohols and related ligands showed limitations when applied to less electrophilic substrates such as imines and ketones.

- The titanium-catalyzed addition of diorganozinc compounds to carbonyl compounds in the presence of chiral diols, *bis*sulfonamide or sulfonamido alcohol ligands provided excellent enantioselectivities but required a large amount (0.6 eq.-1.4 eq.) of $Ti(O\text{-}iPr)_4$.

# Chapter 3

# Sulfonamido Alcohols

## 3.1. Hypothesis

At the starting point of this thesis, the enantioselective catalyzed addition of diorganozinc compounds to aldehydes had already been well documented[22] (see page 20). C-C bond formation through enantioselective addition of diorganozinc to imines was much less developed[23] (see page 23). The use of catalytic amounts of chiral amino alcohol ligands which were so successful for aldehydes had not yet been transposed successfully to C=N bonds. A stoichiometric amount of *N*,O-ligands was required to obtain the chiral amine in good yield with a enantiomeric purity. Our analysis based on the literature of the time was that the lack of reactivity of diorganozinc compounds towards imines was due to insufficient activation of the reaction partners by the active catalyst generated *in situ* from amino alcohols.

How could we achieve a better activation of the reaction partners in the diorganozinc addition to imines? We postulated that a similar active species would be present in the amino alcohol catalyzed addition of diorganozinc to imines as the one described by Noyori for aldehydes[75-79]. The two key features are a Lewis acidic zinc center activating the carbon-heteroatom double bond and an oxygen atom activating the diorganozinc by generating an ate-type complex. The modification of one of these two points could lead to a more active catalyst that could be applied to the less electrophilic imines. In particular, we thought about increasing the Lewis acidity of the zinc center by grafting an electron-withdrawing group (EWG) on the nitrogen atom (Figure 9).

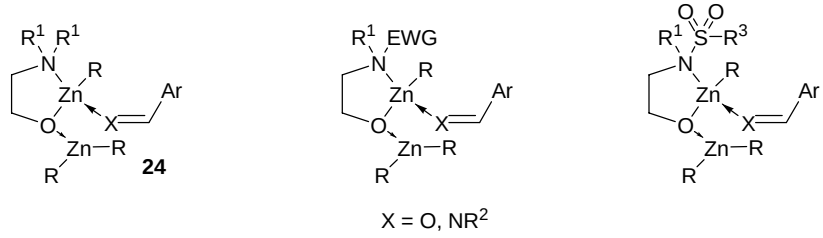



**Figure 9**

Due to previous observations from our laboratory that chiral sulfonamides could influence the course of the diarylzinc addition to *N*-sulfonylimines (see **Scheme 3**), we chose to use a sulfonamide as electron-withdrawing group. The electronic and steric properties of the sulfonamide can be tuned by modifying the nature of the $R^3$ group to provide a variety of chiral 1,2-sulfonamido alcohols. At the time, there were only few reports on the use of β-sulfonamido alcohols ligands for the catalysis of addition of dialkylzinc to aldehydes[129,180,126,128,134,181] and ketones[135]. In the reported examples, the presence of titanium tetraisopropoxide was required (see **51**, **53**, **54**, **55a, 55b** in **Scheme 23** and **Scheme 26**).

It occurred to us that a property of sulfonamide ligands might be of additional interest in enantioselective catalysis. The crystal structures of several metallic complexes carrying a sulfonamide ligand, e.g. **85**[182], **86**[183], **87**[184], showed that the

sulfonamide function could act as a bidentate ligand. However, we have not found such a crystal structure for a zinc complex (Figure 10).

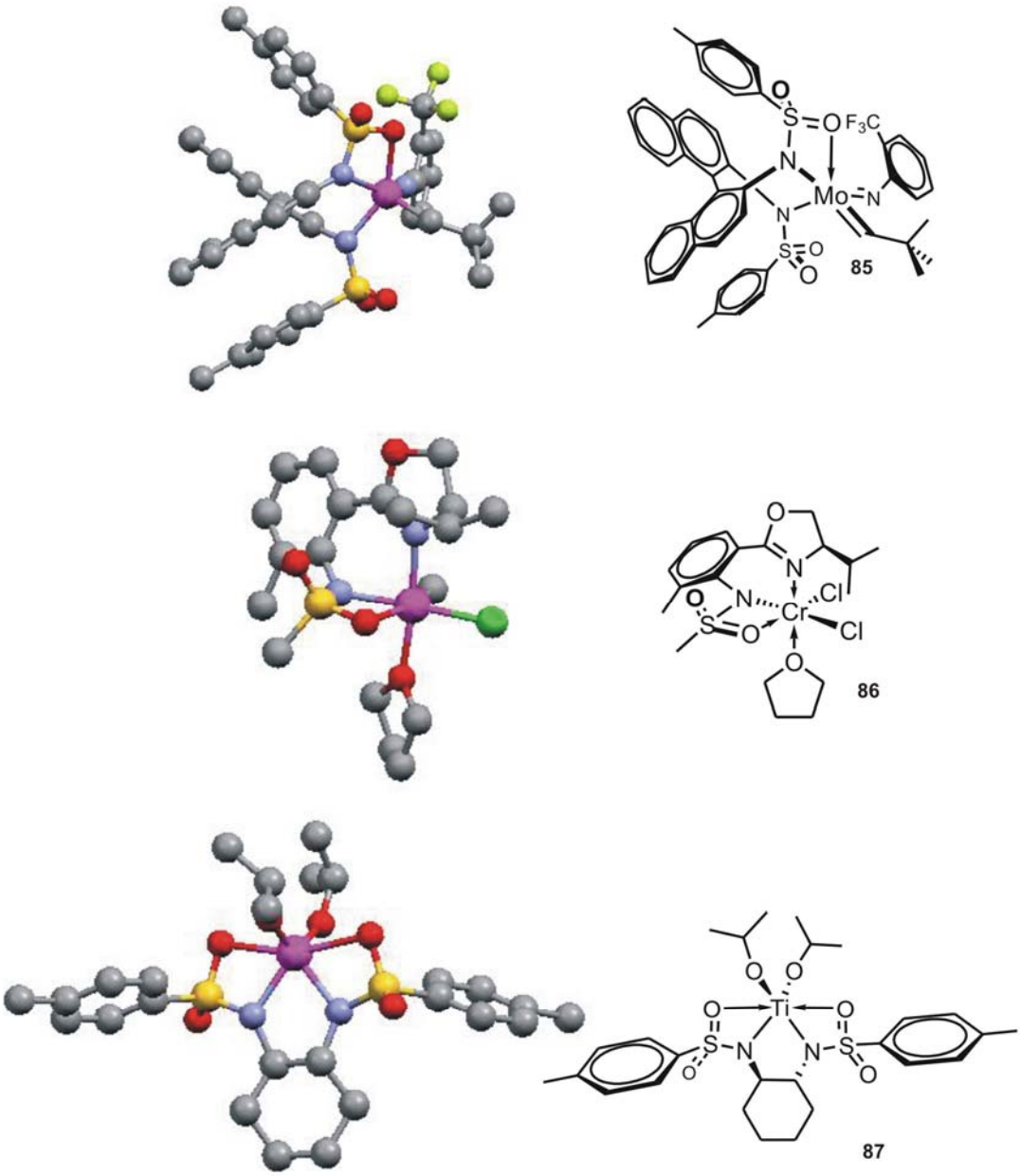



**Figure 10**

If complexation of the metal by one of the oxygen of the sulfonamide occurs, the two oxygen atoms are now different and the sulfur atom becomes a chiral center. If the sulfonamide is part of a chiral ligand, the newly created equilibrating chiral center on sulfur being closer to the reactive center should help with the transfer of the chiral information from the ligand backbone to the prochiral substrate (Figure 11).

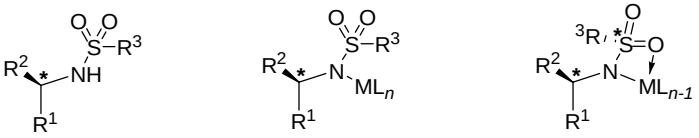


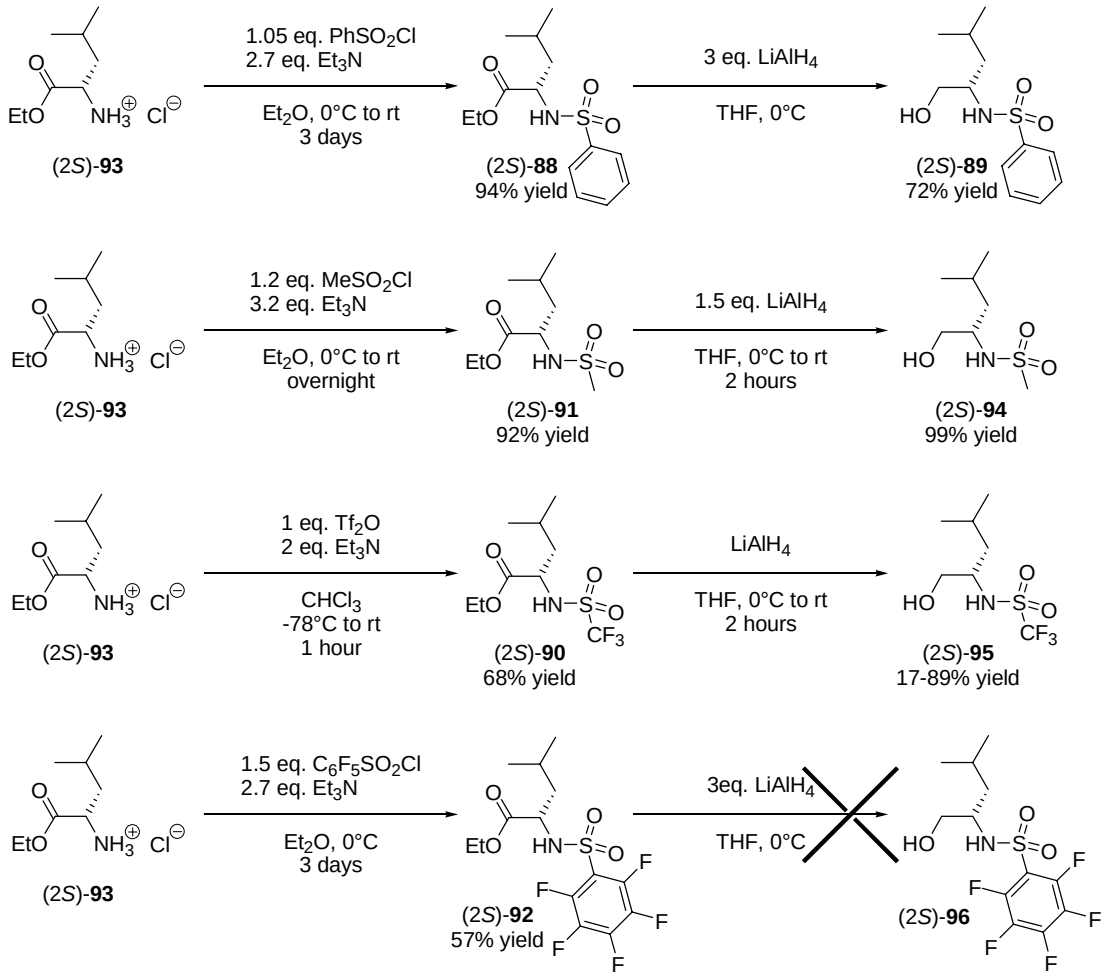

**Figure 11**

# 3.2. Ligand and Substrate Synthesis

## 3.2.1. Ligands

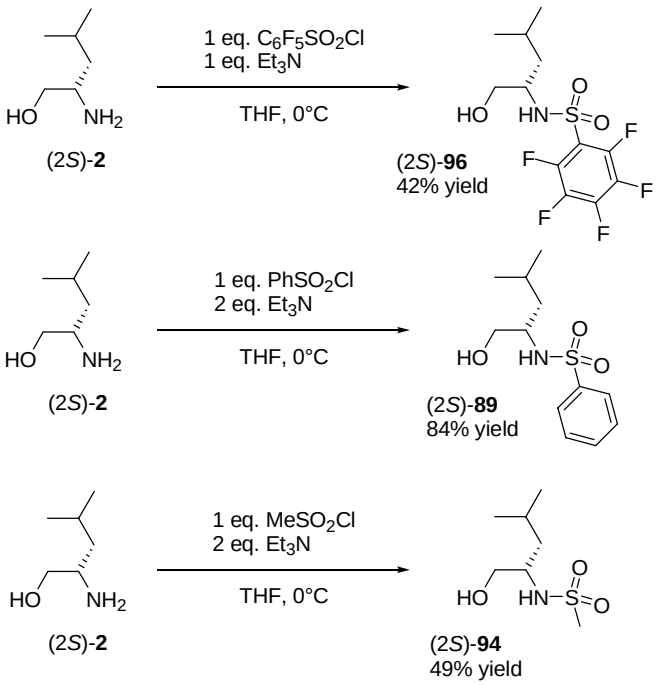
Our first generation of 1,2-sulfonamido alcohols ligands were derived from the natural amino-acid (*S*)-leucine.

The commercial salt of the ethyl ester of (*S*)-leucine was readily sulfonylated with phenyl, methyl and pentafluorophenylsulfonyl chlorides as well as with triflic anhydride in the presence of triethylamine. The reduction of the phenylsulfonamido ester (2*S*)-**88** with lithium aluminum hydride gave the desired sulfonamido alcohol (2*S*)-**89** in high yield. Trifluoromethylsulfonamido ester (2*S*)-**90** and methylsulfonamido ester (2*S*)-**91** were also readily reduced with lithium aluminum hydride but the products could only be extracted from the reaction mixture by direct acidification of the reaction media with aqueous HCl followed by neutralization with aqueous NaOH. The reduction of the pentafluorophenylsulfonamido ester **92** was problematic: the appearance of signals characteristic of aromatic protons in $^{1}$H NMR spectra of the crude mixtures indicated that a nucleophilic substitution of a fluorine by an hydrogen had occurred (Scheme 35).



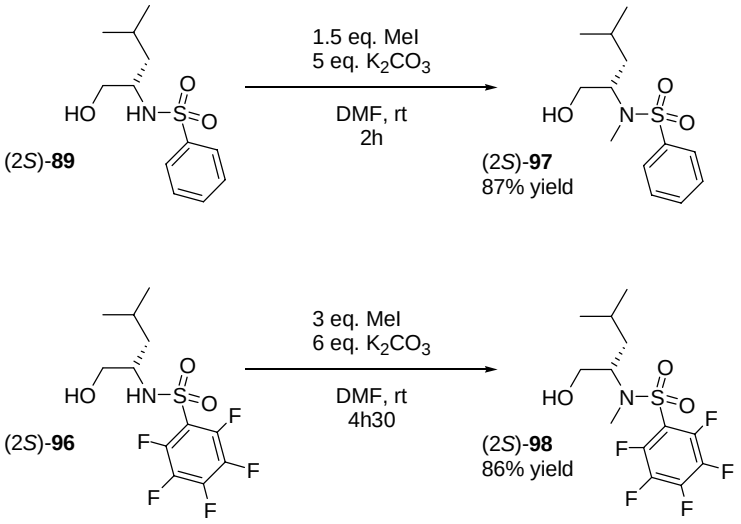

**Scheme 35**

We then carried out the direct and regioselective *N*-sulfonylation of (2*S*)-leucinol. Sulfonamido alcohols (2*S*)-**96**, (2*S*)-**89** and (2*S*)-**94** were obtained in moderate to good yields (Scheme 36).




**Scheme 36**

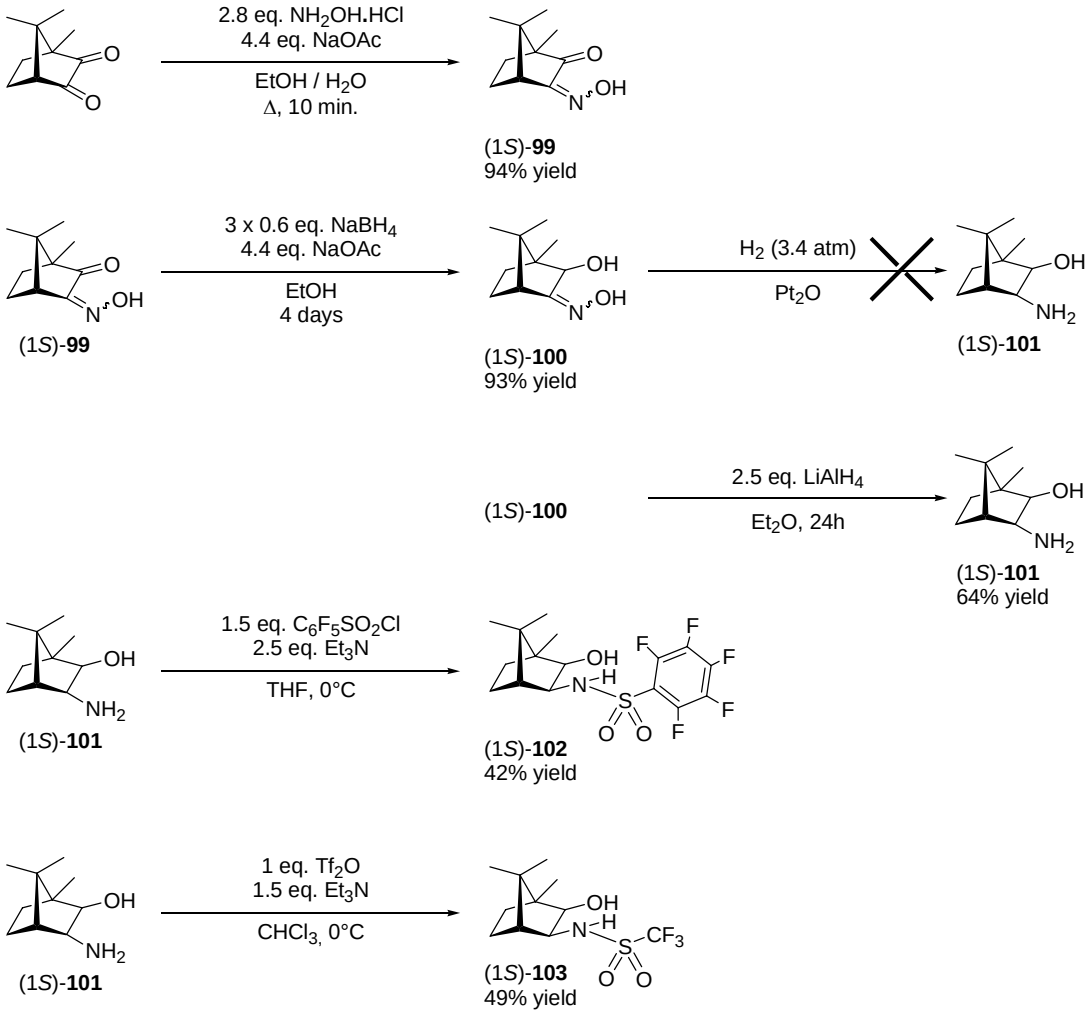
We also performed the methylation of the nitrogen of arylsulfonylamino alcohols (2*S*)-**89** and (2*S*)-**96** and obtained good yields of the two ligands (2*S*)-**97** and (2*S*)-**98** carrying a tertiary amino group (Scheme 37).




**Scheme 37**

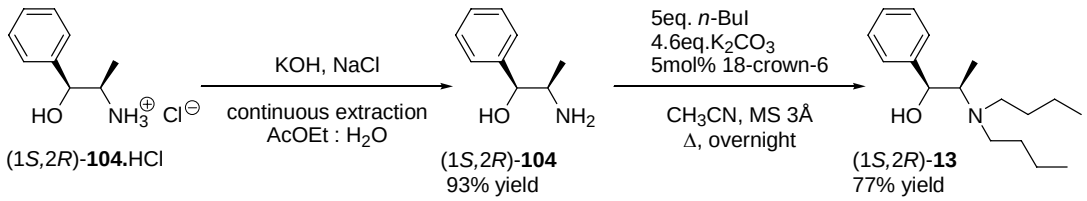
Two sulfonamido alcohol ligands were synthesized based on the 3-aminoisoborneol pattern which is encountered in Noyori's DAIB **12** ligand. These two ligands and their use were investigated by Aurélie Tensy as part of a training stay. A mixture of stereoisomeric oximes **99** was obtained from commercial (1*S*)-camphorquinone [185]. The chemoselective reduction of the ketone function by sodium borohydride yielded a mixture of stereoisomeric oxime-alcohols **100**[185]. Hydrogenation of the oxime catalyzed by platinum(II) oxide following a described procedure[185] did not work. The 3-aminoisoborneol **101** was obtained by lithium

aluminum hydride reduction of the oxime function[186]. The direct sulfonylation of this amino alcohol by pentafluorophenylsulfonyl chloride or triflic anhydride yielded the two sulfonamido alcohols **102** and **103** (Scheme 38).




**Scheme 38**

(1*S*,2*R*)-norephedrine **104** was alkylated with iodobutane to yield Soai's DBNE ligand **13** which has been used to control the diethylzinc addition to aldehydes or imines[187] (Scheme 39).

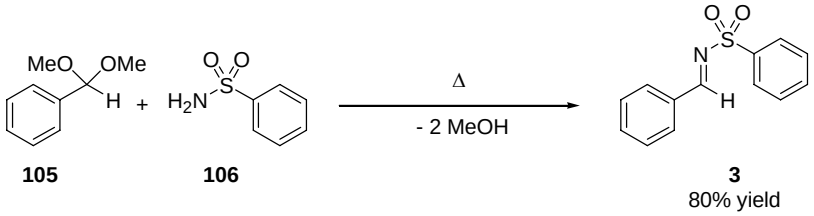



**Scheme 39**

## 3.2.2. Imines Substrates

Two kinds of *N*-activated imines derived from benzaldehyde were synthesized. The *N*-sulfonylimine **3** was obtained in good yield by condensation of the

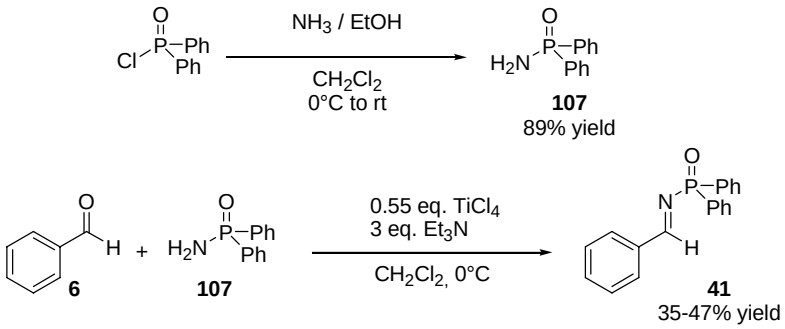
benzaldehyde dimethyl acetal **105** with benzenesulfonamide **106** and concurrent distillation of the methanol produced in the reaction[188] (Scheme 40).




**105** **106** **3**
80% yield

**Scheme 40**

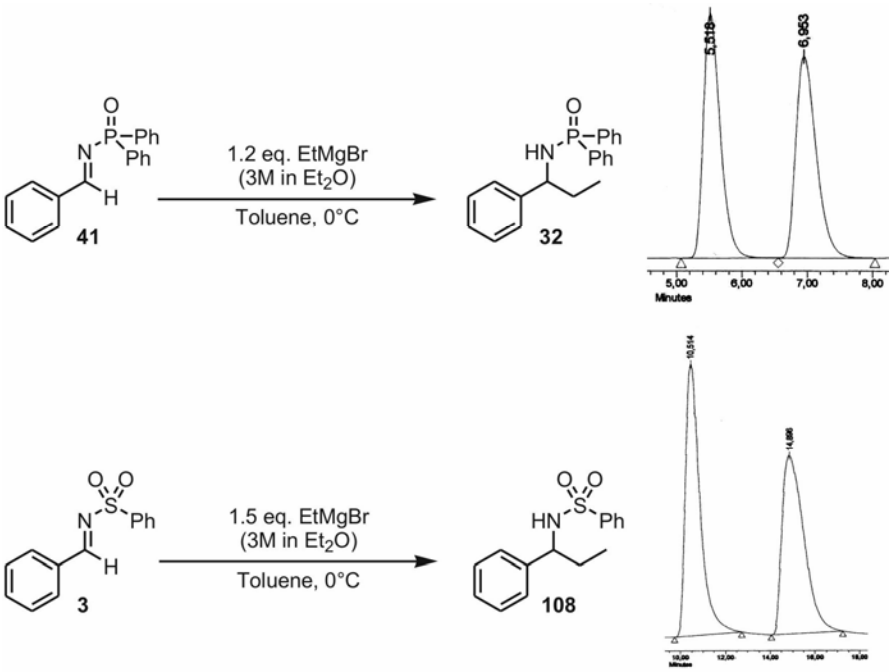
The synthesis of *N*-phosphinoylimine **41** first required the synthesis of diphenylphosphinic amide **107** from the commercial diphenylphosphinic chloride and ammonia[189]. The condensation between benzaldehyde and the phosphinic amide catalyzed by titanium(IV) chloride and in the presence of triethylamine gave moderate yields of imine **41**[189]. The described purification procedure gave *N*-phosphinoylimine samples tainted by traces of the phosphinic amide **107** ($^1$H NMR signal of N$H_2$ around 3.1ppm). A further purification step was therefore added by selectively extracting the imine with warm *n*-hexane in a Soxhlet apparatus. Upon prolonged storage, the imine became contaminated by phosphinic amide **107**. The selective solid-liquid extraction was therefore carried out just before use when deemed necessary (Scheme 41).




**Scheme 41**

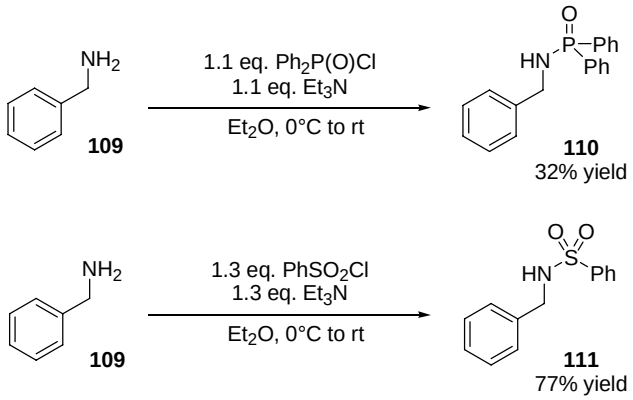
## 3.2.3. Reference Products

The racemic adducts were synthesized by adding ethylmagnesium bromide upon the corresponding imines. The enantiomers of adducts **32** and **108** could be separated satisfactorily by HPLC on a chiral stationary phase (Chiracel OD-H) (Scheme 42).




**Scheme 42**

Authentic samples of the reduction products often obtained in the diethylzinc addition to imines were synthesized from benzylamine (Scheme 43).

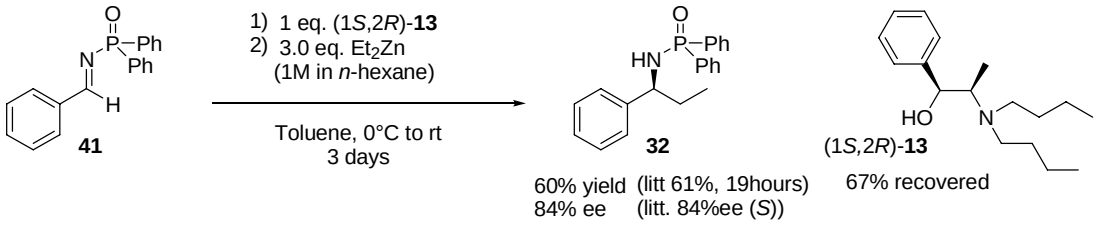



**Scheme 43**

# 3.3. Addition to Imines

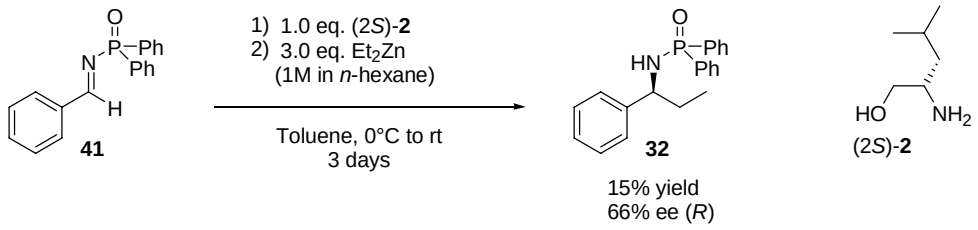
## 3.3.1. Model Experiments

In view of the erratic results previously obtained with N-sulfonylimines, we chose *N*-phosphinoylimine **41** as model substrate. We first repeated the addition of diethylzinc to **41** in the presence of Soai's ligand (1*S*,2*R*)-**13**. Yields and enantiomeric excesses were almost identical to the published results[89] (Scheme 44).



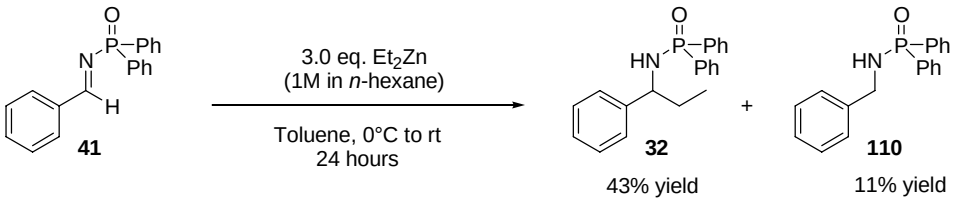

**Scheme 44**

With one equivalent of amino alcohol (2*S*)-**2**, an adduct was obtained with an encouraging enantiomeric excess of 66% albeit in very low yield. The absolute configuration was shown to be (*R*) based on the order of elution in chiral HPLC (Chiracel OD-H) and compared with the assignment made by Soai for the sample obtained with (1*S*,2*R*)-DBNE **13** (Scheme 45).




**Scheme 45**

We checked on the possibility of an uncatalyzed "background" reaction which might diminish the enantiomeric excesses by a non-selective pathway. After 24 hours of reaction, two products could be isolated after careful flash chromatography over silica gel. Adduct **32** was recovered in 46% yield while the reduction product **110** was isolated in 14% yield. This is in sharp contrast with the lack of reactivity of diethylzinc towards benzaldehyde and explains the need for an equivalent of chiral amino alcohol to maximize the ee's (see Scheme 8, Table 2) (Scheme 46).

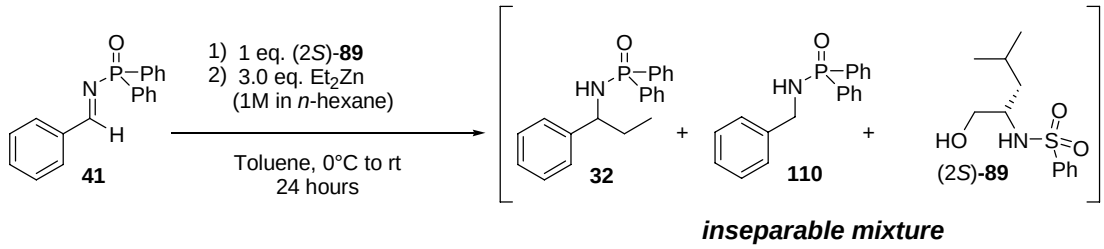



**Scheme 46**

## 3.3.2. Sulfonamido Alcohol-directed Additions $Et_2Zn$ to *N*-Phosphinoylimine 41

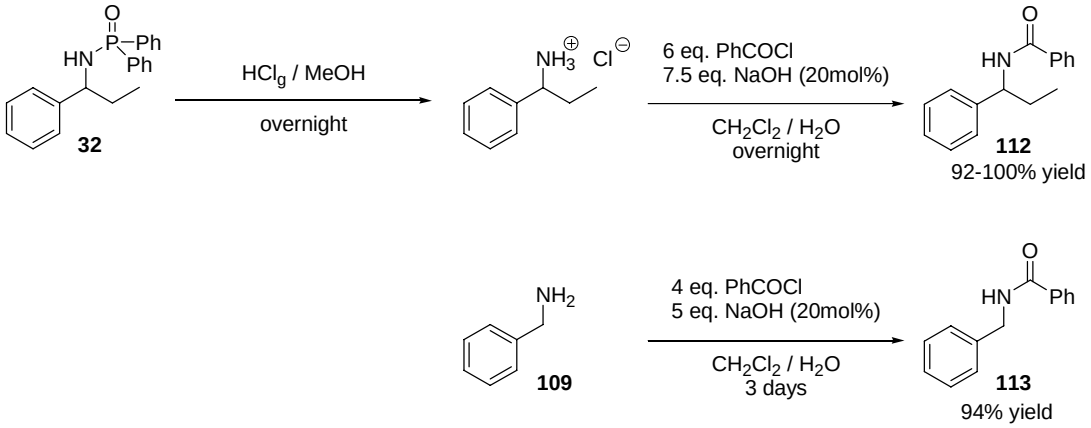
***(2S)-Leucinol Phenylsulfonylamide 89 as Ligand***

We first tested ligand (2*S*)-**89** in the diethylzinc addition to *N*-phosphinoylimine **41** (Scheme 47). An unexpected problem was encountered due to the impossibility to separate the ligand (2*S*)-**89** from the adduct **32** and the reduction product **110.** Moreover, the crude mixture could not provide satisfying information by chiral HPLC or $^1$H NMR (Scheme 47).



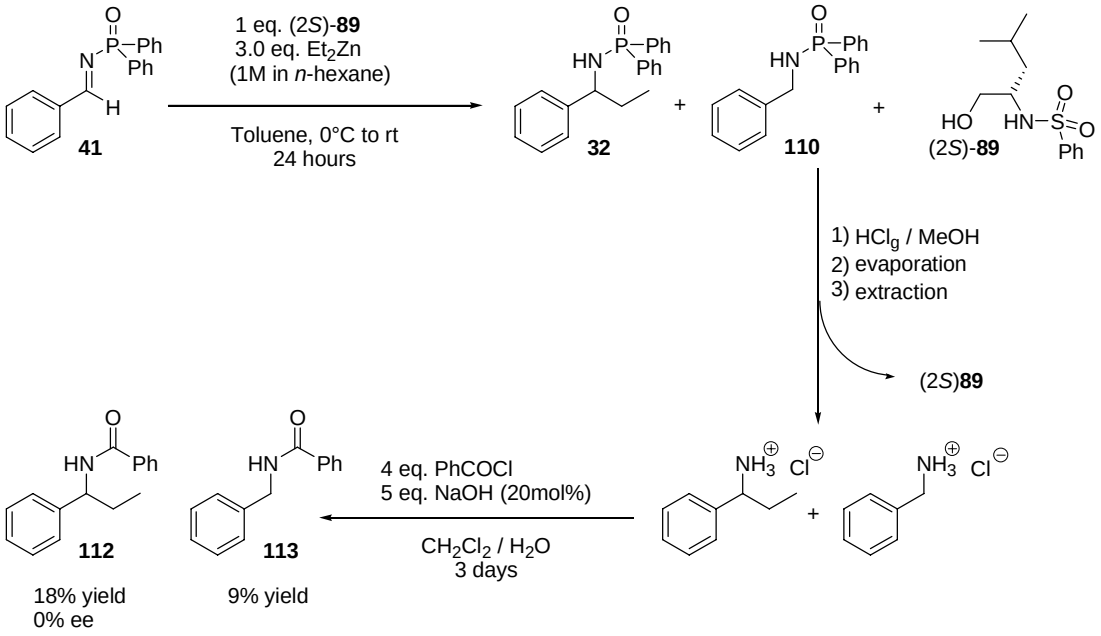

**Scheme 47**

We therefore devised a process to separate the products of the reaction from the ligand through chemical transformation. The cleavage of the N-P bond of **32** was effected in hydrochloric acid saturated methanol. The resulting ammonium was treated with benzoyl chloride and sodium hydroxide (Schotten-Baumann procedure) to yield (92-100%) the *N*-benzoyl phenylpropylamine **112**. The benzoylation of benzyl amine under these conditions was also almost quantitative (95% yield) (Scheme 48).




**Scheme 48**

The addition of diethylzinc to **41** in the presence of stoichiometric of (2*S*)-**89** was thus followed by the acidic deprotection. After evaporation of the solvent, the ligand was separated by extraction from the benzyl ammonium and phenylpropyl ammonium salts. The aqueous phase was basified and the amines were extracted. The recovered amines were benzoylated and separated by column chromatography. The yield in addition product **112** was only of 18% while the reduction product **113** was obtained with 9% yield. The reaction gave a racemic product (Scheme 49).

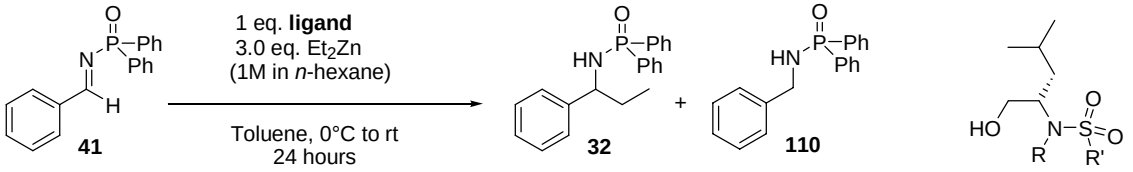



**Scheme 49**

***Other Sulfonamido Alcohols as Ligands***

Four other sulfonamido alcohols derived from (2*S*)-leucinol were tested for the addition of diethylzinc to *N*-phosphinoylimine **41**. When it was impossible to separate the different products by TLC, the crude mixture was subjected to the deprotection-benzoylation procedure. This was the case for all the sulfonamido alcohols with a secondary nitrogen atom (Table 3, entries 1-4). In all case both the addition and the reduction products were obtained in low yields. All the ligands, with the exception of (2*S*)-**95**, gave no enantiocontrol. The trifluoromethylsulfonamido alcohol (2*S*)-**95** did provide a slight enantiomeric excess (11% ee).

**Table 3** : Sulfonamido alcohol directed addition of $Et_2Zn$ to *N*-phosphinoyl-imine **41**



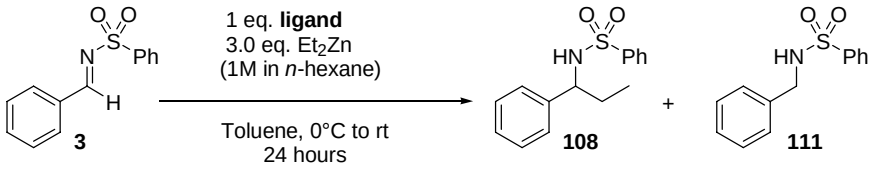

| Entry | Ligand | | | Yield of Addition Product (%) | Enantiomeric Excess (%) | Yield of Reduction Product |
|---|---|---|---|---|---|---|
| | R | R' | | | | |
| 1 | Me | H | (2*S*)-**94** | 8 | 0 | 6 |
| 2 | Ph | H | (2*S*)-**89** | 18 | 0 | 9 |
| 3 | $CF_3$ | H | (2*S*)-**95** | 10 | 11 | 7 |
| 4 | $C_6F_5$ | H | (2*S*)-**96** | 15 | 0 | 10 |
| 5 | $C_6F_5$ | Me | (2*S*)-**98** | 27 | 0 | 5 |

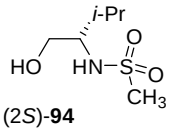
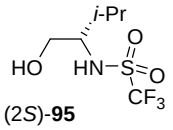
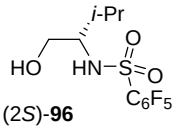
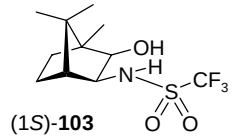
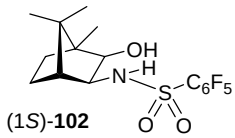
Entries 1-4 required the deprotection-benzoylation procedure to separate the products **32** and **110** from the ligand.

### 3.3.3. Sulfonamido Alcohol-directed Additions of $Et_2Zn$ to N-Sulfonylimine 3

We then looked at the diethylzinc addition to *N*-sulfonylimine **3**. The "background" reaction in the absence of ligand provided almost exclusively the reduction product **111** in 68% yield. Only traces of addition product were observed in the crude mixture. The same reaction was then carried out with one equivalent of our chiral sulfonamido alcohol. Unfortunately, the reduction product **111** remained the major product of the reactions in the presence of our ligands. And with the exception of ligand (1*S*)-**103**, the adduct was only produced in traces (Table 4).

**Table 4** : Sulfonamido alcohol directed addition of $Et_2Zn$ to *N*-sulfonylimine **3**




| Entry | Ligand | Yield of Addition Product 108 (%) | Enantiomeric Excess[b] (%) | Yield of Reduction Product 111 (%) |
|---|---|---|---|---|
| 1 | none | traces[a] | - | 68 |
| 2 |  (2*S*)-**94** | 9 | 11 (*A*) | 80 |
| 3 |  (2*S*)-**95** | traces | 14 (*A*) | 33 |
| 4 |  (2*S*)-**96** | 7 | 1 (*B*) | 69 |
| 5 |  (1*S*)-**103** | 21 | 2.5 (*B*) | 60 |
| 6 |  (1*S*)-**102** | traces[a] | n.d. | 23 |

a : observed by $^1H$ NMR and was not isolated after flash chromatography

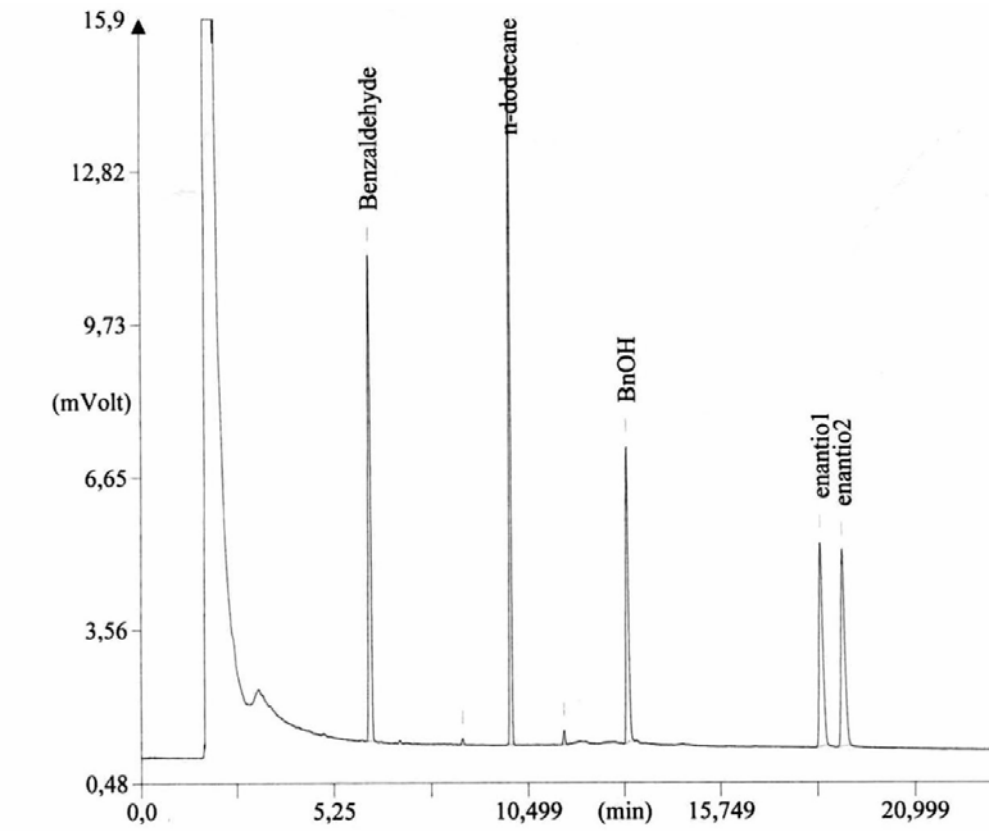
b : (*A*) the first peak in HPLC (Chiralcel OD-H) is the major peak, (*B*) the second peak is the major peak

# 3.4. Addition to Benzaldehyde

## 3.4.1. Sulfonamido Alcohol-directed Addition of $Et_2Zn$ to Benzaldehyde

The potential of our chiral sulfonamido alcohols to direct the addition of diethylzinc to benzaldehyde **6** was assessed. As in most examples of the literature, the addition of diethylzinc on benzaldehyde was used as model reaction. A calibration curve was established to take care of the response factors of benzaldehyde **6** and phenylpropanol **9** in the FID detector (flame ionization detection) and monitor the conversions of the reactions in the presence of *n*-dodecane as internal standard. It was assumed that benzylic alcohol **114**, issued from the reduction of benzaldehyde, had a response factor similar to that of phenylpropanol **9**. A Chirasil Dex (25 m x 0.25 mm – 0.25 µm) column allowed the

separation of all these compounds as well as that of both enantiomers of adduct **9** (Figure 12).

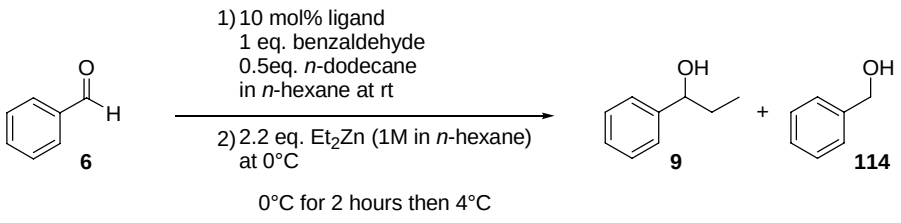


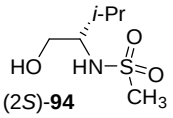
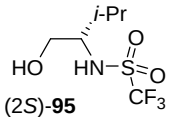
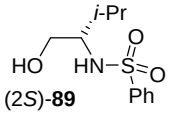
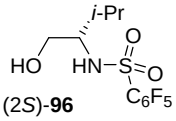
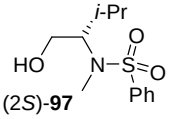
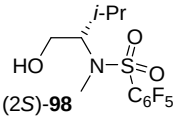
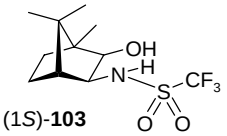
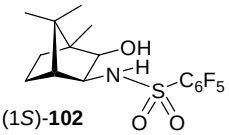

| Peak Number (#) | Retention Time (min) | Component Name | Area (.1*uV*sec) | Area % (%) | Peak Type |
|---|---|---|---|---|---|
| 1 | 6.210 | Benzaldehyde | 433335 | 25.087 | Resolved |
| 2 | 8.722 | | 3803 | 0.220 | Resolved |
| 3 | 10.018 | n-dodecane | 439791 | 25.461 | Fused |
| 4 | 11.482 | | 9388 | 0.544 | Resolved |
| 5 | 13.203 | BnOH | 280444 | 16.236 | Resolved |
| 6 | 18.457 | enantio1 | 280914 | 16.263 | Resolved |
| 7 | 19.050 | enantio2 | 279632 | 16.189 | Resolved |
| | | | 1727306 | | |

**Figure 12**

First of all, the reaction was carried out in the absence of any ligand. Two products were slowly formed. The yield of adduct **9** was 8% after 4 hours, (Table 5, entry 1) and 40% after 24 hours (entry 2). The reduction product **114** was formed in 3% and 6% yield respectively. The reactions were carried out in the presence 10mol% of a sulfonamido alcohol ligand. All the ligands, except those with a tertiary nitrogen (entries 7 & 8), catalyzed the addition of diethylzinc. The reduction product was formed in yields comparable to those observed in the background reaction. Low to modest enantiomeric excesses were observed (maximum 47% ee with leucinol based **96**). Changing the carbon skeleton from leucinol to aminoisoborneol did not improve the reactivity nor the enantioselectivity.

**Table 5** : Sulfonamido alcohol directed addition of $Et_2Zn$ to benzaldehyde **6** after 4 hours (General Procedure J)



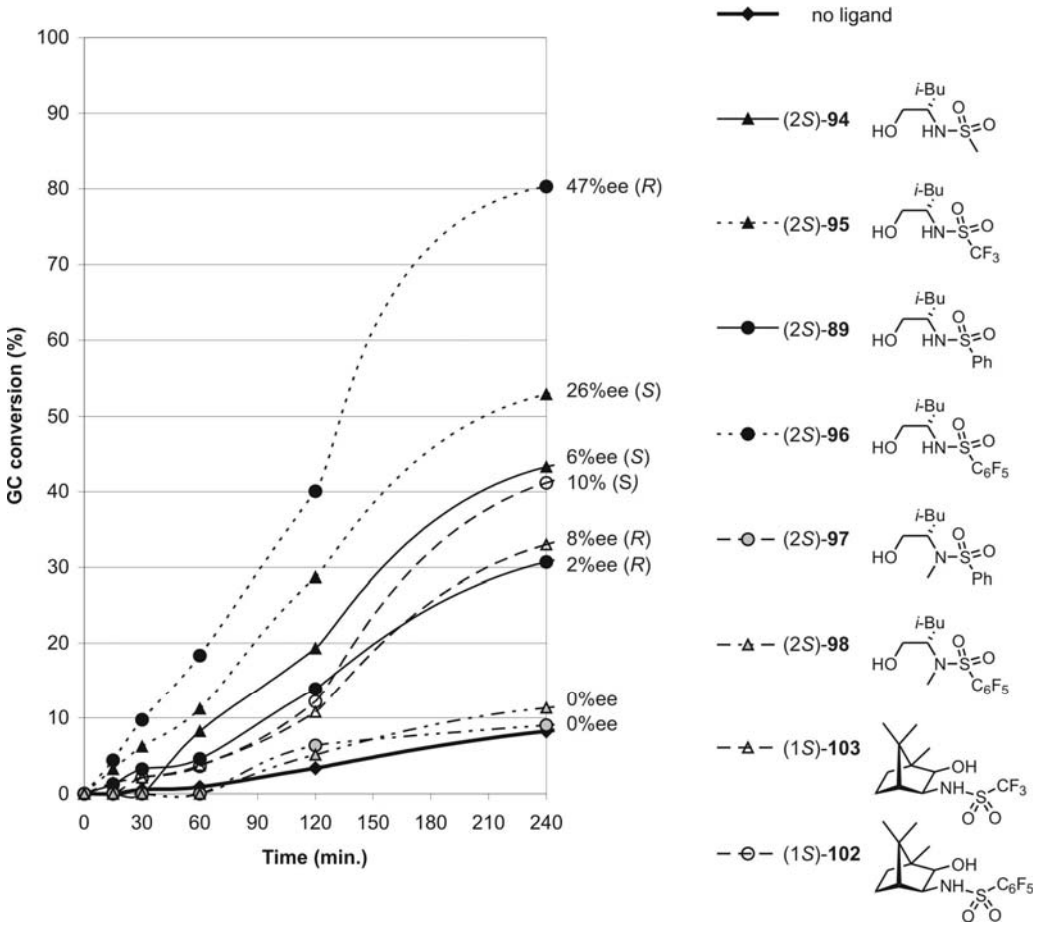

| Entry | Ligand | GC Conversion of Adduct 9 (%) | ee[b] (%) | GC Conversion of Reduction Product 114 (%) |
|---|---|---|---|---|
| 1 | none | 8 | - | 3 |
| 2[a] | none | 40 | - | 6 |
| 3 |  (2*S*)-**94** | 43% | 6 (*S*) | 4 |
| 4 |  (2*S*)-**95** | 53 | 26 (*S*) | 4 |
| 5 |  (2*S*)-**89** | 31 | 2 (*R*) | 2 |
| 6 |  (2*S*)-**96** | 80 | 47 (*R*) | 3 |
| 7 |  (2*S*)-**97** | 9 | 0 | 2 |
| 8 |  (2*S*)-**98** | 11 | 0 | 3 |
| 9 |  (1*S*)-**103** | 33 | 8 (*R*) | 4 |
| 10 |  (1*S*)-**102** | 41 | 10 (*S*) | 4 |

a : after 24 hours

b : based on the order of elution and compared to sample of known optical activity

The rate acceleration as well as the stereocontrol provided by our ligands were weak and synthetically uninteresting. Yet, a clear trend was apparent when the reaction profiles for the different ligands were compared : the sulfonamido alcohols **94** and **89** were less activating than their fluorinated counterparts **95** and **96**. These results vindicated our working hypothesis on the *in situ* generation of a more Lewis acidic and more active chiral zinc catalyst by grafting an electron-withdrawing group on the nitrogen of amino alcohols (see page 41). Unfortunately, the increase in activity was not sufficient with the less electrophilic and more hindered imines as our disappointing results have confirmed (Chart 3).

**Chart 3** : Reaction profiles of the addition of diethylzinc to benzaldehyde with 10 mol% of sulfonamido alcohols (General Procedure J)




An unexpected observation was the reversal of enantioselectivity when going from a chiral trifluoromethylsulfonamide to a pentafluorophenylsulfonamide (Table 5, entries 4 *vs.* 6 & entries 9 *vs.* 10). The enantiocontrol is slightly higher for the pentafluorophenyl ligand **96** (47% ee) compared to the trifluoromethyl ligand **95** (26% ee). A possible explanation for the (*R*) absolute configuration produced with **96** could be a favorable $\pi$-$\pi$ interaction between the phenyl group of the aldehyde and the pentafluorophenyl group of the ligand in an active species such as **115a** (inspired by Noyori's **24** in **Scheme 14**). Such an interaction is absent in the trifluoromethyl substituted ligand **95** and, in that case, an unfavorable interaction between the trifluoromethyl and the phenyl group of the aldehyde could be responsible for the reversal of enantioselectivity and the lower enantiomeric excesses (**116a** *vs* **116b**) (Figure 13).

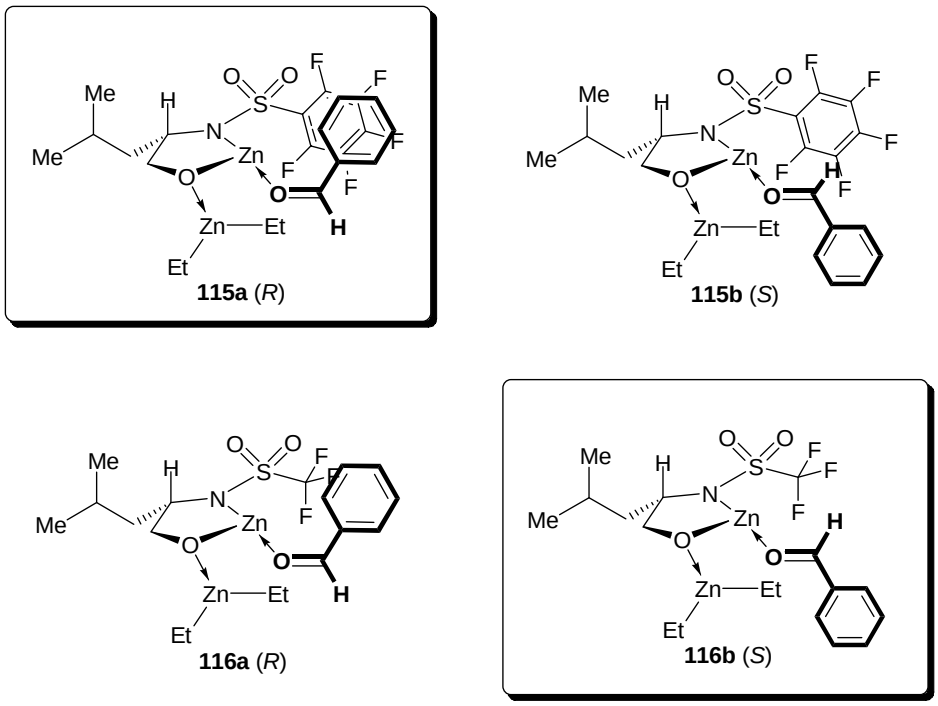



**Figure 13**

## 3.5. Conclusions and Perspectives

The additions of diethylzinc to *N*-phosphinoylimine **41** and *N*-phenylsulfonylimine **3** in the presence of stoichiometric quantities of chiral sulfonamido alcohols did not give synthetically meaningful yields nor enantiomeric excesses. However, some of these chiral sulfonamido alcohols activated the addition of diethylzinc on benzaldehyde **6** even in substoichiometric quantities (10mol%). The best ligands were those bearing electron-withdrawing fluorinated sulfonyl groups on a disubstituted nitrogen atom. The best chiral induction (47% ee) was obtained with the pentafluorophenylsulfonyl leucinol derivative **96**.

While our research was underway, Cho *et al.* published a paper on the enantioselective addition of diethylzinc on benzaldehyde catalyzed by a range of chiral sulfonamido alcohols **117**[190]. They obtained the adduct in good yield with a maximum of 80% ee in the presence of 10mol% of **117e** (Table 6, entry 5). Contrary to our ligand skeletons, the sulfonamide substitution (R) did not lead to any reversal of absolute configuration. Furthermore, their results indicated that the electron-poorer sulfonamido alcohol **117b**, **117d** and **117e** did not improve the acceleration and enantioselectivity of the addition (entries 1 *vs.* 2 and 3 *vs* 4&5).

**Table 6** : Literature results of sulfonamido alcohol directed addition of $Et_2Zn$ to benzaldehyde **6**


**6** (*R*)-**9** **117**

| Entry | Ligand R | | Time | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | Me | **117a** | 9h | 70 | 73 (*R*) |
| 2 | $CF_3$ | **117b** | 18h | 68 | 14 (*R*) |
| 3 | *p*-$MeC_6H_4$ | **117c** | 9h | 86 | 80 (*R*) |
| 4 | 2,4-$(NO_2)_2C_6H_3$ | **117d** | 12h | 30 | 3 (*R*) |
| 5 | *p*-$ClC_6H_4$ | **117e** | 12h | 78 | 76 (*R*) |

These literature results combined with our results show that diorganozinc compounds can be activated by chiral sulfonamido alcohols for the addition to aldehydes. However, these systems are not active for the addition to the more hindered and less electrophilic imines. To obtain a more powerful catalytic system an additional Lewis acid titanium salt must be added as shown by Katsuki[126]. Since then, sulfonamido alcohols combined with titanium salts have been successfully used to direct the addition of diorganozinc compounds to aldehydes[127-129,191] and more recently ketones[134-140]. However, a stoichiometric amount if not an excess of titanium complex is required (see Section 2.4). This project was stopped at this stage.

# Chapter 4

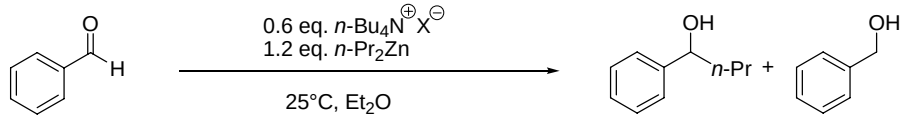
# Fluoride Anion Activation

## 4.1. Fluoride Catalysis

### 4.1.1. Diorganozinc Activation by Halide Anions

In 1970, Chastrette and Amouroux[192] reported on the influence of tetrabutylammonium halides on the reactivity of dipropylzinc towards benzaldehyde. Changing the nature of the counterion, from iodide to bromide and then chloride enhanced the rate of reaction and improved the chemoselectivity. The formation of an undefined complex between the organozinc compound and the ammonium salts was postulated at the time based on the observation of the dissolution of the otherwise insoluble ammonium salts in diethyl ether upon addition of the organometallic compound. The acceleration of the addition reaction paralleled the decreasing radius of the anionic halide (Table 7).

**Table 7** : Tetrabutylammonium halide activation of *n*-$Pr_2Zn$ addition to benzaldehyde

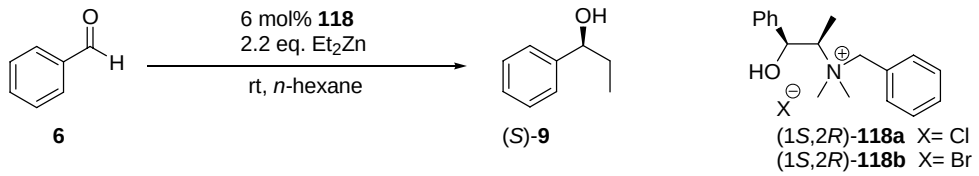



**6**

| Entry | Ammonium Salt | GC Conversion to Adduct (%) | GC Conversion to Reduction Product (%) | k x $10^3$ $l \cdot mol^{-1} \cdot min^{-1}$ |
|---|---|---|---|---|
| 1 | - | 56 | 44 | 2.1 |
| 2 | *n*-$Bu_4NI$ | 77 | 23 | 2.3 |
| 3 | *n*-$Bu_4NBr$ | 92 | 8 | 8.7 |
| 4 | *n*-$Bu_4NCl$ | 94 | 6 | 18.6 |

There is also a report by Soai on the use of chiral ammonium salts as chiral inductors for the addition of diethylzinc to benzaldehyde[193] (Table 8). Catalytic amounts of ephedrine-derived ammonium halides **118** did catalyze the addition reaction and gave good enantioselectivities. Here also the chloride **118a** was superior to the bromide **118b**. A solid residue was present throughout the reaction (Table 8).

**Table 8** : Chiral ammonium halide catalyzed addition of $Et_2Zn$ to benzaldehyde




**6** (*S*)-**9** (1*S*,2*R*)-**118a** X= Cl (1*S*,2*R*)-**118b** X= Br

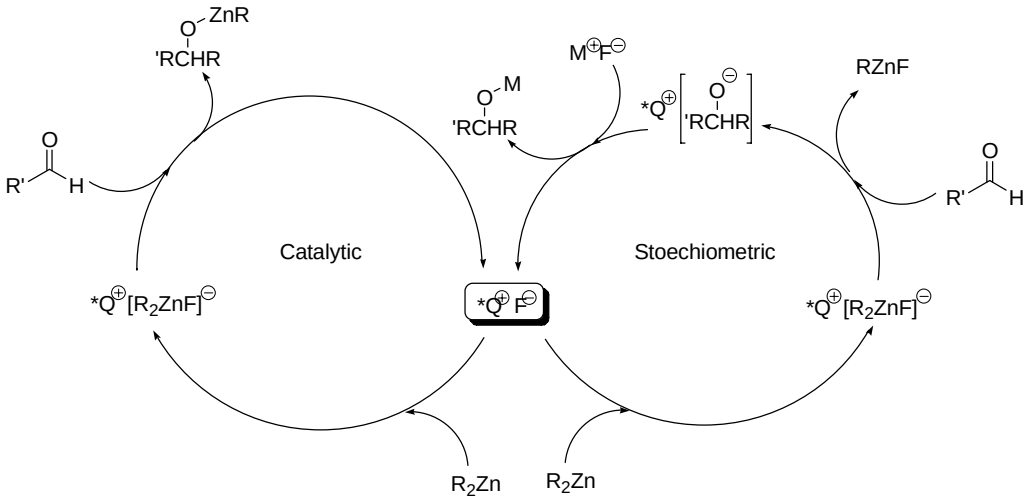
| Entry | Ammonium Salt 118 | Time | Yield of Adduct 9 (%) | Enantiomeric Excess (%) |
|---|---|---|---|---|
| 1 | **118a** X=Cl | 3 d | 90 | 74 (*S*) |
| 2 | **118b** X=Br | 4 d | 72 | 62 (*S*) |

In a patent from 1966 on the preparation of organometallic precursors for galvanization, diethylzinc was described as less susceptible to oxidation and hydrolysis upon mixing with benzyltrimethylammonium fluoride in 1:1 and 1:2 ratios[194]. In 2001, $^1$H NMR studies confirmed the formation of a 1:1 *n*-$Bu_4NCl$ : $Et_2Zn$ complex[82]. The structure of the complex was proposed to be an ammonium zincate *n*-$Bu_4N^+$ $(Et_2ZnCl)^-$.

## 4.1.2. Working Hypothesis

We became interested in using a halide anion in conjunction with a chiral cation to catalyze the addition of diorganozinc compounds to carbon-heteroatom double bonds and induce a facial selection. We expected the stronger activation of the diorganozinc compound by the smaller and more nucleophilic fluoride atom. The use of a chiral cation ($^*Q^+$), such as a chiral ammonium or a alkaline cation complexed to a chiral crown ether, could control the stereoselectivity of the zincate's addition on the prochiral aldehyde. A zinc alkoxide could be produced, the chiral fluoride would then be regenerated. In that case, the process will be catalytic in fluoride. Another possibility is the formation of an organozinc fluoride and an alkoxide. This process will be stoichiometric in fluoride salt[§]. It can be rendered catalytic in chiral cation if the fluoride salt is regenerated through anion metathesis in a phase transfer process. (Scheme 50).

[§] Note that an alkoxide-activation can also be imagined. Then, the chiral fluoride salt would only be the catalyst precursor.

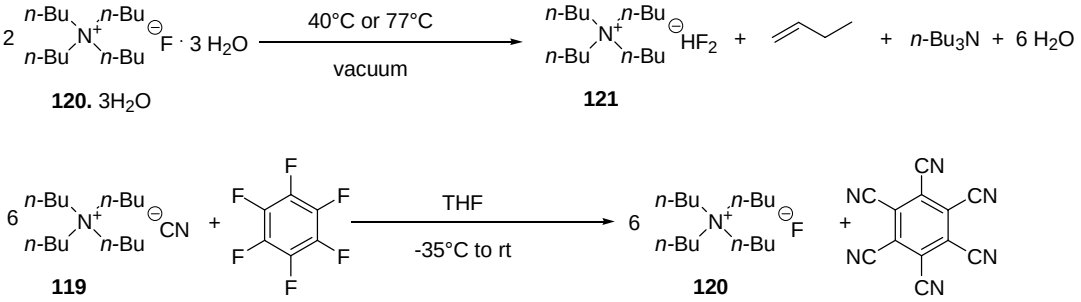



**Scheme 50**

# 4.2. Reactions in the Presence of Ammonium Fluorides

## 4.2.1. Literature

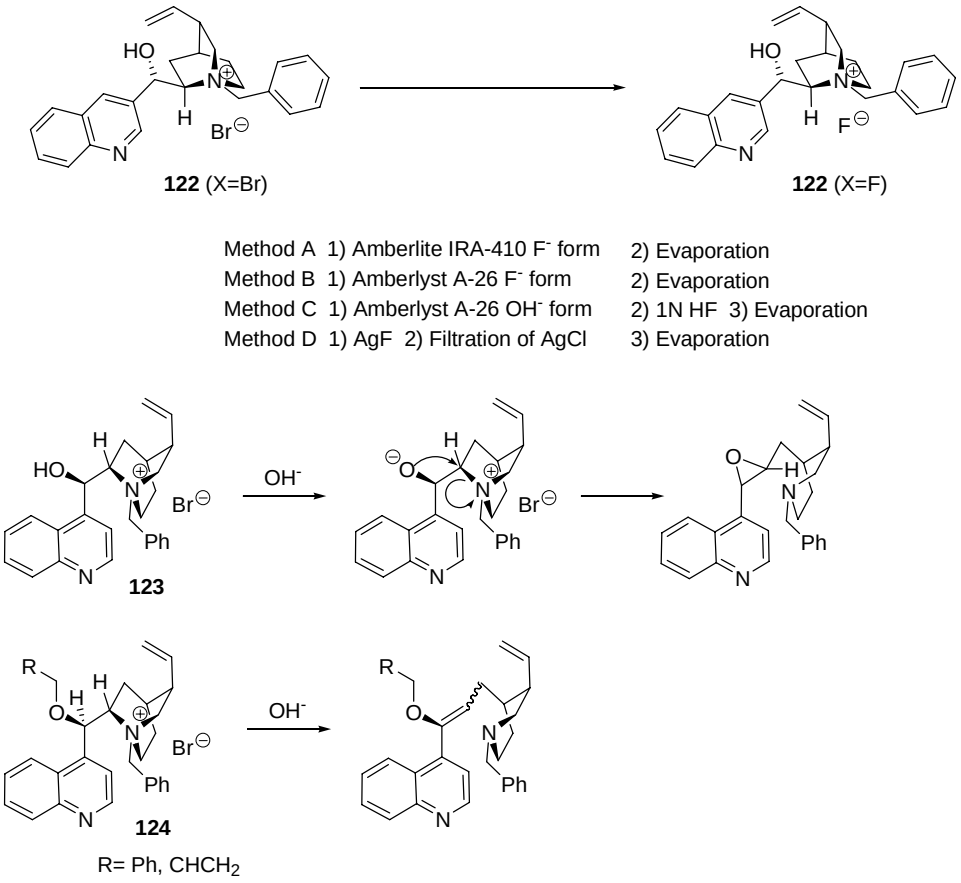
The synthesis of ammonium fluorides is not trivial since the fluoride anion is a strong base in the absence of a proton donor. Therefore attempts to obtain anhydrous ammonium fluorides very often lead to degradation of the ammonium cation. For example, tetrabutylammonium fluoride trihydrate decomposes upon drying through an Hofmann elimination leading to tributylamine, tetrabutylammonium bifluoride ($HF_2^-$) and butene[195]. In 2005, DiMagno *et al.* reported the synthesis of anhydrous tetrabutylammonium fluoride starting from the corresponding cyanide **119** and showed that tetrabutylammonium fluoride **120** was stable in the solid state and in dry THF at -35°C but decomposed slowly above 0°C[196] (Scheme 51).




**Scheme 51**

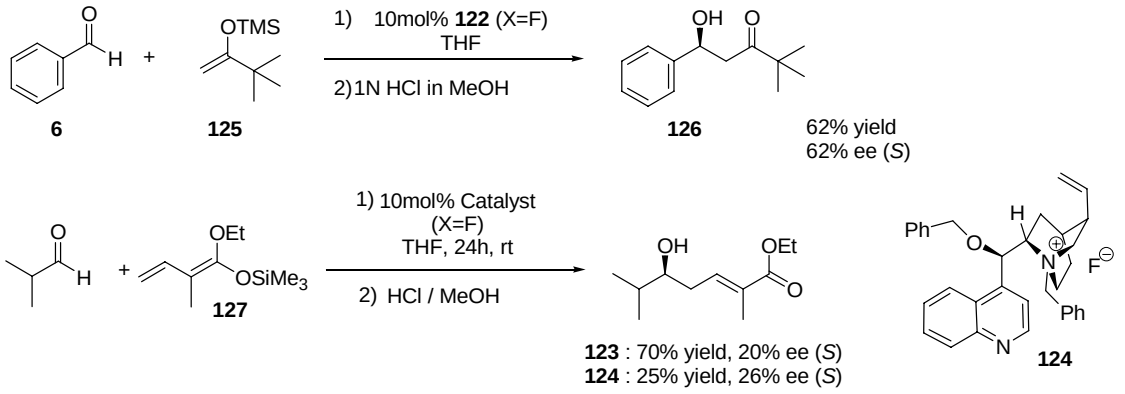
In spite of this, several chiral ammonium fluorides have been prepared and used as catalysts for enantioselective transformations. The ammonium cation were often prepared by *N*-alkylation of natural alkaloids. The resulting chloride and bromide salts must then be transhalogenated to produce the corresponding fluorides. Shirori *et al.* have developed different techniques for the preparation of *N*-benzylcinchonium fluoride **122** (X=F) by anion metathesis[197]. In methods A and B, the exchange was effected by passing the bromide **122** (X=Br) through an

ion-exchange resin in the fluoride form. Method C consist in exchanging the bromide for an hydroxide and then neutralizing the ammonium hydroxide salt with hydrogen fluoride. The halide exchange can also be carried out with silver fluoride (Method D). The resulting fluorides were dried overnight over $P_2O_5$ at 40°C under vacuum with no sign of degradation ($^1H$ and $^{19}F$ NMR). This contrasts with the decomposition of the cinchonidine-derived salts **123** and **124** in basic conditions through the formation of an oxirane or an Hofmann elimination as shown by O'Donnell[198] (Scheme 52).




**Scheme 52**

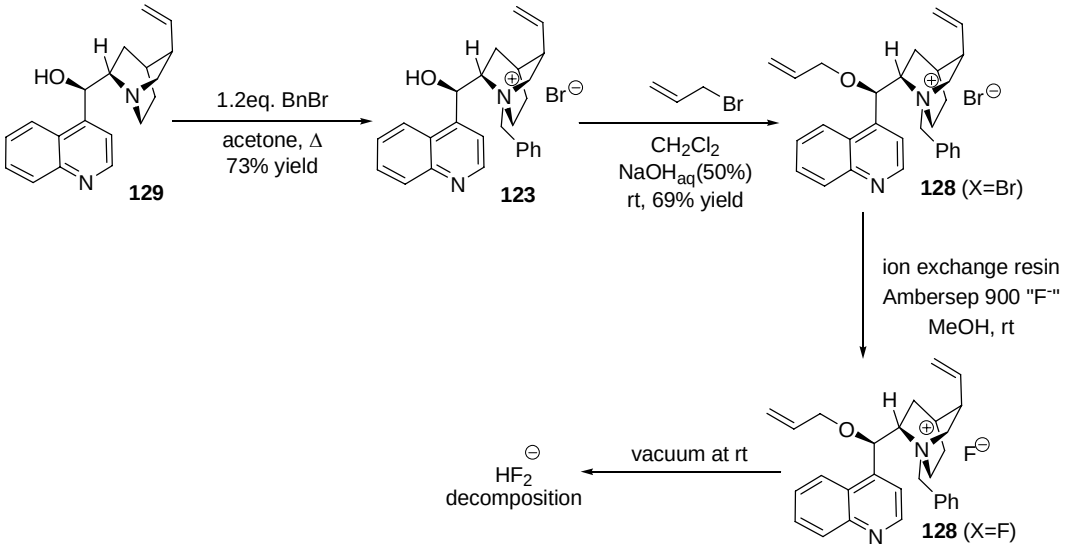
Chiral ammonium fluorides have been shown to catalyze reactions of silyl enol ethers or ketene acetals with carbonyl groups[199,200]. Cinchonium salt **122** (X=F) was used to control the asymmetric Mukaiyama-aldol condensation[197]. Attempts to catalyze the vinylogous Mukaiyama-aldol reaction were made by Campagne with the cinchonidinium fluoride salt **123** providing good yields but poor enantioselectivity. The *N,O*-benzyl cinchonidinium fluoride **124** was also synthesized and tested but provided lower yields[201] (Scheme 53).




**Scheme 53**

## 4.2.2. Results

We attempted to synthesize an ammonium fluoride salt by *N*-benzylating cinchonidine with benzyl bromide and then grafting an allyl group on the hydroxyl residue[198]. The anion exchange was done with an anion exchange-resin loaded with fluoride. The sample of the fluorinated cinchonidinium salt **128** was analyzed by $^{19}F$ NMR after submitting it briefly to vacuum to remove traces of solvent. Two peaks were present. The major signal (82%) at -121 ppm was attributed to the fluoride anion of **128**. A minor signal (18%) at -150 ppm was attributed to the bifluoride anion ($HF_2^-$). The sample was again submitted to vacuum for an entire day at room temperature and analyzed by $^{19}F$ NMR spectroscopy. Only one signal was observed and corresponded to the bifluoride anion. The ease with which this ammonium salt decomposed while trying to dry it surprised us and we did not make any other attempt at isolating an ammonium fluoride salt.



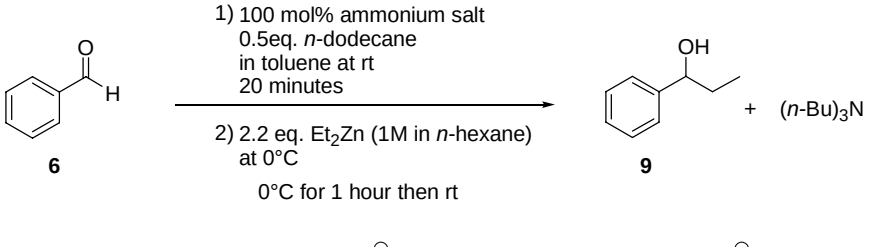

**Scheme 54**

Interactions of the fluoride anion with protic sources, such as water and HF, decrease its basic properties. In the same perspective, the complexation between the fluoride anion and silicon or tin leads to pentavalent species stable enough to be isolated[202,203]. Tetrabutylammonium difluorotriphenylsilicate **130**, known as TBAT, has been described by DeShong as a fluoride source which less basic but also

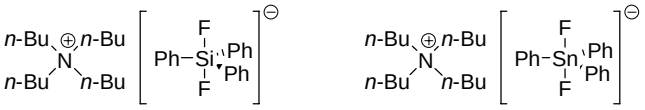
less nucleophilic than tetrabutylammonium fluoride **120** with the additional advantage of being anhydrous and non-hygroscopic[204]. Another synthetic equivalent of TBAF is the tetrabutylammonium difluorotriphenylstannate **131** introduced by Gingras[205]. Both are commercially available.

We tested the influence of stoichiometric amounts of **130** and **131** on the addition of diethylzinc to benzaldehyde. To our great pleasure, both salts activated the addition reaction and no reduction product was observed. The difluorotriphenylsilicate **130** led to 68% conversion to the adduct in 4 hours (Table 9, entry 1) but the reaction was not complete when left to run for 24 hours (entry 2). In the case of the tin analog **131**, the reaction was much faster since it was complete in one hour. (entry 3).

**Table 9** : $Et_2Zn$ addition to benzaldehyde **6** in the presence of "masked" fluoride sources (General Procedure I)



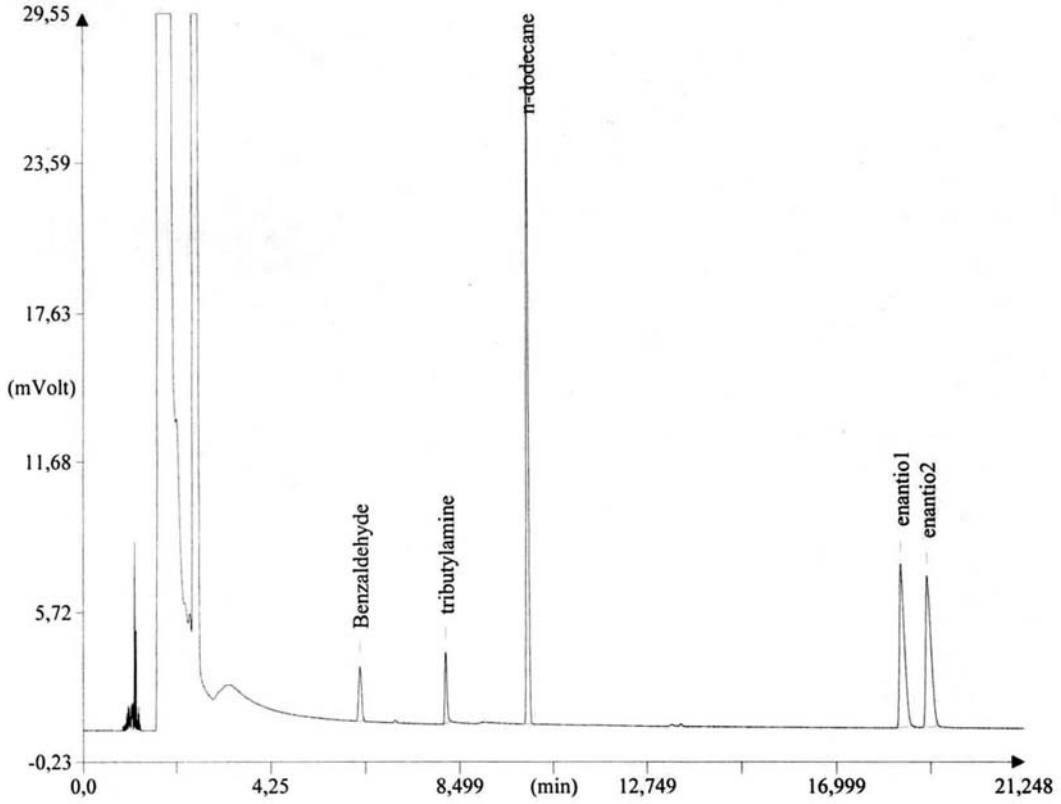

**6** **9**



**130** **131**

| Entry | Fluoride Source (1 eq.) | Time | GC Conversion of Adduct 9 (%) |
|---|---|---|---|
| 1 | **130** | 4 hours | 68 |
| 2 | " | 24 hours | 83 |
| 3 | **131** | 1 hour | 100 |

The results are quite encouraging since they might indicate that "masked" fluoride sources **130** and **131** can activate the nucleophilicity of benzaldehyde. Yet, the analysis by gas chromatography of our samples for these two reactions revealed the presence of an unidentified product. GC-MS allowed identification of this peak as *n*-tributylamine. The identification was then confirmed by comparing the retention time of a commercial sample. The observation of such degradation product did not encourage us to synthesize asymmetric versions of **130** or **131** (Figure 14).



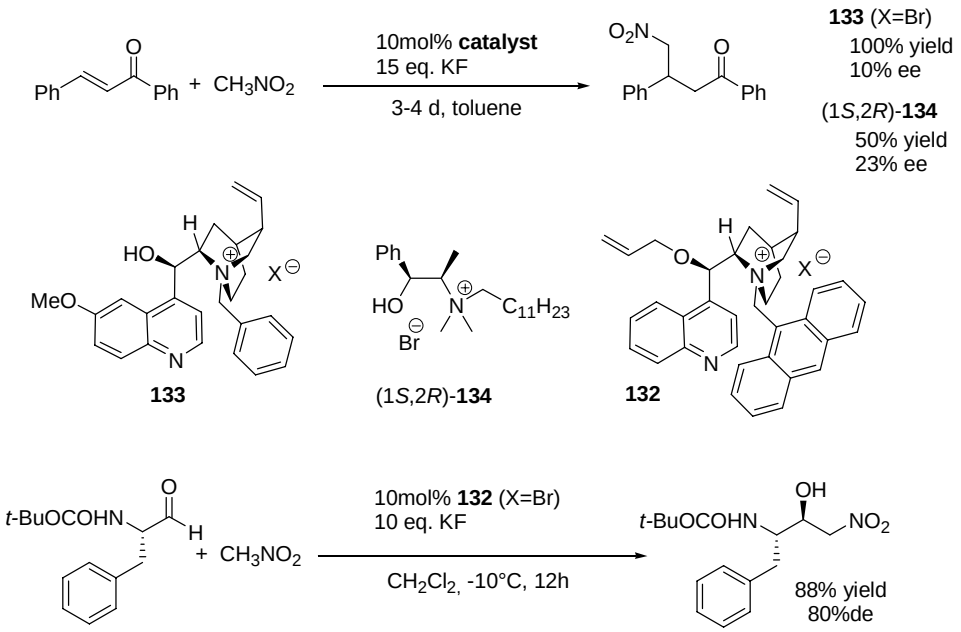

| Peak Number (#) | Retention Time (min) | Component Name | Area (.1*uV*sec) | Area % (%) | Peak Type |
|---|---|---|---|---|---|
| 1 | 6.247 | Benzaldehyde | 97026 | 4.698 | Resolved |
| 2 | 8.177 | tributylamine | 96015 | 4.649 | Resolved |
| 3 | 10.025 | n-dodecane | 873707 | 42.308 | Resolved |
| 4 | 18.445 | enantio1 | 498133 | 24.121 | Resolved |
| 5 | 19.042 | enantio2 | 500239 | 24.223 | Resolved |
| | | | 2065119 | | |

**Figure 14**

# 4.3. Fluoride Phase-Transfer Catalysis

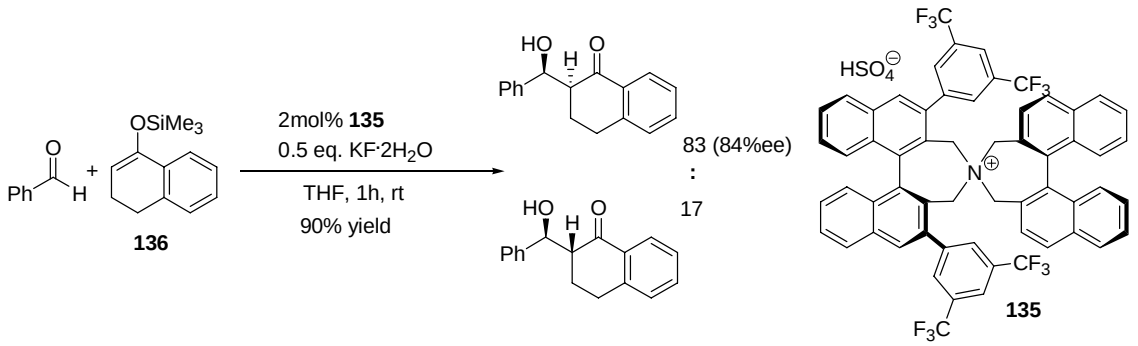
## 4.3.1. Literature

Chiral ammonium salts have been used previously to transfer the fluoride anion from insoluble potassium salts to the organic phase in the case of enantioselective reactions [206-209]. The first application of this kind of catalyst system is due to Wynberg *et al.* in 1978 with the Michael addition of nitromethane to chalcones[206]. Corey *et al.* have used *N,O*-alkylated cinchonidinium salts such as **132** and potassium fluoride to promote an enantioselective nitroaldol condensation[208]. In these cases, it is the Bronsted basic properties of fluoride that are sought and not its nucleophilic properties[210] (Scheme 55).



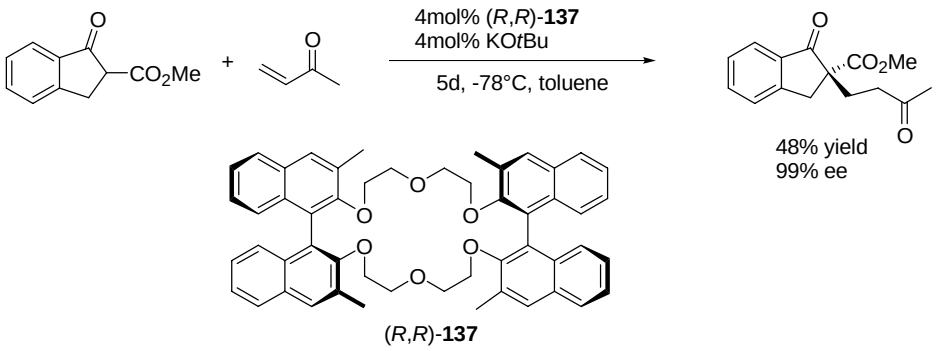

**Scheme 55**

In the last few years, Maruoka has designed chiral ammonium salts lacking hydrogens in β-position relative to the nitrogen and therefore more stable in basic media[211,212,209]. For instance, **135** been used in conjunction with potassium fluoride to control the stereoselective Mukaiyama-aldol addition of silyl enol ether **136** on benzaldehyde with 84% ee for the *erythro* adduct[212] (Scheme 56).




**Scheme 56**

Crown ethers have a strong affinity for specific cations which helps in the solubilisation of their salts[213]. Cram has been the first to exploit their phase transfer properties to an asymmetric reaction by using chiral crown ether **137**: the addition of β-keto esters to methylvinylketone in the presence of potassium *tert*-butoxide providing the product with modest yield but excellent enantioselectivities. To our knowledge there is no report of a combined use of a chiral crown-ether with a fluoride salt (Scheme 57).

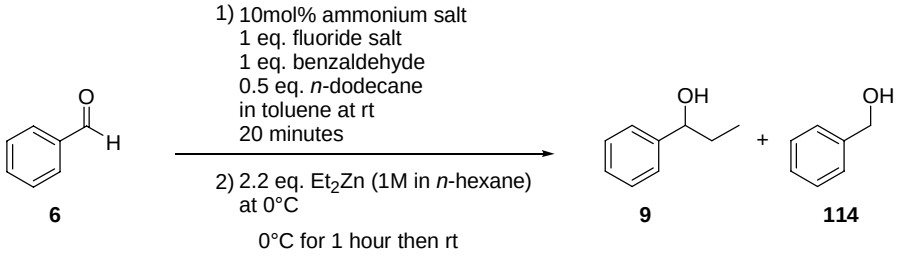



**Scheme 57**

## 4.3.2. Results

In parallel to our attempts at isolating a chiral ammonium fluoride (see Scheme 54), we explored the possibility of using a phase-transfer process to synthesize *in situ* the ammonium fluoride salt and catalyze the addition of diethylzinc on benzaldehyde. Three inorganic fluoride sources were first tested in the absence of ammonium salt. After 4 hours of reaction, an equivalent of potassium fluoride provided the same conversion level than in the absence of any catalyst (Table 10, entries 1 & 2). Another source of fluoride anion we planned to use was silver fluoride which did accelerate somewhat the reaction leading to a conversion level of 10% of adduct (entry 3). Cesium fluoride alone however led to almost full conversion in 4 hours (entry 4). This is certainly due to the increase in solubility of cesium salts compared to potassium salts. This last result confirms our hypothesis on the activation of the diethylzinc nucleophilicity by the fluoride anion.

**Table 10** : $Et_2Zn$ addition to benzaldehyde **6** after 4 hours in the presence of inorganic fluoride and cinchodinium salts (General Procedure I)




**6** **9** **114**

| Entry | Fluoride Source (1 eq.) | Cinchodinium Salt (10mol%) | GC Conversion of Adduct 9 (%) | ee(%)[a] | GC Conversion of Reduction Product 114 (%) |
|---|---|---|---|---|---|
| 1 | - | - | 3 | - | 1 |
| 2 | KF | - | 1 | - | 0 |
| 3 | AgF | - | 10 | - | 3 |
| 4 | CsF | - | 94 | - | 0 |
| 5 | - | **123** (X=Cl) | 20 | 5 (*R*) | 0 |
| 6 | KF | **123** (X=Cl) | 50 | 0 | 0 |
| 7 | AgF | **123** (X=Cl) | 33 | 3 (*R*) | 1 |
| 8 | CsF | **123** (X=Cl) | 100 | 0 | 0 |
| 9 | - | **128** (X=Br) | 13 | 3 (*S*) | 1 |
| 10 | KF | **128** (X=Br) | 20 | 0 | 1 |

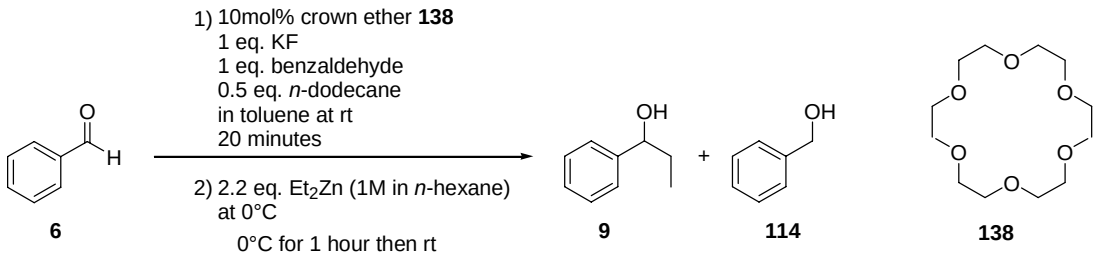
a : absolute configuration based on the order of elution and compared to sample of known optical activity

Chiral ammonium salts **123** (X=Cl) and **128** (X=Br) in the absence of any fluoride source did lead to a small increase in reactivity compared to the background reaction but with negligible enantiocontrol (Table 10, entries 5 & 9). Yet, when a fluoride source such as potassium fluoride or silver fluoride was added, the reactivity increased but led to the adduct **9** with insignificant enantiomeric excess (entries 6, 7 & 10). The addition of an ammonium salt to cesium fluoride provided essentially the same result than the fluoride source taken alone (entries 4 & 8). These results seem to indicate that the phase transfer of fluoride anions does take place with the ammonium salts **123** (X=Cl) and **128** (X=Br) but it does not lead to any enantioselectivity.

Crown ethers are other commonly used transfer agents. By adding potassium fluoride and 10 mol% of crown ether 18-C-6 **138** which has a high complexation affinity for potassium, the addition of diethylzinc to benzaldehyde was greatly accelerated since it was over in a little bit more than 2 hours (Table 11, entry 3).

The crown ether by itself does not activate the reaction[**] (entry 2). We were greatly enthusiastic about this result since only a substoichiometric amount of phase transfer agent is used.

**Table 11** : $Et_2Zn$ addition to benzaldehyde **6** after 4 hours in the presence of inorganic fluoride and crown ether **138** (General Procedure I)




**6** **9** **114** **138**

| Entry | Fluoride Source (1 eq.) | Crown ether (10mol%) | GC Conversion of Adduct 9 (%) | GC Conversion of Reduction Product 114 (%) |
|---|---|---|---|---|
| 1 | KF | - | 1 | 0 |
| 2 | - | 138 | 3 | 2 |
| 3 | KF | 138 | 100 | 0 |

## 4.4. Conclusions

In this chapter we have looked at the potential activation by fluoride anion of diorganozinc compounds for the addition to an electrophile such as benzaldehyde. Our attempts at synthesizing an anhydrous cinchonidine-based ammonium fluoride salt failed presumably due to the basic properties of the fluoride anion in aprotic conditions. The use of "masked" tetrabutylammonium fluoride salts, **130** and **131**, led to strong acceleration of the diethylzinc addition to benzaldehyde but the conditions of reaction are basic enough for degradation of the tetrabutylammonium cation through β–elimination to occur.

To circumvent these problems, the catalysis by *in situ* generated fluoride salts was studied. Substoichiometric amounts of chiral ammonium salts in the presence of 1 eq. of KF or AgF led to some activation of the addition reaction but with insignificant enantiocontrol. When studying the use of phase transfer conditions to generate a soluble fluoride source, we discovered that CsF alone is soluble enough in the organic phase to activate the reaction.

[**] Crown ether **138** is known to interact with diorganozinc species and form species where the diorganozinc is threaded through the crown ether (crystallographic evidence)[214] Pajerski, A. D.; BergStresser, G. L.; Parvez, M.; Richey, H. G. *J. Am. Chem. Soc.* **1988**, *110*, 4844-4845, [215] Fabicon, R. M.; Parvez, M.; Richey, H. G. *Organometallics* **1999**, *18*, 5163-5169..

In the presence of otherwise insoluble KF (1 eq.), achiral crown ether 18-C-6 **138** (10 mol%) acts as a phase transfer agent leading to strong activation of the diethylzinc addition to benzaldehyde.

By looking at the literature, it appeared to us that very few chiral crown ethers are described and they are challenging to synthesize[††]. In addition, it was not clear if the chiral environment provided by the chiral crown-ether around the fluoride anion would be adequate to induce enantiocontrol in the addition of diorganozinc to the aldehyde. We therefore preferred to invest our time in an alternative strategy.

[††] At that time, attempts in the laboratory by Patrick Schanen to synthesize chiral crown-ethers for his own projects were met with failure[11] Schanen, P. *PhD Thesis*, Université catholique de Louvain, Unité de Chimie Organique et Médicinale, **2003**.

# Chapter 5

# Ambifunctional Catalysts

## 5.1. Introduction

Our previous results showed that the activation of diorganozinc compounds by addition of a fluoride anion and, presumably, the formation of a zincate intermediate, did lead to a rapid and efficient addition of diethylzinc on benzaldehyde. Yet, the introduction of chirality in such systems was problematic since the chiral crown ethers were not easily accessible and might hinder the optimization of the chiral induction. Moreover, we still did not believe that the activation obtained with the fluoride anion was strong enough to be applied to the less electrophilic imines. We therefore wanted to develop a new more powerful system still based on our discovery of diorganozinc activation by fluoride anions but with an ease in the introduction and diversification of the chiral information.

If we look back at the mechanism proposed by Noyori[75,21,76-79], part of the success of 1,2-amino alcohol catalyzed addition of dialkylzinc to aldehydes resides in the ambifunctional properties of the active catalyst **139** generated *in situ*. The deprotonation of the 1,2-amino alcohol by dialkylzinc generates an electrophilic zinc atom capable of activating the carbonyl group through complexation. Complexation of the oxygen atom by another molecule of dialkylzinc leads to an equivalent of an ate complex which can deliver an alkyl group to the activated carbonyl group (Figure 15).

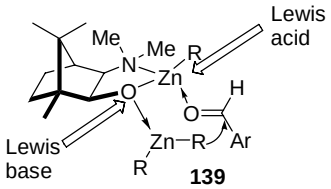



**Figure 15**

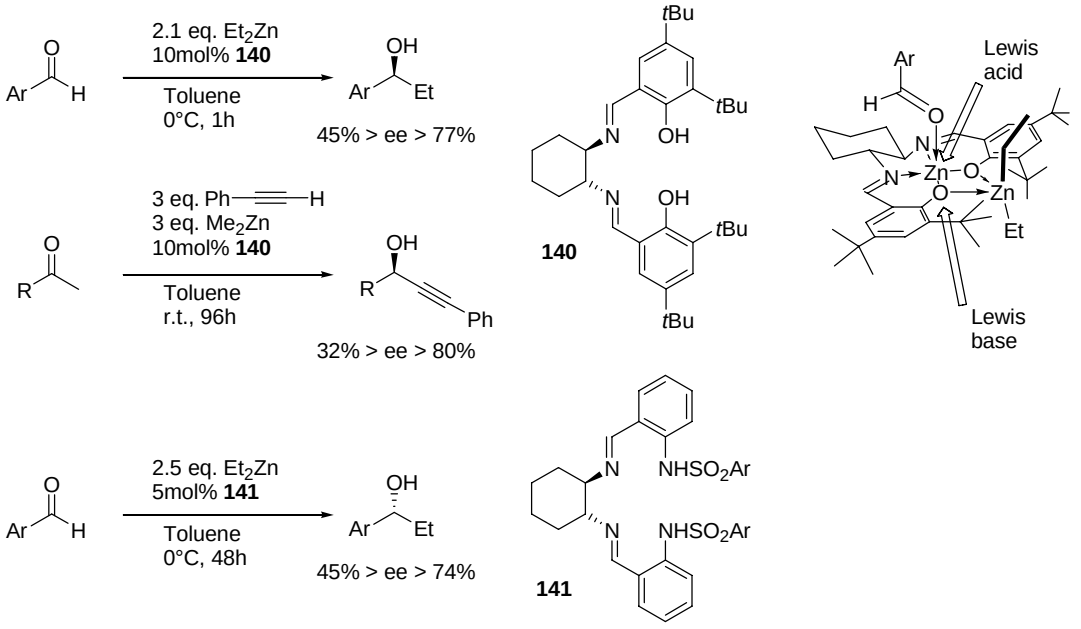
Both reaction partners are thus activated which leads to a strong reaction acceleration. Additionally, this ambifunctional catalysis brings the two reactants in close proximity, thus "intramolecularizing" the reaction – which entropically favors the reaction [216,217].

The high rate of the catalyzed asymmetric pathway decreases the erosion of enantiomeric excess due to the achiral uncatalyzed reaction. In addition, an ambifunctional catalyst also controls the orientation of both the prochiral aldehyde and the nucleophile, hopefully ensuring a better transfer of the chiral information from the asymmetric ligand. In principle, an ambifunctional catalyst should result in a high enantiomeric excess without compromising the reaction's speed[218].

## 5.2. Examples

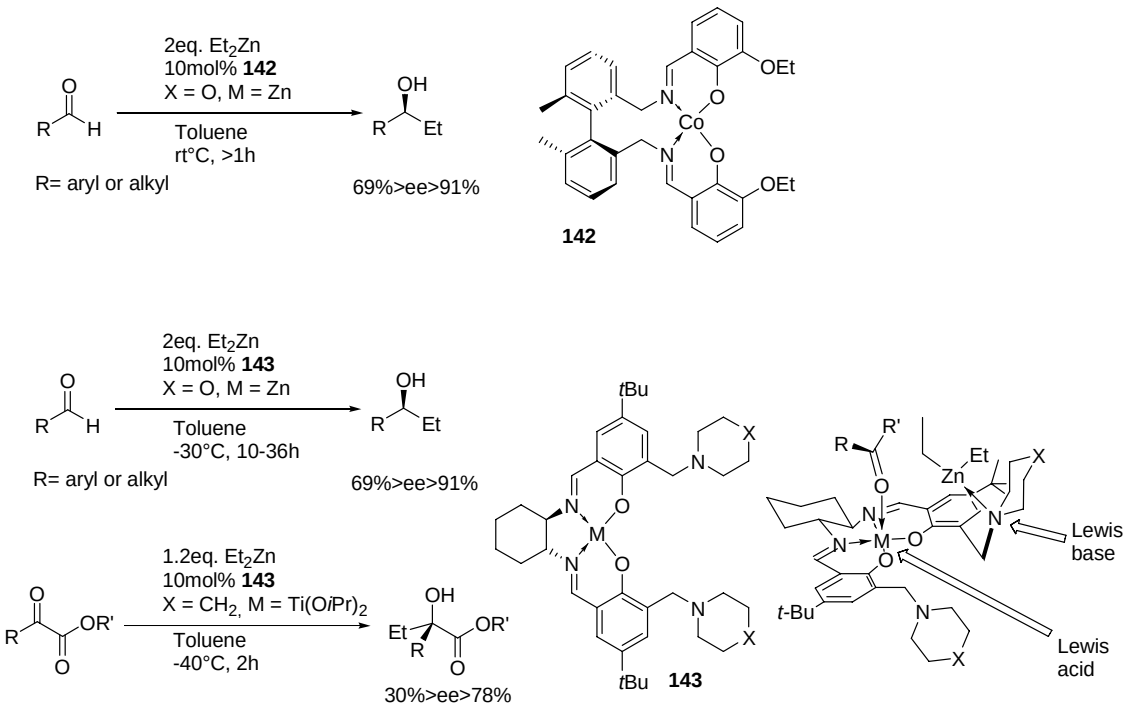
While looking over the body of literature on $R_2Zn$ addition to C=O double bonds, we found a few examples of systems built around the principle of ambifunctional activation but which were not directly related to 1,2-amino alcohols.

Among these, Cozzi and Umano-Ronchi reported the use of salen zinc complexes **140** generated *in situ* for the promotion of the asymmetric diethylzinc addition on aldehydes[219] and, later on, the asymmetric dialkynylzinc addition to ketones[220]. In both cases, they proposed that the zinc complex played the role of a Lewis acid by coordination to the carbonyl group while the two oxygen atoms bound to the organometallic reagent. The maximum enantioselectivity registered for these systems was respectively 77% ee and 81% ee. The related tetradentate sulfonamide ligand **141** reported by König induces moderate enantiocontrol (<74% ee) in the diethylzinc addition to aldehydes[221]. In this case, it was proposed that an oxygen atom of the sulfonamide plays the role of the Lewis base (Scheme 58).



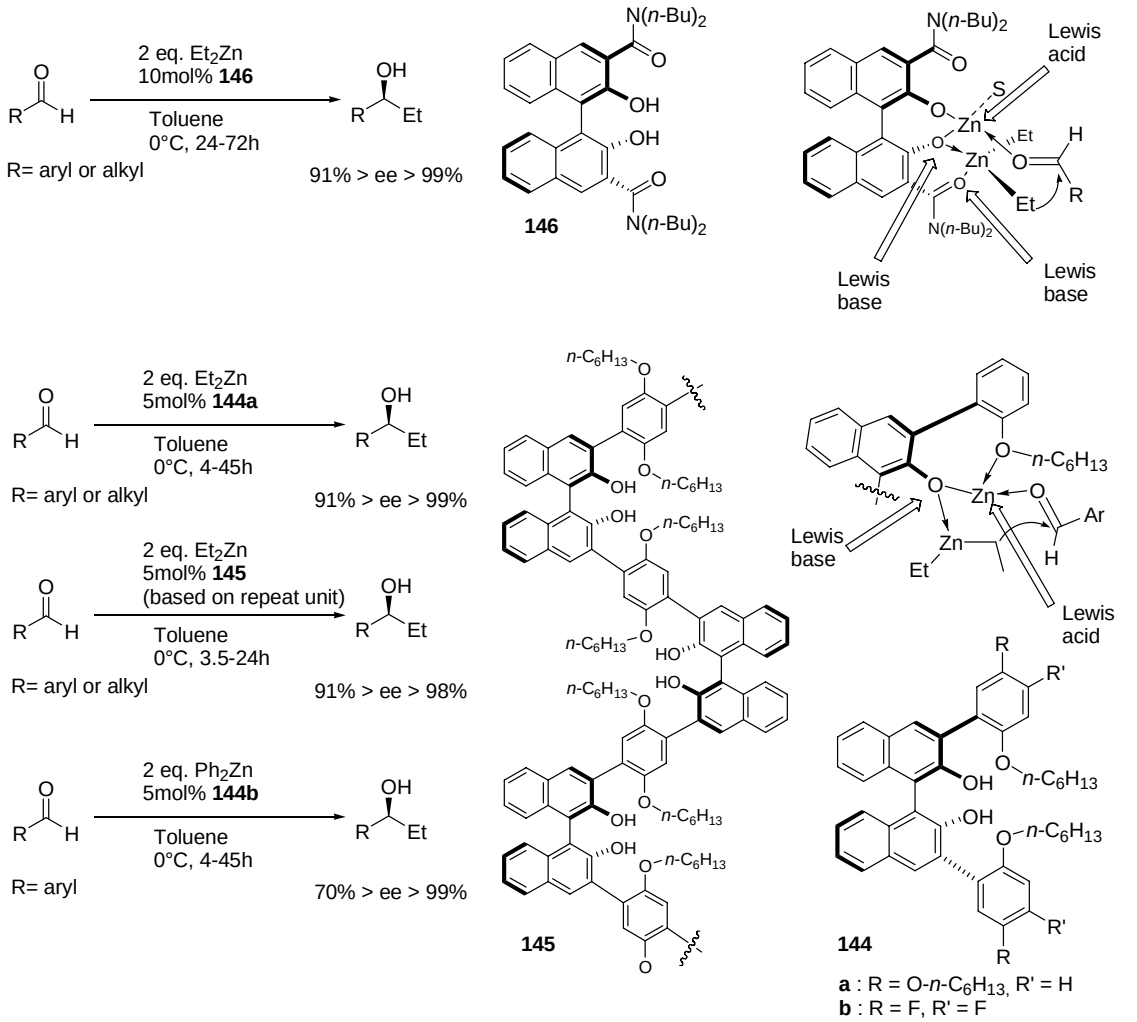

**Scheme 58**

Salen complexes with additional heteroatoms located to play the role of Lewis bases have been reported. Cobalt salen complex **142** based on a chiral axial diamine and substituted salicylaldehydes was evaluated by Rippert for the addition of dialkylzinc to aryl aldehydes[222]. Kozlowski introduced the modified salen complexes **143** carrying an nitrogen-bearing-arm and applied them to the enantioselective addition of dialkylzinc compounds to aldehydes[223] and $\alpha$-ketoesters[224,225] (Scheme 59).



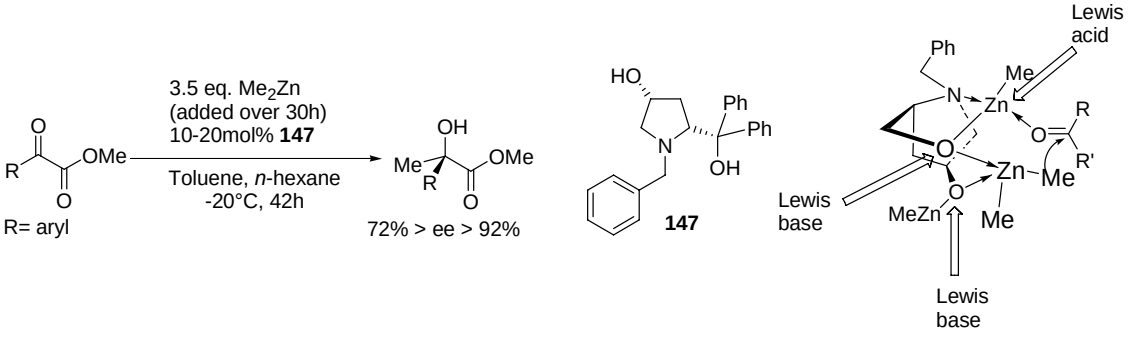

**Scheme 59**

Two research groups have prepared chiral binaphtols with substituents allowing ambifunctional catalysis of the diorganozinc addition to aldehydes. Binaphtols 146 carrying amide functions adjacent to the hydroxy groups were shown by Katsuki to catalyze $Et_2Zn$ addition to aldehydes[226,227]. Monomeric ligands **144** and polymeric ligands **145** based on binaphtol units bearing diaryl ethers next to the hydroxy groups were synthesized and tested by Pu for the asymmetric addition of $Et_2Zn$ and $Ph_2Zn$ to aldehydes with high enantioselectivity[228-233]. These ligands exhibit higher catalytic activity than unsubstituted binaphtol underlining the importance of the additional heteroatom in the catalytic events. Katsuki postulated double deprotonation of the binaphtol unit by one diethylzinc generating a Lewis acidic zinc alkoxide center. However, Pu proposes that only one hydroxy group is deprotonated by a unit of diorganozinc leading to an active species akin of the Noyori's amino alcohol based active catalyst **139** (Scheme 60).




**Scheme 60**

More recently, Shibasaki introduced ligand **147** bearing one tertiary nitrogen and two hydroxyl functions[234]. The *syn* relationship of the two alcohol substituents was shown to be crucial for the successful enantioselective addition of dimethylzinc to $\alpha$-ketoesters. Again, a zinc atom was assigned the role of a Lewis acid while the two oxygen acted as Lewis bases directing and activating the dimethylzinc nucleophile (Scheme 61).




**Scheme 61**

## 5.3. Proposal

The few examples presented in the previous section indicate that the use of a ligand or catalyst showing both Lewis acid and Lewis base properties was a winning solution for the asymmetric addition of diorganozinc compounds to carbon-oxygen double bonds. Both reaction partners are activated in close proximity and with defined positions leading to a low energy transition state with a good transfer of the chiral information from the chiral auxiliary to the asymmetric center.

How could we introduce the fluoride anion in an ambifunctional catalyst to take advantage of its Lewis base properties? When comparing the ambifunctional systems found in the literature, we observed that in the amino-alcohol transition state **139** as well as in the system of Cozzi and Umani-Ronchi (**140** in Scheme 58), the Lewis basic and acidic features were directly linked together as schematized in **148**. Following that line, the simplest idea we could find was to directly link the fluoride atom to a Lewis acidic metal center as is the case in a metal-fluoride species. The complexation of the metal center by optically active ligands could then lead to some enantiocontrol in a transition state such as **149** (Figure 16).

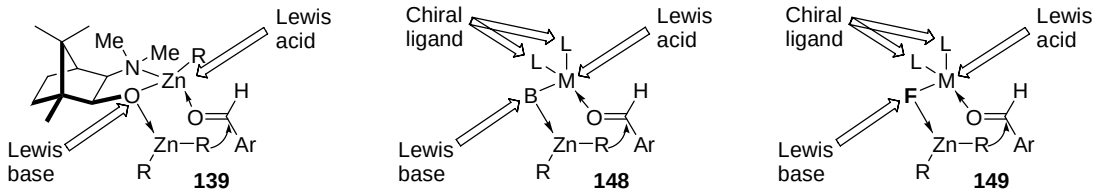



**Figure 16**

# Chapter 6

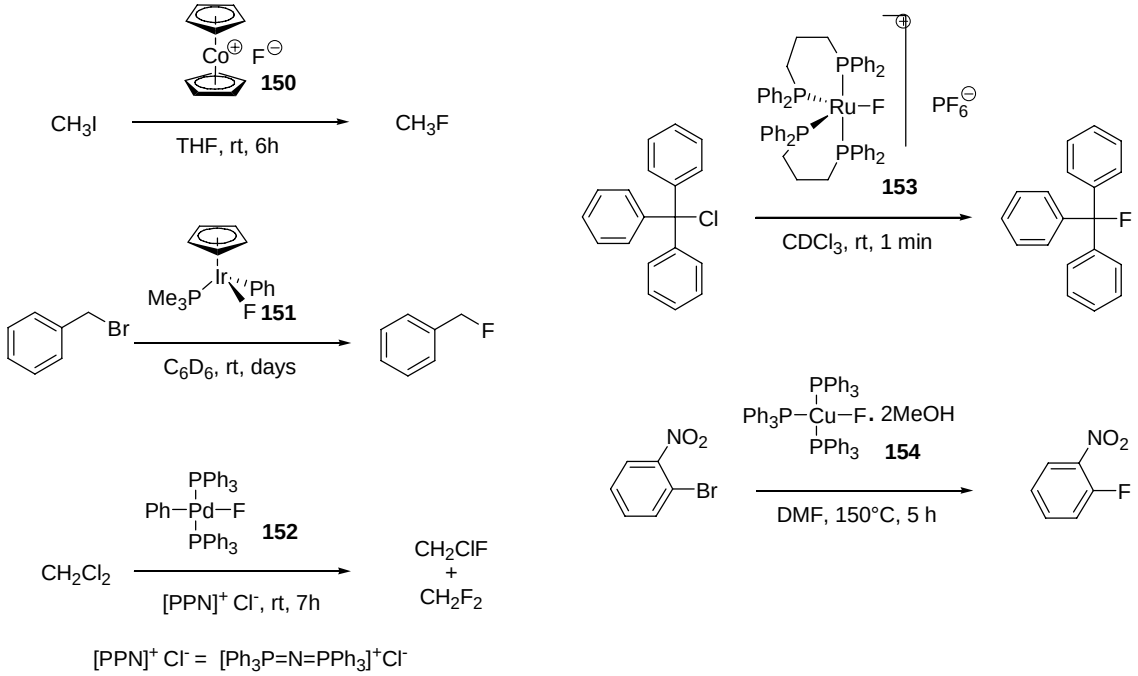
# Introduction to Metal Fluorides

## 6.1. Metal-Fluoride Compounds

### 6.1.1. Introduction

As we have seen in the preceding chapters, the use of a Lewis base such as a fluoride anion is an attractive approach to increase the nucleophilicity of diorganozinc compounds. However, after our investigation of ammonium salts and crown ethers, a practical chiral source of fluoride anions had yet to be found.

We have turned our attention to transition metal fluorides[235-238] as potential catalyst for the addition of diorganozinc compounds to carbonyl compounds and imines. Several metal fluoride complexes, such as **150**[239], **151**[240], **152**[241,242], **153**[243], **154**[244], exhibit a highly reactive metal fluoride bond and are highly potent sources of nucleophilic fluoride anions (Scheme 62).




**Scheme 62**

### 6.1.2. Properties of the Metal-Fluoride Bond

Metal fluoride complexes are not as common as metal chloride, bromide and iodide complexes. This could be partly ascribed to a mismatched combination of the fluoride anion with a transition metal from the point of view of the HSAB (hard/soft

acid/base) principle formulated by Pearson[245]. The fluoride anion is a hard base. The polarizability of transition metals varies with their hardness increasing for smaller metal nuclei and higher oxidation state[246]. Thus, according to this theory, the more stable metal fluoride complexes are those combining a fluoride ion with a hard Lewis acid metal center. With a soft metal center, the metal fluoride will be less stable. This reflects in the experimental metal-fluoride bond energies. Fluoride form strong bonds with hard metal partners ($E_{Ti-F}$= 140 kcal.mol$^{-1}$ in $TiF_4$) and weaker bonds with softer metal centers ($E_{Cu-F}$= 88 kcal.mol$^{-1}$ in $CuF_2$)[247].

The metal-fluoride bond could be described by two binding components: (1) a σ bond and (2) a π bond resulting from the back donation of electrons from a lone pair on fluorine to a d orbital on the transition metal[248]. For the fluoride lone pairs to be able to interact with the metal through π interactions, an empty d orbital of the appropriate symmetry and energy level should be available on the metal. When such an empty orbital is available, the metal-fluoride π interaction would be stabilizing. However, if the d orbital is filled by an electron doublet, the interactions would be destabilizing[249] (Figure 17)

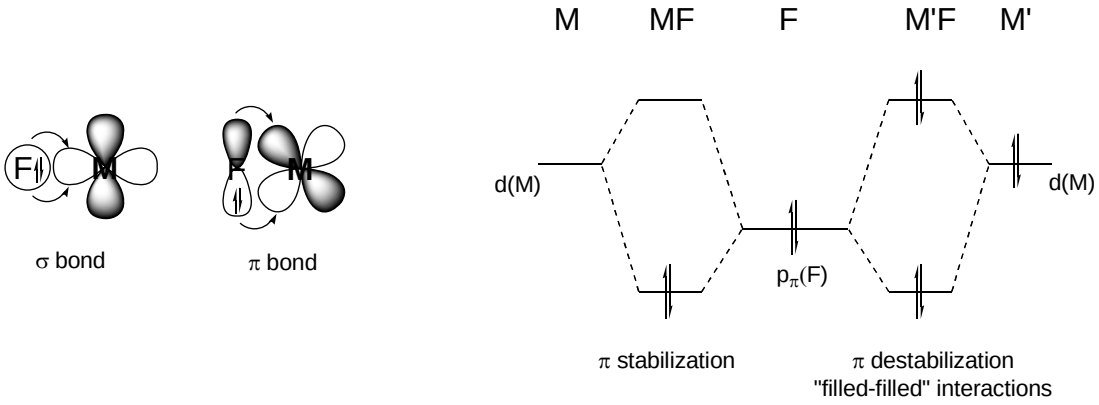



**Figure 17**

The stability of these complexes is not only influenced by the nature of the metal but also by the surrounding ligands. Electron-withdrawing co-ligands lead to a decrease of the electron density on the metallic center thereby stabilizing the metal-fluoride bond in a "push-pull" interaction. The most studied ligands are π acceptor ligands, such as carbonyl (*i.e.* iridium complex **155** (X=F), see Figure 19) and phenyl (*i.e.* palladium complex **152**, see Scheme 62), which are located *trans* to the fluoride (Figure 18).

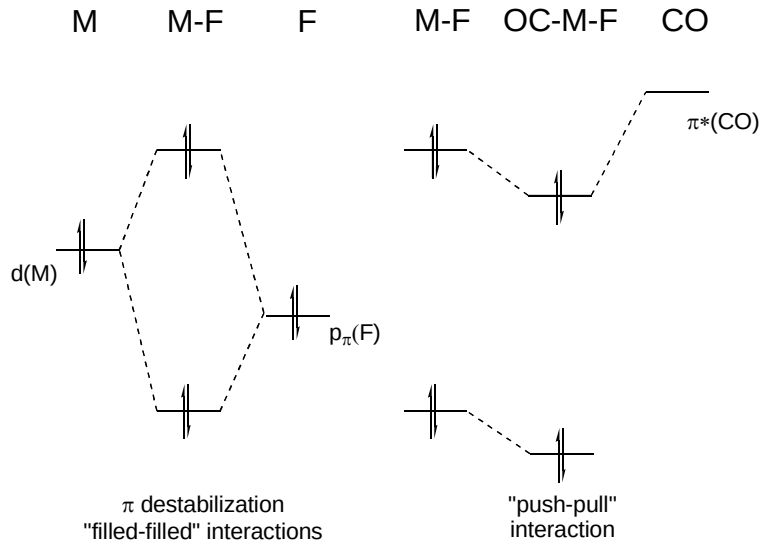



**Figure 18**

Mezzetti pointed that fluoride, being the most electronegative element in the periodic table, is not inherently a good "π donor". The π donor ability of the fluoride should be reconsidered even if it could partially explain the existence of most metal-fluoride complexes. It is proposed that the experimental observations previously assigned to π donation by the fluoride towards the metal are the results of electrostatic interactions between the metal orbitals and the fluoride negative charge[250]. Indeed computational studies of *trans*-[IrX(CO)($PR_3$)$_2$] **155** by Goldman and Krogh-Jespersen[251] showed that the bonding π orbital of the Ir-F bond had strong F character while the antibonding π* was localized on the metal. This confirmed the ionic character of the Ir-F bond. On the other hand, the π donation by iodide and the covalent character of the Ir-I bond were obvious from the coefficients of the molecular orbitals in the iodide complex **155** (Figure 19).

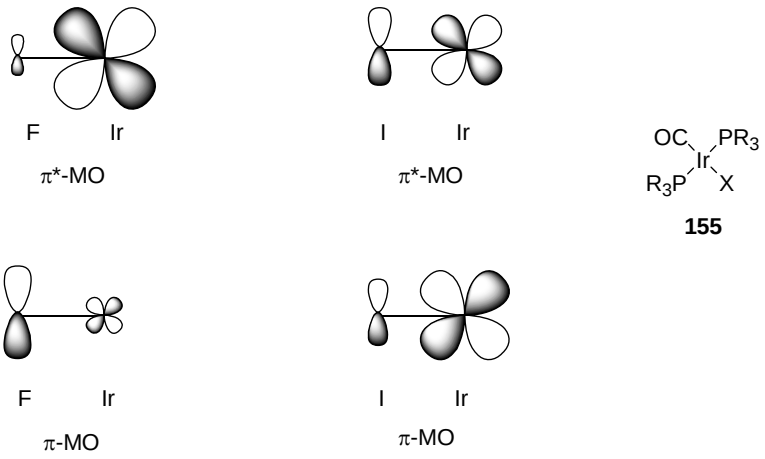
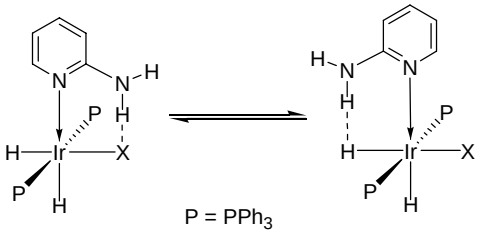



**Figure 19**

The lone pairs of the fluoride can also participate in weak interactions such as hydrogen bonding. The hydrogen bond between the fluoride anion and water is one of the stronger hydrogen bonds known ( 13.5 kcal.mol$^{-1}$) [247]. A good illustration of

hydrogen bonding involving halide ligands is the quantitative analysis, by Eisenstein and Crabtree[252], of the competitive hydrogen bonding to halide and hydride ligands. The determination of the relative population of the two rotamers **156** and **157** showed that the fluoride ligand is the best halide partner for hydrogen bonding with an estimated bond strength of 5.2 kcal.mol$^{-1}$ (Scheme 63)[‡‡]

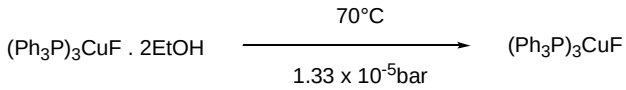



**156** **157**

| X | IrX···HN (kcal.mol$^{-1}$) | IrX···HH (kcal.mol$^{-1}$) |
|---|---|---|
| I | <1.3 | 3.3 |
| Br | 1.8 | 3.0 |
| Cl | 2.1 | 2.9 |
| F | 5.2 | <2.9 |

**Scheme 63**

This hydrogen bonding has several consequences on the properties of fluoride complexes. First of all, several metal-fluoride complexes crystals were obtained with tightly bound solvent molecules. It can be difficult to remove the solvent molecules from the complex as shown for **158**[254]: the unsolvated complex could only be obtained after heating the complex at 70°C for four hours under high vacuum (1.33x10$^{-5}$ bar) (Scheme 64).




**158**

**Scheme 64**

In the case of the $Pd_2(\mu\text{-}F)_2$ complex **159**, three molecules of the relatively non-acid, $CH_2Cl_2$ are hydrogen-bonded to fluoride.[255] Hydrogen bonding of the fluoride ligand by hydrogen fluoride can lead to a bifluoride as in the molybdenum complex **160.**[256] In the case of complex **152**, some intermolecular and intramolecular hydrogen bonds between fluoride ligands and non-acidic hydrogens were observed in the solid phase[255]. These examples show that in these complexes the fluorine atom retains its Lewis basicity even when complexed to a metal (Figure 20).

[‡‡] For further information on protonation and hydrogen bond formation of metal halide complexes, see the review article by Kuhlman[253] Kuhlman, R. *Coord. Chem. Rev.* **1997**, *167*, 205-232.

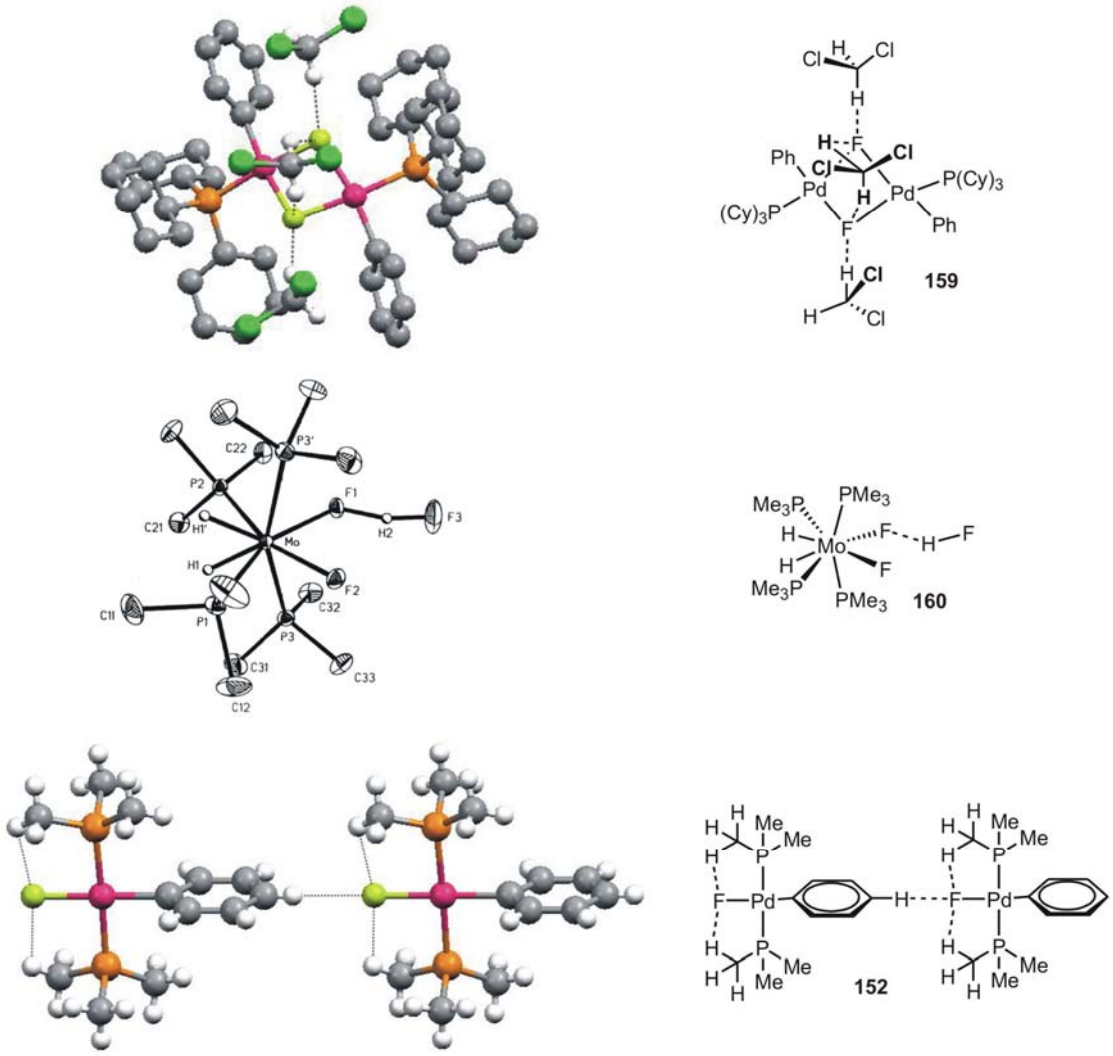
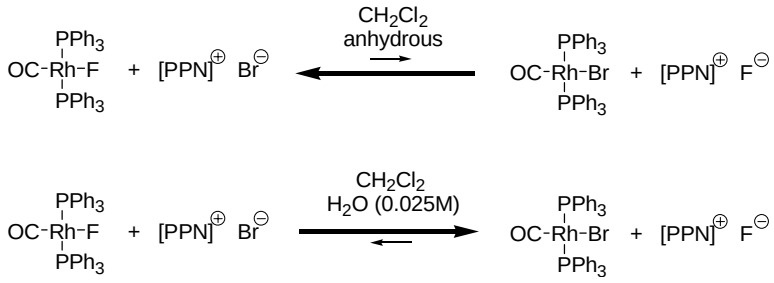


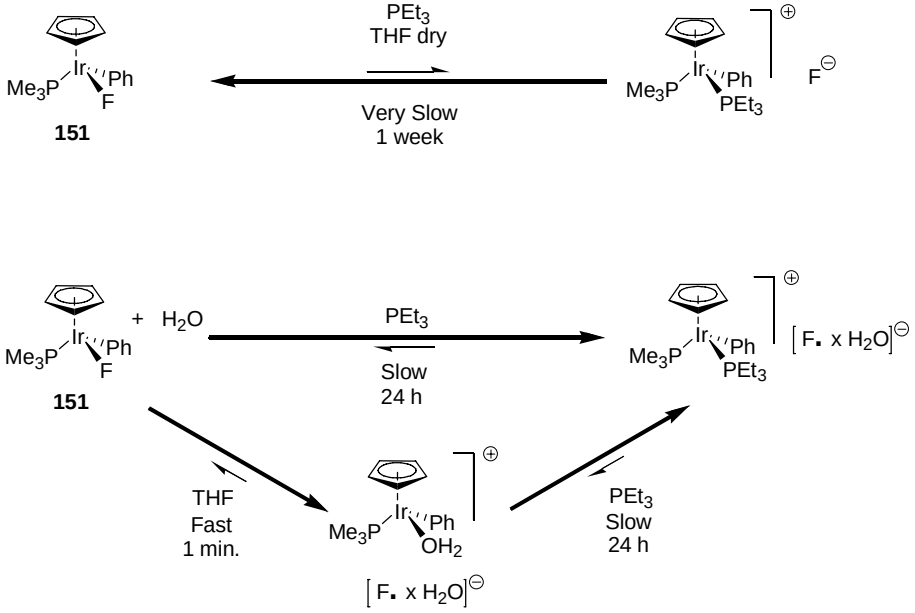

**Figure 20**

Given the propensity of fluoride to form hydrogen bonds, the properties of metal fluorides complexes should be expected to be strongly influenced by protic solvents. This is illustrated in Scheme 65 : traces of water shift the equilibrium completely to the right. This sensitivity to water is not observed with the other halides[257,258].




**Scheme 65**

From a kinetic point of view, the lability of the metal fluoride bond is increased in the presence of protic solvents. For instance, in iridium complex **151**, fluoride substitution by triethylphosphine was slow and in the absence of water. In the presence of water, the substitution reaction was much faster (1 day *vs* 1 week) and the equilibrium lied to the right. However, the interpretation of the kinetic data has to take into account the nucleophilic displacement of fluoride ligand by water[240] (Scheme 66).




**Scheme 66**

Mechanistic studies by Grushin of the ionization of the palladium fluoride bond induced by water showed that, indeed, that both electrophilic activation by hydrogen bonds and nucleophilic attack of water on the metal have to be taken into consideration[241,259]. Two "push-pull" mechanisms have been proposed combining both ionization's activation modes (Figure 21).

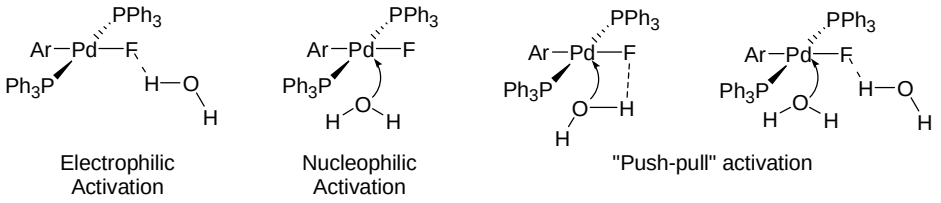
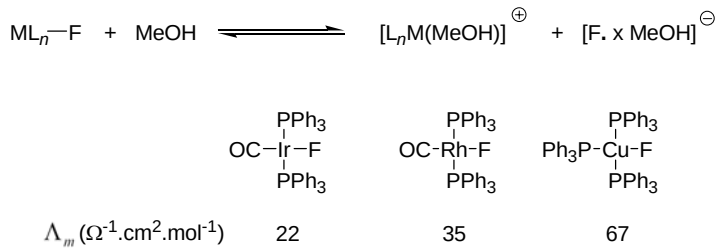



**Figure 21**

The ionization of the metal fluoride bond as also been observed through conductivity experiments in a protic solvents such as methanol. The molar conductivity values ($\Lambda_m$) of the fluoride complexes, compared to those of strong electrolytes which range between 80 and 110 $\Omega^{-1}.cm^2.mol^{-1}$, indicate the presence of a solvolytic equilibrium[260,254] (Scheme 67).




**Scheme 67**

To conclude, the metal fluoride bond will be destabilized if we go from early to late transition metals or if the oxidation state of the metal is decreased. These conclusions parallel the ones of the HSAB principle. The description of the metal fluoride bond itself is problematic. The description through σ bonding and π backbonding components conflicts with the high electronegativity and weak polarizability of the fluoride anion. Therefore, Mezzetti has proposed that the metal-fluoride bond could be best described by an electrostatic interaction between the electron-rich fluoride anion and a positively charged metal. The fluoride in metal fluoride complexes is also involved in secondary interactions. In the presence of traces of water or protic solvents, the fluoride atom is susceptible to participate in hydrogen bonding. These will either lead to dissociation of the metal fluoride bond or stabilization of the metal-fluoride bond by decreasing the electronic density on the fluoride. In aprotic media, the metal fluoride bond is kinetically more stable. By choosing the right conditions, metal fluoride complexes can be synthesized, isolated, characterized and potentially used in catalysis.

# 6.2. Catalysis by Metal Fluorides

## 6.2.1. Introduction

Metal halide salts are a convenient and abundant[§§] entry point for the synthesis of complexes. It is therefore normal that halide complexes are quite numerous and are widely used in catalysis. In a recent review, Lautens has highlighted the role of the halide ion as an tunable ligand in transition metal catalysis[248]. However, catalysts where fluoride is a ligand are less common than with the other halides. Duthaler highlighted, in 1997, the emergence of fluorotitanium species as catalyst for the addition of nucleophiles towards aldehydes[262]. In 1999, a short review on homogeneous catalysts involving fluoride ligands was compiled by Carreira *et al.*[247]. Since then, several metal fluoride based catalysts have been developed.

In the following pages, we have gathered examples of metal fluoride catalyzed reaction with an emphasis on mechanistic hypothesis or observations. The metal fluoride catalytic systems are presented in two classes : (1) those involving silicon reagents and (2) those not involving silicon reagents.

---

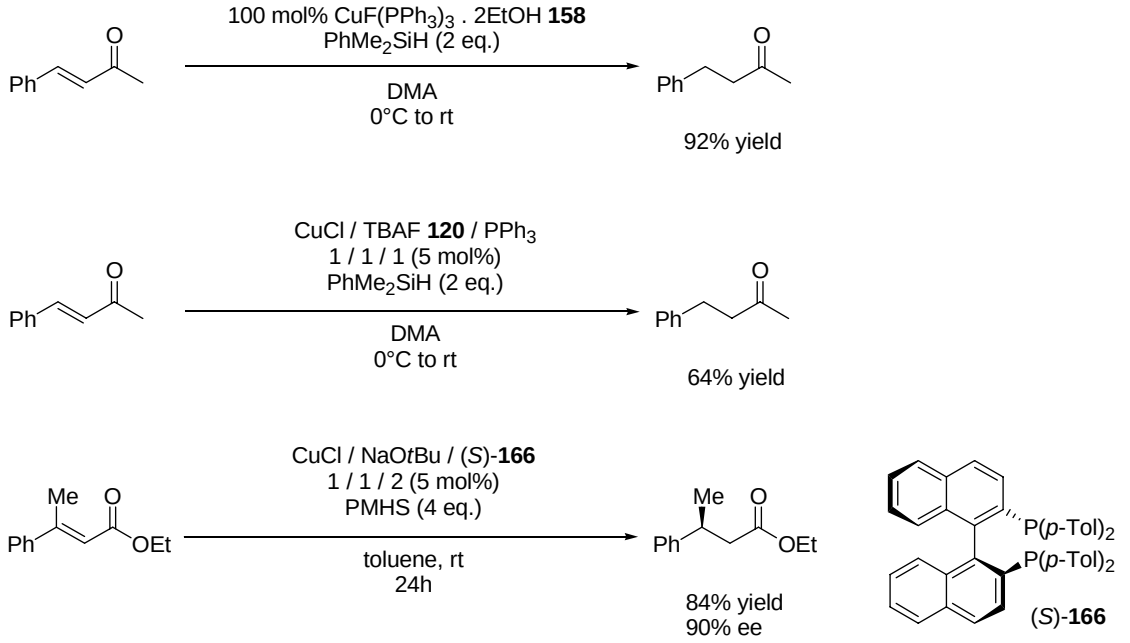
[§§] The term "halogen" has been introduced, in 1811 by J.S.C. Schweigger, based on the greek root meaning "to produce sea salt" to describe the property of elemental chlorine which combines directly with metals[261] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*; Pergamon Press: New York, **1984**..

## 6.2.2. Metal Fluoride Catalysts and Silicon Reagents

The strength of the silicon-fluoride bond ($D$ ($H_3Si$-F)=150 kcal.mol$^{-1}$ and $D$ ($F_3Si$-F)=166 kcal.mol$^{-1}$)[263] has been the key to the development of metal fluoride catalysts. Many authors have used silicon reagents to purposefully abstract the fluoride atom from the metal-fluoride complexes.

***Copper Catalysts***

The reduction of α,β-unsaturated ketones by hydrosilanes mediated by copper(I) salt **158** has been described by Mori[264,265]. In the same article, the combination of copper(I) chloride, tetrabutylammonium fluoride (TBAF) **120** and triphenylphosphine was revealed to be quite efficient with loadings as low as 5mol%. Even though no experimental proof was provided, it was assumed that the reaction involved the formation of a copper hydride species. This hypothesis was strongly supported by the reported conjugated reduction of enones by the copper(I) hydride cluster $[(PPh_3)CuH]_6$, the so-called Stryker's reagent[266]. Buchwald *et al.* have developed an enantioselective catalyst for this reaction based on copper(I) chloride and chiral diphosphine *p*-TolBINAP **166** [267]. This reaction was also applied to the α,β-unsaturated lactones and lactams[268] (Scheme 68).

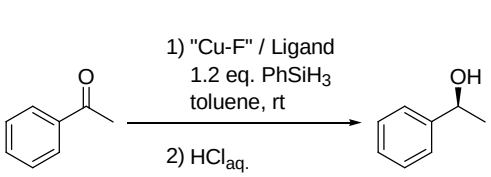


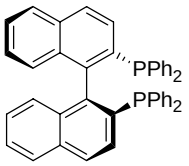

**Scheme 68**

The asymmetric hydrosilylation of ketones by phenylsilane has been shown by Riant *et al.* to be catalyzed by a copper(II) fluoride-chiral diphosphine system (Table 12, entries 1 & 2) as well as by the copper(I) fluoride complex **154** with a chiral diphosphine (entries 3 & 4)[269,270]. No reaction was observed when other copper halide salts were used. However the catalytic activity was recovered when a copper(I) iodide and a diphosphine were used in the presence of a fluoride source such as TBAT **130** ($n$-$Bu_4NPh_3SiF_2$) (entry 5). These systems have the peculiar property of being accelerated by oxygen. In a recent development, Chan *et al.* have applied their dipyridylphosphine ligand **161** to this reaction with improved

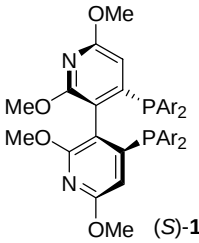
enantiocontrol (entry 6)[271]. The precise mechanism is not known. Lipshutz *et al.* has shown that copper(I) chloride and a chiral diphosphine in conjunction with sodium *tert*-butoxide catalyze the hydrosilylation of ketones by polymeric silane PMHS (in these conditions $PhSiH_3$ is inactive) (entry 7)[272-274]. It can therefore be speculated that the copper fluoride species are only pre-catalysts and that the catalytic cycle involves copper hydride and copper alkoxide species.

**Table 12** : Copper fluoride catalyzed asymmetric ketone hydrosilylation



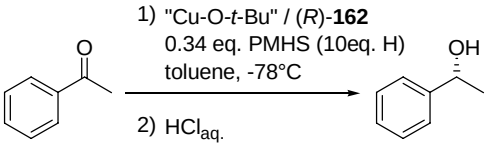



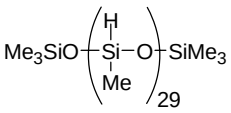

(*S*)-**75**



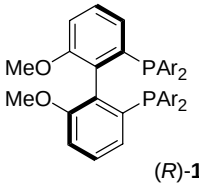

(*S*)-**161**

Ar = 3,5-$Me_2(C_6H_3)$




PMHS



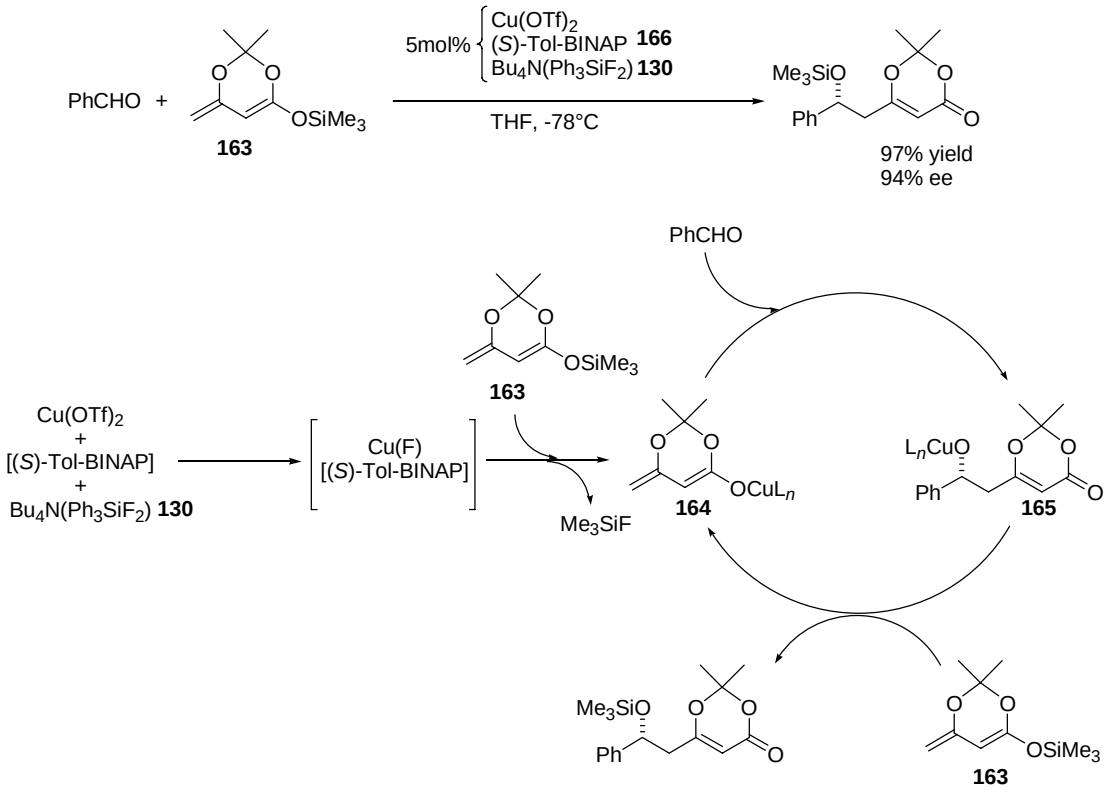

(*R*)-**162**

Ar = 3,5-$Me_2(C_6H_3)$

| Entry | [Cu] | Ligand | "Si-H" | atm. | time | conv. (%) | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | $CuF_2$ (1mol%) | (*S*)-**75** (1mol%) | $Ph_3SiH$ | air | 2h | 98 | 78 (*S*) |
| 2 | $CuF_2$ (1mol%) | (*S*)-**75** (1mol%) | $Ph_3SiH$ | Ar | 16h | 99 | 79 (*S*) |
| 3 | [$CuF(PPh_3)_3$.2MeOH] (2mol%) | (*S*)-**75** (2mol%) | $Ph_3SiH$ | air | 1h | 100 | 74 (*S*) |
| 4 | [$CuF(PPh_3)_3$.2MeOH] (4mol%) | (*S*)-**75** (4mol%) | $Ph_3SiH$ | Ar | 40h | 91 | 71 (*S*) |
| 5 | CuI / TBAT **130** (1mol%) | (*S*)-**75** (1mol%) | $Ph_3SiH$ | Ar | 24h | 40 | 76 (*S*) |
| 6[a] | $CuF_2$ (3mol%) | (*S*)-**161** (1mol%) | $Ph_3SiH$ | air | 6h | 99 | 87 (*S*) |
| 7[b] | CuCl / *t*-BuONa (3mol%) | (*S*)-**162** (3mol%) | PMHS | Ar | 5h | 98 | 94 (*R*) |

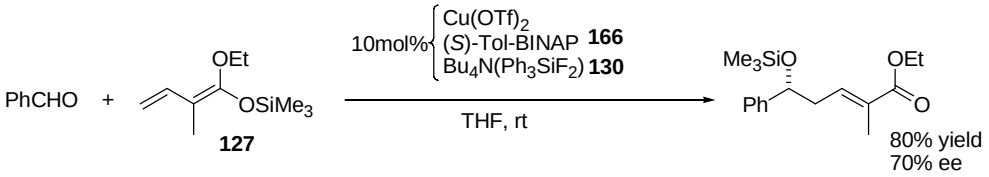
a : -20°C; b : -78°C

The use of copper fluoride species has been reported by Carreira et *al.* to mediate C-C bond formation by enantioselective addition reaction of dienol silanes **163** to aldehydes[275]. Mechanistic studies[247] point towards the removal of the fluoride counterion from the copper metal center by desilylation of **163** and the generation of a reactive copper dienolate **164**. Silylation of the copper alkoxide **165** by the dienolsilane **163** releases the reaction product from the catalyst and regenerates the reactive copper dienolate **164**. (Scheme 69)




**Scheme 69**

Later, Campagne reported the use of Carreira's catalyst system for the asymmetric addition of the simpler silyl dienolate **127** to aldehydes with good yields and enantioselectivities[201,276,277] (Scheme 70).

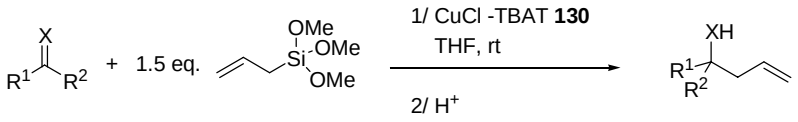


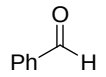
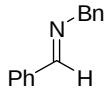
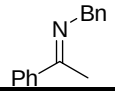

**Scheme 70**

Copper(I) fluoride species have been used by Shibasaki[278] as catalysts for the allylation of carbon-oxygen and carbon-nitrogen double bonds by allyltrimethoxysilane. It would be tempting to deduce based on the reaction

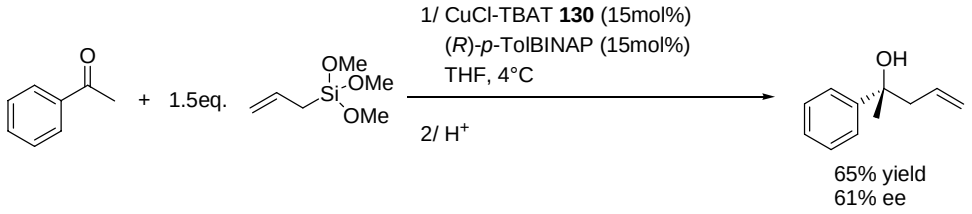
mechanisms proposed by Carreira (see Scheme 69) that the fluoride anion works only as an initiator to generate an active species such as a copper alkoxide. Indeed, CuO*t*Bu alone did not catalyze the allylation reaction on benzaldehyde. The addition to CuO*t*Bu of $(EtO)_3SiF$ in catalytic amounts (10mol%) did restore the catalytic activity. The fluoride anion has an active role in the catalytic cycle (Table 13).

**Table 13** : Shibasaki's allylation of C=O and C=N[278]



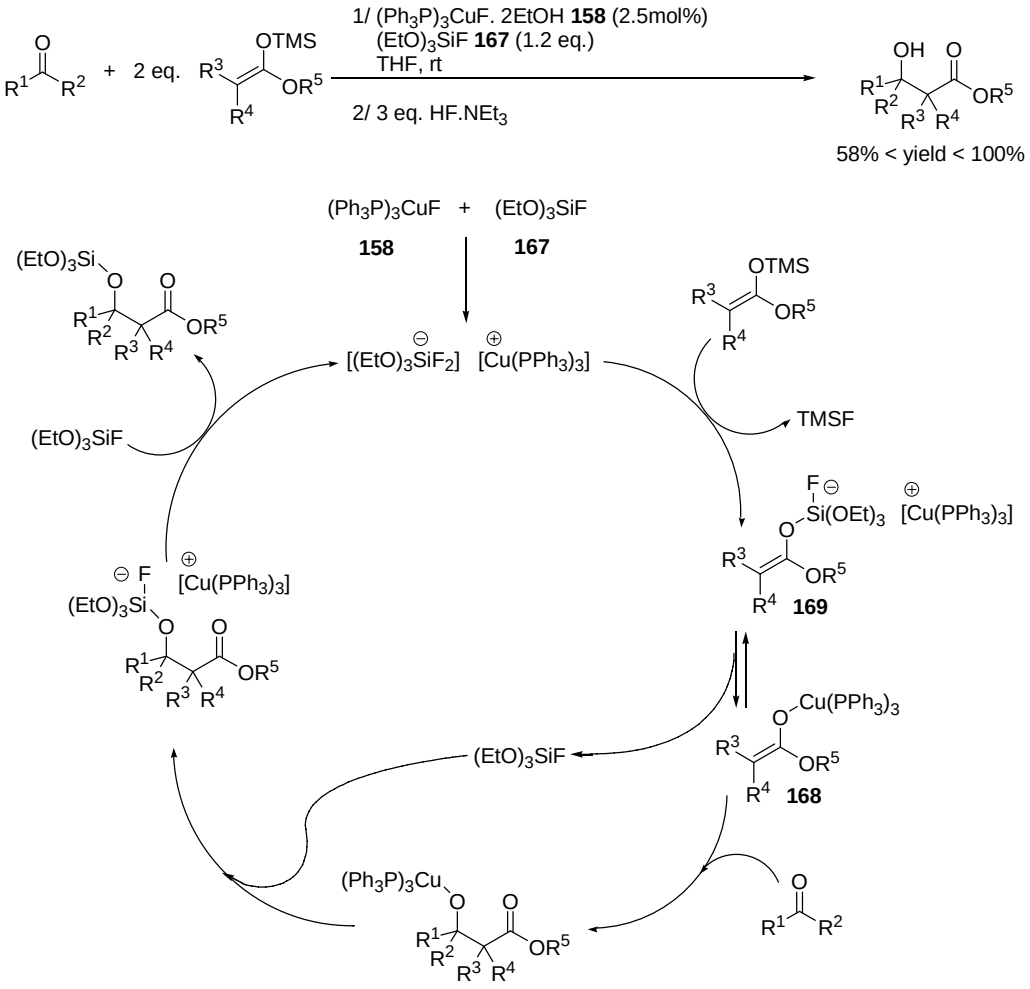

| Substrate | CuCl - TBAT 130 | time | yield (%) |
|---|---|---|---|
|  | 1mol% | 2.5 h | 94 |
|  | 2mol% | 4 h | 90 |
|  | 2mol% | 8 h | 96 |
|  | 5mol% | 26 h | 68 |

Preliminary attempts to apply this reaction in the chiral series by adding a chiral diphosphine are promising. The allylation of acetophenone in the presence of (*R*)-*p*-TolBINAP **166**-CuCl-TBAT **130** proceeds with 61% ee and 65% yield[278] (Scheme 71).



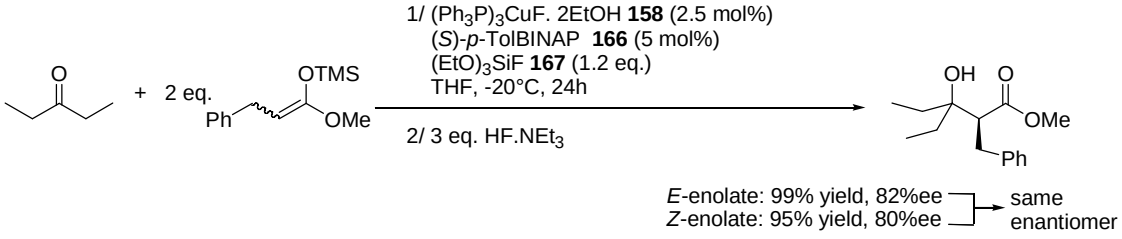

**Scheme 71**

Shibasaki *et al.* have used copper(I) fluoride complex **158** to catalyze the aldol addition of silyl ketene acetal to ketones[279]. The reaction did only proceed in the presence of stoichiometric quantities of triethoxysilyl fluoride **167**. This result, coupled with further mechanistic studies, indicated that the reaction involved a complex and dynamic ligand exchange between silicon and copper atoms. The actual nucleophilic species seems to be the copper enolate **168** and not the enol silicate **169**. The fluoride anion is involved throughout the catalytic cycle but it is not bound to the copper atom except in the catalyst precursor (Scheme 72).



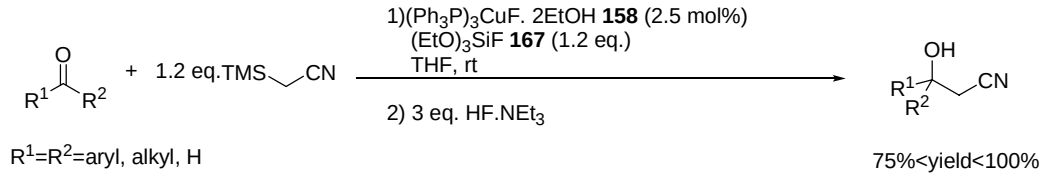

**Scheme 72**

Preliminary results in the chiral series show that the enantioselectivity is dictated almost entirely by the chiral ligand, (*S*)-*p*-TolBINAP **166**, and not by the geometry of the initial silyl ketene acetal (Scheme 73).



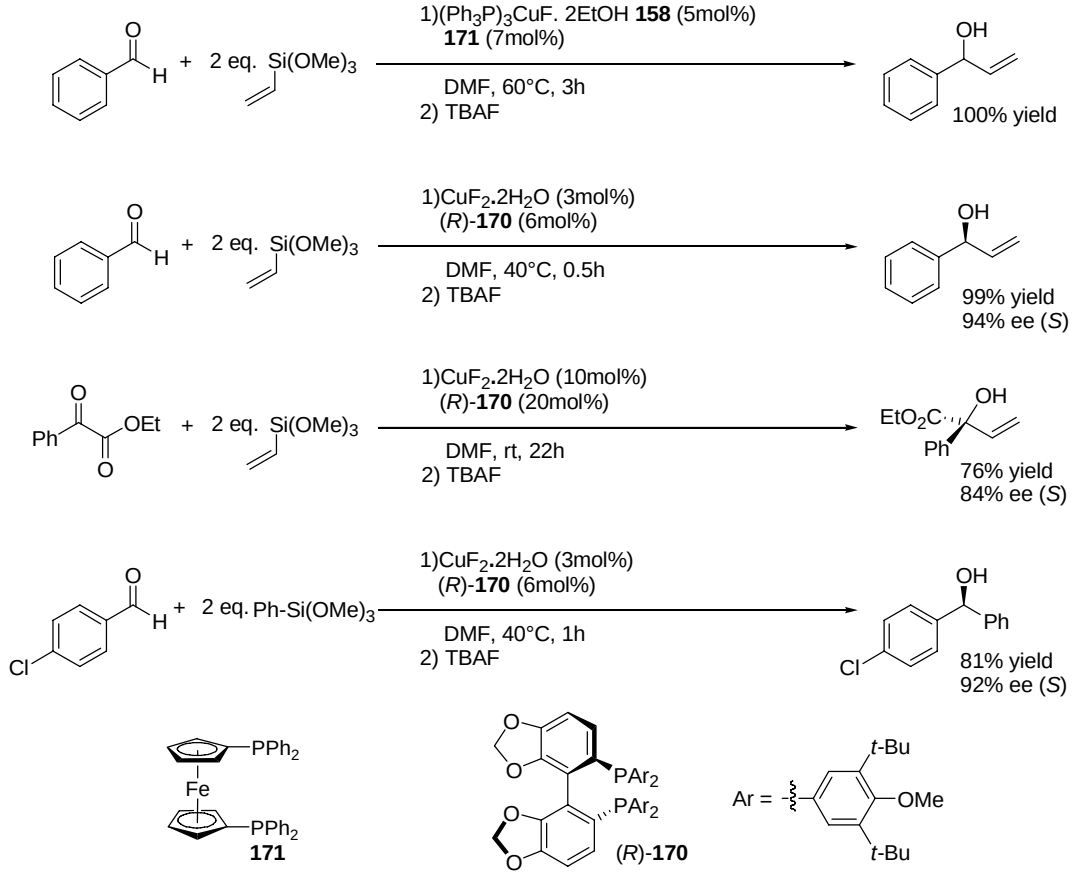

**Scheme 73**

The same catalyst combination has been used to promote the cyanomethylation of ketones and aldehydes by $TMSCH_2CN$[280] (Scheme 74).




**Scheme 74**

In a recent development, Shibasaki *et al*.[281] showed that copper fluoride and diphosphines catalyzed the alkenylation and phenylation of aldehydes and ketoesters by trimethoxyvinylsilane and trimethoxyphenylsilane. When using the chiral diphosphine **170**, the adducts were obtained with high enantiomeric excesses. Note that in the asymmetric version, the catalyst had to be prepared by reducing the copper(II) fluoride by one equivalent of expensive chiral diphosphine in wet methanol. In the catalytic cycle proposed by the authors, the fluoride anion is abstracted by the organosilane at the beginning of the reaction generating an organocopper reagent but is not involved in the rest of the catalytic cycle (Scheme 75).

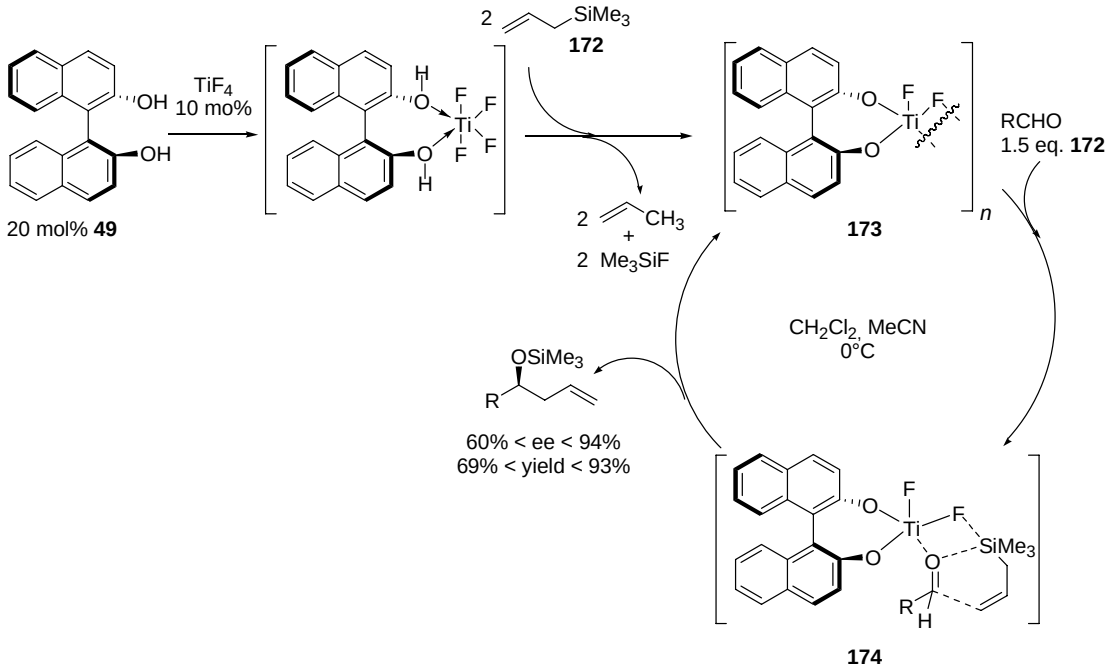



**Scheme 75**

***Titanium Catalysts***

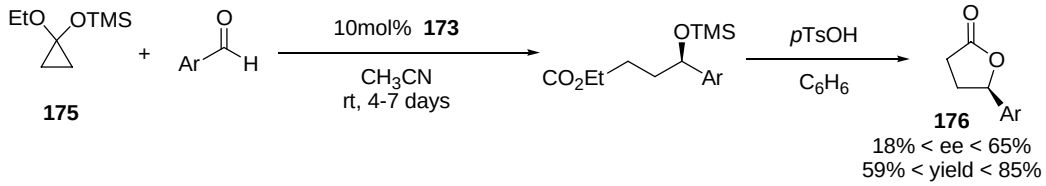
The use of titanium(IV) fluoride in the presence of chiral binaphtol **49** was shown by Carreira[247,282] to be instrumental in the enantioselective allylation of

aldehydes by allylsilanes. The allylic alcohols were produced at 0°C in up to 94% ee and good to high yields with a catalyst loading of 10mol%. Although the structure of the catalyst is unknown, a mechanism has been proposed which involves the *in situ* generation of the active catalyst through the formal elimination of HF from $TiF_4$ and binaphtol **49** in the presence of allylsilane **172**. The aldehyde would be activated by the chiral Lewis acid "titanium-binaphtol-fluoride" complex **173**. The remaining fluoride ligand could activate the nucleophilic allylsilane **172** through the formation of a bridged structure **174**[262,247] (Scheme 76).



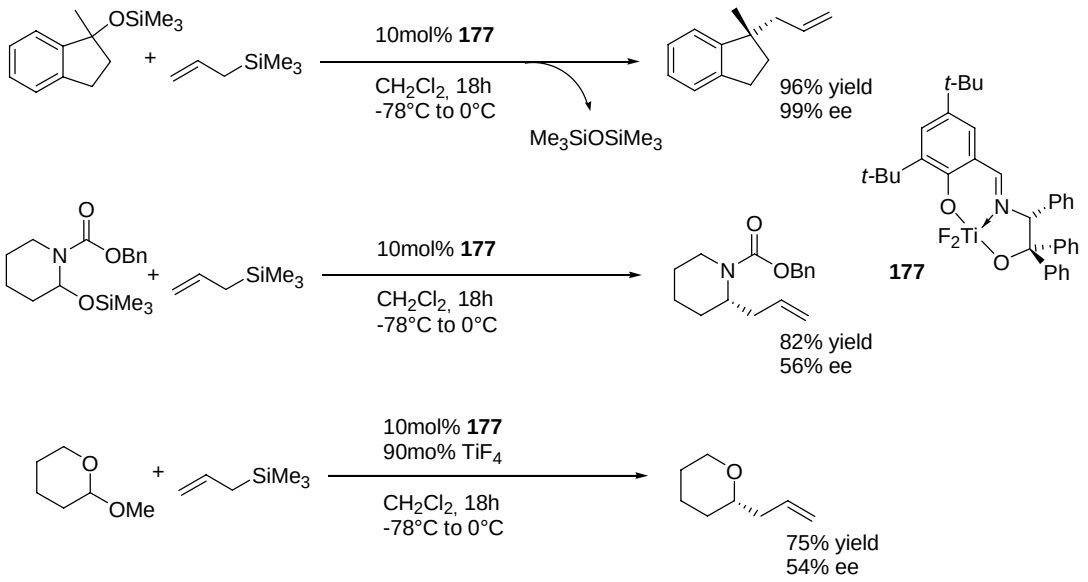

**Scheme 76**

The same catalyst **173** has been reported by Gleason to catalyze the ring opening of 1-ethoxy-1-(trimethylsilyloxy)cyclopropane **175** and the subsequent asymmetric addition to aldehydes [283]. The silylated mixed homo-aldol adduct is then deprotected to generate the corresponding lactone **176** with good yields and low to moderate enantioselectivity (Scheme 77)



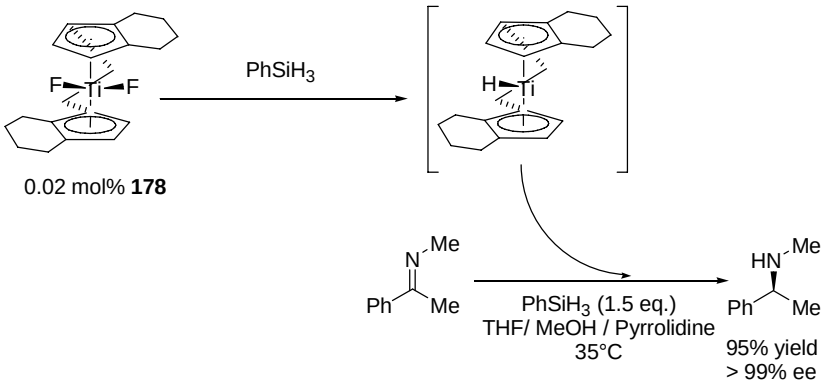

**Scheme 77**

Chiral titanium(IV) fluoride complex **177** has been used to control the dynamic kinetic asymmetric allylation of silylethers and silylacetals[284]. Starting from the racemic substrates, the allyl adducts were obtained in good to high yields and with moderate to excellent enantioselectivity. The role of the fluoride anion has not been elucidated (Scheme 78).




**Scheme 78**

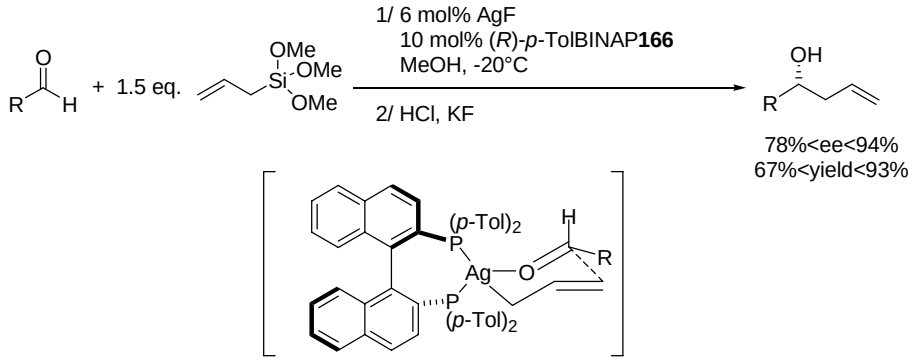
One of the most impressive reaction in this category is the asymmetric ketimine reduction reported by Buchwald[285]. The chiral *ansa*-titanocene(IV) catalyst **178** is supposedly activated through *in situ* abstraction of the two fluorides and reduction to Ti(III). This reaction produces secondary amines in high yields and up to 99% ee with catalyst loadings as low as 0.02mol%. A similar catalytic system has been applied successfully to the asymmetric hydrosilylation of ketones[286] (Scheme 79).




**Scheme 79**

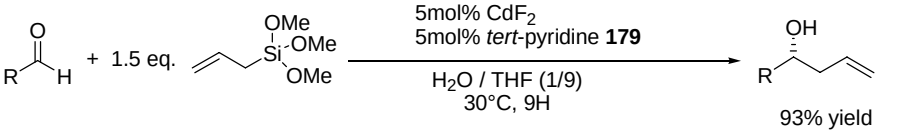
***Miscellaneous Metals***

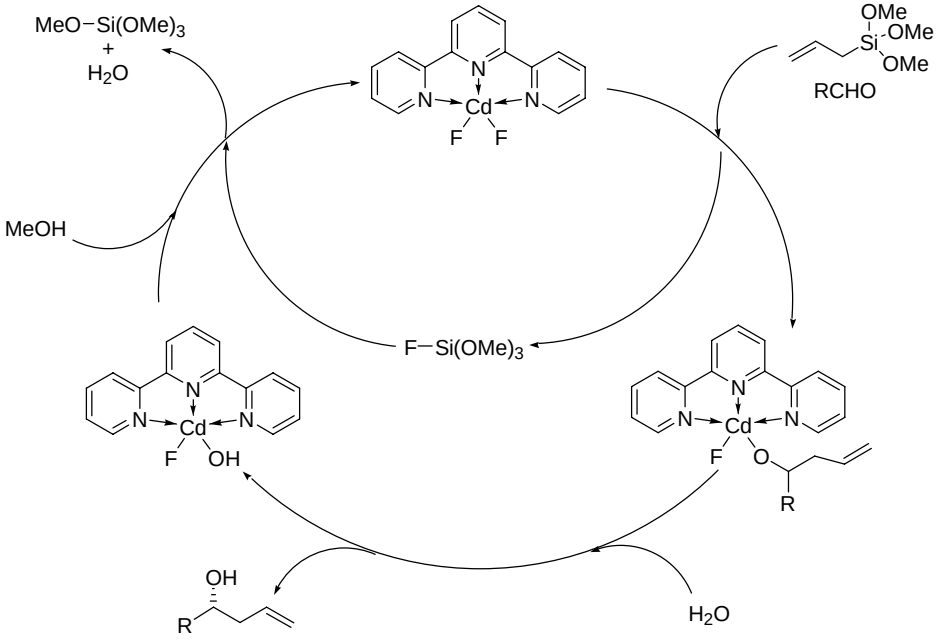
A chiral *p*-TolBINAP silver(I) fluoride **166** was shown by Yamamoto to catalyze the addition of trimethoxyallylsilane to aromatic and conjugated aldehydes[287]. A transmetallation of the allylsilane to generate an allylsilver species was supposed to occur through abstraction of the fluoride from the silver atom. The allylsilver complexed by the chiral diphosphine then delivers the allylic fragment to the aldehyde (Scheme 80).




**Scheme 80**

Cadmium(II) fluoride in the presence of *tert*-pyridine **179** was found to catalyze the allylation of aldehydes[288,289]. The mechanistic investigation showed that one of the fluoride anions was removed during the activation of the silane. Yet, the cadmium(II) fluorohydroxide complex reacted with fluorotrimethoxysilane to regenerate a cadmium(II) fluoride species (Scheme 81). In the same publication, Kobayashi *et al.* showed that the silver(I) fluoride-diphosphine was also regenerated in a reaction such as the one exposed in Scheme 80[288].

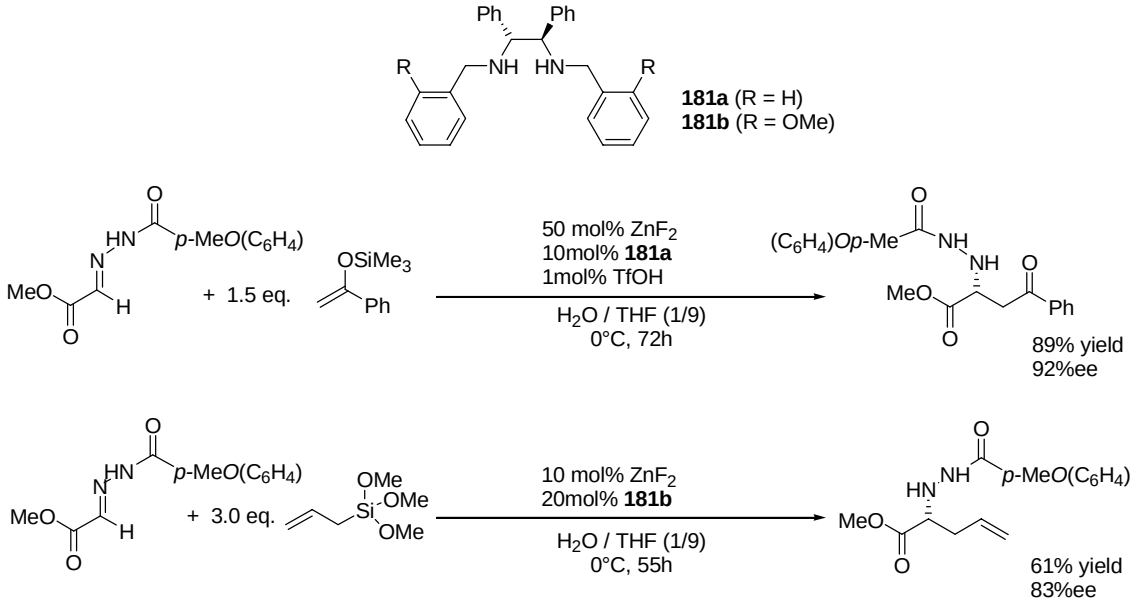



**Scheme 81**

The asymmetric additions of silyl enolethers[290] and trimethoxyallylsilane[291] to activated hydrazones **180** are catalyzed by zinc(II) fluoride in the presence of chiral

diamines **181**. In both cases, the fluoride anion proved decisive. Yet, in the case of the Mannich-type reaction, the fluoride is not recycled and therefore a minimum of 50mol% of $ZnF_2$ proved to be necessary. Concerning the allylation reaction, experimental observations point towards a catalytic cycle similar to the one proposed for cadmium(II) fluoride (see above) (Scheme 82).

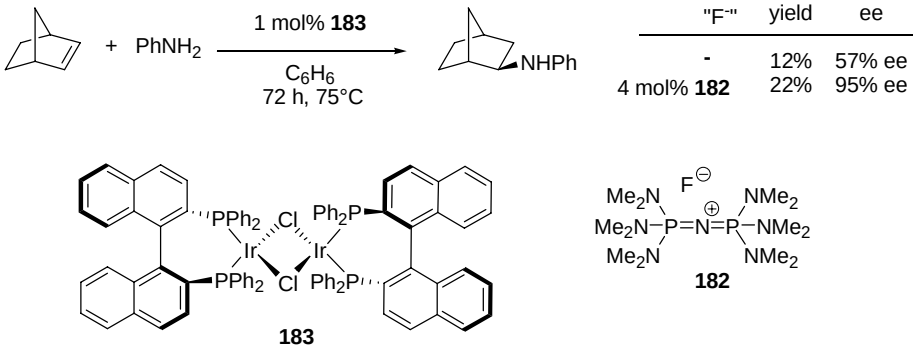



**Scheme 82**

## 6.2.3. Type II Catalysts

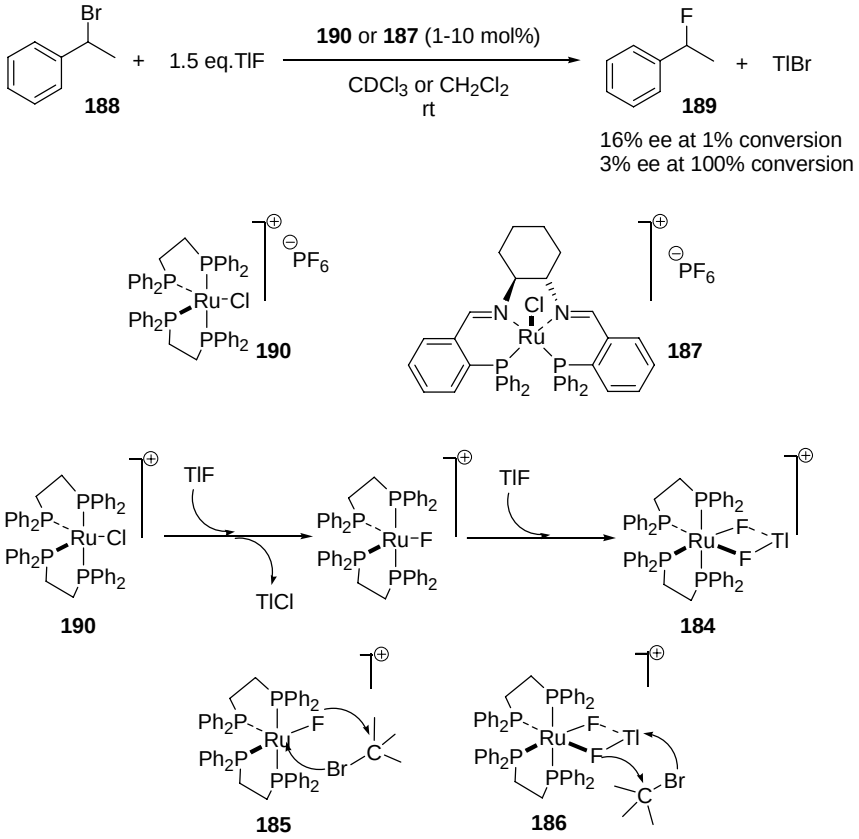
In this second category, the "metal-fluoride" catalyzed reactions do not involve silicon reagents. Reports on this kind of catalyzed reactions are seldom. The catalysts are very often produced *in situ* and are not defined. The mechanism of the reactions and the role of the fluoride anion are therefore based more on speculation than on scientific observations. Even, the position of the fluoride anion on the metal is not always established[250].

An improvement of the asymmetric catalytic hydroamination of a C-C double bond by the presence of a fluoride ion has been described by Togni[292,293]. The addition of an anhydrous source of fluoride **182**, to an iridium-chloride diphosphine dimer **183** increased both the catalytic activity and the enantioselectivity of the reaction. The structure of the catalyst and the role of the fluoride are as yet unknown (Scheme 83).



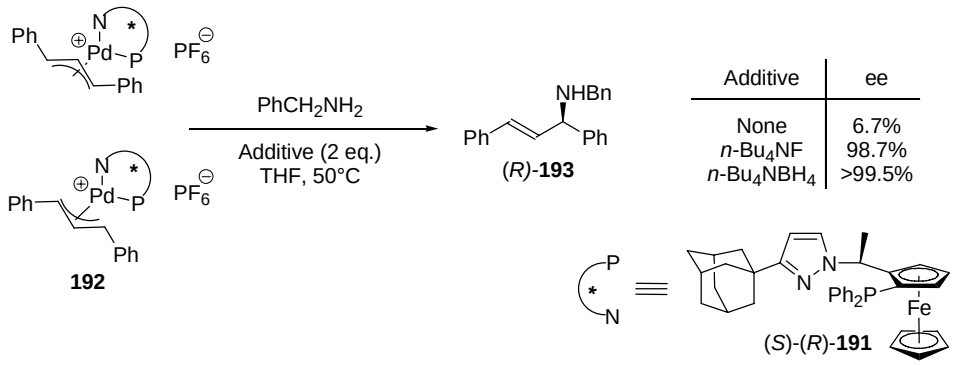

**Scheme 83**

As we already mentioned in Scheme 62, some metal fluoride complexes can transfer their fluoride atom to organic electrophiles through nucleophilic displacement. The ruthenium fluoride system reported by Togni is the only system able to fluorinate catalytically activated organic electrophiles in the presence of a primary fluoride source (TlF)[294]. The reaction probably proceeded via a σ-bond metathesis. Given that the authors have been able to isolate the difluoro-bridged thallium ruthenium complex **184**, the transition states **185** and **186** have been postulated. In the asymmetric version, the chiral ruthenium complex **187** fluorinates a racemic mixture of 1-bromo-1-phenylethane **188** to give non-racemic compound **189**. However, the enantioselectivities are very low (Scheme 84).




**Scheme 84**

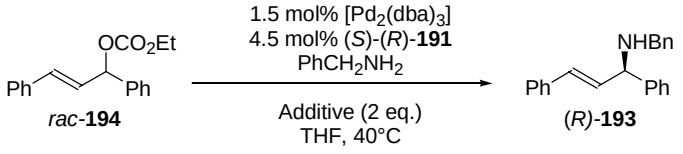
Togni's group has shown that a fluoride anion can have a spectacular effect on the asymmetric allylic alkylations of amines in the presence of the chiral ligand **191**[295]. When the $PF_6^-$ allyl-palladium salt **192** (mixture of two isomers) was subjected to benzylamine, the product **193** was generated with only 6.7% ee. Upon addition of an ammonium fluoride or borohydride, the enantiomeric excesses increased respectively up to 98.7% ee and 99.5% ee (Scheme 85).




| Additive | ee |
|---|---|
| None | 6.7% |
| *n*-$Bu_4NF$ | 98.7% |
| *n*-$Bu_4NBH_4$ | >99.5% |

**Scheme 85**

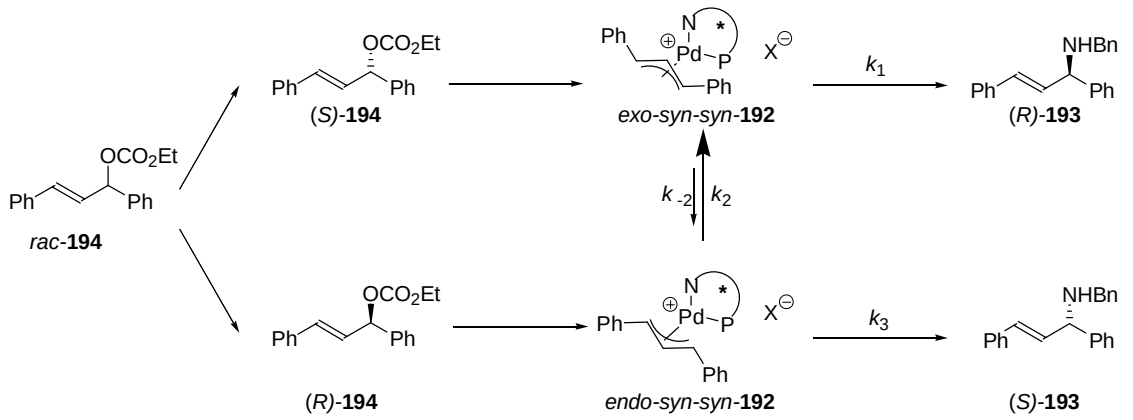
The effect of salt additives was also investigated in the catalytic version of the reaction. Although the enantioselectivity was already high in the absence of any added anion, the addition of hard anions, *e.g.* $F^-$, $BH_4^-$, increased further the facial selectivity. A puzzling result is the decrease in enantioselectivity observed when a weakly non-coordinating anion, *e.g.* $PF_6^-$, is added (Scheme 86).




| Additive | ee |
|---|---|
| None | 99.1% |
| *n*-$Bu_4NPF_6$ | 68% |
| *n*-$Bu_4NF$ | 99.5% |
| *n*-$Bu_4NBH_4$ | >99.5% |

**Scheme 86**

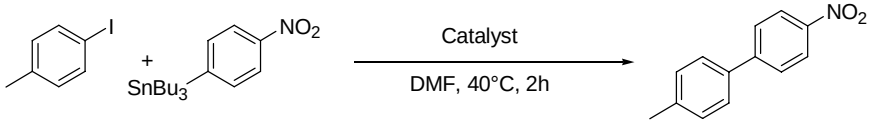
The explanation proposed by Togni is that in the absence of a coordinating counterion, the equilibrium between the *endo-syn-syn* and the more stable *exo-syn-syn* $\pi$-allyl palladium complexes is slow. In the presence of the fluoride which is supposedly in closer interaction with the palladium, the rate of isomerization between the two $\pi$-allyl palladium intermediates, $k_2$ and $k_{-2}$, is fast compared to the rate of the nucleophilic attack ($k_1$), thus establishing a Curtin-Hammett regime (Scheme 87).



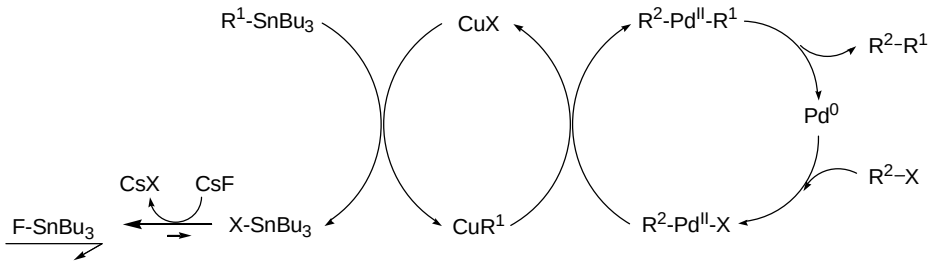

**Scheme 87**

Copper(I) salts and fluoride ion have been found by Baldwin *et al.* to have a synergetic effect on the palladium catalyzed Stille's coupling[296]. The copper salt was believed to mediate the transfer of the organic moiety from the organostannane to the palladium catalyst by first generating a more reactive organocopper intermediate through Sn/Cu transmetallation. It was proposed that the fluoride anion facilitated the preliminary transmetallation step by transforming the $Bu_3SnCl$ by-product in the insoluble polymeric $Bu_3SnF$, thus shifting the successive transmetallation equilibria towards the products. The authors did not mention the possible involvement of a copper-fluoride species. Prior to this report, other laboratories had used separately copper salts or fluoride anion to improve the Stille's coupling (Table 14, Scheme 88).

**Table 14** : Stille coupling improved by combination of copper salt and fluoride anion

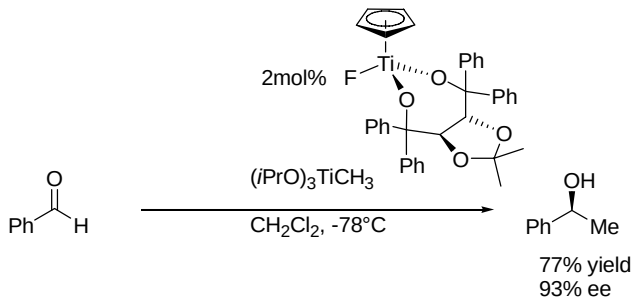



| Entry | Palladium | Copper | $F^-$ | Yield (%) |
|---|---|---|---|---|
| 1 | - | CuI (20mol%) | CsF (2.0 eq.) | 0 |
| 2 | $Pd(PPh_3)_4$ (10mol%) | - | - | 2 |
| 3 | $Pd(PPh_3)_4$ (10mol%) | - | CsF (2.0 eq.) | 8 |
| 4 | $Pd(PPh_3)_4$ (10mol%) | CuI (20mol%) | - | 46 |
| 5 | $Pd(PPh_3)_4$ (10mol%) | CuI (20mol%) | CsF (2.0 eq.) | 98 |



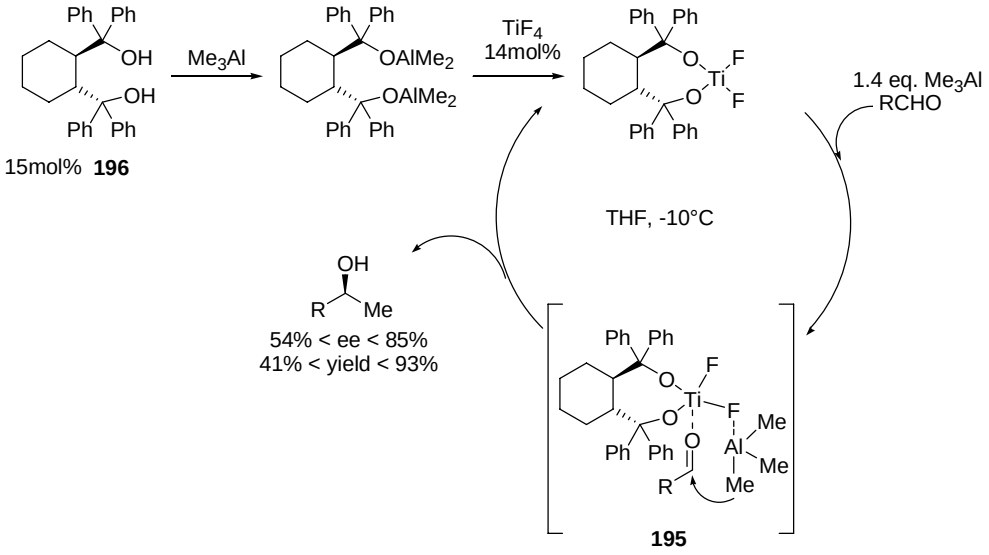

**Scheme 88**

Duthaler has reported the enantioselective addition of methyltriisopropoxide titanium on benzaldehyde directed by a chiral fluoride titanocene with good enantioselectivity (93% ee) for a low catalyst loading (2mol%)[262] (Scheme 89).




**Scheme 89**

Carreira has published a system based on titanium(IV) fluoride and a chiral diol to catalyze the enantioselective addition of trimethylaluminum to aldehydes[297]. The rationale behind this catalytic system is that the fluoride on the titanium Lewis acid center could serve as a bridging unit with trimethylaluminum. The bimetallic species **195** would enforce a tight and rigid transition state combining the nucleophile and the electrophile partners. This system provided the addition product with good to excellent yields and with enantiomeric excesses ranging between 54% ee and 85% ee for conjugated and aromatic aldehydes (Scheme 90).



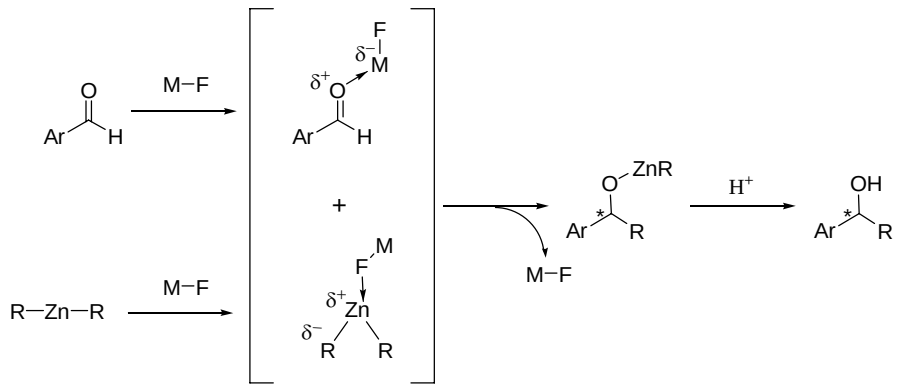

**Scheme 90**

### 6.2.4. Conclusions

From all the examples discussed in this chapter, it is clear that metal fluoride species are not oddities and that they have already been used to catalyze a wide range of reactions. Even if the mechanistic details are most often unknown, it appears that the metal fluoride bond can be broken if doing so provides a thermodynamic well (strength of the Si-F bond). Breaking the metal fluoride bond can generate the active catalyst, in which case, the metal fluoride species is only a convenient catalyst precursor. The metal fluoride bond can also be broken to activate one of the reagents and regenerated later on in the catalytic cycle. In other cases, the metal fluoride bond is not broken in the catalytic process. In which case, the role of the fluoride anion is to interact through its free electron pairs with metal centers to generate a tight and controlled transition state. In all three cases, the fluoride anion acts as a Lewis base towards one of the reagent.

## 6.3. Metal Fluoride Selection

The addition of diorganozinc species can be activated through : (1) the binding of a Lewis acid to the carbonyl or imine therefore activating the electrophilicity of the substrate; (2) the interaction of a Lewis base with the diorganozinc to form a more nucleophilic zincate complex. Ambifunctional catalysts possessing both features have been shown to be quite successful (Chapter 5). Our hypothesis was that metal fluoride species could be ambifunctional catalysts : the metal center acting as a Lewis acid and the fluoride anion acting as a Lewis base (Scheme 91).




**Scheme 91**

From the examples of the literature, it seems that the fluoride in metal fluoride catalysts often acts as Lewis base towards one the reagents. The question is which metal would leave the fluoride counterion with the best ability to form a zincate. The HSAB mismatch between a soft late transition metal and the hard fluoride anion seems attractive since the involvement of the electronic pairs of the fluoride with the soft metal would be limited. The electrons of the fluoride counterion would still be available to form a nucleophilic zincate.

The introduction of the chiral information can be achieved by *in situ* complexation of the metal by a chiral ligand. This facilitates the search for an optimal catalyst since it avoids the preparation of the chiral catalyst before the reaction. A large number of chiral ligands are now available from commercial sources and others can be made by well described synthetic procedures. These cover a range of binding atoms, steric properties and electronic nature which will be helpful in the optimization process.

# Chapter 7

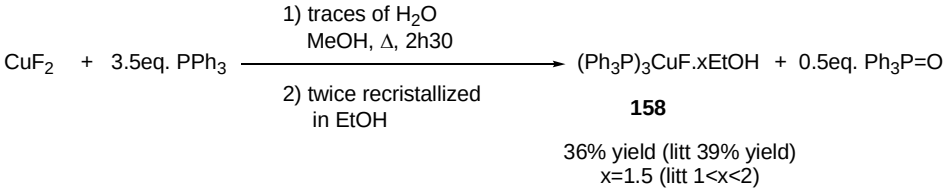
# A Copper Fluoride Catalyst

## 7.1. Introduction

This chapter covers our first attempts at using a metal-fluoride complex to catalyze the addition of diorganozinc on aldehydes. As we have rationalized in the preceding chapter, we focused our bibliographic search on late transition metals fluoride complexes. Fully characterized and stable metal fluoride complexes such as the copper fluoride complex **158** were much more appealing from a rational point-of-view than species supposedly prepared *in situ*. The choice of a copper complex had the additional advantage that copper was already well known to mediate reactions involving diorganozinc compounds[144,143,298,142,299].

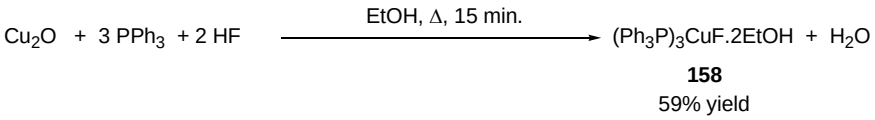
## 7.2. Synthesis and Properties

The first synthesis of copper(I) fluoride complex **158** is due to Jardine *et al.* in 1970. It involved the reduction of commercially available copper(II) fluoride in the presence of triphenylphosphine and water (they used $CuF_2.H_2O$, we used anhydrous $CuF_2$ and a drop of water)[300]. A subsequent double recrystallization of the complex in ethanol allows for the separation from triphenylphosphine oxide byproduct and permits to change the coordination solvent from methanol to ethanol. We have prepared this complex in 36% yield on a 10mmol scale. $^1$H NMR signal area integration showed an average of 1.5 molecules of ethanol per copper center. Over the course of our study, we did not notice any variation of the ethanol content of the complex. The complex is very stable and can be stored on the benchtop for a couple of years with only a slight yellowing of the crystalline solid (Scheme 92).



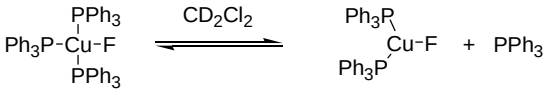

**Scheme 92**

Another route towards copper(I) fluoride complex has been more recently described by Chaudhuri *et al.* The fluorination of copper(I) oxide by aqueous hydrogen fluoride in the presence of triphenylphosphine leads to **158**[301]. This method presents several advantages: a cheaper source of copper ($27^{€}/_{kg}$ for $Cu_2O$ and $144^{€}/_{kg}$ for $CuF_2{\cdot}3H_20$), no phosphine oxide byproduct. We did not use this method during the course of our study (Scheme 93).




**Scheme 93**

The physical properties of complex **158** have been investigated by Levason *et al.*[254]. Variable temperature $^{31}P$ NMR experiments revealed an equilibrium due to reversible phosphine ligand dissociation in halocarbon solvents. The equilibrium was fast enough, on the NMR time scale, for the peaks to coalesce at -70°C. Therefore, ligand exchange between a triphenylphosphine and an added chiral ligand should not be problematic (Scheme 94).

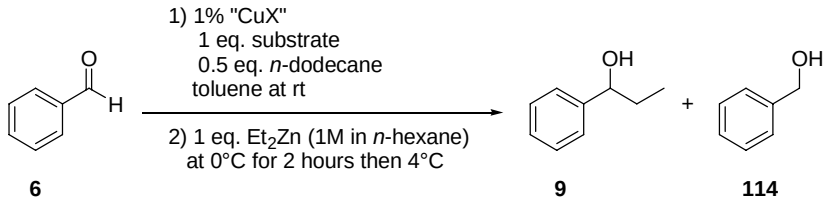



**Scheme 94**

# 7.3. First Steps in Catalysis

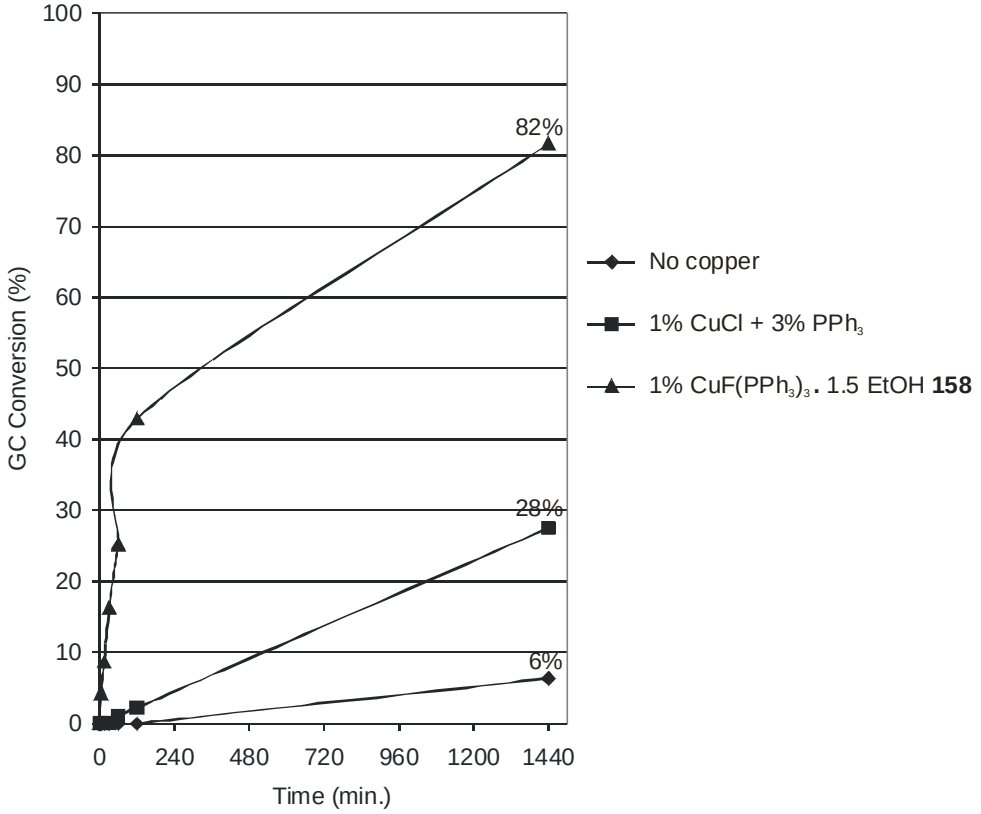
## 7.3.1. Catalytic Activity of Copper-Fluoride Complex 158

As we have already stated, dialkylzinc compounds alone are not nucleophilic towards electrophiles such as aldehydes, ketones, enones and imines. They are therefore greatly appealing for catalysis since they will only react "on demand" when a catalyst is added. We thus wanted first to check the rates of addition of diethylzinc to benzaldehyde in the absence and in the presence of copper(I) fluoride **158**. To ascertain the influence of the fluoride, a catalytic amount of copper(I) chloride was complexed by three triphenylphosphines *in situ*[302] prior to the addition of benzaldehyde and diethylzinc (Scheme 95, Chart 4).



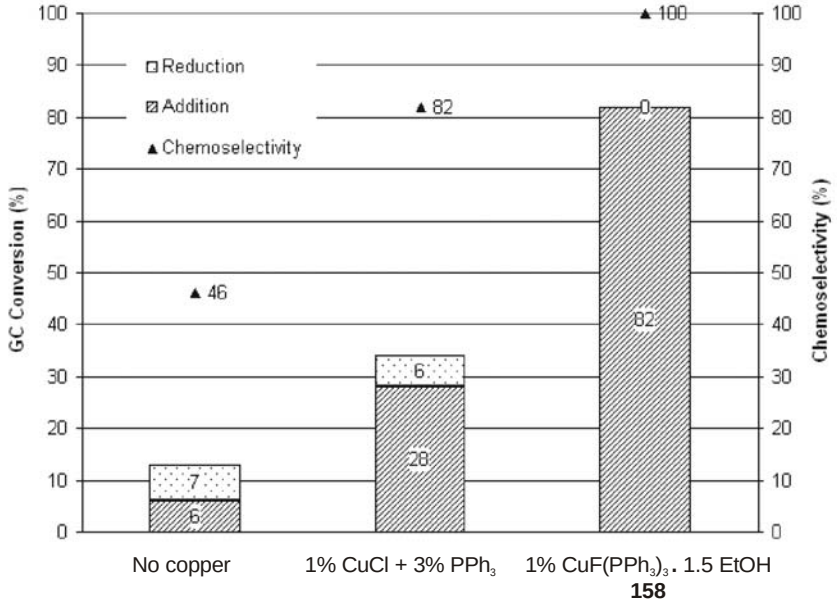

**Scheme 95**

**Chart 4 :** Rate acceleration of addition reaction by copper(I) fluoride **158** using **General Procedure J**



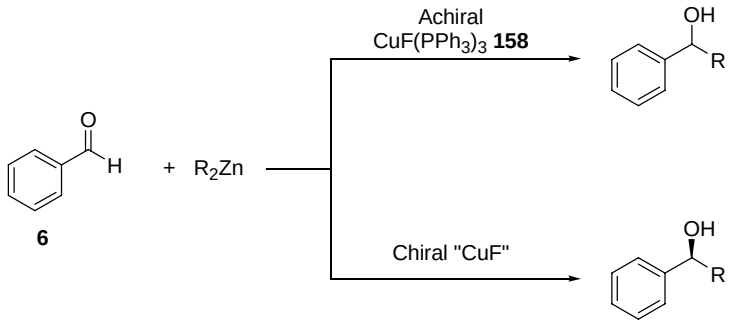

To our delight, we observed a large acceleration of the addition of diethylzinc in the presence of the copper(I) fluoride complex **158**. This was not only due to the presence of the copper metal because there was also a strong effect linked to the fluoride counterion. Moreover, the presence of fluoride complex improves dramatically the chemoselectivity of the reaction as no reduction product **114** was observed.

**Chart 5** : Chemoselectivity in the absence and presence of copper catalysts after 24 hours using **General Procedure J**



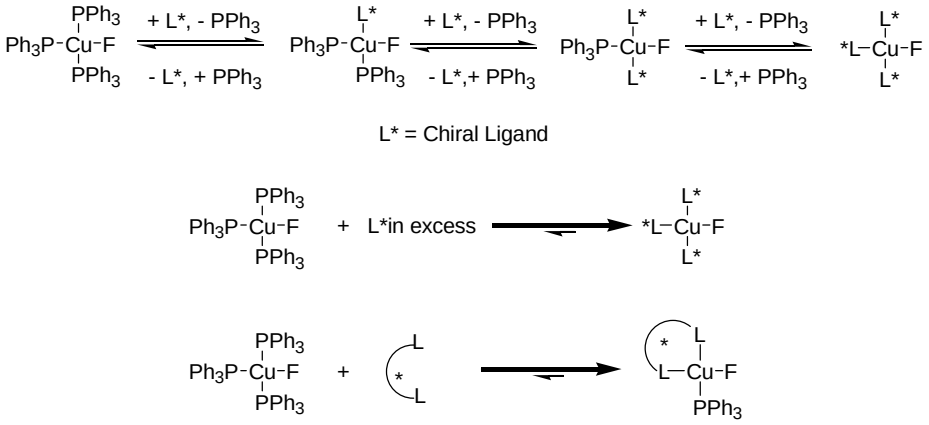

## 7.3.2. Preliminary Screening of Ligands

The addition of an external chiral ligand to complex **158** should provide a chiral copper(I) fluoride complex through ligand-exchange and possibly lead to enantioselective catalysis. However, this enantioselective pathway has to compete with the background reaction due to the presence of some achiral fluoride complex **158** (Scheme 96).



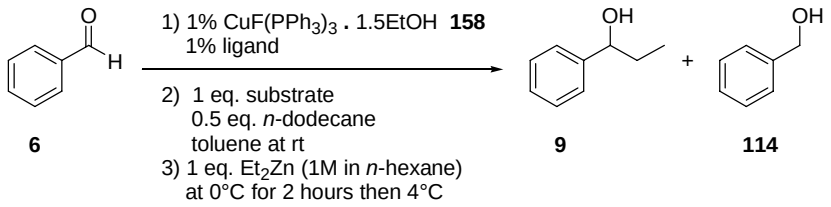

**Scheme 96**

To diminish the deleterious effect of achiral complex **158** on the enantioselectivity, the ligand-exchange with the external ligand has to be complete so that no achiral catalyst remains in solution. To displace completely the equilibrium towards the chiral complex, we could use an excess of external ligand, but this method is rather costly in regard to the prize of chiral ligands. A more satisfactory solution of this problem is to take advantage of the chelate effect[246]. The substitution of two triphenylphosphines from the original copper(I) fluoride complex by a bidentate ligand should indeed be favored for entropic reasons (Scheme 97).




**Scheme 97**

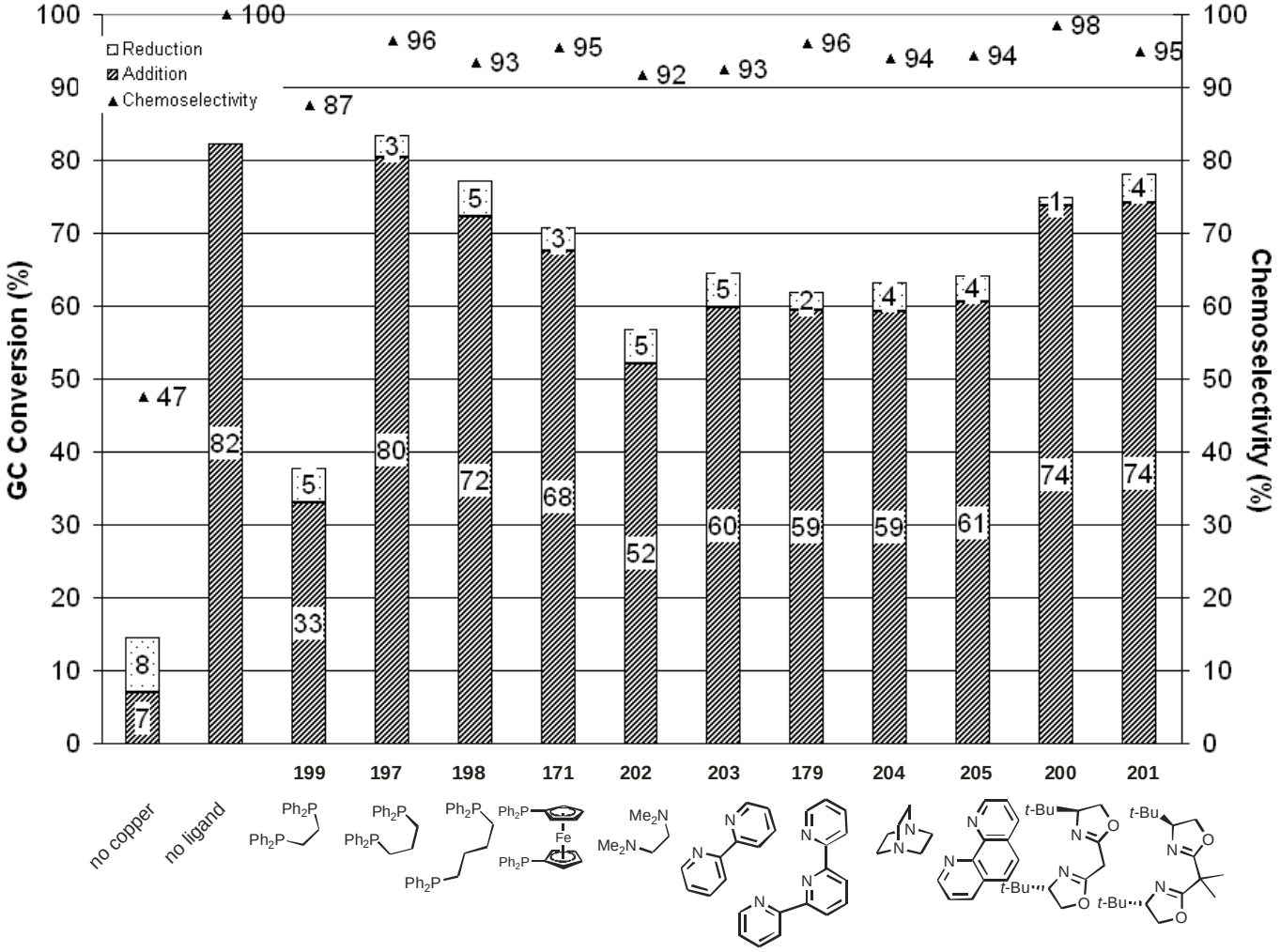
We tested a variety of common chelating agents. The reported data have been collected after 24 hours (Scheme 98).




**Scheme 98**

The results of this first screening of ligands were not very impressive. The diphosphines **197**, **198**, **171** gave sensibly the same results as complex **158** alone but with a slight loss of chemoselectivity. Diphosphine dppe **199** however inhibited the reaction. Diamino ligands gave lower conversion and poorer chemoselectivity than complex **158** alone. Chiral *bis*oxazolines **200** and **201** did not decrease the conversion as much as the other diamines. The deleterious effect of these bidentate ligands on the conversion and chemoselectivity of the addition of diethylzinc to benzaldehyde indicates that they complex the copper metal. However the newly generated species seem less active than the *tris*-triphenylphosphine copper fluoride complex **158**.

**Chart 6** : Chelating ligands screening after 24 hours of reaction using General Procedure J



The results presented in Chart 6 only reflect the status after 24 hours when the reaction are complete or evolving slowly. By plotting the GC conversion results from samples taken during the first hours as a function of time, we noticed that amino bidentate ligands slowed the reaction as compared with the reaction with copper(I) fluoride **158** alone (Chart 7)[***]. By contrast, reactions are accelerated by the presence of diphosphine ligands except for dppe **199** which slowed down the reaction (Chart 8). Also, during the first two hours of the reaction, we did not observe any reduction product **114** except, again, in the case of the dppe ligand **199** which led to some reduction of benzaldehyde from the very beginning of the reaction.

[***] Jardine *et al.* have observed that the displacement of a phosphine of copper fluoride complex **158** by amino ligands leads to species that readily decomposed.[300] Jardine, F. H.; Rule, L.; Vohra, A. G. *J. Chem. Soc. A* **1970**, 238-240.

**Chart 7** : Rates of addition reaction in the presence of complex **158** and diamino bidentates using General Procedure J

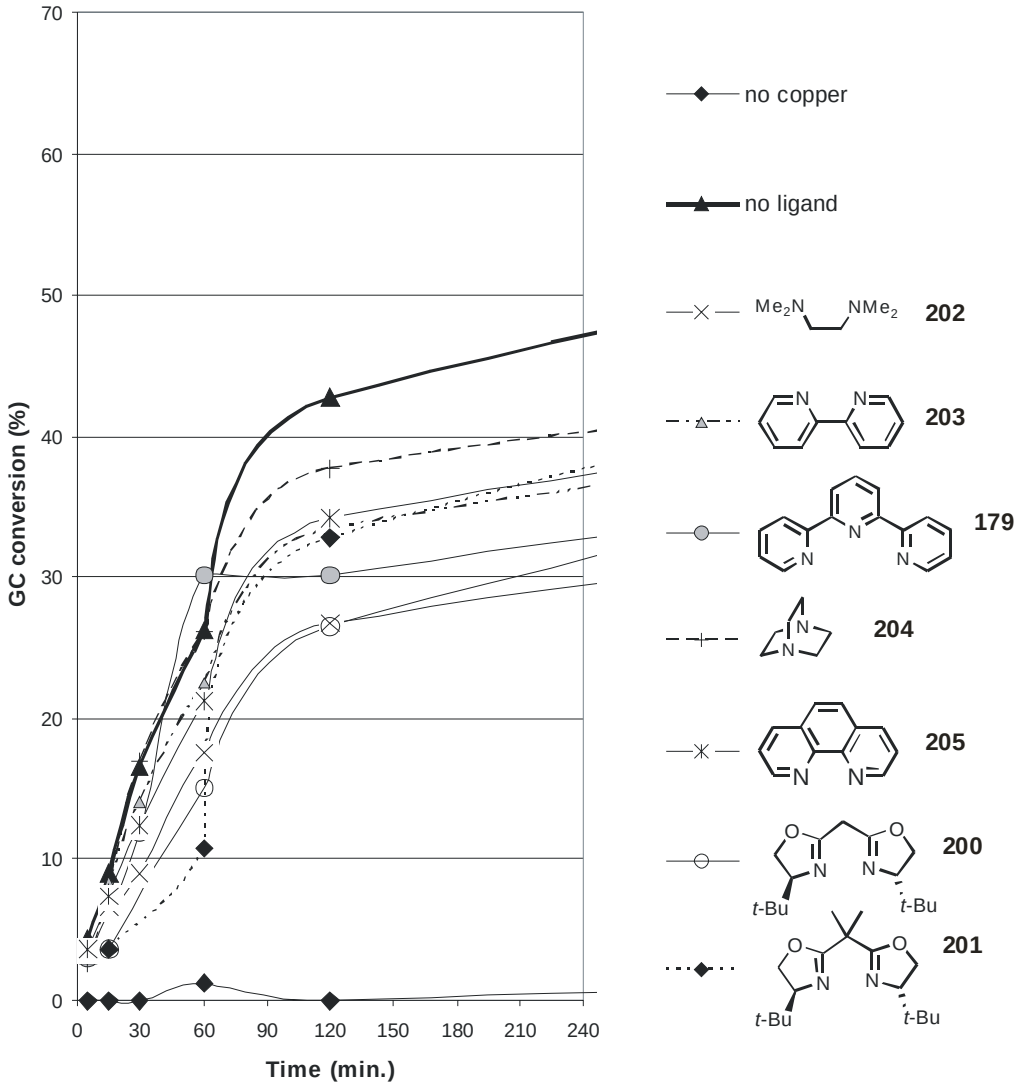
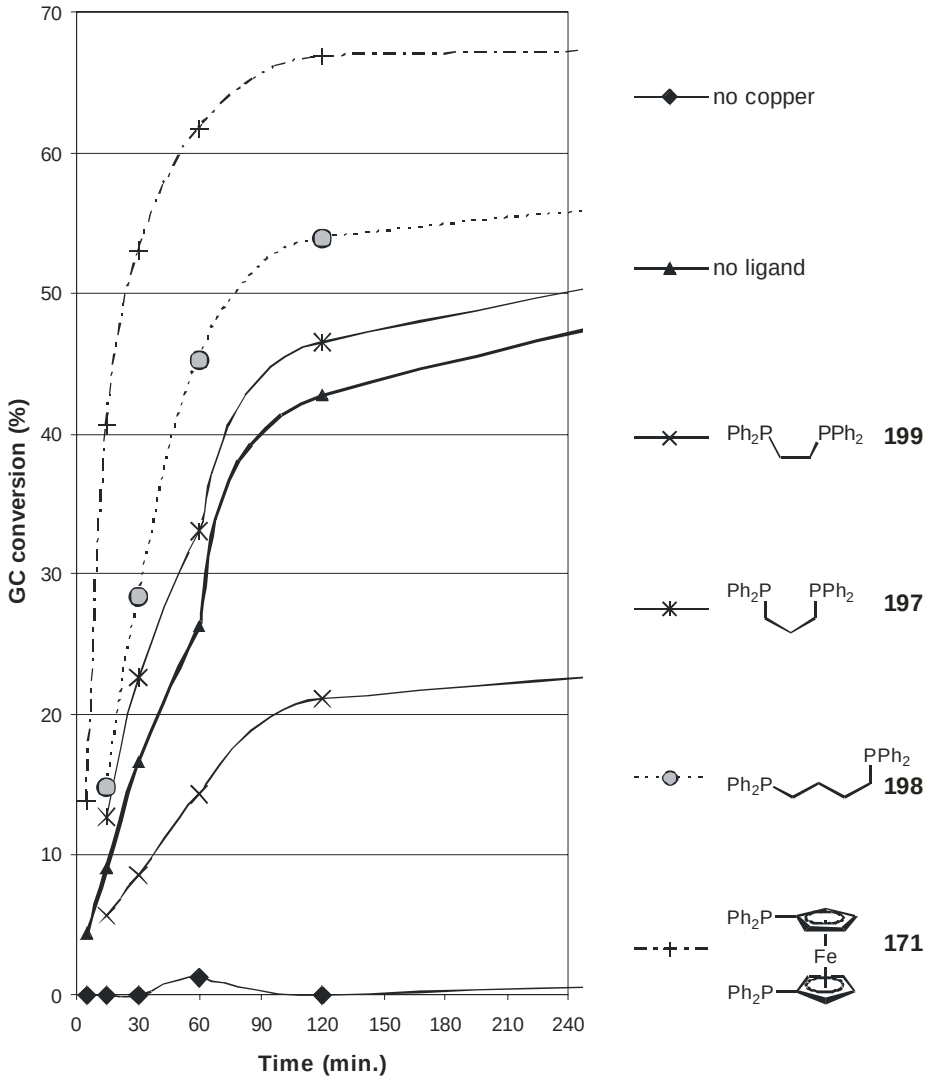
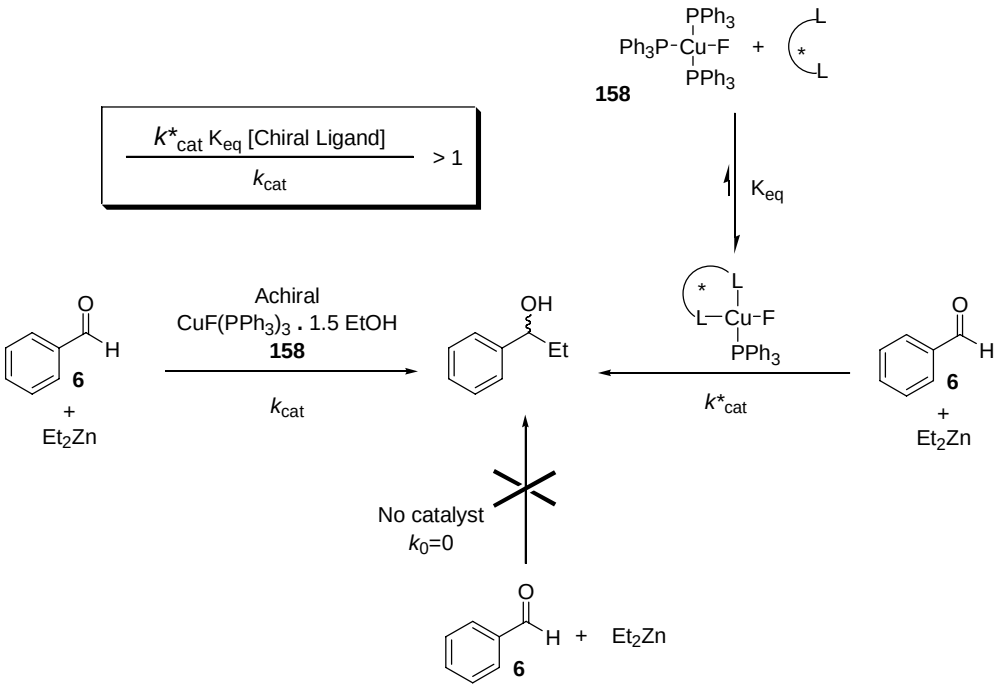


**Chart 8** : Rates of addition reaction in the presence of complex **158** and diphosphine ligands using **General Procedure J**.




To have a successful enantioselective catalysis, the achiral or "background" reaction has to be negligible compared to the chiral pathway. The achiral copper complex precursor **158** is catalytically active, therefore the addition of a chiral chelate should completely displace the equilibrium towards the formation of a chiral copper catalyst (see Scheme 97). Also the chiral pathway should be much faster than the achiral pathway. The first tests with diphosphines **197**, **198**, **171** showed such a "ligand-acceleration"[303]. Chiral diphosphines were therefore a logical choice for the continuation of our investigation (Scheme 99).




**Scheme 99**

# 7.4. Enantioselective Catalysis with Copper(I) Fluoride Complexes

## 7.4.1. Screening of Chiral Ligands

Since diphosphine ligands showed so much promise in the first ligand screening, it was logical to first test the available chiral diphosphines. As before, the experimental conditions were those described in **General Procedure J**. For sake of clarity, only results after two hours will be shown. There were several reasons for this choice :

- Fast reactions are our ultimate goal. In this reaction series, either the reaction is almost finished after two hours or it is going to drag on slowly. Only the first situation was of interest to us.

- We also aim for a good enantiocontrol. Enantiomeric excesses were stable during the first two hours but we often noticed a slight decrease of enantioselectivity when longer reaction times were used. This suggests some degradation of the catalyst overtime and the occurrence of a competing achiral process.

To our delight, several chiral ligands gave some enantiocontrol of the alkylation of benzaldehyde (Chart 9 and Chart 10). BINAP **75**, *p*-tolyl-BINAP **166**, MeO-BIPHEP **206** and JosiPHOS **207** gave the addition product in more than 40% ee (with a maximum of 57% ee for **166**). Diphosphines with an axis of chirality seemed to have an edge in the induction of chirality.

The presence of BINAP **75**, MeO-BIPHEP **206**, tetraMe-BITIOP **208**, Et-FerroTANE **209** and the JosiPHOS ligands **210** and **211** gave the addition product at approximately the same rate or faster than the copper(I) fluoride complex **158** alone[†††]. Quite astonishingly, the reaction in the presence of ligand **209** was extremely fast: it was close to completion after only one hour. Unfortunately, a strong ligand acceleration effect does not necessarily match with a good enantiocontrol.

The analysis of Chart 8, Chart 9, Chart 10 permits to extract a general trend in the acceleration of the reaction as a function of the ligand geometry. Ligands where the two phosphorus atoms are only separated by two carbon atoms, **199** and **212**, slow down the reaction and decrease the chemoselectivity compared to **158** alone. However diphosphines with more than two carbon atoms between the two phosphorus atoms do not inhibit the reaction or even accelerate it (with the unexplained exception of **79**).

The nature of the two coordinating atoms was also of importance. As we already showed, diamines do not accelerate the reaction compared to diphosphines. Mixed chelates such as QUIPHOS **213**[304], oxazoline-phosphite **214**[153] (both used in the Michael addition of $Et_2Zn$ to enones in the presence of copper salts) and *bis*imine-*bis*phosphine **215**[305] gave poor results. However, oxazoline-phosphine **216** gave an honorable 30% ee but with only 24% conversion after 2 hours of reaction. Diphosphines were thus the obvious choices for further investigations.

[†††] The qualitative estimate of reaction's rate is based on the GC conversion levels observed for samples taken at regular intervals (normally 5, 15, 30 minutes, 1, 2 and 24 hours).

**Chart 9** : Chiral Ligand Screening with copper(I) fluoride complex **158** after 2 hours using General Procedure J - Part 1

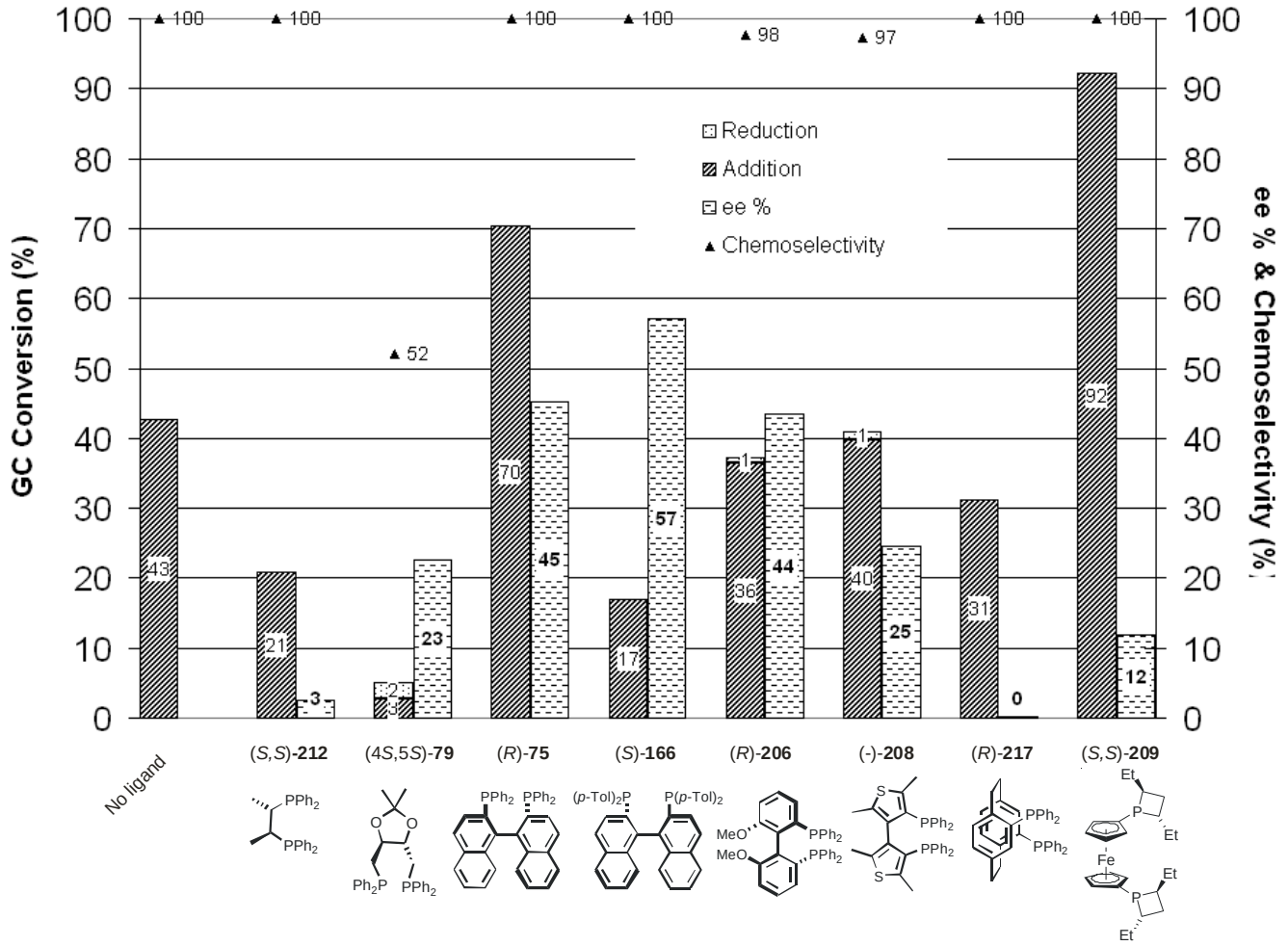
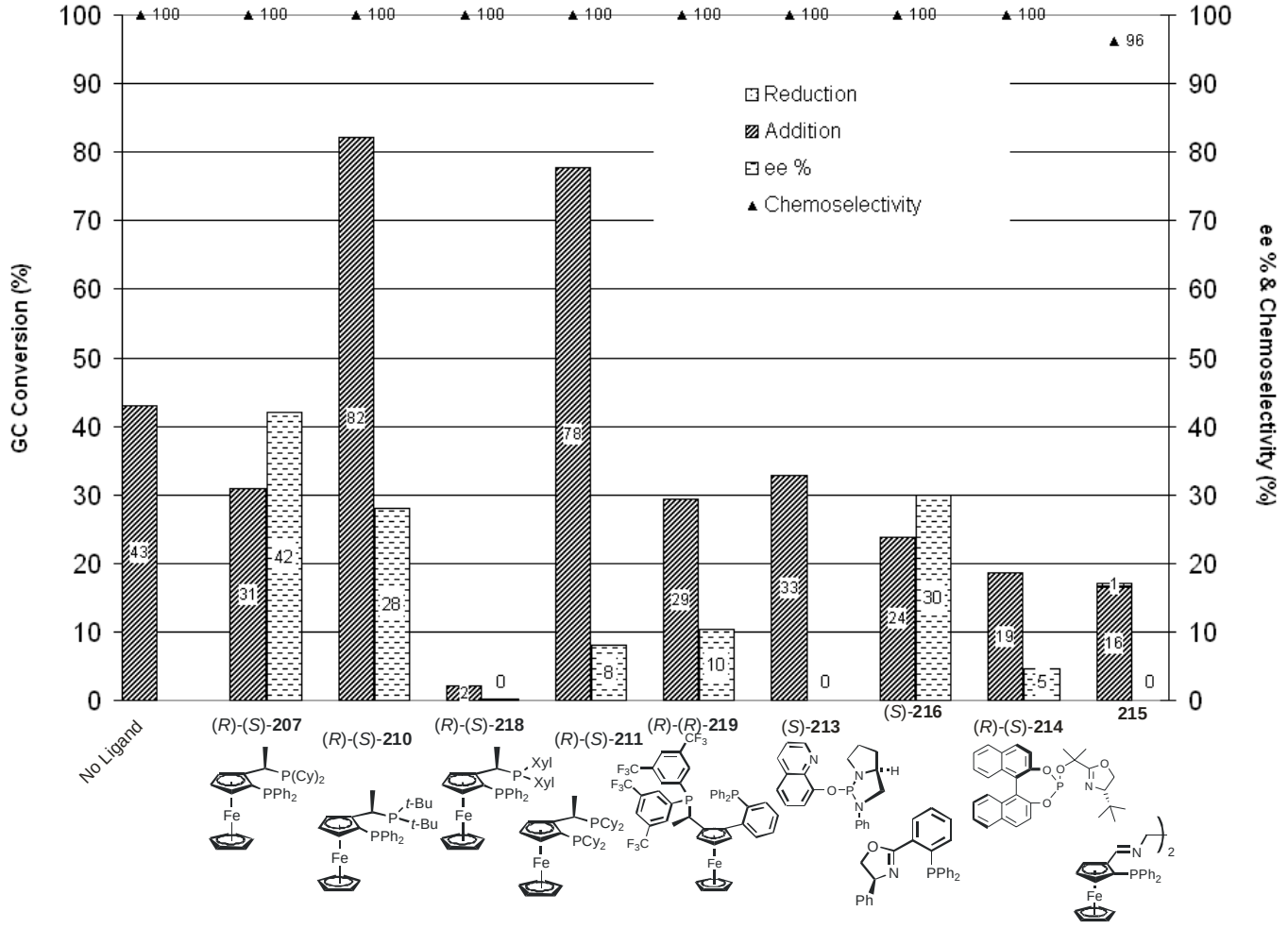


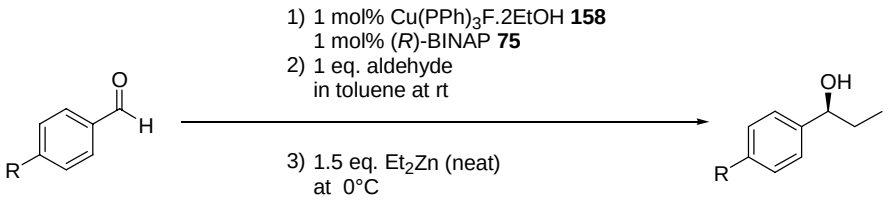
**Chart 10 :** Chiral Ligand Screening with copper(I) fluoride complex **158** after 2 hours using **General Procedure J**- Part 2



## 7.4.2. Isolated Yields

The above results were obtained by glc with an internal standard. We then made a serie of preparative experiments using the chiral ligand (*R*)-BINAP **75** which gave the best combination of enantioselectivity and catalytic activity. We modified slightly the experimental conditions : first of all, an excess of diethylzinc was used (1.5 eq. compared to 1 eq. used in the screening) to attain a total conversion. Neat diethylzinc was used instead of a solution in hexane. The substrate concentration was increased from *ca*. 0.33M to *ca.* 0.8M.

**Table 15** : $Et_2Zn$ addition to various arylaldehydes catalyzed by complex **158** and (*R*)-BINAP




| Entry | R | Time | GC Conversion[a] (%) | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | H | <30 min. | 100 | 85 | 49.1 (*S*[b]) |
| 2 | Me | <1 hour | 99 | 77 | 57.9 (*S*[c]) |
| 3 | Cl | <30 min. | 100 | 85 | 55.8 (*S*[c]) |
| 4 | OMe | >3 hours | 98 | 89 | 63.4 (*S*[b]) |

a : based on the area of the remaining aldehyde divided by the sum of the area of all the peaks (no correction for response factor)

b : attributed by comparison of optical rotation sign with the literature

c : based on the order of elution of enantiomers in chiral GC and compared to sample of known optical activity

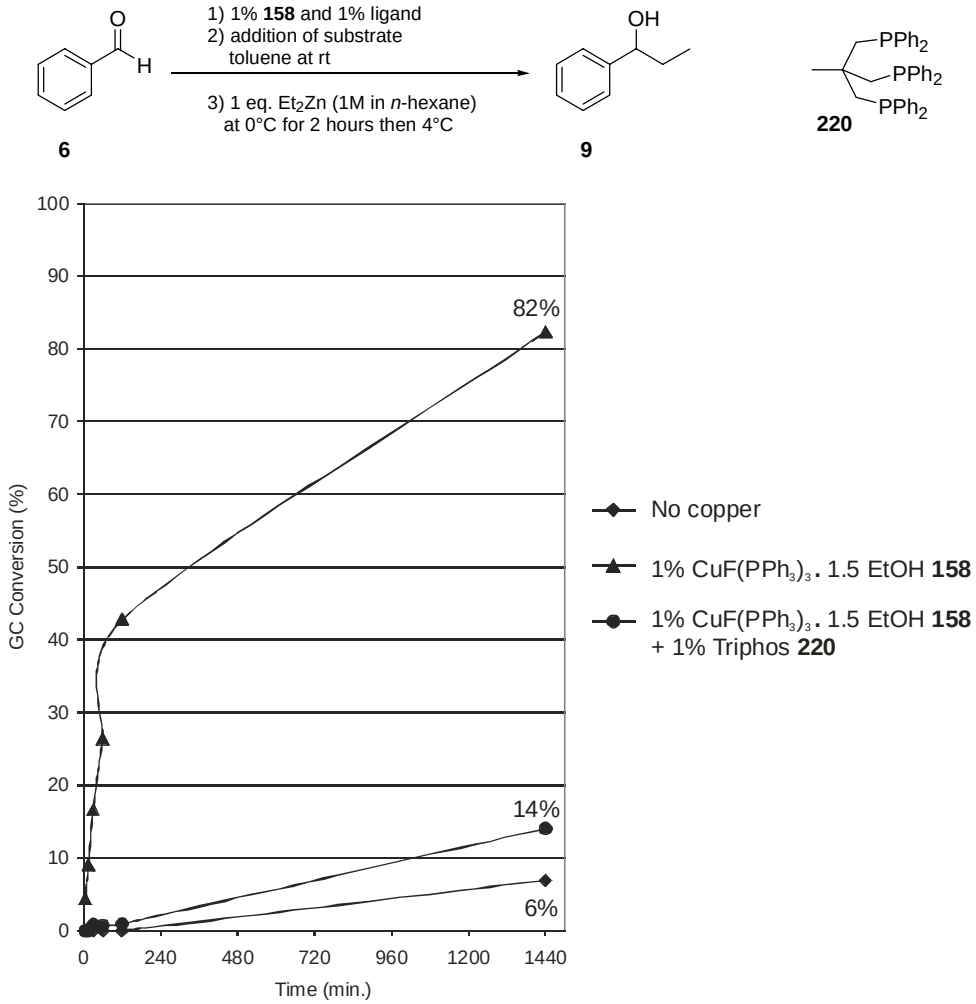
The addition products were obtained in good yields and moderate enantiomeric excesses. The electron-donating substituent of *p*-anisaldehyde led to a slow down of the addition reaction. This could be due to the fact that the nucleophilic addition step is the rate determining step or that the electron-richer alcoholate has difficulty leaving the active site of the catalyst.

# 7.5. Conclusions

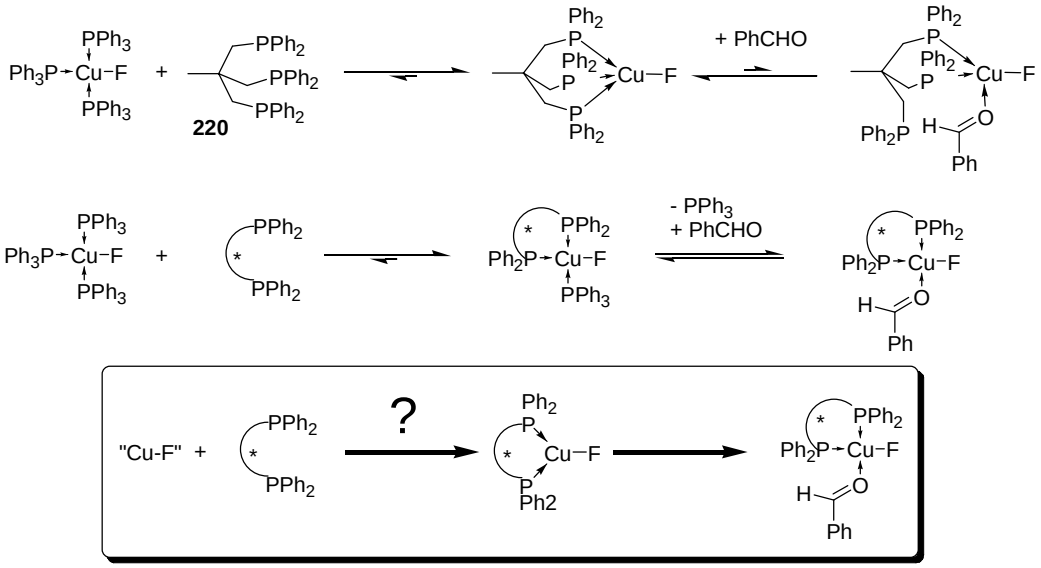
Copper(I) fluoride complex **158** catalyzed the addition of diethylzinc to benzaldehyde. An acceleration of the reaction was noticeable in the presence of some diphosphine ligands. The use of chiral diphosphines, such as BINAP **75**, *p*-tolyl-BINAP **166**, MeO-BIPHEP **206** and **207** from the JosiPHOS family, gave the addition product in more than 40% ee, proving that enantiocontrol is possible. Of course, a systematic screening of the chiral diphosphines described in the literature or available from commecial sources could have been performed…

However, some experimental observations led us to another approach. We had indeed observed a dramatic decrease of the reaction rate when the tridentate ligand, triPHOS **220**, was used in conjunction with the copper(I) fluoride **158** (Chart 11)

**Chart 11** : Tridentate phosphine **220** influence on the rate of addition using **General Procedure J**




Such a behavior pointed to the importance that only two phosphorus atoms be present in the coordination sphere of the copper metal center, presumably to allow the complexation of the substrate. In order to improve the catalytic activity, it was essential to find a synthetic route to a chiral copper(I) fluoride complex in the absence of spectator phosphines (Scheme 100).


PPh3
Ph3P–Cu–F
PPh3
+
PPh2
PPh2
PPh2
220
Ph2
P
Ph2
P
Cu–F
P
Ph2
+ PhCHO
Ph2P
H
O
Ph
- PPh3
+ PhCHO
"Cu-F" +
?
Ph2
Ph2P
Ph

**Scheme 100**

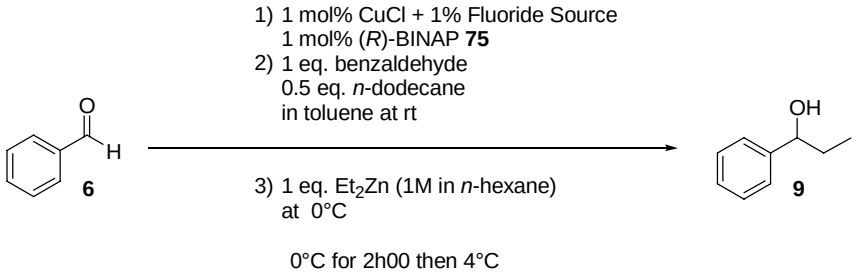
# Chapter 8

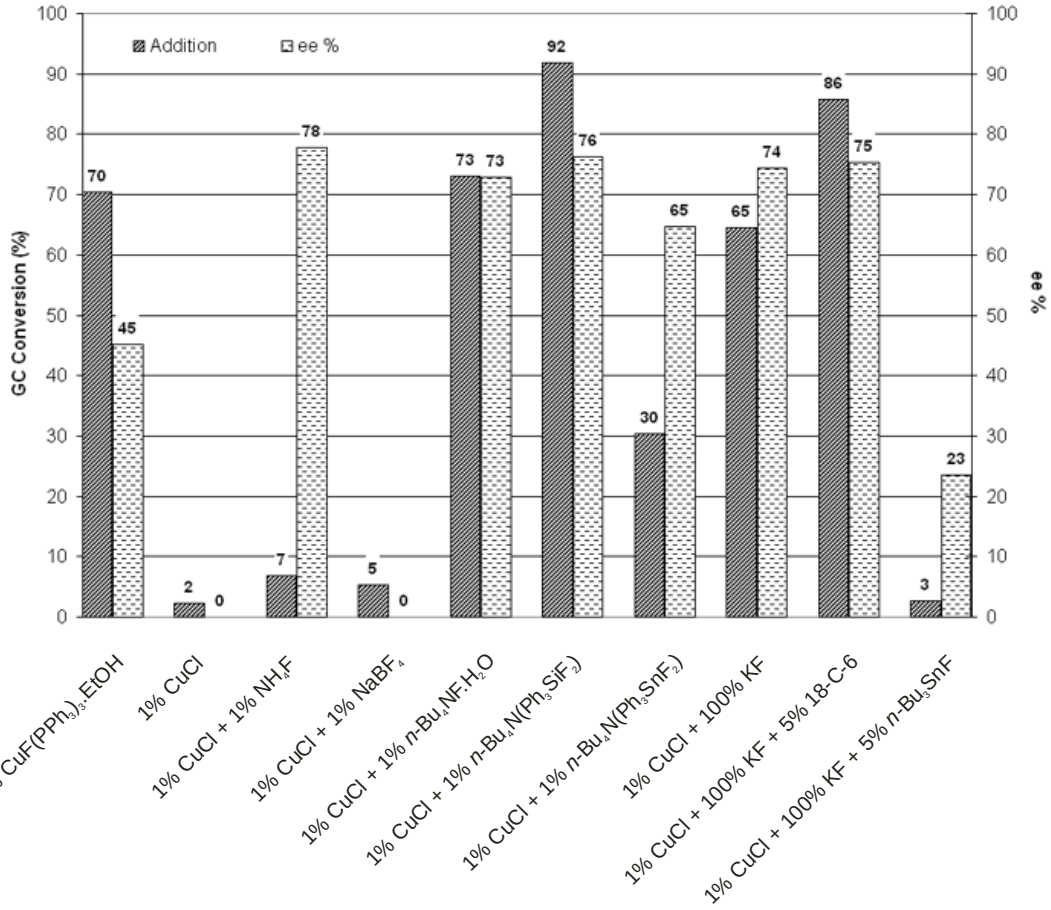
# Second Generation Copper Fluoride Catalysts

## 8.1. Preliminary Experiments

To avoid the use of the copper(I) fluoride complex **158**, we could build the copper fluoride complex *in situ* through anion metathesis of a copper salt with a fluoride source in the additional presence of a chiral diphosphine. In fact, such a strategy has been used by several groups to generate copper fluoride catalysts. Most examples use a combination of copper(I) chloride and a fluoride source (see pages 84 and following). We thus investigated the use of copper(I) chloride with several fluoride sources in the presence of chiral BINAP **75** (Chart 12).

**Chart 12** : Copper(I)chloride, (*R*)-BINAP and various fluoride sources as catalyst's precursors for the ethylation of benzaldehyde using **General Procedure L** (results after 2 hours)




The use of $NH_4F$ only led to a slight improvement of the conversion as compared to the blank experiment in the absence of a fluoride source. However there was a significant increase of enantioselectivity. $NaBF_4$[306] did not show any improvement in reactivity nor enantioselectivity. The use of organic fluoride sources, tetrabutylammonium fluoride monohydrate **120** or tetrabutylammonium triphenyldifluorosilicate (TBAT) **130**[204] which had already been used in copper(I) fluoride catalysis[264,247,307,275], resulted in a spectacular increase in reactivity and enantioselectivity. Tetrabutylammonium triphenyldifluorostannate[205] **131** also led to some enantiocontrol but the conversion was lower.

An unexpected result was the acceleration of the reaction upon addition of solid potassium fluoride. The use of crown ether 18-C-6 was not necessary to obtain a good enantiocontrol but it increased the rate of the reaction. The addition of 5% tributyltin fluoride [308,309] had a strong deleterious effect.

*In situ* generation of a copper(I) fluoride species with only two chelating phosphorus atoms is beneficial to the enantiocontrol of the reaction ( up to 75% ee) as compared to the use of copper(I) fluoride complex **158** (45% ee).

We decided to avoid the use of potassium fluoride in the following investigations to avoid complications in the interpretation of results due to phase-transfer phenomena. The handling of tetrabutylammonium fluoride monohydrate was not very practical due to its hydrophilicity and its instability during drying[195]. On the other hand, TBAT **130** is a practical, stable, non-hygroscopic and soluble source of fluoride ion[204]. It also gave good enantiocontrol (75% ee) and the highest conversion of all the fluoride sources (see Chart 12).

# 8.2. Screening of the Reaction Parameters

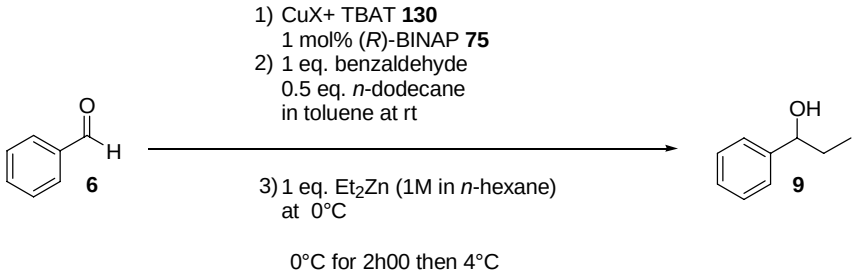
## 8.2.1. The Copper Source

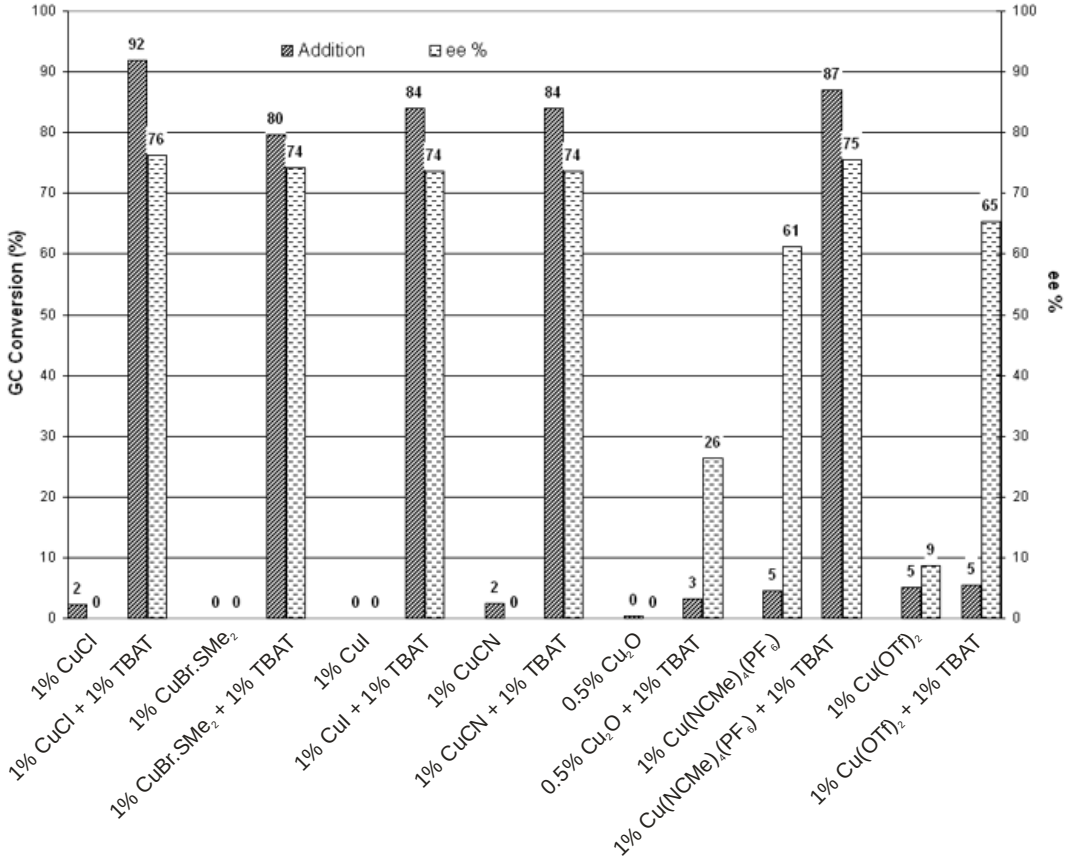
The success obtained when a copper(I) fluoride complex was generated *in situ* from copper(I) chloride, a fluoride source and chiral ligand (*R*)-BINAP **75** encouraged us to explore the influence of various reaction parameters. Several copper salts were selected to be tested in the absence and in the presence of TBAT **130** (Chart 13).

In the absence of TBAT **130**, copper salts complexed by (*R*)-BINAP **75** did not significantly catalyze the addition reaction. This was surprising since the Lewis acidic copper(II) triflate[148] and *tetrakis*(acetonitrile)copper(I) hexafluorophosphate[154] as well as copper(I) cyanide[310] have been used to catalyze the Michael addition of diorganozinc to enone[142].

However in the presence of **130**, the majority of copper salts led to an increase in reactivity and enantioselectivity. Copper(I) halides, copper(I) cyanide and *tetrakis*(acetonitrile)copper(I) hexafluorophosphate gave similar conversions (80-92%) and enantioselectivities (around 75% ee) when (*R*)-BINAP was used as ligand. Copper(I) –chloride[264] and –iodide[270] as well as copper(II) triflate[275,247,307] have been used by others to generate *in situ* copper(I) fluoride catalysts with TBAT **130** and phosphine ligands (see pages 84 and beyond). Yet in our case, the addition of TBAT **130** to copper(II) triflate did not improve the reactivity but did affect positively the enantioselectivity (65% ee). Copper(I) oxide did not show an increase in rate of reaction and enantioselectivity (26% ee) upon addition of fluoride source **130**. Since copper(I) chloride provided slightly better conversions, it was selected for the rest of our studies.

**Chart 13** : Effect of TBAT on the catalysis by various copper salts on the benzaldehyde alkylation by diethylzinc after 2 hours using **General Procedure L**

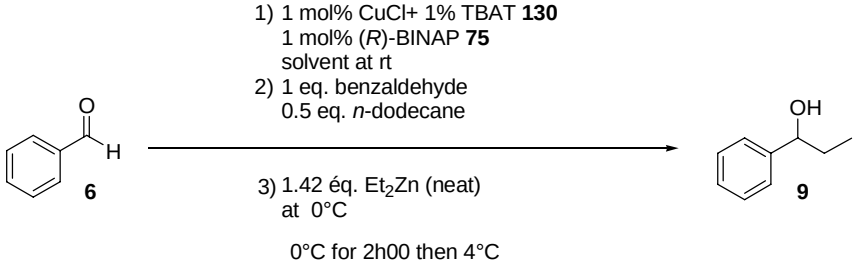



## 8.2.2. Solvents

A screening of various solvents was undertaken using the diethylzinc addition to benzaldehyde in the presence of CuCl, TBAT **130** and (*R*)-BINAP **75**. Yields and ee's were measured after 2 hours. Chart 14 clearly shows that *n*-hexane, toluene, chlorobenzene, diethylether and *tert*-butylmethylether gave the best conversions and the best enantioselectivities.

**Chart 14** : Solvent's effect on the diethylzinc addition to benzaldehyde in the presence of CuCl, TBAT and (*R*)-BINAP after 2 hours following **General Procedure M**



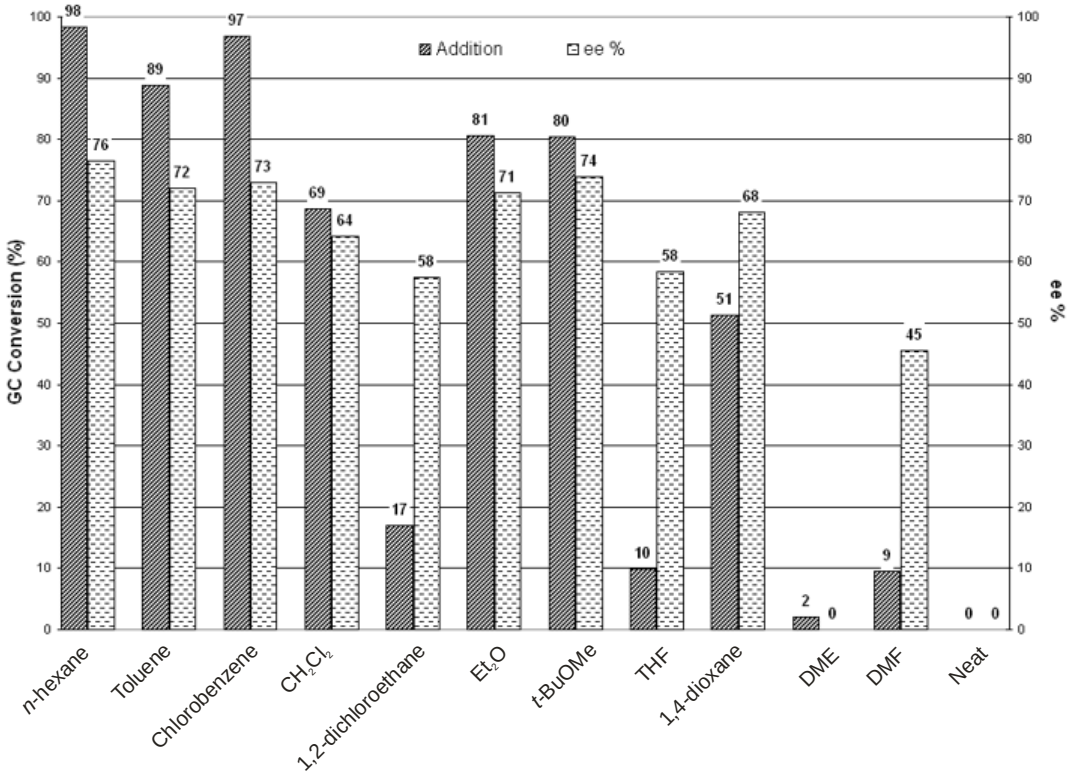
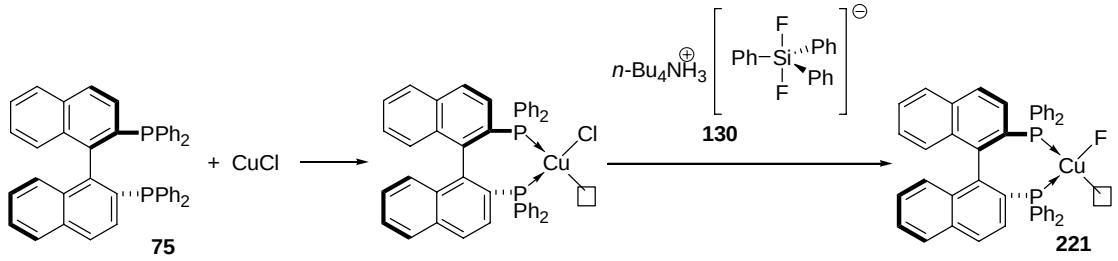




Chart 4 shows that non-coordinating solvents (*n*-hexane, toluene, chlorobenzene and dichloromethane), with the exception of 1,2-dichloroethane, gave good conversions (>69% after 2 hours) and good ee's (64-76% ee). However the effect of coordinating atoms in ethereal solvents is ambiguous. Diethylether and *tert*-butylmethylether gave results analogous to the non-coordinating solvents. However, the more basic THF gave a very low conversion (10% after two hours) with non-negligeable enantiocontrol (58% ee). Coordination thus seemed detrimental to the reaction. In 1,2-dimethoxyethane (DME) which can act as a bidentate, the reaction almost stopped. On the other hand, 1,4-dioxane gave the addition product with 51% conversion after 2 hours and 68% ee. However, in that case, the reaction medium became strongly viscous ($m_p$=10.8°C for 1,4-dioxane). Nevertheless, the reaction is not inhibited by the diffusion barrier. Also a more basic solvent such as DMF slowed down the reaction. Finally, in the absence of any solvent, the reaction did not proceed at all. We decided to run further reactions in aromatic solvents (dichlorobenzene or preferably toluene) which would readily solubilize our substrates.

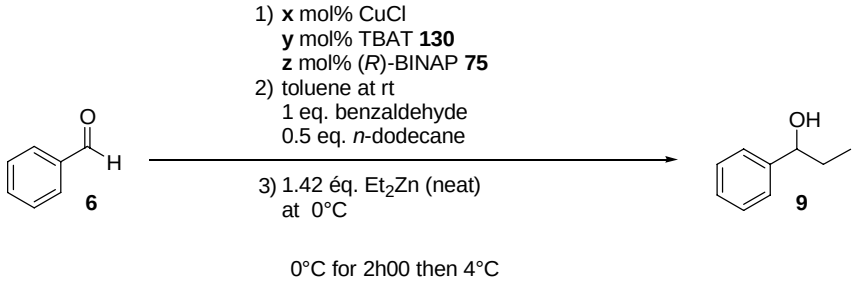
## 8.2.3. Catalyst's Precursors Stoichiometry

In our preliminary studies, we had used a 1:1:1 ratio of copper(I) salts, TBAT **130** and chiral diphosphine. This was the stoichiometry previously used by Carreira[307] and more recently by Shibasaki[278]. It suggested a complex like **221** or one of its oligomers (Scheme 101).




**Scheme 101**

We explored the influence of the stoichiometry of the catalyst's precursors on the addition of diethylzinc to benzaldehyde following the General Procedure N (Scheme 102, Chart 15, Chart 16).




**Scheme 102**

**Chart 15** : Influence of the relative stoichiometry of (*R*)-BINAP on the addition of diethylzinc to benzaldehyde after two hours following **General Procedure N**

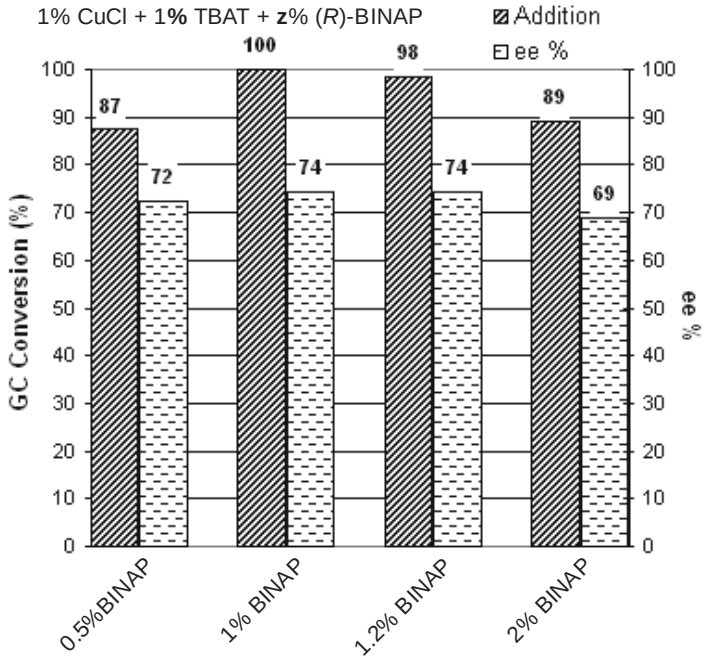
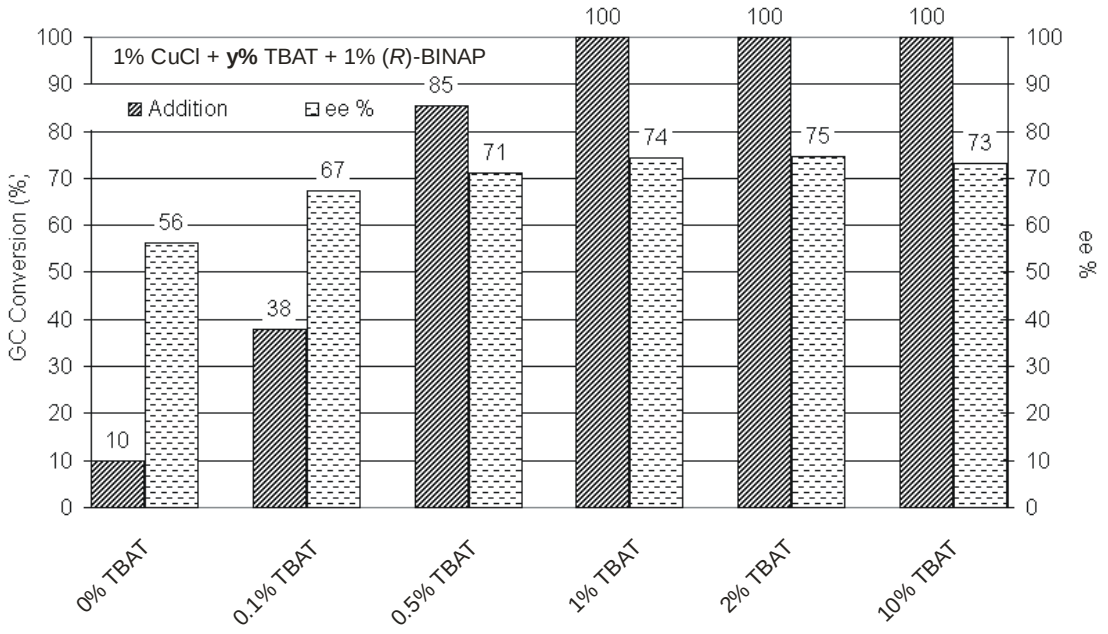



Chart 16 shows that the amount of (*R*)-BINAP **75** relative to copper(I) chloride and the fluoride source had little influence on the conversion and the enantioselectivity of the reaction. The use of a deficit (0.5mol%) or a two-fold excess of diphosphine slowed down the reaction. Also an excess (2mol%) of chiral ligand slightly decreased the enantiomeric excesses.

**Chart 16** : Influence of the relative stoichiometry of TBAT on the addition of diethylzinc to benzaldehyde after two hours following **General Procedure N**

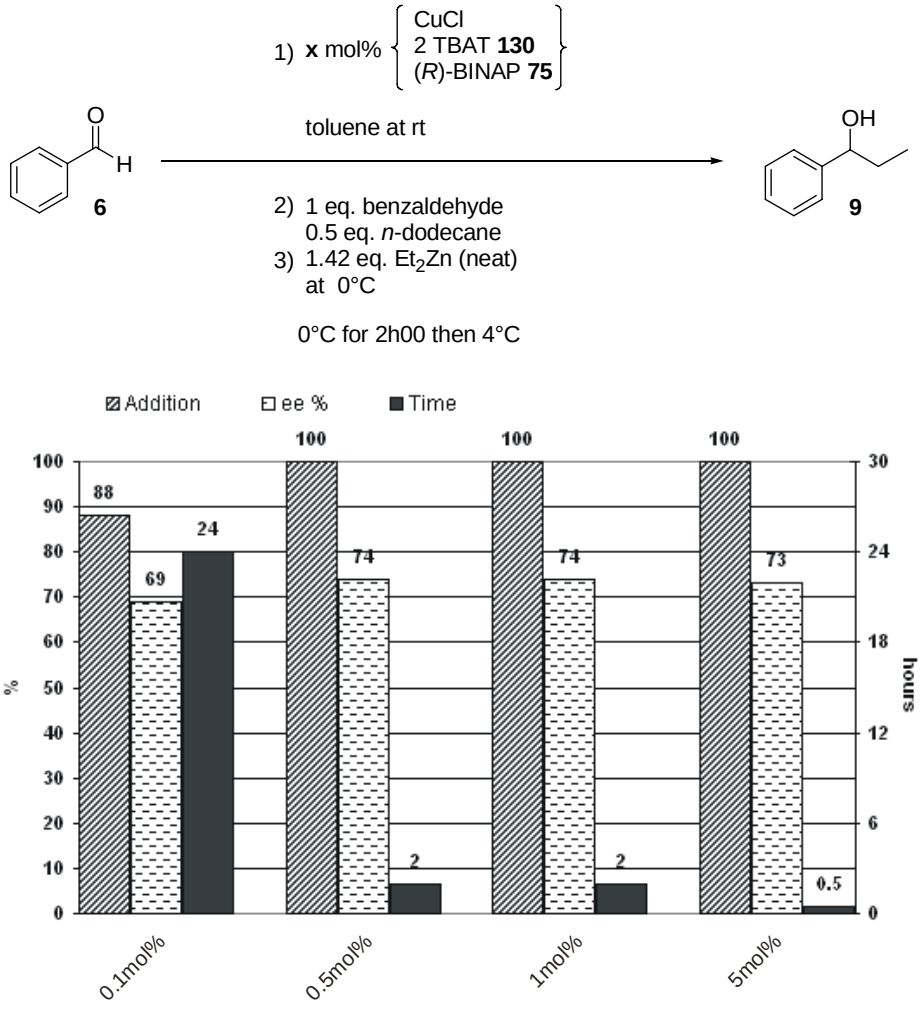



At least one equivalent of TBAT **130** was needed to form the catalyst. It was discovered that an excess of fluoride source insured better reproducibility. It seems reasonable to believe that a copper-fluoride-diphosphine complex such as **221** is formed. An excess of fluoride was used to ensure the complete formation of such a species. From now on, we will use a 1:2:1 ratio of copper(I) chloride, TBAT **130** and diphosphine (Chart 16).

## 8.2.4. Catalyst's Loading

The effect of the catalyst loading on the model reaction was also investigated. The catalyst's loading mostly affected the reaction's rate. With 5mol%, the reaction was complete in thirty minutes but the enantioselectivity was the same than with 1mol% or 0.5mol% catalyst. However, with only 0.1mol% catalyst, the reaction was not only much slower but the enantioselectivity was also slower. This could be the result of a slow decomposition of the catalyst and the occurrence of an uncatalyzed pathway (Chart 17).

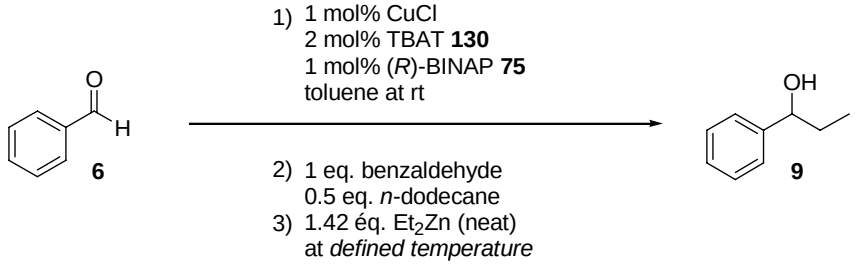
**Chart 17** : Influence of the catalyst's loading (**General Procedure N**)

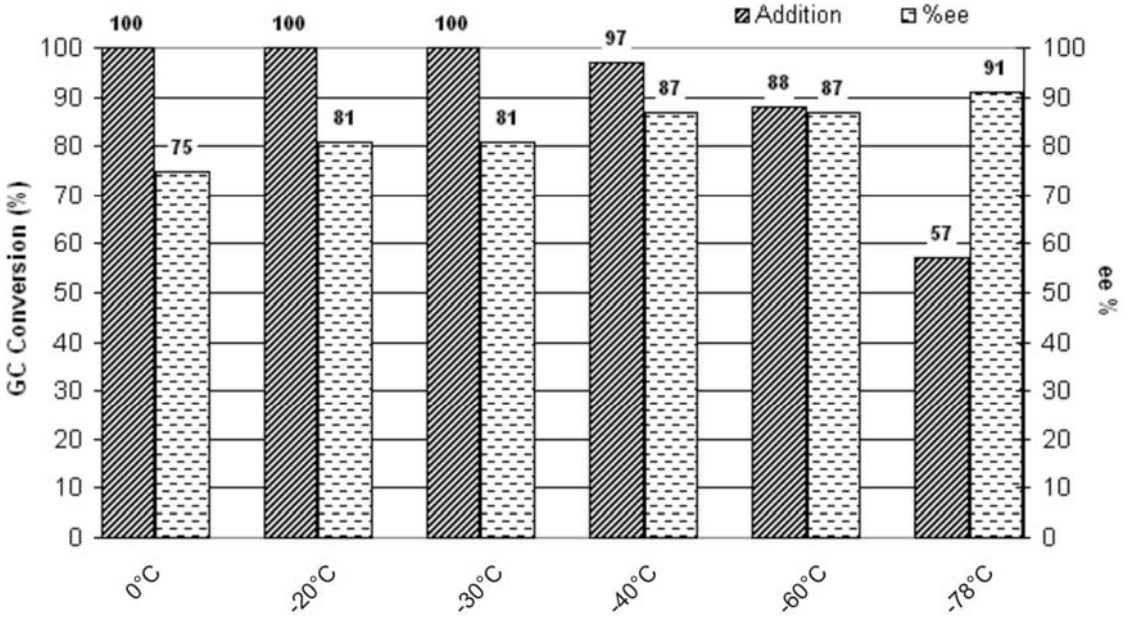



## 8.2.5. Temperature

One of the most common ways to increase the enantioselectivity of a reaction is to vary the reaction's temperature. In the case of our model reaction, an increase of the enantioselectivity was obtained by decreasing the temperature. However, it was accompanied by a decrease in reactivity. When the temperature was set lower than -40°C, the reaction was incomplete after 2 hours (Chart 18).

**Chart 18** : Influence of the temperature after 2 hours using (**General Procedure N**)




## 8.2.6. Ligand Screening

(*R*)-BINAP had been quite promising but the enantiomeric excesses could not be further increased. Other phosphorus based ligands were therefore tested. Most were commercial, some were synthesized and a few were gifts from laboratories and companies which we sincerely thank (see **0** for a list of ligands and their source). The results are reported following a classification based on the structural characteristics of the ligands.

The reactions were carried out at 0°C (ice-bath) for two hours and then at 4°C (cold room) for the remaining 22 hours under the conditions of **General Procedure N**. To provide the reader with a sense of the ligand's impact on the reaction's rate, the results are reported at reaction times corresponding either to the reaction's completion if under 2 hours or otherwise after 24 hours[‡‡‡].

A range of $C_2$-symmetric diphosphines were tested. "Classical" ligands such Chiraphos **212**[311], Norphos **222**[312,313] as well as Knowles' DIPAMP **223**[314,315] and BIPNOR **224**[316-318] did not increase substantially the reaction rate (40-50%

[‡‡‡] Samples were taken at regular intervals (5, 15, 30 minutes, 1, 2 and 24 hours).

conversion after 24 hours). Other diphosphines such as Phanephos **217**[319,320], and Trost's ligand **225**[321,322] did not further accelerate the reaction eventhough the two chelating phosphorus were separated by more than two carbons compared to the previous four ligands. With Kagan's DIOP **79**[323-325], the reaction was over in two hours but enantiomeric excesses were very low (Chart 19).

Families of ligands that cover a range of steric and electronic properties would certainly help in tuning the ligand to achieve better results. One of these families consist of the atropisomeric ligands[326] used in Chart 20 with Noyori's BINAP **75**[327,328] being its most famous representative. *p*-TolBINAP[329] **166** and BINAP gave similar results. Other atropoisomeric diphosphines such as Hoffman-la Roche's MeO-BIPHEP, Bayer's Cl,MeO-BIPHEP **226**[330,331] and Sannicolo's TMBPT **208**[332] showed good catalytic activities with the exception of the sterically crowded **227**. On the other hand enantioselectivities were not better than that observed with BINAP **75**. (Chart 20).

Another family of ligands commonly known as Josiphos has been developped by Togni in collaboration with Ciba-Geigy (now Solvias)[333,334]. These diphosphines contain a 1,2-disubstituted ferrocene core and possess both an axis and a center of asymmetry. We tested seven ligands of that family. All showed an excellent activitiy. Reactions were complete in 15 minutes to two hours except in the case of **218** which is the only Josiphos ligand with two diaryl-substituted phosphorus atoms and thus the least nucleophilic ligand of the series. Four Josiphos ligands led to moderate enantioselectivities (48% ee-67% ee) while the other three gave practically no enantiocontrol (0% ee-8% ee) (Chart 21).

The Walphos ligands **219**, **228**, **229** and **230** developped by Weissensteiner and Solvias[335,336] afforded the addition product with excellent to total conversion but quite slowly (2 to 24 hours). Interestingly, the Walphos ligand **219**, bearing electron-withdrawing groups, provided the highest enantiocontrol, while the most basic Walphos **230** formed the most active catalytic complex. Taniaphos ligands **231**, **232**, **233**, developped by Knochel[337,338], led to less than total conversion in more than 24 hours and with very little enantiocontrol (Chart 22).

Diphosphines, based on 1,1'-disubstituted ferrocene, were also tested. FerroTANE **209**[339-341], developped by ChiroTech[§§§], gave the addition product with total conversion after one hour but the enantioselectivities were low. Hayashi's ligand **234**, known as (*S*),(*R*)-BPPFA [343-345], did not show a good catalytic activity (24 hours were needed to attain total conversion) nor a satisfactory enantioselectivity (11% ee) (Chart 23).

Three ligands **235**, **236** and **237**, from the MandyPhos or FerriPhos family devellopped by Knochel's group, did not accelerate strongly the reaction[346-348]. Two of them, **235** and **236** led to enantiomeric excesses of 34% and 48% respectively (Chart 23).

The Feringa's phosphoramidite ligand **60**, known as PAMID, has been successfully used for the 1,4 addition of dialkylzinc compounds to enones and other

---

[§§§]Ferrocene ligands similar to FerroTANE have been independently reported by Marinetti and Genêt at approximately the same time [342] Marinetti, A.; Labrue, F.; Genêt, J.-P. *Synlett* **1999**, 1975-1977.

Michael acceptors in the presence of a copper salt[149,349]. Yet the 1,2-addition on benzaldehyde in the presence of 2mol% of the monophosphonamidite **60** was rather slow and showed little enantiocontrol. BINAPHOS **242**, Nozaki and Takaya's ligand for the asymmetric hydroformylation reaction[350], was also inefficient (Chart 23).

**Chart 19** : $C_2$-symmetric diphosphine ligands

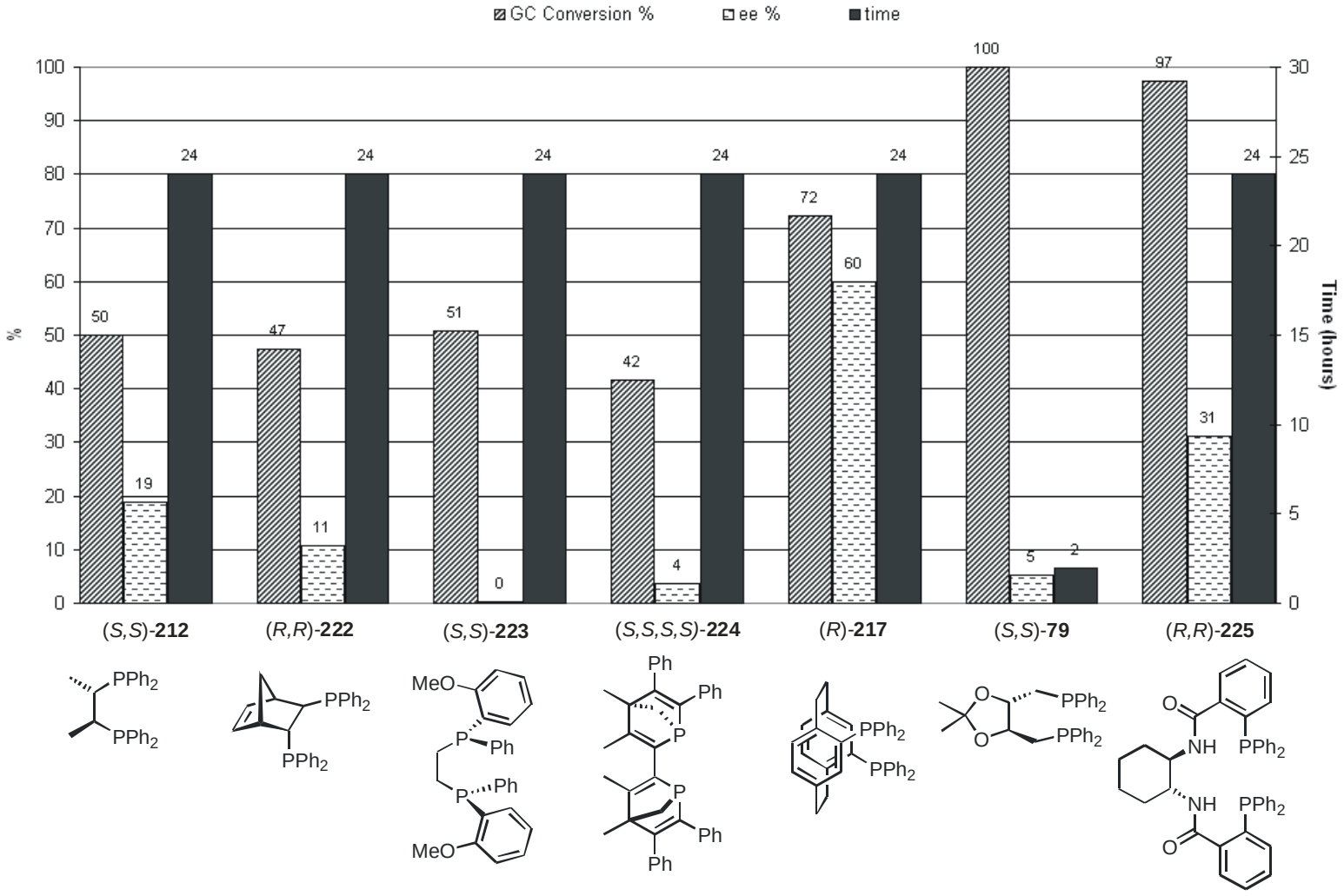


**Chart 20 :** $C_2$-symmetric atropisomeric diphosphine ligands

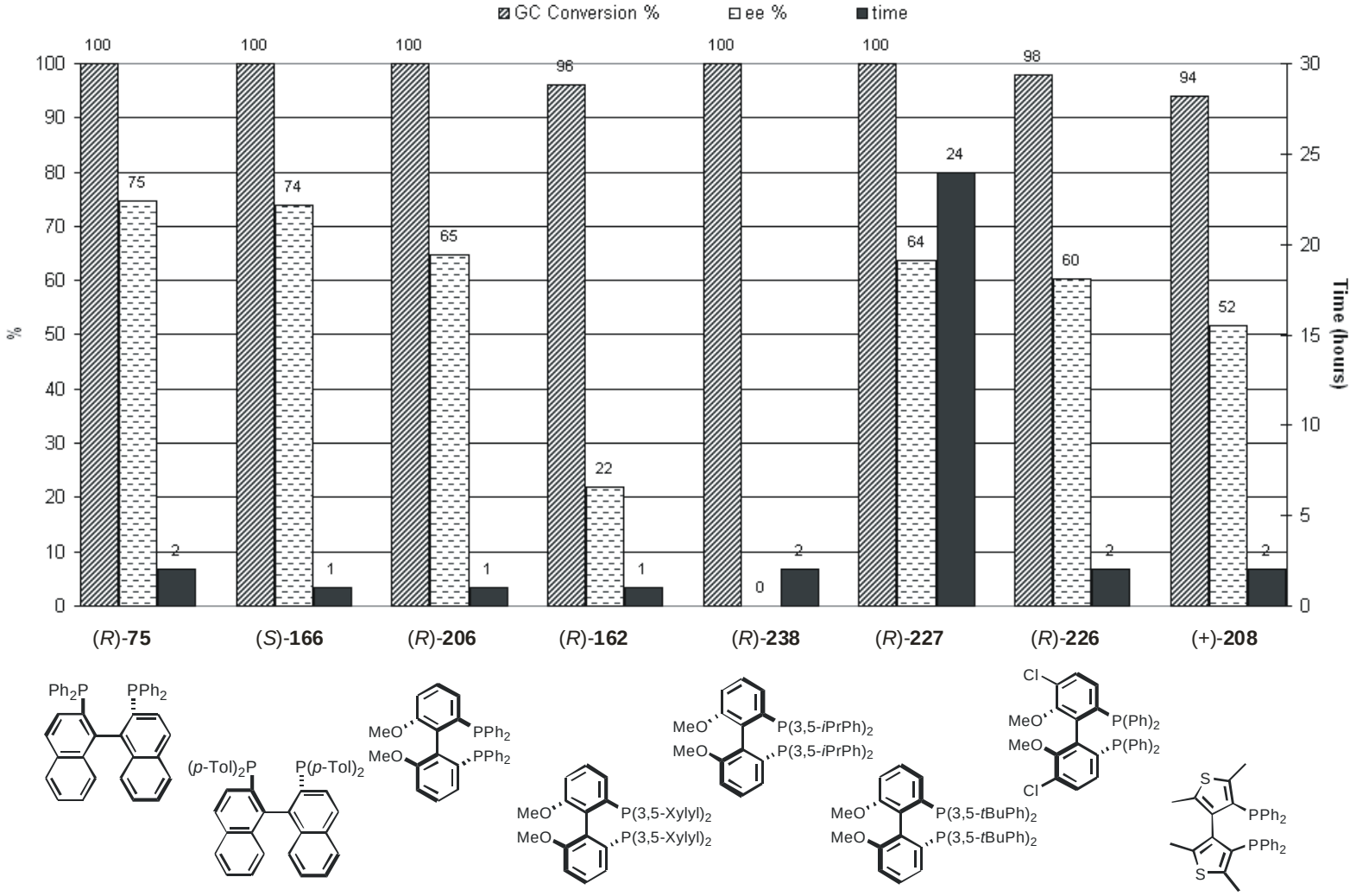


**Chart 21** : 1,2-Ferrocenyl diphosphines (Josiphos family)

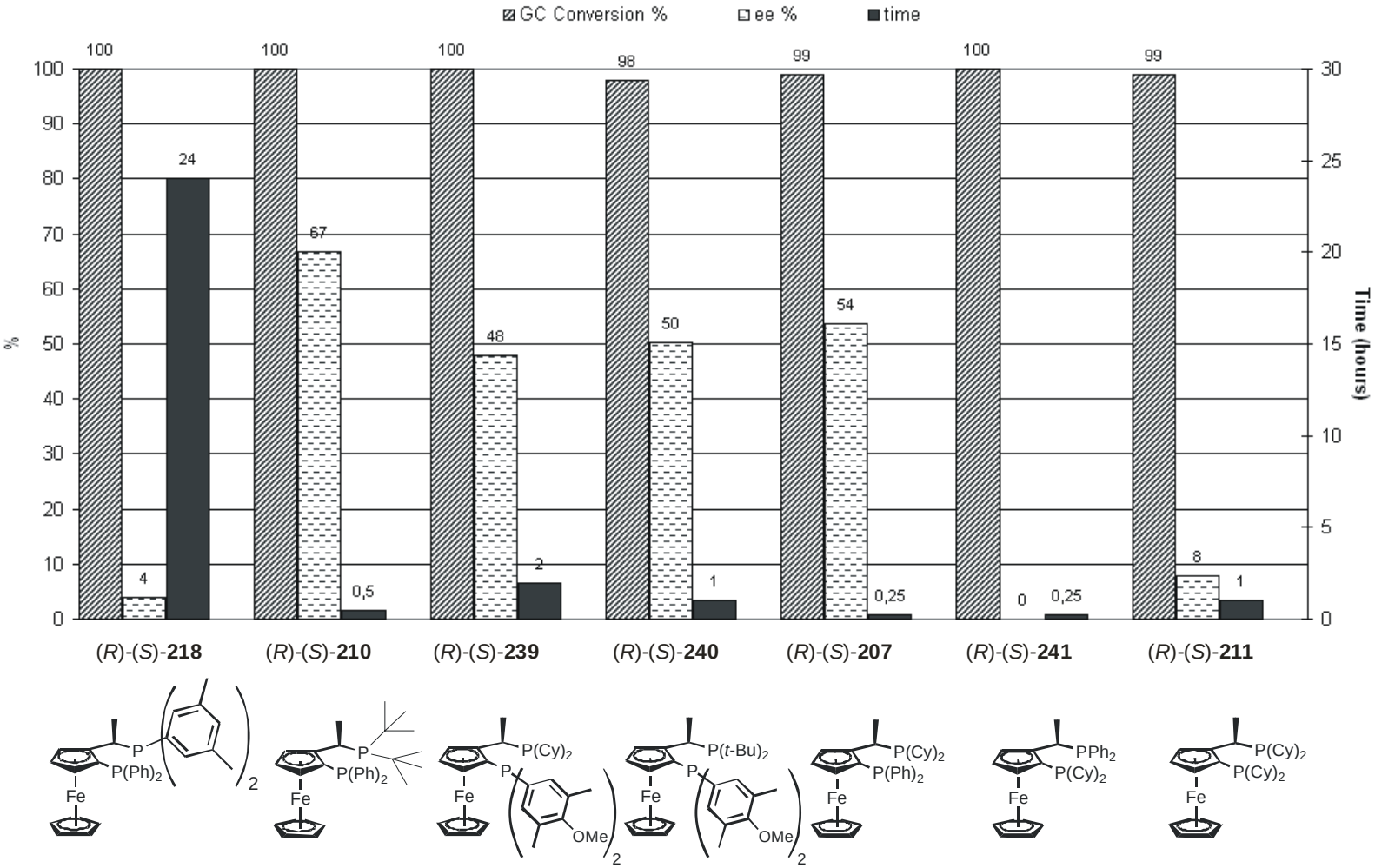


**Chart 22 :** 1,1'-Ferrocenyl diphosphines (Walphos and Taniaphos family)

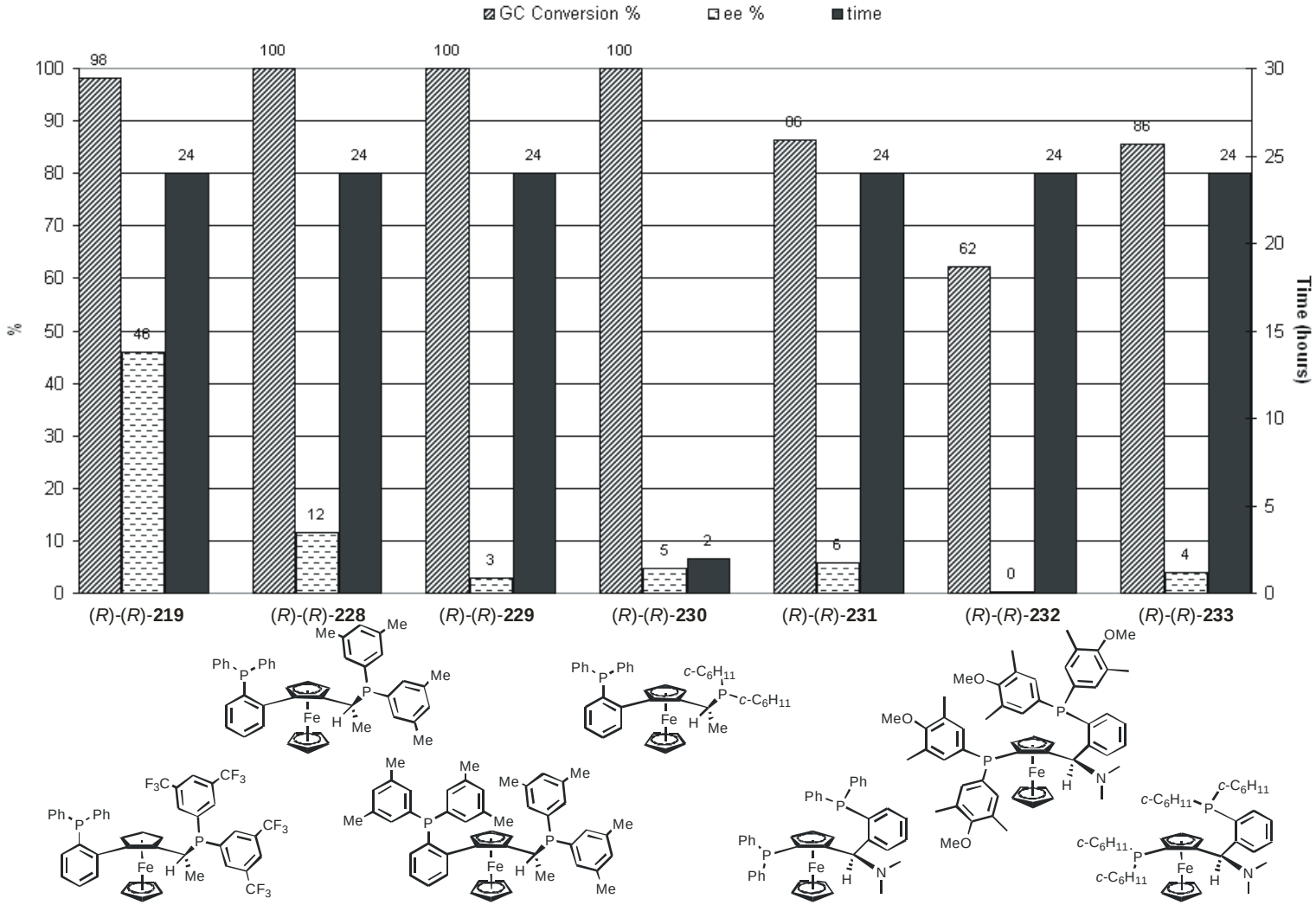
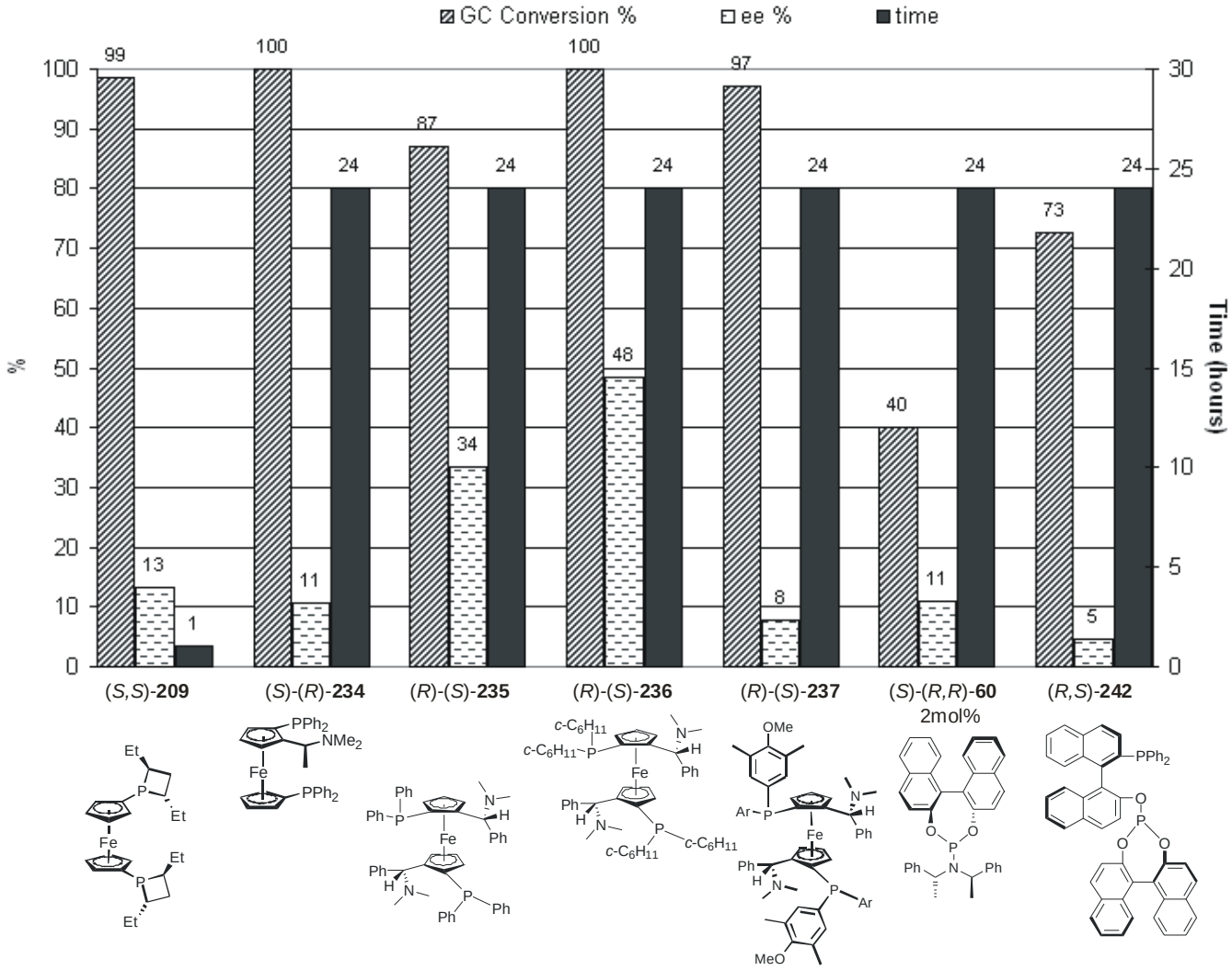


**Chart 23** : 1,1'-ferrocenyl diphosphines (including Mandyphos family)

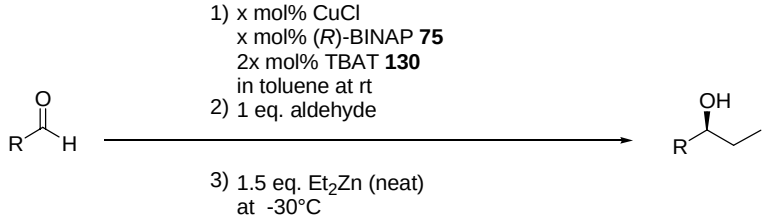


Unfortunately, we have been unable to extract any structure-activity relationship from the ligand screening. However, a few leading ligands emerge from this body of work. Atropoisomeric diphosphines **75**, **166**, **206**, **226**, **208** and Josiphos ligands **210**, **239**, **240**, **207** combined encouraging enantiocontrol (48-75% ee) with satisfying reactivity (2 hours or less). It might prove useful to have such a collection of ligands at hand when tuning reaction conditions for a specific substrate. In this work, no specific subtrate has been targeted, therefore the choice of ligand was based on commercial availability and cost. Therefore, BINAP **75** will be used throughout the rest of our study (409€ for 5g)

# 8.3. Applications

## 8.3.1. Diethylzinc Addition to Aldehydes

Conditions were selected to prepare the addition products in the best possible yields and the highest enantiomeric purities. The reaction time should be as short as possible and as little as possible of the catalyst should be used. With this aim the temperature of the reaction was set at -30°C (see Chart 18). The reaction time could be diminished by adding an excess (1.5 eq) of diethylzinc. A slight decrease in the enantioselectivity occured when going from 1mol% to 0.1mol% of catalyst (Scheme 103, Table 16). However the reaction became very slow and did not reach completion when 0.1mol% of catalyst was used even if the quantity of diethylzinc was increased from 1.5 eq. to 2 eq. (entries 1-4). From this reason, we used 1mol% catalyst for the study of the scope and limitation of the method.




**Scheme 103**

The reaction was quite general for aromatic aldehydes, yields were very good and enantiomeric excesses ranged between 75% and 87% (entries 1-10, 12-13,15). Mono-substitution in *ortho* or *para* position of the phenyl group had little influence on the yield or the enantioselectivity. However, there was no reaction at all with the 2,4,6-trisubstituted substrate. This difference in reactivity between mono-*ortho*-substituted substrates and mesitylaldehyde is probably due to steric factors.

**Table 16** : $Et_2Zn$ addition to various aldehydes catalyzed by second generation copper fluoride and (*R*)-BINAP (General Procedure O)

| Entry | R | $Et_2Zn$ ( eq.) | x | Time[a] | Yield[b] (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | 1.5 | 1mol% | 3h | 83 | 81 (*S*) |
| 2 | " | " | 0.5mol% | 17h | 84 | 81 (*S*) |
| 3 | " | " | 0.1mol% | 48h | 42 | 78 (*S*) |
| 4 | " | 2 | 0.1mol% | 48h | 43 | 75 (*S*) |
| 5 | *p*-$ClC_6H_4$ | 1.5 | 1mol% | >1h | 92 | 84 (*S*) |
| 6 | *p*-$CNC_6H_4$ | " | " | 8h | 80 | 81 (*S*) |
| 7 | *p*-$MeC_6H_4$ | " | " | 8h | 93 | 85 (*S*) |
| 8 | *p*-$MeOC_6H_4$ | " | " | 17h | 96 | 87 (*S*) |
| 9 | *o*-$MeC_6H_4$ | " | " | 19h | 79 | 80 (*S*) |
| 10 | *o*-$MeOC_6H_4$ | " | " | 3h | 92 | 83 (*S*) |
| 11 | 2,4,6-$Me_3C_6H_2$ | " | " | 24h | 0 | - |
| 12 | 1-naphtyl | " | " | 24h | 73 | 75 (*S*) |
| 13 | 2-furyl | " | " | 5h | 64 | 81 (*S*) |
| 14 | 2-pyridyl | " | " | <3h | 71 | 2 |
| 15 | 4-pyridyl | " | " | 24h | 67 | 81 (*S*) |
| 16 | Fc[c] | " | " | >3h[d] | 92 | 65 (*S*) |
| 17 | *c*-$C_6H_{11}$ | " | " | 24h | 66 | 19[e] |
| 18 | 3-$PhCH_2CH_2$ | " | " | 1h | 81 | 2 |
| 19 | *t*-Bu | " | " | 24h | 0 | - |

a : followed by GC until complete or until no noticeable evolution, quenched with MeOH after 24 hours (or more when indicated)

b : isolated yields

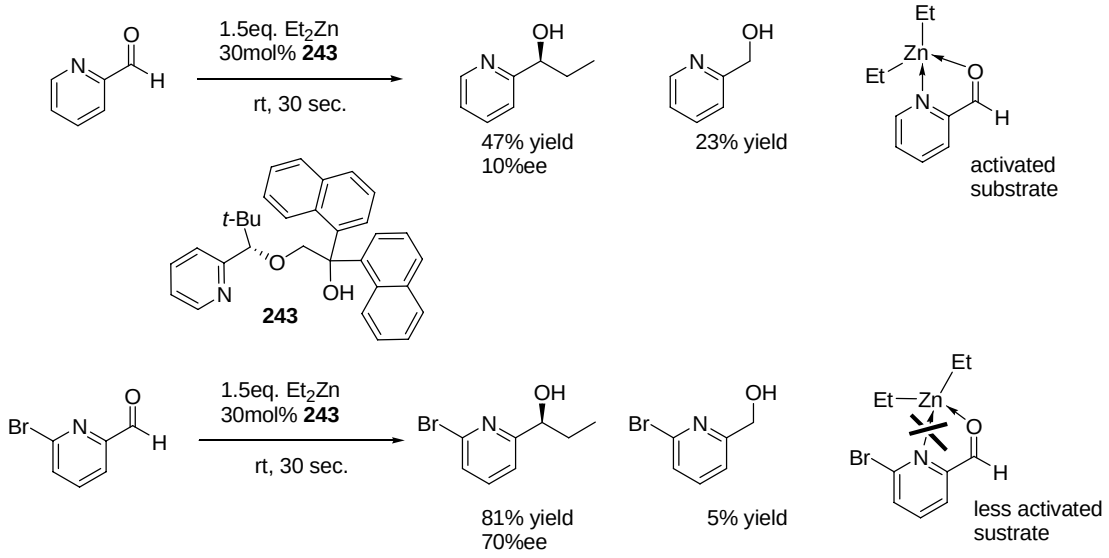
c : ferrocenylcarboxaldehyde, reaction at 0°C

d: followed by TLC on silica gel

e : measured on the benzoate derivative

Both 2-furyl- and 4-pyridyl-carboxaldehydes yielded the corresponding adducts with 81% enantiomeric excesses (entries 13 & 15). However 2-pyridine

carboxaldehyde gave a quasi-racemic adduct in less than three hours (entry 14). A similar result had been observed by several authors[351-353****]. When Hoshino *et al.* introduced a bromine at the 6-position of the pyridine ring, the addition of product was obtained with 70% ee as compared to 10% ee with the unsubstituted 2-pyridine carboxaldehyde in the presence of ligand **243**. The steric influence and electron-withdrawal of bromine apparently inhibits the activation of the substrate through chelation by $Et_2Zn$ thus favoring the asymmetric catalyzed pathway[353] (Scheme 104).




**Scheme 104**

Aliphatic aldehydes gave good yields of addition product except the sterically demanding pivaldehyde (entries 17-19). The enantioselectivities of the addition to these aldehydes (entry 17,18) were surprisingly low. A ligand screening might bring about the discovery of suitable ligands for alkylaldehydes.

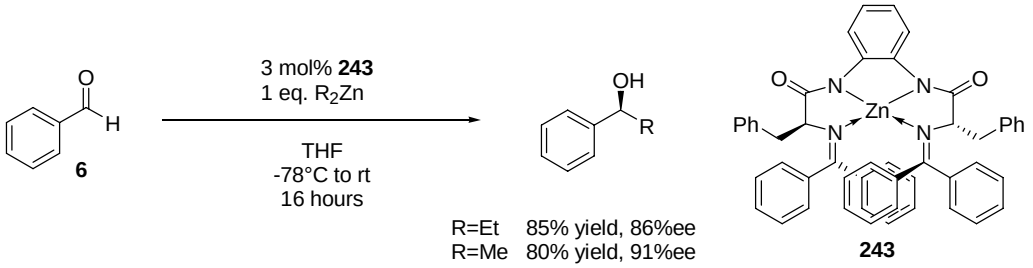
## 8.3.2. Dimethylzinc Addition to Benzaldehyde

***Literature***

The additions of dimethylzinc to aldehydes in the presence of 1,2-diamino alcohols are slower than those of diethylzinc[355-357,86,358,40,359] and the enantioselectivities are lower. This difference might arise from the fact that the active catalyst formed *in situ* by deprotonation of the amino-alcohol bears one of the alkyl residue. On the other hand $Me_2Zn$ and $Et_2Zn$ behaved similarly towards benzaldehyde in the presence of the tetracoordinate zinc complex catalyst **243** designed by Polt[360]: in this case the zinc atom is only complexed by the dianionic

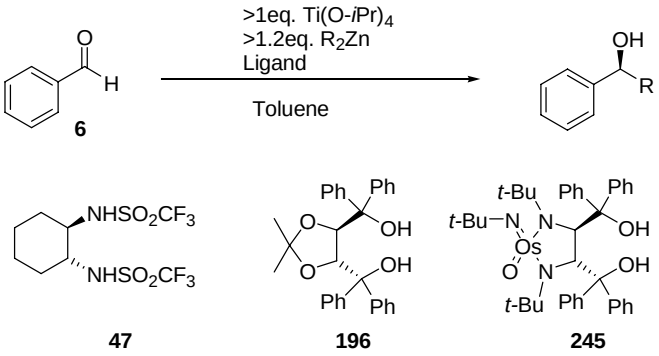
**** Soai's group has reported auto-catalysis of the dialkylzinc addition with nitrogen-heteroaromatic aldehydes, yet there is no mention of 2-pyridine carboxaldehyde as a substrate[14]Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382-390, [354] Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982-983.

ligand. Quite interestingly, this system also induces high enantioselectivity with aliphatic aldehydes (Scheme 105).




**Scheme 105**

The titanium tetraalkoxide-based systems, first developped by Ohno and Kobayashi[114,113], have been successful in catalyzing the asymmetric addition of dimethylzinc on aldehydes. In the presence of a catalytic amount of ligands[361,362], such as *bis*sulfonamide **47**[115], TADDOL **196**[50] or its osmium derivative **245**[363], the addition products were obtained with good yields and enantioselectivities. These reactions involve a catalyst which does not carry an alkyl residue (**Scheme 25**). Yet, dimethylzinc seems to be less reactive than diethylzinc when using ligands **47** and **196** (Scheme 106, Table 17, compare entries 1&2 to 3&4). This difference in reactivity should therefore be attributed to the intrinsic lack of nucleophilicity of dimethylzinc.



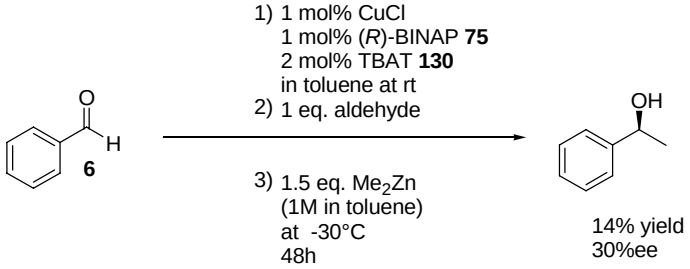

**Scheme 106**

**Table 17** : $Ti(O\text{-}iPr)_4$ mediated diethylzinc and dimethylzinc addition to benzaldehyde

| Entry | Ligand | $Ti(O\text{-}iPr)_4$ (eq.) | $R_2Zn$ ( eq.) | Temp. | Time | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | **47** (0.5mol%) | 1.2 | $Et_2Zn$ (1.2 eq.) | -30°C | 2.5h | 98 | 99 |
| 2 | **47** (4mol%) | 1.2 | $Me_2Zn$ (1.2 eq.) | 0°C | 48h | 99 | 73 |
| 3 | **196** (8mol%) | 1 | $Et_2Zn$ (1.2 eq.) | -78°C to -30°C | 1 day | 70 | 98 |
| 4 | **196** (8mol%) | 1 | $Me_2Zn$ (1.2 eq.) | -78°C to -30°C | 1 day | 55 | 94 |
| 5 | **245** (20mol%) | 1.45 | $Et_2Zn$ (1.8 eq.) | -30°C | 1 day | 87 | 87 |
| 6 | **245** (20mol%) | 1.45 | $Me_2Zn$ (1.8 eq.) | -30°C | 1 day | 92 | 91 |

***Result***

The addition of dimethylzinc to benzaldehyde in the presence of the *in situ* generated copper-fluoride catalyst was desperately slow. The addition product was obtained in very low yield (14%) and low enantiomeric excess (30% ee) after 48 hours (Scheme 107). There was still a lot of starting material as shown by the strong gas evolution upon treatment of the reaction media with methanol.



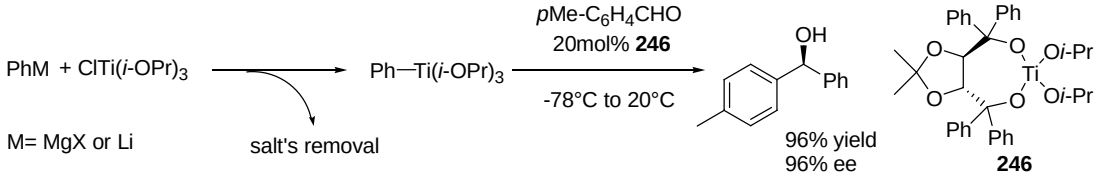

**Scheme 107**

## 8.3.3. Arylzinc Addition to Aldehydes

***Introduction***

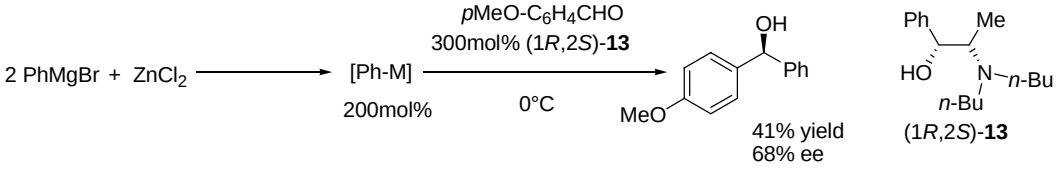
Seebach *et al.* reported in 1985 the first stoichiometric enantioselective aryl addition to an aromatic aldehyde[31] and, in 1994[132], a catalyzed version of the reaction using a titanium-TADDOLate complex. The aryl titanium was obtained

from the the reaction of the corresponding aryl Grignard or aryllithium reagent with chlorortriisopropyllithium. In this procedure, the magnesium or lithium salts must be removed by centrifugation and filtration prior to addition to the electrophile and a catalyst loading of 20mol% is needed. This is somewhat unpractical (Scheme 108).




**Scheme 108**

In 1991, Soai reported the use of an arylzinc species generated *in situ* from phenylmagnesium bromide and zinc chloride in the presence of an large excess of chiral amino alcohol **13**[364]. In these conditions, diarylcarbinols were obtained in good enantiomeric excesses. Here the presence of the metal salts is needed to the catalytic activity (Scheme 109).




**Scheme 109**

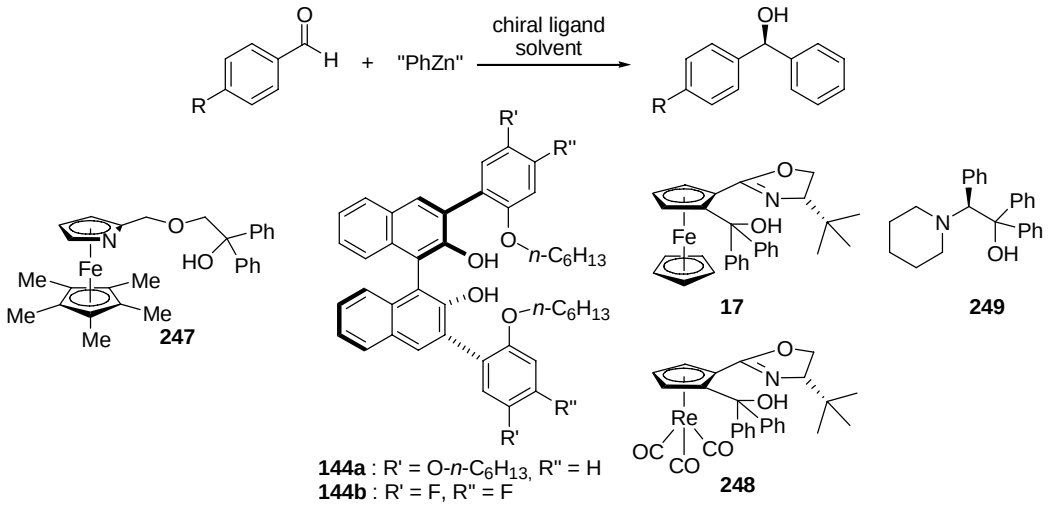
In 1997, Fu reported the first addition of pure diphenylzinc on *para*-chlorobenzaldehyde in the presence of a catalytic amount (3mol%) of chiral azaferrocene **247**[43] (Table 18, entry 2). In 1999, Huang and Pu reported the enantioselective addition of diphenylzinc to arylaldehydes catalyzed by chiral binaphtol **144a**[231]. Preliminary deprotonation of the ligand by addition of diethylzinc led to a more enantioselective catalyst active catalyst (entries 3&4). Oligomeric versions of these chiral binapthol sensibly gave the same results than the monomer[232] but can be recovered by simple precipitation in methanol. The presence of an electron-withdrawing group such as fluorine on the monomeric binaphtol led to an improved active catalyst **144b**[233] (entry 5). In 1999, Bolm *et al.* used ferrocene-based oxazolidine alcohol **17** to generate *in situ* a catalyst for the addition of diarylzinc to aldehydes. Enantiomeric excesses were high[365] (entry 6).

In all reported examples of the diphenylzinc addition to aldehydes, only one of the phenyl group was transferred. Bolm *et al.* found that mixing diphenylzinc and diethylzinc (in a ratio of 1:2) led to the selective transfer of the aryl group in the presence of **17** with an increase in enantioselectivity compared to pure $Ph_2Zn$[68] (Table 18, entries 6 vs 7). It was proposed that an equilibrium was established between diphenylzinc, diethylzinc and a mixed "PhZnEt" species. The electronic and structural factors responsible for the preferred aryl transfer in the mixed diorganozinc species have been explored through theoretical calculations[69]. The impact of this mixed diorganozinc species on the enantioselectivty has been attributed to two factors:

- Contrary to diethylzinc, diphenylzinc reacted with aldehydes in the absence of catalyst. The mixed reagent, $Ph_2Zn/Et_2Zn$, was less reactive than $Ph_2Zn$ in the absence of any catalyst decreasing thus the impact of the background reaction leading to a racemic adduct[69,366]

- The active catalyst generated from a chiral aminoalcohol bears spectator phenyl or ethyl groups depending on the diorganozinc compound used. In the case of a sterically demanding ligand such as **17**, the less bulkier ethyl groups could lead to a more enantioselective pathway[367] (this is a similar effect to the one observed by Pu with **144**).

**Table 18 :** Asymmetric aryl transfer on aromatic aldehydes : Literature results




| Entry | R | Catalyst | "PhZn" | T (°C) | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1[a] | Cl | - | $Ph_2Zn$ (1.3 eq.) | 0°C | 88 | - |
| 2 | Cl | **247** (3mol%) | $Ph_2Zn$ (1.3 eq.) | r.t. | 99 | 57 |
| 3 | MeO | **144a** (5mol%) | $Ph_2Zn$ (2 eq.) | 0°C | 76 | 54 |
| 4 | MeO | **144a** + $2Et_2Zn$ (5mol%) | $Ph_2Zn$ (1 eq.) | 0°C | 87 | 77 |
| 5 | Cl | **144b** + $2Et_2Zn$ (20mol%) | $Ph_2Zn$ | r.t. | 92 | 95 |
| 6 | Cl | **17** (5mol%) | $Ph_2Zn$ (1.5 eq.) | 0°C | 99 | 82 |
| 7 | Cl | **17** (5mol%) | $Ph_2Zn$ + $2Et_2Zn$ (0.65 eq.) | 0°C | 92 | 95 |
| 8 | Cl | **248** (2mol%) | $Ph_2Zn$ + $2Et_2Zn$ (0.65 eq.) | 10°C | >80 | 96 |
| 9 | Cl | **249** (10mol%) | $Ph_2Zn$ + $2Et_2Zn$ (0.64 eq.) | r.t. | 82 | 95 |
| 10 | Cl | **17** (1mol%) | $Ph_2Zn$ + $2Et_2Zn$ (0.65 eq.) | 10°C | 84 | 79 |
| 11 | Cl | **17** (1mol%) | $Ph_2Zn$ + $2Et_2Zn$ (0.65 eq.) + 25mol% DiMPEG | 10°C | 71 | 93 |

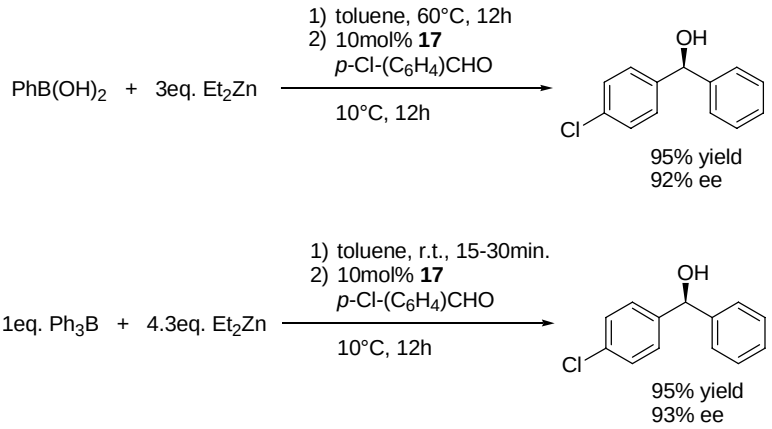
a : Personnal result

Modifications of the metallocene moiety by Bolm *et al.* lead to the discovery of cyclopentadienylrhenium(I) tricarbonyl **248** which showed higher activity so that

catalyst loading could be reduced to less than 5mol% with still high ee's[368]. In 2004, Péricas *et al.* have reported that the mixed organozinc species in the presence of catalytic amounts of amino-alcohol **249** as low as 1.5mol% furnished the aryl adduct of different aromatic aldehydes with excellent enantioselectivities (up to 99% ee)[366] (Table 18).

In a recent development, Bolm *et al.* have shown that adding DiMPEG (dimethoxy poly(ethylenegycol)) allowed a lower loading of chiral ligand **17** (1mol%) with almost no loss of enantioselectivity. Such an effect was linked to the suppression of nonselective contribution from traces of zinc salts (such as $ZnCl_2$, $ZnBr_2$)[59] (Table 18, entries 10 & 11)

Bolm *et al.* have used arylboronic acids[60] and organoborane[59] as the primary aryl source in this type of reactions. Through a transmetallation process with diethylzinc, an arylzinc species is supposedly formed which can then be added enantioselectively to aryl aldehydes in the presence of chiral ligand 17. The ease of access to substituted boronic acids make this a very promising route to optically active diarylmethanols (pure diphenylzinc is commercial but expensive and no substituted diarylzinc is commercial. (Scheme 110).



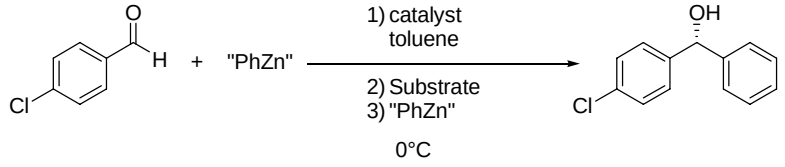

**Scheme 110**

The asymmetric addition of diarylzinc to ketones has been reported in a few publications[43,140,139] but this will not be exposed in this document. The reader is also lead to a review on catalytic asymmetric aryl transfer on a range of substrates by Bolm *et al.* published in 2001[369].

***Results***

We were curious to see how our second generation copper(I) fluoride system fared in the asymmetric addition of an aryl group to an aryl aldehyde. For the sake of comparison with published results, we chose *p*-chlorobenzaldehyde as substrate. A larger loading of catalyst was used in order to favor the catalytic pathway over the uncatalyzed addition. The ratio of copper chloride to TBAT **130** was only 1:1.25 so as to diminish the mass of the catalyst precursor introduced in the reaction (Table 19).

**Table 19** : Phenyl addition on *p*-Cl-($C_6H_4$)CHO with second generation copper fluoride catalyst




| Entry | CuCl | (*R*)-BINAP | TBAT | "PhZn" | Time | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|
| 1[a] | - | - | - | $Ph_2Zn$ (1.3 eq.) | <1h | 88 | - |
| 2[a] | 4mol% | 4mol% | 5mol% | $Ph_2Zn$ (1.3 eq.) | <1h | 90 | 3 |
| 3[a] | - | - | - | $Ph_2Zn$ (0.65 eq.) + $Et_2Zn$ (1.3 eq.) | >6h | 87 | - |
| 4[a] | 4mol% | 4mol% | - | $Ph_2Zn$ (0.65 eq.) + $Et_2Zn$ (1.3 eq.) | >6h | 88 | 2.5 |
| 5[a] | 4mol% | 4mol% | 5mol% | $Ph_2Zn$ (0.65 eq.) + $Et_2Zn$ (1.3 eq.) | 6h | 86 | 5 |
| 6[b] | 4mol% | 4mol% | 5mol% | $Ph_2Zn$ (0.65 eq.) + $Et_2Zn$ (1.3 eq.) | >3h | 78 | 8 |

a: $Ph_2Zn$ from STREM, b: : $Ph_2Zn$ from Aldrich

Table 19 confirmed that diphenylzinc reacted in the absence of any catalyst (entry 1) and showed that our second generation catalyst was unable to compete effectively : the ee was only 3% ee (entry 2). The addition of diethylzinc as proposed by Bolm[68] did slow the uncatalyzed aryl transfer (entry 3 vs. entry 1). The presence of copper chloride and (*R*)-BINAP did not lead to a significant facial selection (2% ee) (entry 4). The additional presence of a fluoride source, 130, did not accelerate the reaction and the enantioselectivity was only slightly higher (entry 5). As reported by Bolm *et al.*, no ethyl addition product was observed by GC and $^1$H NMR of the crude. The product was assigned the R configuration based on the order of elution and comparison with published data[60].

Professor Carsten Bolm pointed to us that results were sometimes dependent on the commercial source of the diphenylzinc. When diphenylzinc from Strem was replaced by Aldrich's, the reaction was only slightly faster and slightly more enantioselective (entry 6). We did not make any further investigation on this reaction.

## 8.4. Conclusions

By changing the access route to copper-fluoride complexes to the combination of a fluoride source with a copper salt in the presence of a chiral diphosphine and optimizing several reaction parameters such as copper and fluoride sources, solvent, temperature, catalyst stoichiometry and ligand structure, we have been able to improve the asymmetric addition of diethylzinc on benzaldehyde as

compared to the pre-formed copper(I) fluoride complex **158** in the presence of (*R*)-BINAP.

This new system was then tested on a range of aldehydes, giving very good enantioselectivities (75 to 87% ee) with functionalized arylaldehydes and heteroarylaldehydes? In the presence of (*R*)-BINAP **75**, alkyl aldehydes were alkylated in good yields but with poor enantioselectivity (2 to 19% ee). Our system showed no catalytic activity with sterically hindered substrates. The application of the copper(I)chloride, TBAT **130**, (*R*)-BINAP system to the phenyl transfer on an arylaldehyde gave the diarylcarbinol in good yields but low enantiomeric excesses (up to 8% ee).

# Chapter 9

# Mechanistic Studies

## 9.1. Introduction

Having shown that the presence of copper(I) fluoride complexed by a chiral diphosphine efficiently catalyzed the addition of diethylzinc to aldehydes, we now want to describe literature data and new experiments aiming at understanding the role of the active copper species.

## 9.2. Mechanistic Hypotheses

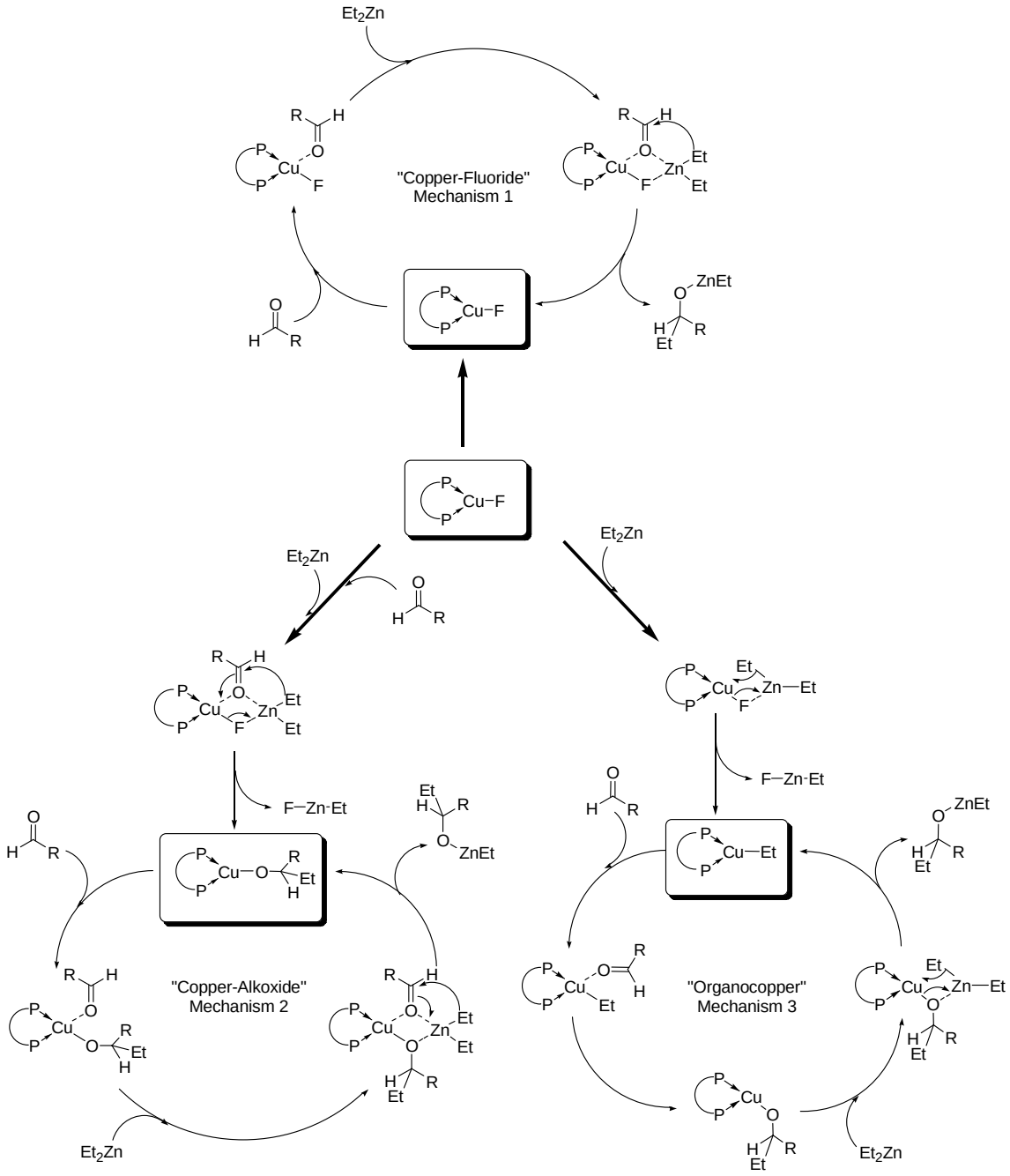
We hereby propose three different mechanisms which accommodate for the role of the fluoride anion in the copper mediated-diethylzinc addition.

The first proposal (Scheme 111, mechanism 1) is based on the hypothesis that the active catalyst is the copper(I) fluoride itself. The interaction of diethylzinc with the fluoride leads to the formation of a more nucleophilic zincate. The aldehyde is activated through complexation with the Lewis acid copper center. The coordination of the second electronic pair of the oxygen atom by the zinc atom could further activate the electrophile. The copper fluoride complex would be regenerated after transfer of the ethyl group and the production of the zinc alkoxide.

Another possibility (Scheme 111, mechanism 2) would be the formation of a copper alkoxide species instead of copper fluoride with the concomitant formation of ethylzinc fluoride. The copper alkoxide complex would then be the propagating catalyst. The role of Lewis base activating the diethylzinc would be played by the oxygen atom of the alkoxide.

A third mechanism (Scheme 111, mechanism 3) would involve the formation of an organocopper species. $Zn^{2+}$ is a harder cation than $Cu^{+}$; hard anions would therefore be expected to preferably bind to zinc[246]. The metathesis between a copper(I) fluoride species and a dialkylzinc compound could therefore result in the formation of an organocopper species. The same should be true between copper(I) alkoxide and dialkylzinc.

These mechanistic hypothesis in fact raise one important point : is the fluoride anion involved throughout the catalytic cycle (mechanism 1) or is fluoride only needed to generate some active catalyst (mechanisms 2 & 3)?

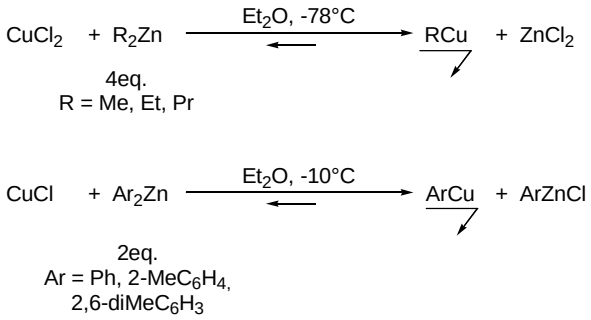



**Scheme 111**

## 9.3. Organocopper Reagents

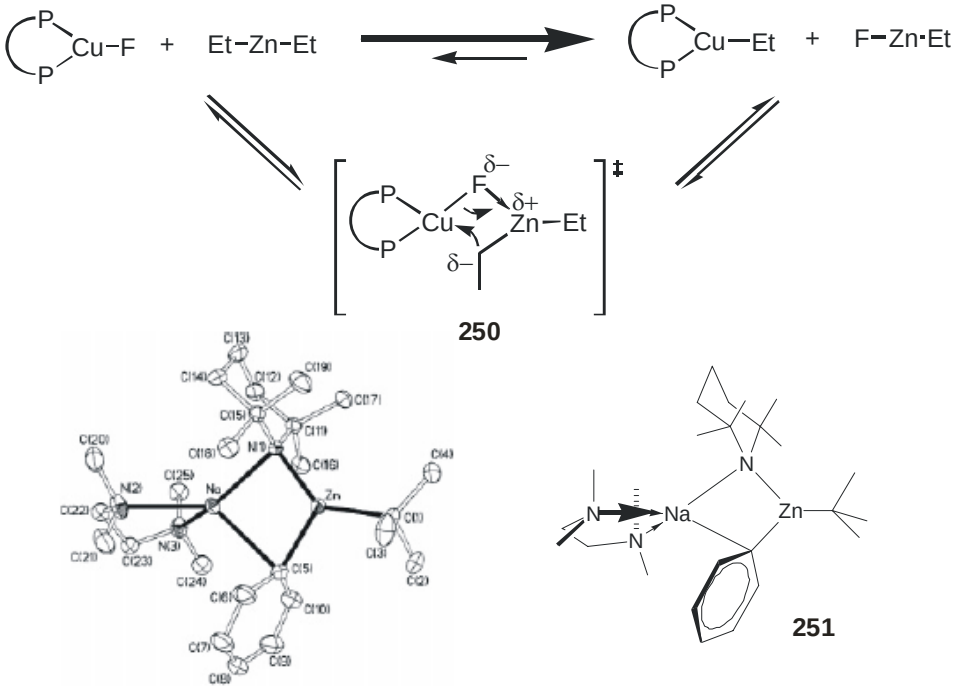
In mechanism 3 of Scheme 111, the alkyl fragment is transferred through the intermediate of an organocopper species. Transmetallation should proceed readily because the metal in the parent organometallic reagent ($R_2Zn$) is more electropositive than the copper salt ( $\chi_P^b(Cu^{+1})=1.9$ *vs* $\chi_P^b(Zn^{+2})=1.6$ )[246]. We have already said in the introduction that the synthesis of alkyl copper and aryl copper species could be carried out by transmetallation of copper chloride salts and

diorganozinc compounds in the absence of any ligand (Scheme 112). It is thus reasonable to think that an organocopper reagent participates in the catalytic cycle.




**Scheme 112**

What is the role of the fluoride anion in our catalyst systems? The interaction between the halide counterion and dialkylzinc in a four-membered transition state **250** will lead to the formation of an nucleophilic zincate complex. Such a four member ring transition state finds support from the recently published X-ray structure of sodium diorgano-amidozincate **251** with a μ-bound phenyl group bridging the sodium and zinc centers[370]. From HSAB principle's point-of-view, fluoride being a harder Lewis base than chloride, the interaction between the fluoride anion and the zinc metal should be stronger and facilitate the transmetallation step (Scheme 113).




**Scheme 113**

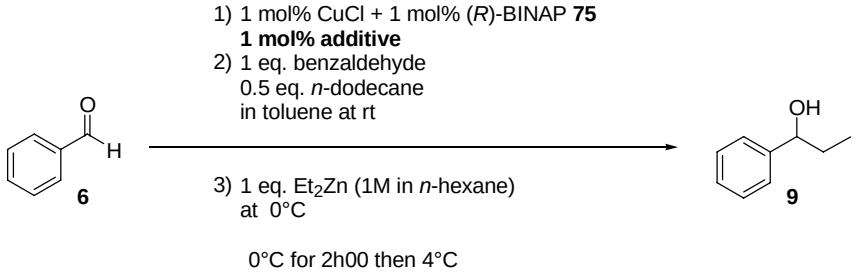
# 9.4. Copper Alkoxide Catalyzed 1,2-Addition

In mechanism 3 (Scheme 111), the fluoride anion is only involved in the generation of the active species and is not implicated in the catalytic cycle itself. The catalytic active species would be best described as a copper alkoxide species. Could the diorganozinc addition to aldehydes be catalyzed starting from a copper(I) alkoxide instead of a copper(I) fluoride species?

Copper alkoxides are readily generated by anion metathesis between copper chloride and an alkaline alkoxide[371]. However, their isolation is usually difficult due to their instability towards moisture and air[372,373]. Most often, experiments involving copper(I)alkoxide are carried out with *in situ* generation of the sensitive copper species[374,267,375,376].

We generated *in situ* the copper(I) *tert*-butoxide complex from copper(I) chloride, sodium *tert*-butoxide and (*R*)-BINAP and reacted this complex with diethylzinc and benzaldehyde. The addition of $Et_2Zn$ to benzaldehyde took place in 46% conversion after 2 hours and 72% ee (Table 20, entry 1). Similar results were obtained with potassium trimethylsilyloxide[377] (entry 2). However we found that these results were not easy to reproduce (entry 4). It is therefore hazardous to conclude if copper(I) alkoxide is involved in the catalytic cycle.

**Table 20** : Copper alkoxide catalyzed addition of $Et_2Zn$ to benzaldehyde and influence of the reagents' addition order after 2 hours following **General Procedure L**.




| Entry | Copper / Ligand (1 mol%) | Additive (1 mol%) | GC Conversion of Adduct 9 (%) | ee (%) |
|---|---|---|---|---|
| 1 | CuCl / (*R*)-BINAP **75** | NaO*t*-Bu | 46 | 72 (*S*) |
| 2 | " | KOTMS | 56 | 67 (*S*) |
| 3 | " | TBAT **130** | 92 | 76 (*S*) |
| 4 | " | NaO*t*-Bu | 1 | 0 |

# 9.5. Copper-Catalyzed Dialkylzinc 1,4-Addition

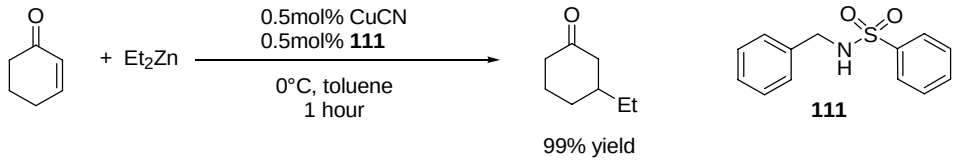
## 9.5.1. Introduction

In the last decade, tremendous efforts have been made to use diorganozinc reagents as the nucleophilic source in copper catalyzed Michael addition[298,143,142].

Even though such a reaction presents differences with the 1,2-addition reactions, we would like to bring forward the work of Noyori and Kitamura[378,379,310] and Alexakis[380] as it might enlighten our understanding of the role of the copper counterion.

## 9.5.2. Literature

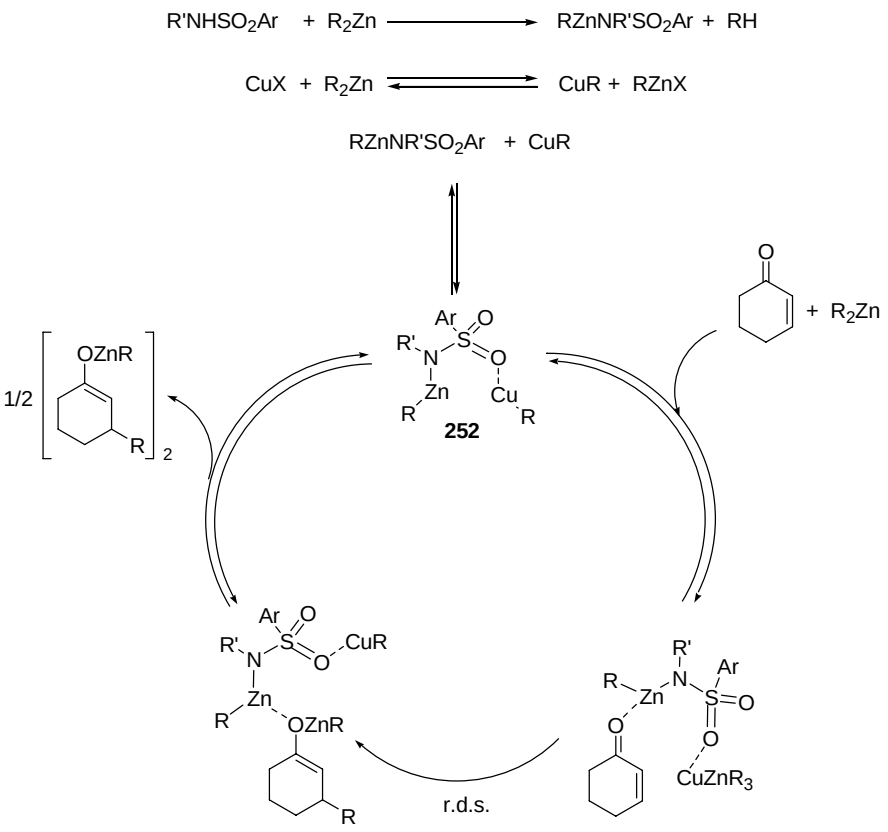
In 1996, Noyori and Kitamura reported on the influence of *N*-monosubstituted sulfonamide ligands on the copper(I) catalyzed addition of diethylzinc to enones. In contrast with the situation with Grignard and organolithium reagents, the addition of a copper(I) salt (including CuCN, CuOTf, CuO*t*Bu, CuCl, CuBr, CuI) did not activate the Michael addition of diethylzinc to 2-cyclohexenone. The addition of a catalytic quantity of *N*-benzylbenzenesulfonamide **111** to a catalytic amount of copper salt (CuCN, CuOTf, CuMes, CuO-*t*-Bu, CuBr) activated the conjugated addition of diethylzinc[310] (Scheme 114).




**Scheme 114**

A mechanism was proposed (Scheme 115). A first molecule of dialkylzinc deprotonates the sulfonamide R'N(H)$SO_2$Ar while a second molecule undergoes a transmetallation reaction in the presence of the copper(I) salt. The resulting organocopper CuR reacts with RZnNR'$SO_2$Ar to yield a mixed-metal complex **252** which acts as a bifunctional catalyst for the addition of dialkylzinc to enones. The sulfonamide ligand acts as a three-atom spacer linked to the oxygen atom and the C-C double bond of the enone.

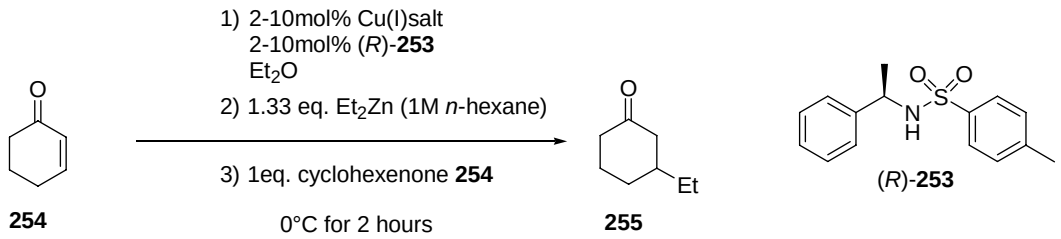
The kinetic studies suggested that the rate determining step is the alkyl transfer. The determination of first order kinetics in $Et_2Zn$, 2-cyclohexenone and copper-sulfonamide, led the authors to propose the alkyl transfer was not due to the Cu-R moiety but involved a copper-zinc cluster. However, no spectroscopic evidence supporting the formation of that cluster or any other bimetallic species was presented (Scheme 115).




**Scheme 115**

Sewald reported the use of chiral sulfonamides and a copper salt for the addition of diethylzinc to 2-cyclohexenone[381]. Even if poor enantioselectivities were obtained, these results provided additional evidence of the direct involvement of the sulfonamide in the catalytic cycle. Furthermore, copper(I) triflate, copper(I) thiophenolate and all copper(I) halides gave a slight excess of the (*S*)-adduct in the presence of (*R*)-**253** (Table 21, entries 1-3) while copper(I) cyanide produced a small excess of the (*R*)-3-ethylcyclohexanone (entry 4). The influence of the anion of the starting copper salt is not to be overlooked. Sewald proposed that the strongly coordinating cyanide anion was involved in the catalytic cycle in contrast to the other anions. Based on Noyori and Kitamura's mechanism (see Scheme 115), the active nucleophile in the presence of cyanide might then be best described as RZn(NR*SO2Ar)CuR(CN)(ZnR).

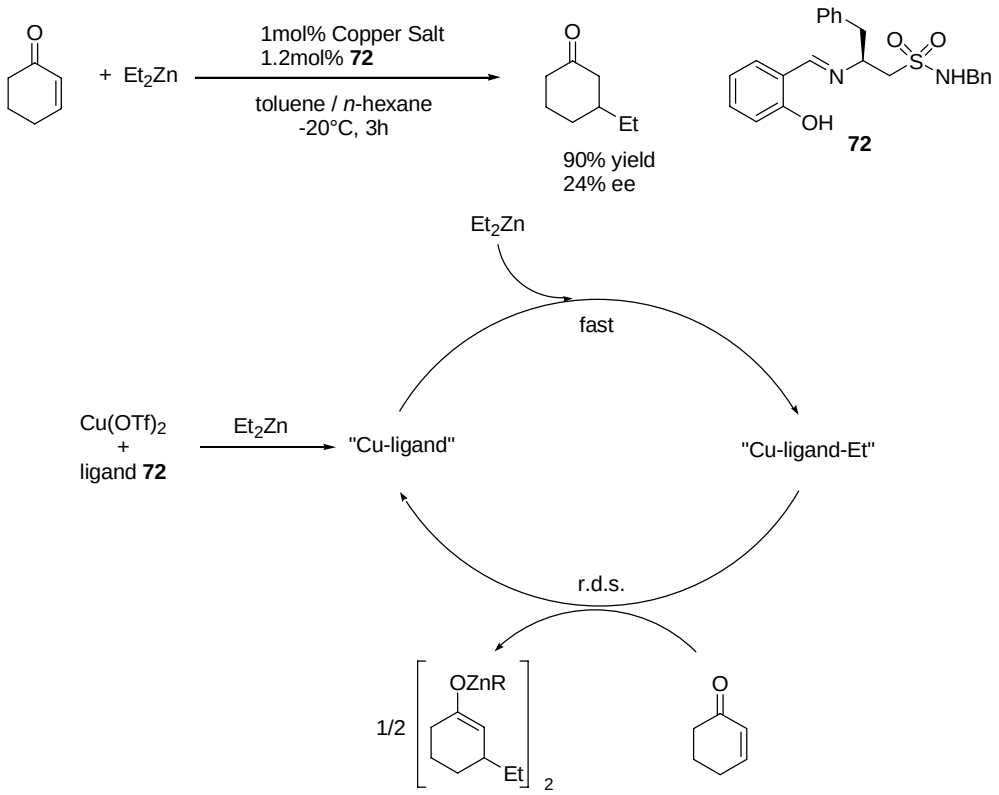
**Table 21** : Influence of the copper source on the 1,4-addition of $Et_2Zn$ to 2-cyclohexenone with chiral sulfonamide **253**[381]




**254** **255** (*R*)-**253**

| Entry | Copper Salt | (*R*)-253 | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 9.3 mol% CuOTf | 9.3 mol% | 77 | 16 (*S*) |
| 2 | 9.3 mol% CuSPh | 9.3 mol% | 84 | 22 (*S*) |
| 3 | 5.9 mol% CuCl | 5.9 mol% | 6 | 6 (*S*) |
| 4 | 5.6 mol% CuCN | 5.6 mol% | 80 | 30 (*R*) |

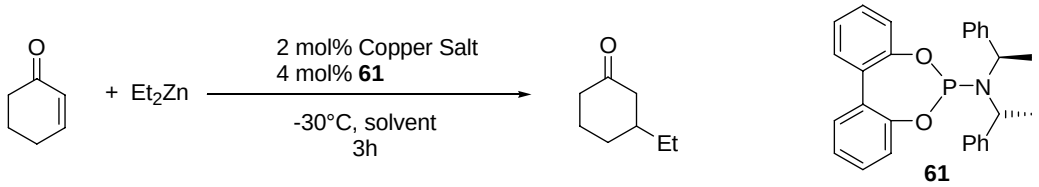
High-throughput screening of a family of chiral salicylimine-sulfonamide ligands for the enantioselective copper-catalyzed Michael additions of diethylzinc to enones[382] and nitroolefins[383] was reported by Gennari *et al.*. In 2004, Gallo, Piarulli, Gennari *et al.* also published the results of their mechanistic investigation of the Michael addition on cyclohexenone in the presence of ligand **72**[384]. The reduction of the copper(II) triflate by $Et_2Zn$ was evidenced by the disappearance of the paramagnetic of copper(II) species (EPR measurements). A first order in copper-ligand and cyclohexenone was observed. However, in contrast with the results of Noyori (Scheme 115), the order of $Et_2Zn$ was close to zero. This might translate into a fast step where diethylzinc generates a nucleophilic species through transmetallation to the copper complex. This nucleophilic species then coordinates with 2-cyclohexenone and the ethyl group is transferred in a rate-determining step generating a zinc enolate and a copper-ligand complex (Scheme 116).




**Scheme 116**

In 2002, Alexakis *et al.* reinvestigated the enantioselective conjugate addition of dialkylzinc to Michael acceptors in the presence of a copper salt and chiral phosphoramidite ligands[380]. They screened 21 different copper salts in different solvents (selected results in Table 22). A study of the influence of the solvent showed that a non-coordinating solvent like toluene was not compulsory and that $Et_2O$ improved the rates and enantioselectivities of most copper catalysts. Most inorganic copper salts behaved poorly, except for CuCl, $Cu(ClO_4)_2.6H_2O$ and $Cu(BF_4)_2.6H_2O$. Organic copper salts, such as 1,3-diketonates and carboxylates, led respectively to similar and better enantioselectivities than copper(II) triflate. Interestingly, the Lewis acidity of the copper source did not affect the conversion nor the enantiomeric excesses (entries 7 and 8). By analogy with the copper-sulfonamide mechanism proposed by Noyori (see Scheme 115), the carboxylate residues were assigned the role of the bridge in a bifunctional mixed-metal active species.

**Table 22** : Conjugate addition of $Et_2Zn$ to 2-cyclohexenone catalyzed by phosphoramidite **61** and different copper salts




**61**

| Entry | Copper Salt | Toluene | | $Et_2O$ | |
|---|---|---|---|---|---|
| | | Conversion (%) | ee (%) | Conversion (%) | ee (%) |
| 1 | $Cu(OTf)_2$ | >99 | 82 | >99 | 90 |
| 2 | CuCl | >99 | 80 | >99 | 82 |
| 3 | $Cu(ClO_4)_2.6H_2O$ | 65 | 73 | >99 | 86 |
| 4 | CuCN | 50 | 0 | >99 | 79 |
| 5 | $Cu(acac)_2$ | >99 | 80 | >99 | 90 |
| 6 | $Cu(F_3acac)_2$ | 80 | 75 | >99 | 90 |
| 7 | $Cu(OAc)_2$ | 95 | 89 | >99 | 92 |
| 8 | $Cu(O_2CCF_3)_2$ | >99 | 91 | >99 | 92 |
| 9 | CuTC[a] | 90 | 93 | >99 | 96 |
| 10 | $Cu(O_2CR)_2$[b] | >99 | 91 | >99 | 94 |

a. CuTC : copper(I) thiophene-2-carboxylate

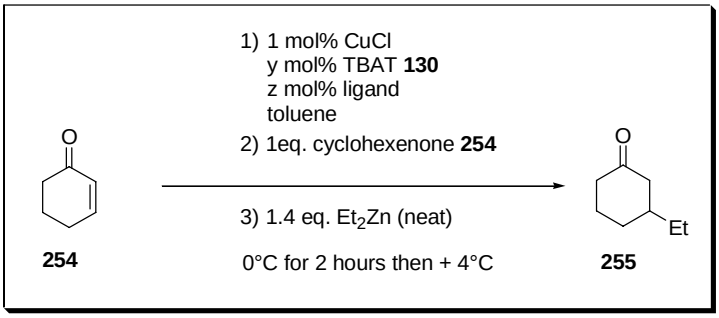
b. $Cu(O_2CR)_2$ : copper(naphtenate)$_2$

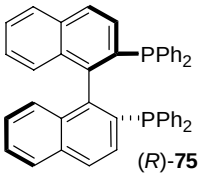
## 9.5.3. Results and Discussion

The literature examples indicated that the counterion has an influence on the copper catalyzed conjugate addition of dialkylzincs with enones. What would be the influence of copper fluoride catalysts in such reactions? We thus carried out the addition of diethylzinc to 2-cyclohexenone in the presence of copper chloride, TBAT **130** and a chiral ligand. For comparison, the reaction in the absence of any fluoride source was also examined. Two ligands were studied: (*R*)-BINAP **75** and the highly successful phosphoramidite ligand **60** for conjugated addition[149,349] (Table 23).

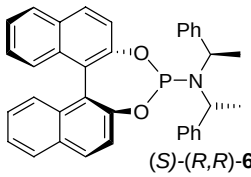
The addition of diethylzinc to 2-cyclohexenone was carried out in the presence of copper chloride, TBAT **130** and a chiral ligand. For comparison purposes, the reaction in the absence of any fluoride source was achieved under the same conditions. Two ligands were chosen: (*R*)-BINAP **75** and the highly successful phosphoramidite ligand **60** for conjugated addition[149,349].

**Table 23** : Influence of fluoride on the 1,4-addition of $Et_2Zn$ to 2-cyclohexenone in the presence of copper chloride and chiral ligands




(*R*)-**75**




(*S*)-(*R*,*R*)-**60**

| Entry | Ligand | TBAT | Time | Yield (%) | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | 2 mol% **60** | - | <5min[a] | 67 | 84 (*S*) |
| 2 | 2 mol% **60** | 2 mol% | (<1 hour)[a] | 49 | 83 (*S*) |
| 3 | 1 mol% **75** | - | 19 hours | 52 | 20 (*S*) |
| 4 | 1 mol% **75** | 2 mol% | 1 hour | 66 | 31 (*S*) |

a: first sample taken

b: measured by integration of $^{13}C$ NMR signals of diastereomeric aminal derivatives of **255**[385]. For further details see in the experimental section **16.2.2**

The complete disappearance of the enone **254** and the sole production of the conjugate addition product **255** was observed by gas chromatography. The product being volatile **255**, yields (isolated products) were moderate and not representative.

The reactions in the presence of ligand **60** and a copper source were extremely fast. It was over in less than 5 minutes with copper(I) chloride ! We did not take a sample early enough when the reaction was carried out in the presence of copper(I) chloride and fluoride source **130** (entry 2). The enantioselectivity of the reaction did not differ significantly with and without fluoride.

The picture was much clearer with (*R*)-BINAP **75**. In the absence of fluoride, the reaction took 19 hours for complete conversion and afforded the addition product with 20% ee (entry 3). When **130** was added, the reaction only took 1 hour and the enantioselectivity was improved to 31% ee. The addition of fluoride to the copper(I) chloride-BINAP complex accelerated greatly the 1,4-addition of diethylzinc to enones. The small difference of enantiomeric excesses (20% ee *vs.* 31% ee) in the absence or presence of fluoride is not significant from a structural and energetic point-of-view. The addition of fluoride seems to decrease the energy level of the rate determining transition step but does not lead to significant structural changes in the enantioselective-determining step.

Alexakis had reported the use of copper(II) triflate and BINAP in the asymmetric conjugate addition of $Et_2Zn$ to enones [386] (Table 24, entry 1). The enantioselectivity reached 24% ee for the reaction of 2-cyclohexenone. (*S*)-BINAP gave the (*S*)-adduct **255**. Under our conditions, the addition of diethylzinc to 2-cyclohexenone in the presence of copper(II) triflate and (*R*)-BINAP **75** led to the (*R*)-3-ethylcyclohexanone **255** in 30% ee (entry 2). This is exactly the reverse enantioselectivity than the one obtained with (*R*)-BINAP and copper(I) chloride or copper(I) chloride and TBAT **130** (entries 3 & 4).

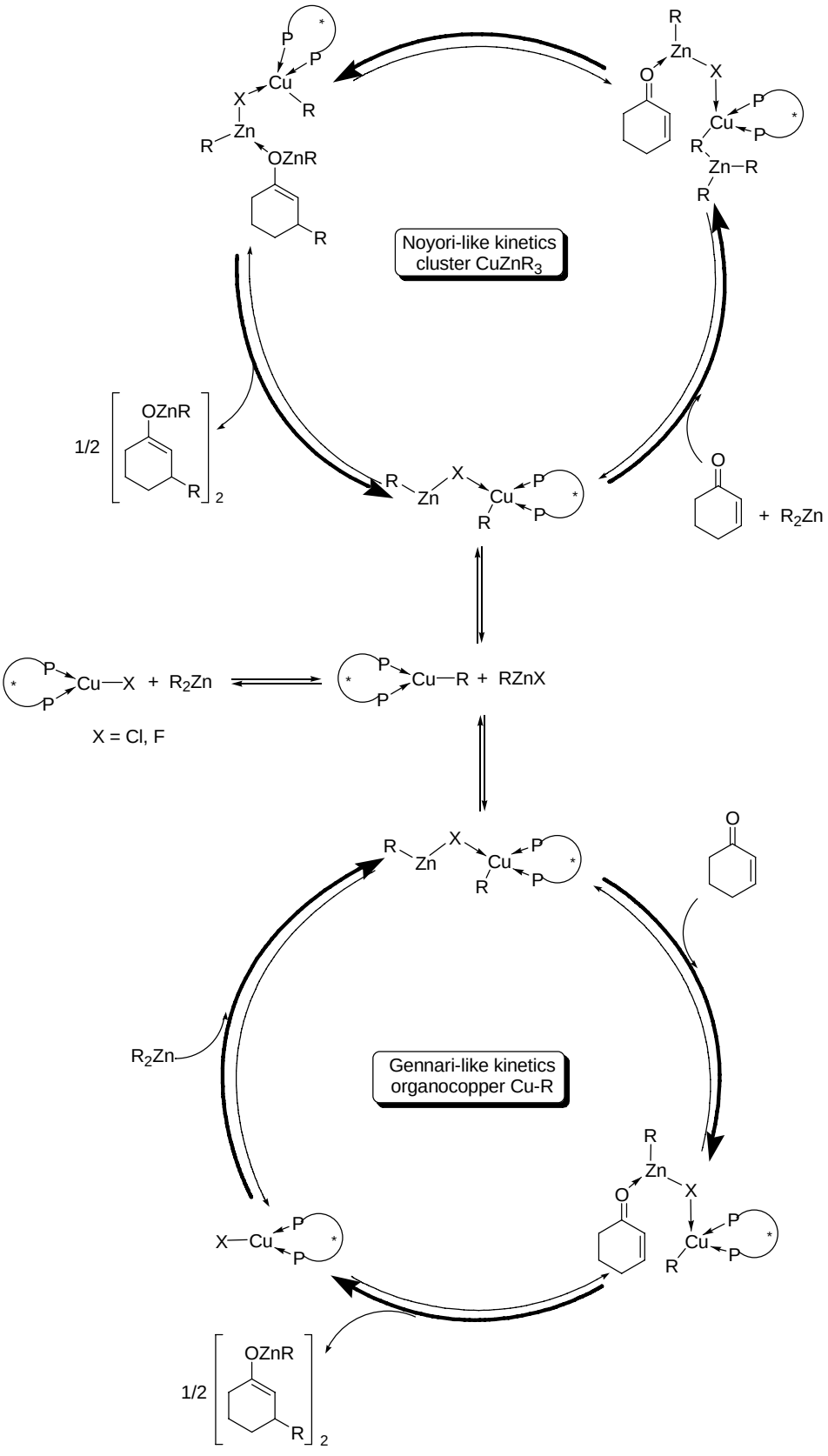
**Table 24** : Influence of the nature of the copper source on the 1,4-addition of $Et_2Zn$ to 2-cyclohexenone with chiral BINAP **75**

| Entry | Copper Salt | Ligand | Temp | Time | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1[a] | 0.5 mol% $Cu(OTf)_2$ | 0.5 mol% (*S*)-**75** | 0°C | 1 hour | 80 | 24 (*S*) |
| 2 | 1 mol% $Cu(OTf)_2$ | 1 mol% (*R*)-**75** | 0°C | 2 hours | 56 | 30 (*R*)[b] |
| 3 | 1 mol% CuCl | 1 mol% (*R*)-**75** | 0°C | 19 hours | 52 | 20 (*S*)[b] |
| 4 | 1 mol% CuCl + 2 mol% TBAT | 1 mol% (*R*)-**75** | 0°C | 1 hour | 66 | 31 (*S*)[b] |

a : see reference[386]

b :: measured by integration of $^{13}C$ NMR signals of diastereomeric aminal derivatives of **255**[385]. For further details see in the experimental section **16.2.2**

This unexpected inversion of chirality indicates important structural changes of the transition state in the enantioselective step depending on the anion and its properties. The halide anions, chloride or fluoride, could bridge a copper and zinc center in analogy with the sulfonamide in Noyori's mechanism. The triflate anion however is a non-nucleophilic anion which should not be able to interact with metal centers. The nature of the nucleophilic species involved, $CuZnR_3$ cluster or organocopper Cu-R, is undefined at this stage.


Noyori-like kinetics
cluster CuZnR3
Gennari-like kinetics
organocopper Cu-R
X = Cl, F
+ R2Zn
R2Zn
1/2

**Scheme 117**

# 9.6. Nonlinear effects

## 9.6.1. Introduction

An easy probe to obtain information on the mechanism of asymmetric reactions is the measure of nonlinear effects[387,388]. Nonlinear effects (NLE) in asymmetric reactions are observed when the enantiomeric excesses of the product ($ee_{prod}$) are not directly proportional to the enantiomeric excesses of the chiral inductor ($ee_{aux}$). Figure 22 shows examples of a linear effect, a positive nonlinear effect and a negative nonlinear effect.

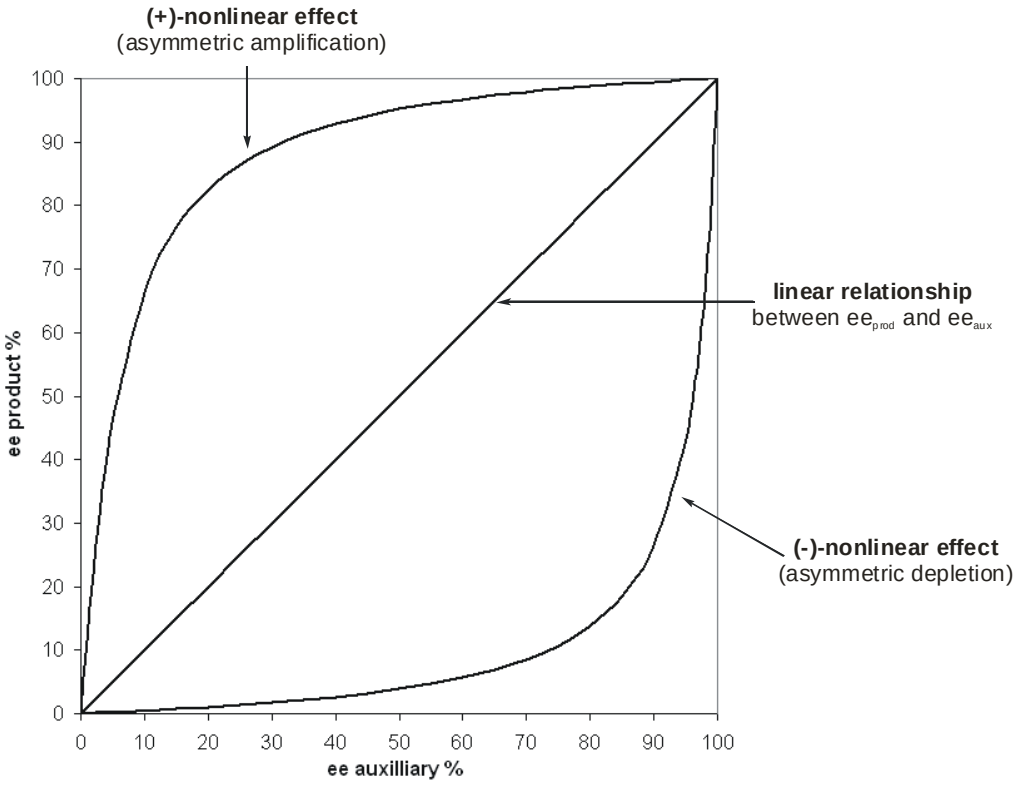
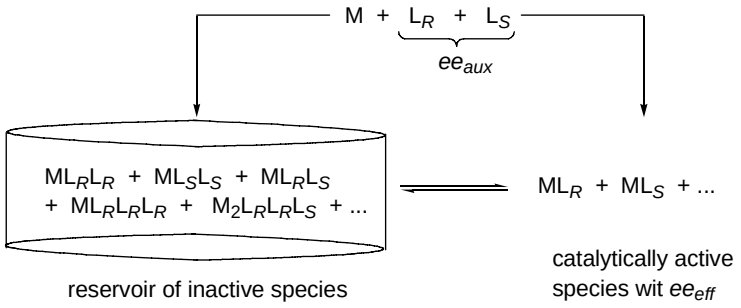



**Figure 22**

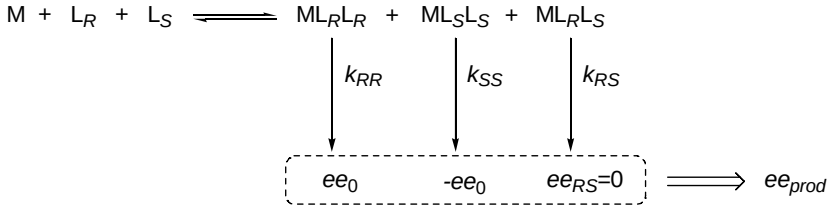
The first report of a non-linear effect in asymmetric catalysis was published by Kagan in 1986.[389] Many efforts have been made by Kagan, Noyori and others to rationalize these effects.[390-392,75]. The potential perturbations generated by the use of partially resolved chiral ligand in asymmetric catalysis reflect the formation of diastereomeric complexes. Kagan *et al*. have developed two models to account for such behaviour[392].

A first explanation involves the presence of diastereomeric species at the periphery of the catalytic cycle (Scheme 118). Starting with a certain amount of ligand with a defined optical activity ($ee_{aux}$), the diversion of ligand to a reservoir or pool of unproductive species modifies the enantiomeric excess of the catalytically active species (effective ee or $ee_{eff}$). This "reservoir effect" allows for non-linear effects with catalytically active species bearing only one ligand.




**Scheme 118**

The other rationale implicates the formation of catalytic species bearing two or more chiral auxiliaries ($ML_n$ model ($n \geq 2$). The simplified case where two ligands are involved is shown in Scheme 119 and leads to curves as in Figure 22. The fast ligand exchange between reactive species involving two chiral ligands ($L_R$, $L_S$) can lead to three different complexes: chiral complexes $ML_RL_R$ and $ML_SL_S$, as well as the *meso* complex $ML_RL_S$. The two asymmetric complexes yield the product with the same rate constant ($k_{RR}=k_{SS}$) with the same enantiomeric excess ( $|ee_0|$ ) but of opposite sign ($ee_0$ corresponding to the ee obtained in the presence of enantiopure ligand). The *meso* complex $ML_RL_S$ yields a racemic product with a specific rate constant $k_{RS}$. The experimental enantiomeric excess will thus reflect the relative concentration of the three possible catalytic species ($ML_RL_R$, $ML_SL_S$, $ML_RL_S$) and their respective rate constants.




**Scheme 119**

The use of partially resolved ligand has also an impact on the reaction rate of a system presenting NLE[391,393]. It is easily understood that in the case of the reservoir effect, the concentration of the active species is decreased when using enantiomeric impure ligand, therefore decreasing the reaction's rate. In the case of an $ML_n$ system with a positive NLE, the rate of the reaction will also drop with the ligand's enantiopurity to account for the decrease in the concentration of the catalytically active homochiral species and the increase in the catalytically less active achiral species. Conversely in the presence of a negative NLE, the reaction's rate will be increased by the lowering of the ligand optical activity. The kinetic impact of aggregate formations in the case of an $ML_n$ model or a reservoir effect model will be different, permitting to distinguish between the two. However, the precise kinetic measurements to discriminate between the two cases have been very rarely undertaken[391,393-395].

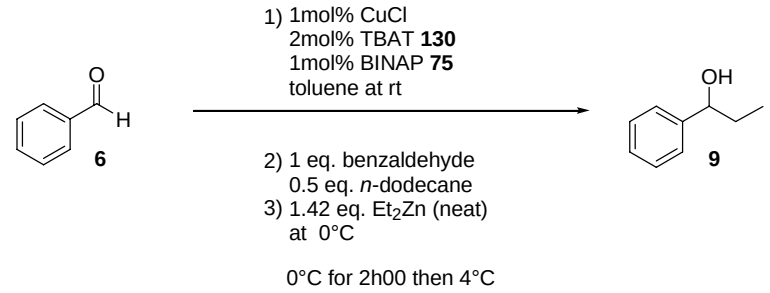
In summary, non-linear effects are due to the formation of diastereomeric species by aggregation or complexation with different chemical reactivities which directly or indirectly affect the asymmetric catalytic cycle. However, the two models

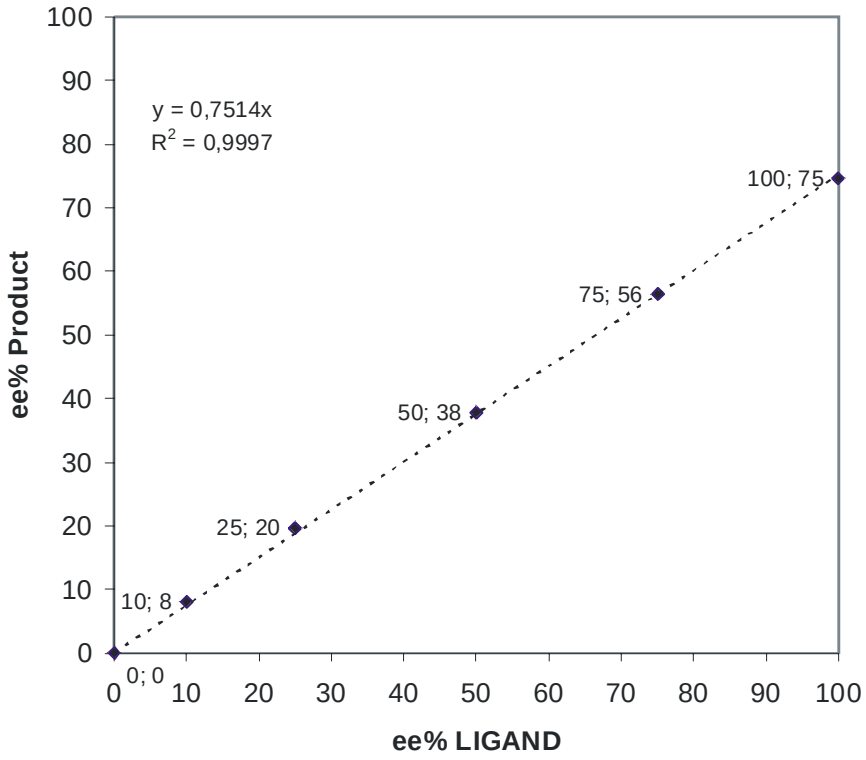
presented are extremes and a combination of the two is not to be excluded leading to complex situations.

## 9.6.2. NLE in Copper Fluoride Catalyzed 1,2-Addition of $Et_2Zn$ to Benzaldehyde

We decided to find out whether our copper fluoride catalyzed additions showed nonlinear effects revealing the presence of diastereomeric aggregates in the catalytic cycle or its periphery. We varied the enantiomeric excess of the BINAP **75** using only 1mol% of catalyst. The plot of the enantiomeric excess of the diphosphine against the enantiomeric excess of addition product **9** yielded a linear relationship. The linear regression among the data points describes a straight line with a slope of 0.7514 (with a coefficient of determination, $r^2$, equal to 0.9997) (Chart 24).

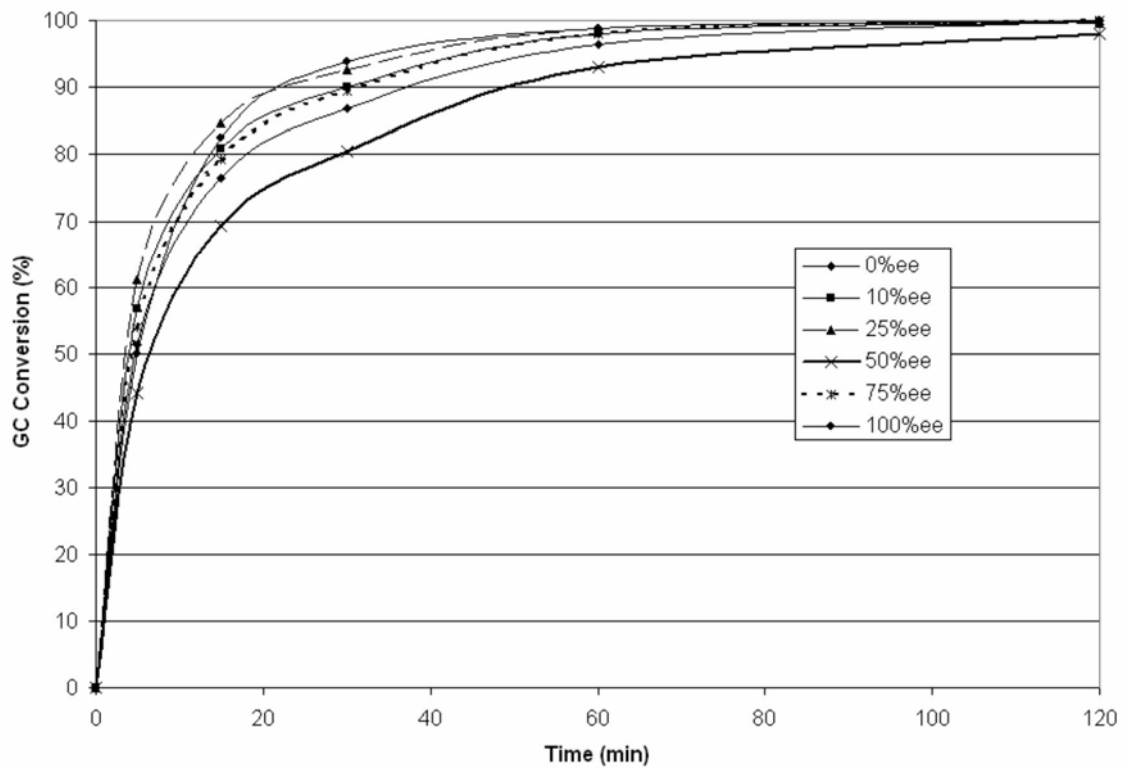
**Chart 24** : Influence of BINAP's optical activity on the enantioselectivity of the "copper-fluoride" catalyzed addition of $Et_2Zn$ to benzaldehyde following **General Procedure N**



The rates of the reaction for different optical purities of the BINAP ligand are qualitatively the same (Chart 25). The conclusion is that there are no diastereomeric aggregates stable enough to influence the catalytic cycle. As a consequence, the active catalyst should bear only one unit of BINAP.

**Chart 25** : Influence of BINAP's optical activity on the rate of addition of $Et_2Zn$ to benzaldehyde catalyzed by the "copper-fluoride" system following **General Procedure N**




# 9.7. NMR Experiments

## 9.7.1. Introduction

Nuclear magnetic resonance is without doubts the "eyes and ears"[396] of the modern synthetic chemist. We followed the reactions involving the copper fluoride catalyst by NMR spectroscopy. Deuterated dichloromethane was used instead of toluene due to the higher solubility of the various organometallic complexes in chlorinated solvents . We also chose to use *p*-tolylBINAP **166** instead of BINAP **75**. Both ligands provide the same reactivity and enantioselectivity in the reactions (see Chart 20) but *p*-tolylBINAP gives additional information in $^1$H NMR. The singlet signal (2.18ppm) corresponding to the methyl protons of the free ligand **166** is split in two singlets (2.16 & 1.86ppm) in the copper chloride complex. This behavior is readily explained by the formation of a seven membered ring upon complexation to copper resulting in different spatial environment of each tolyl groups on a same phosphorus atom. In the uncomplexed ligand, the two tolyl groups can readily exchange at room temperature though a rotation around the P-$C_{naphtyl}$ bond and their methyl $^1$H NMR signal are indistinguishable. We were expecting the shape of these two signals to be sensitive to the nature of the anions that might be present on the copper center (Figure 23).

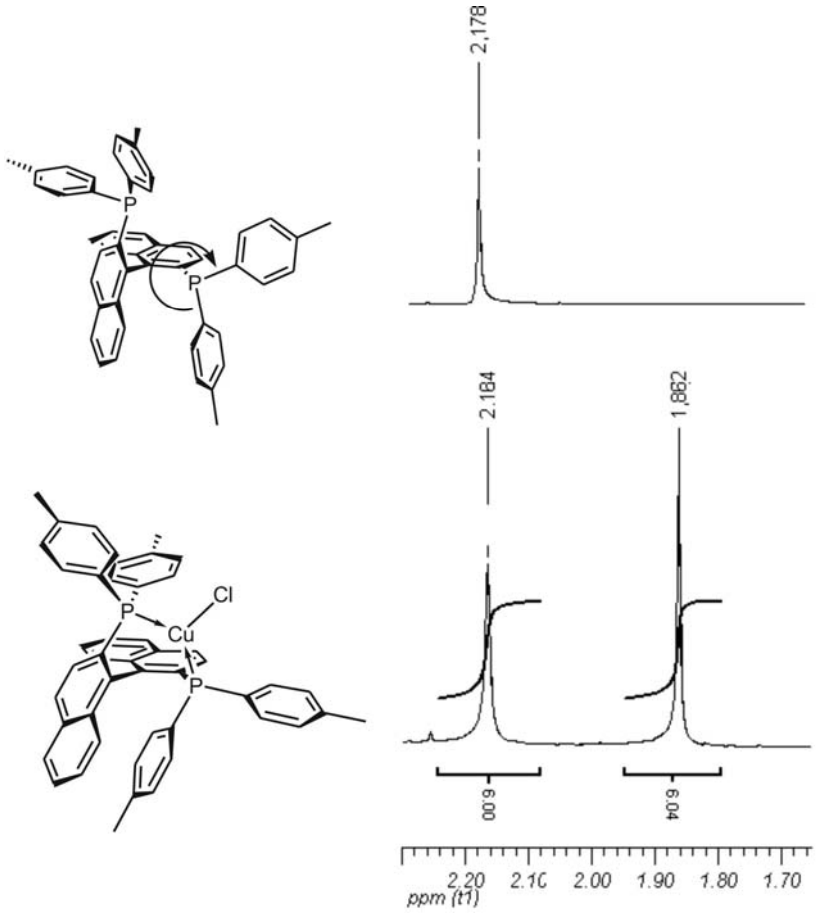
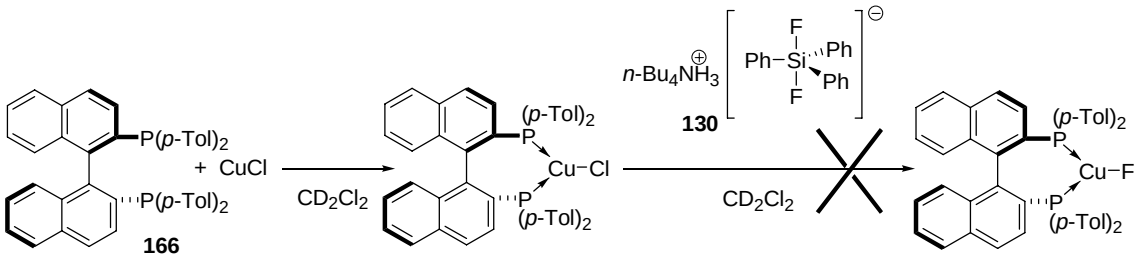



**Figure 23**

## 9.7.2. *In situ* Generation of the Catalyst

Upon the addition of one equivalent of TBAT **130** to (*S*)-*p*-Tol-BINAP**.**CuCl complex, the formation of a copper(I) fluoride species complexed by the diphosphine was expected. Carreira had mentioned that a copper(I) fluoride complex could be prepared *in situ* from [CuOTf**.**$C_6H_6$], (*S*)-*p*-Tol-BINAP and TBAT[307]. Shibasaki *et al.* have used a combination of CuCl, (*S*)-*p*-Tol-BINAP **166** and TBAT **130** to promote the asymmetric allylation of ketones (see **Scheme 71**). In the framework of that reaction, Shibasaki had stated that a new signal (-155.7ppm) could be observed upon mixing CuCl and TBAF **120** in deuterated THF and was attributed to a copper fluoride species by comparison with the signal (-208.7ppm in $CD_2Cl_2$) reported for copper(I) fluoride complex **158**[278]. Nevertheless, we did not observe any change in the $^{1}H$, $^{19}F$ and $^{31}P$ NMR spectra upon mixing CuCl, (*S*)-*p*-Tol-BINAP **166** and TBAT **130** (Figure 24). There is no formation of copper(I) fluoride species! This was also confirmed when KF was used as fluoride source, in which case, no signal due to soluble fluorinated products were observed in the $^{19}F$ spectrum (Scheme 120).


P(p-Tol)2
+ CuCl
P(p-Tol)2
166
CD2Cl2
(p-Tol)2
P
Cu−Cl
P
(p-Tol)2
n-Bu4NH3
130
F
Ph−Si
Ph
Ph
F
CD2Cl2
(p-Tol)2
P
Cu−F
P
(p-Tol)2

**Scheme 120**

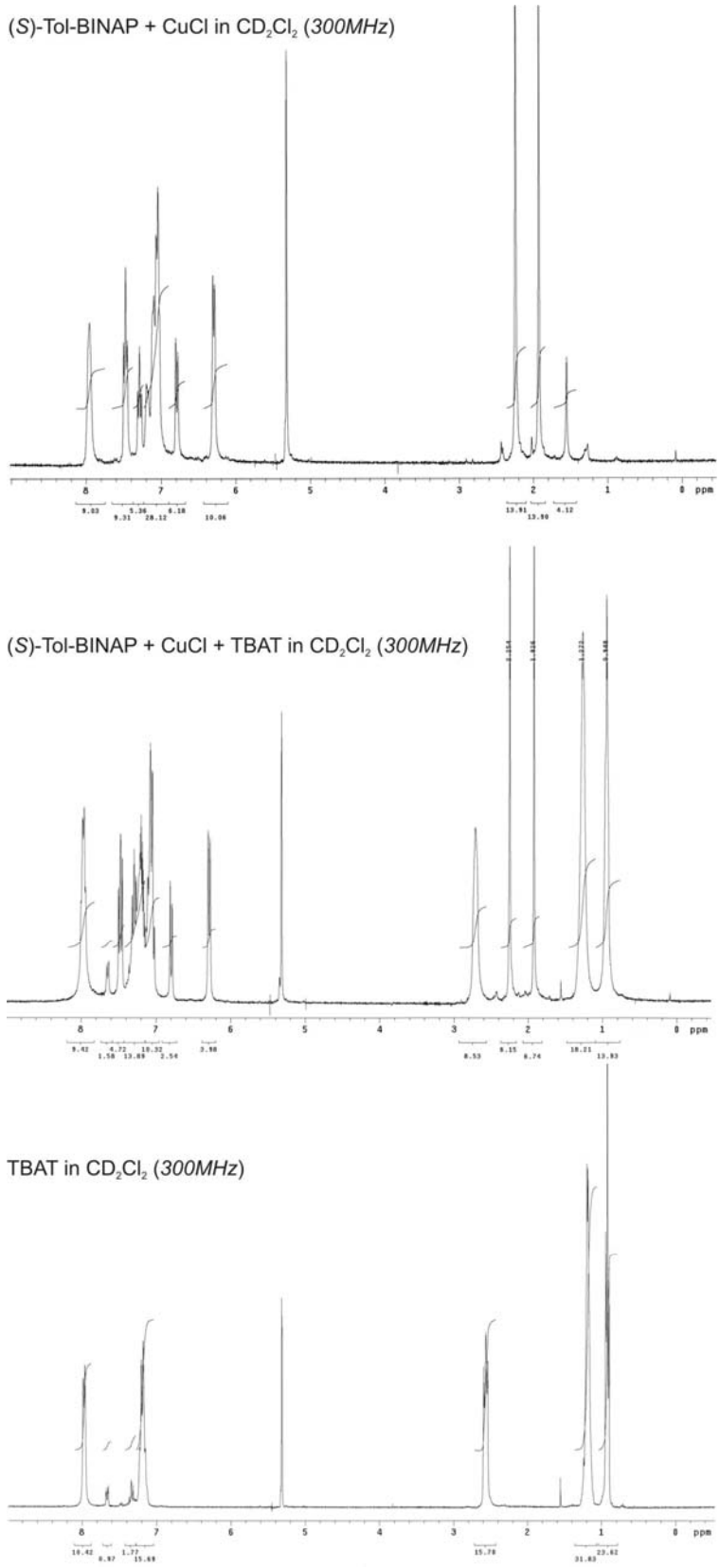
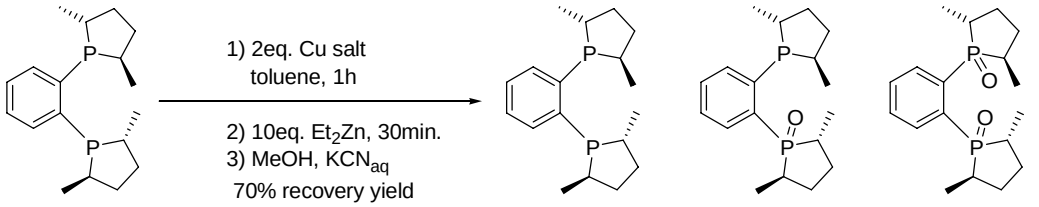
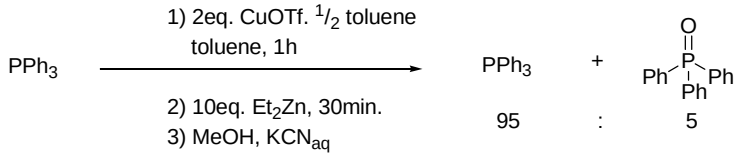

(S)-Tol-BINAP + CuCl in CD2Cl2 (300MHz)
(S)-Tol-BINAP + CuCl + TBAT in CD2Cl2 (300MHz)
TBAT in CD2Cl2 (300MHz)

**Figure 24**

If a copper-fluoride bond was not formed, what was the role of the fluoride anion? Recently, Charette showed that DuPhos **80** in the presence of a copper salt and traces of oxygen could be oxidized to the corresponding monoxide **81** and dioxide **81.**[172] The diphosphine monoxide ligand **81** was shown to be a more effective enantioselective catalyst than the diphosphine **80** in the asymmetric diethylzinc addition to *N*-diphenylphosphinoylimine **41** (see **Scheme 32**). Unlike copper(II) and copper(I) triflates, copper(I) chloride did not lead to any significant phosphorus oxidation. The nature of the phosphine was also important since copper(I) triflate only provided 5% of oxidized triphenylphosphine **81**[170] (Scheme 121).




| | | | | | | |
|---|---|---|---|---|---|---|
| $CuOTf \cdot {}^1/_2$ toluene | 55 | : | 39 | : | 5 |
| CuOAc | 90 | : | 8 | : | 2 |
| CuCl | 96 | : | 3 | : | 1 |
| $Cu(OTf)_2$ | 76 | : | 20 | : | 4 |
| $Cu(OTf)_2 \cdot 2.3H_2O$ | 52 | : | 42 | : | 6 |




**Scheme 121**

Could the diphosphine ligand be oxidized by a combination of copper(I) chloride and a fluoride source[††††] ? The presence of a single peak in the $^{31}P$ NMR spectra of the (*S*)-*p*-Tol-BINAP**.**CuCl complex (-6.5ppm) which remained almost (-6.8ppm) upon addition of fluoride led us to exclude a copper- and/or fluoride-induced oxidation of the phosphorus ligand.

The addition of 1 equivalent of $Et_2Zn$ to the (*S*)-*p*-Tol-BINAP**.**CuCl, TBAT mixture did lead to small changes in the NMR spectra. In the $^1H$ NMR, no peak corresponding to $Et_2Zn$ is observed (triplet at 1.13ppm and quadruplet at 0.26ppm). A singlet, at 0.86ppm, was assigned to the formation of ethane. In the $^{19}F$ NMR spectra, two minor signals appeared at -128 and -170ppm. The second signal was assigned (comparison with an authentic sample) to the formation of

[††††] Verkade has reported a fluoride-catalyzed oxidation of triphenylphosphine coupled to the reduction of a palladium(II) salt in the presence of water[397] McLaughlin, P. A.; Verkade, J. G. *Organometallics* **1998**, *17*, 5937-5940..

$Ph_3SiF$ through loss of a fluoride anion from the pentavalent $[Ph_3SiF_2]^-$ anion (Figure 25 & Figure 26).

The addition of four more equivalents of $Et_2Zn$ led to more profound changes. In the $^1H$ NMR spectrum, the protons of the tetrabutylammonium cation have completely disappeared. Degradation through β-elimination was considered. However, no peaks of the corresponding tributylamine were observed. Yet, the resulting amine could be complexed by metallic species and account for some of the new signals. There were signals in the olefinic region (5.45 & 5.35ppm). Peaks in the olefinic region are present (5.45 & 5.35ppm). Yet, it is unclear if they attest the presence of 1-butene since no signal for the internal olefinic proton is present (expected around 5.8ppm). Another possibility would be formation of ethylene through decomposition of an organometallic species by β-elimination[398-400] (Figure 25).

Unexpectedly, signals assigned to ethylzinc ethoxide were also observed. This resulted from the presence of ethanol in the deuterated dichloromethane. More interestingly, signals that might correspond to ethyl fragments of newly formed organometallic species (triplet at 0.56ppm and quadruplet at -0.45ppm) are present (chemical shifts for $Et_2Zn$ : triplet at 1.15ppm and quadruplet at 0.25ppm), However, the chemical shifts of the two singlets assigned to the protons of the tolyl groups were unchanged by the addition of $Et_2Zn$ as if the (*S*)-*p*-Tol-BINAP copper complex was unmodified (Figure 25).

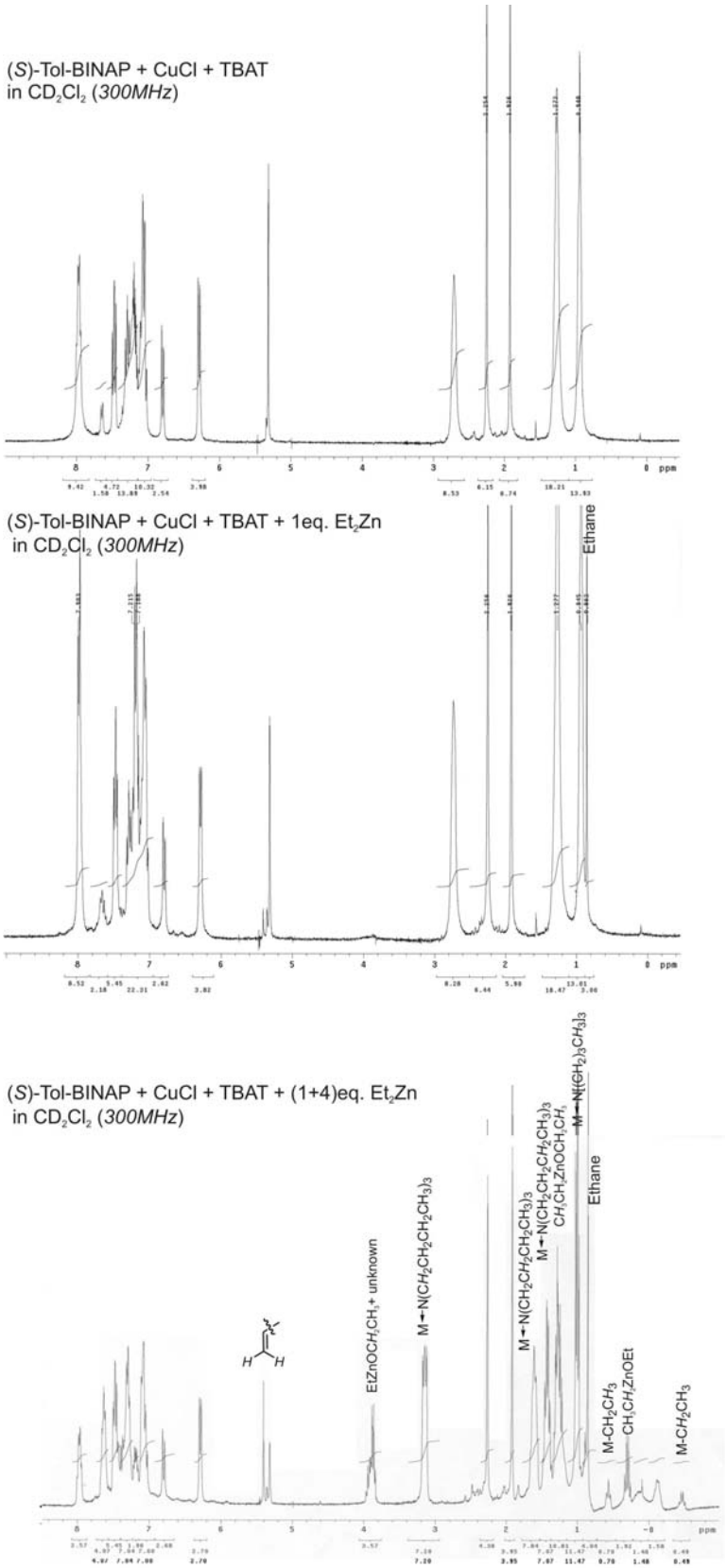

(S)-Tol-BINAP + CuCl + TBAT
in CD2Cl2 (300MHz)
(S)-Tol-BINAP + CuCl + TBAT + 1eq. Et2Zn
in CD2Cl2 (300MHz)
Ethane
(S)-Tol-BINAP + CuCl + TBAT + (1+4)eq. Et2Zn
in CD2Cl2 (300MHz)
EtZnOCH2CH3 + unknown
M-N(CH2CH2CH2CH3)3
M-N(CH2CH2CH2CH3)3
M-N(CH2CH2CH2CH3)3
CH3CH2ZnOCH2CH3
M-N(CH2CH2CH3)3
Ethane
M-CH2CH3
CH3CH2ZnOEt
M-CH2CH3

**Figure 25**

The signal at -95.5ppm in the $^{19}F$ NMR spectrum corresponding to the $[Ph_3SiF_2]^-$ anion completely disappeared after addition of four more equivalents of $Et_2Zn$. The singlet at -170ppm ($Ph_3SiF$) was still present but several yet unassigned signals appeared (-172.5, -176.5, -178, -179 & -181ppm) (Figure 26)[‡‡‡‡].

During the $^1H$ and $^{19}F$ NMR analysis, the sample turned brown. Such a rapid decomposition was not observed in the catalytic runs which let us to believe that the aldehyde must stabilize the catalyst species.

[‡‡‡‡] A sealed capillary containing a reference dissolved in $CD_2Cl_2$ is placed in the NMR tube. Two references were used : $CFCl_3$ (0ppm) or hexafluorobenzene (-163ppm).

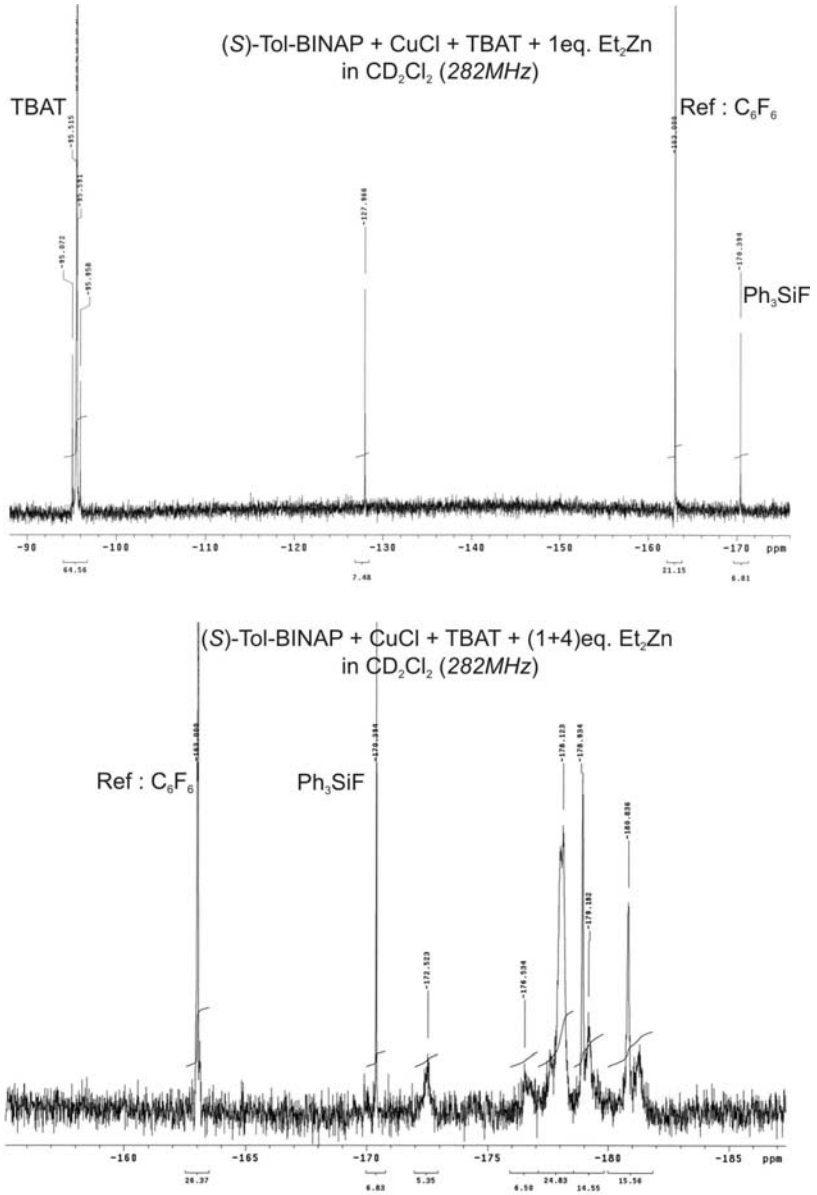
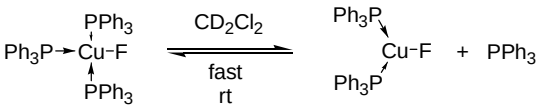


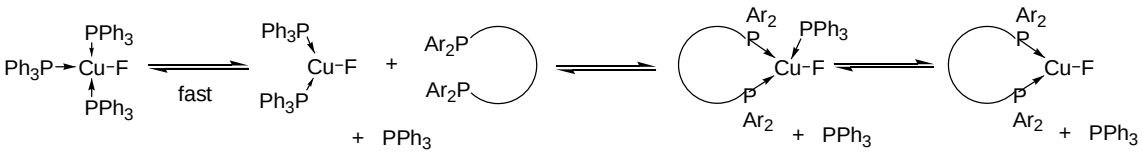

**Figure 26**

## 9.7.3. Copper(I) fluoride Complex 158

The complexation of the preformed copper(I) fluoride complex **158** by one equivalent of (*S*)-*p*-Tol-BINAP **166** was studied. The $^{1}H$ NMR spectra indicated that the entirety of (*S*)-*p*-Tol-BINAP **166** was not bound to the copper metal ($CH_3$ of coordinated ligand : 2.26ppm & 1.76ppm; $CH_3$ of uncoordinated ligand : 2.20ppm) (Figure 27). However, in the $^{19}F$ NMR spectrum and after addition of the chiral bidentate, only one fluoride signal (-209.5ppm) was present with almost unchanged chemical shift compared to the starting copper fluoride complex **158** (-208.7ppm). The $^{31}P$ NMR spectra revealed the presence of uncomplexed (*S*)-*p*-Tol-BINAP (-17.2ppm) and two other peaks (-4.5ppm and 1.4ppm). The signal expected for uncomplexed triphenylphonsphine is not observed (-5.1ppm). The two signals (-4.5ppm and 1.4ppm) are also present in the starting copper(I) fluoride complex

**158**. Gulliver [254] *et al.* proposed that these resulted from a dissociation equilibrium. The broadening of the signals in the $^{1}H$ NMR spectra seem to corroborate such a dynamic behavior (Scheme 122).




**Scheme 122**

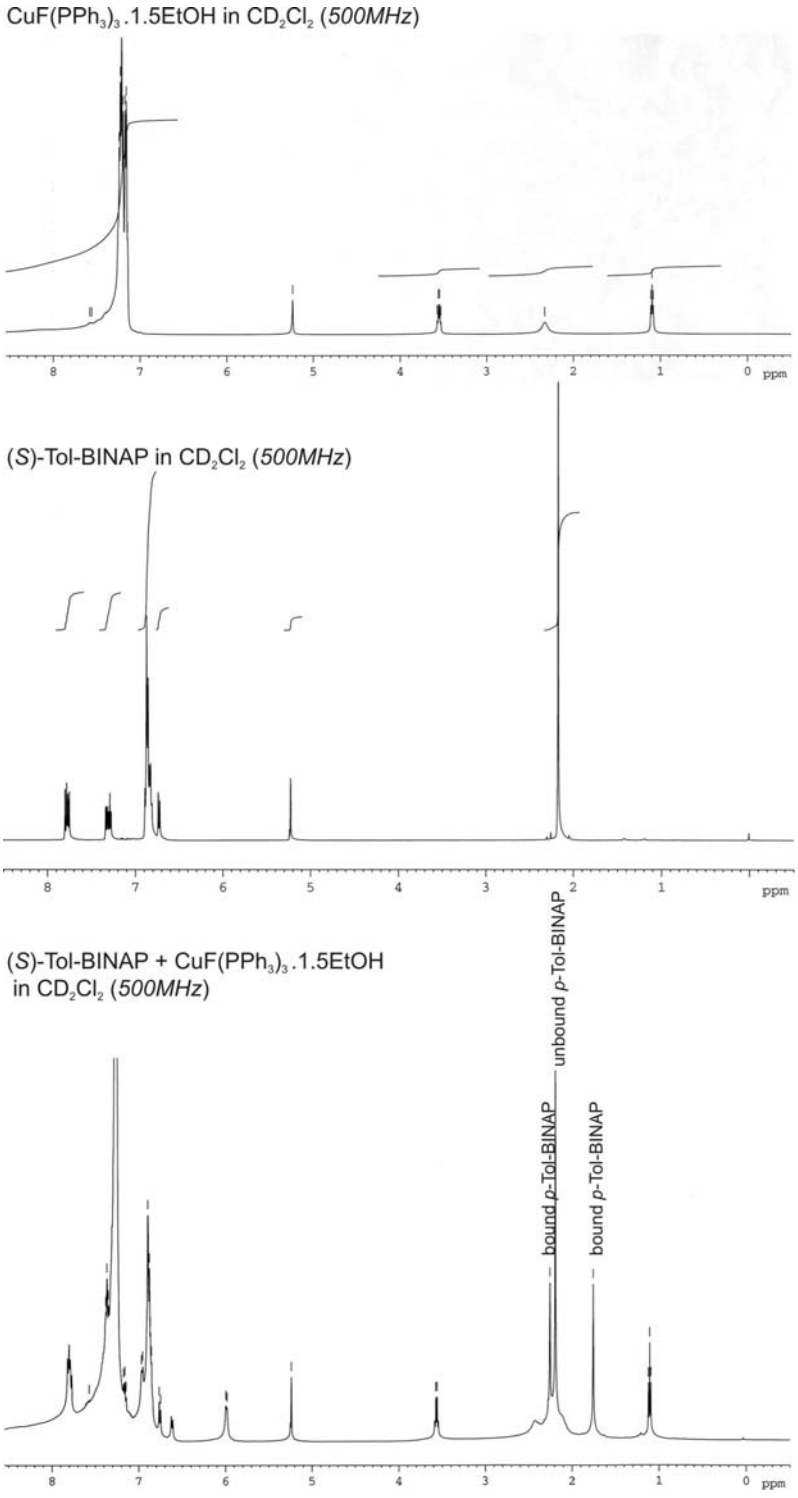



**Figure 27**

After addition of *ca.* 2 equivalents of $Et_2Zn$ on the mixture of copper(I) fluoride **158** and (*S*)-*p*-Tol-BINAP **166**, the $^1H$ NMR spectra showed the disappearance of the signals corresponding to the complexed ethanol and the appearance of new signals that were assigned to ethane (singlet at 0.87ppm) and EtZnOEt (3.89 (q); 1.1-1.4 (2t); 0.32 (q)). The addition of 8 more equivalents of

$Et_2Zn$ led to no change in the $^{1}H$ spectrum. After addition of a total of 10 equivalents of $Et_2Zn$, the $^{19}F$ NMR spectra showed no signal around -209ppm indicating the absence of copper(I) fluoride species. There were no other resolved signals in the spectrum. This probably reflects the degradation of the complexes. Specks of dark brown solid were present in the NMR tube upon retrieval from the spectrometer.

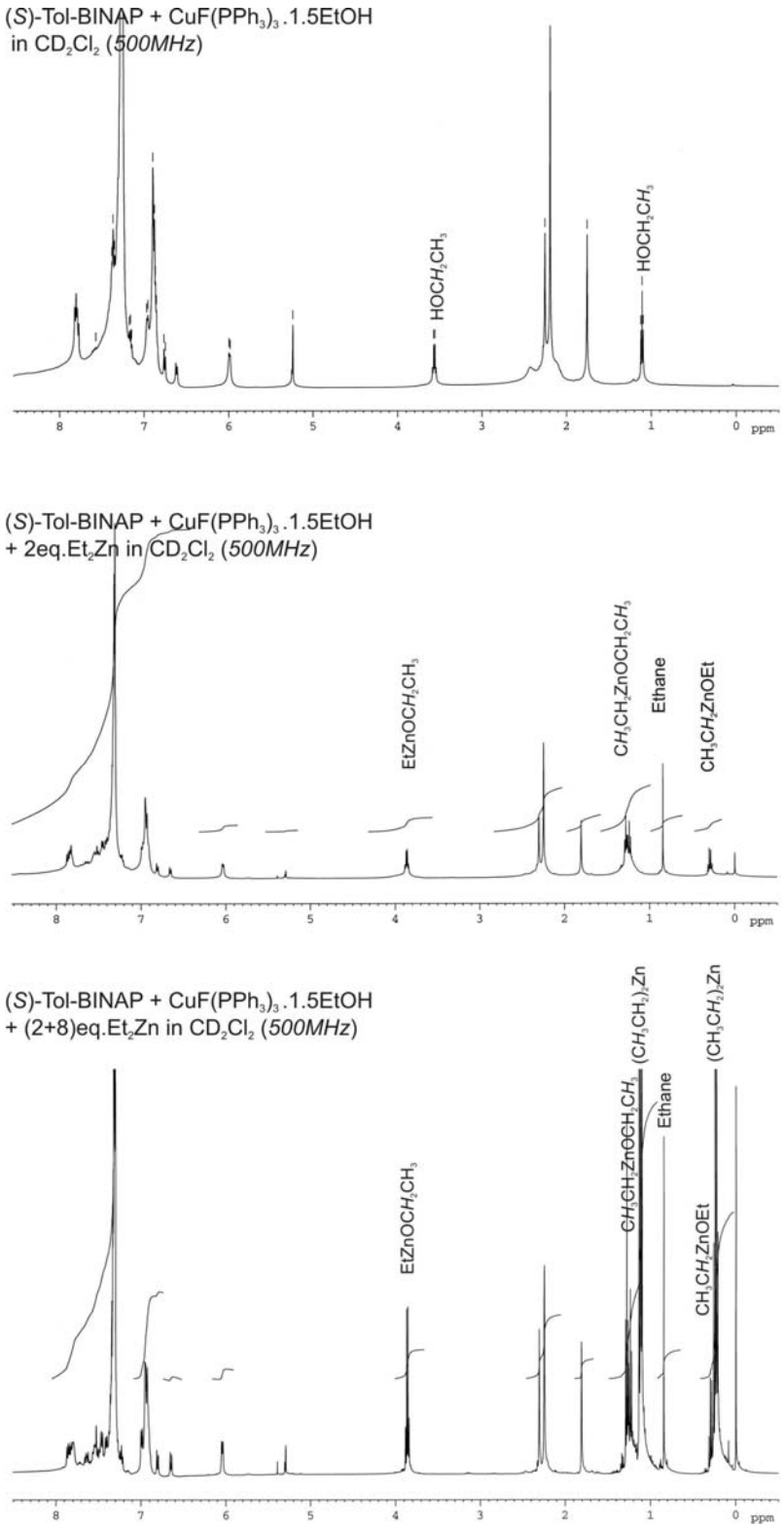

(S)-Tol-BINAP + CuF(PPh3)3.1.5EtOH
in CD2Cl2 (500MHz)
HOCH2CH3
HOCH2CH3
ppm
(S)-Tol-BINAP + CuF(PPh3)3.1.5EtOH
+ 2eq.Et2Zn in CD2Cl2 (500MHz)
EtZnOCH2CH3
CH3CH2ZnOCH2CH3
Ethane
CH3CH2ZnOEt
ppm
(S)-Tol-BINAP + CuF(PPh3)3.1.5EtOH
+ (2+8)eq.Et2Zn in CD2Cl2 (500MHz)
EtZnOCH2CH3
CH3CH2ZnOCH2CH3
(CH3CH2)2Zn
Ethane
CH3CH2ZnOEt
(CH3CH2)2Zn
ppm

**Figure 28**

### 9.7.4. Conclusions

The NMR experiments led to some unexpected observations. First of all, the addition of a fluoride source to copper(I) chloride and a chiral diphosphine did not produce a copper(I) fluoride species as was expected from reports in the literature. The addition of an excess of $Et_2Zn$ to a mixture of CuCl, (*S*)-*p*-Tol-BINAP **166** and TBAT **130** led to the decomposition of the tetrabutylammonium cation and the loss of a fluoride anion by the pentavalent $[Ph_3SiF_2]^-$ anion to form $Ph_3SiF$ and a range of unknown fluorinated species. The appearance of small quantities of an unknown Et-Metal moiety let us believe that an organocopper might be generated, but that it decomposes through β-elimination to generate ethylene.

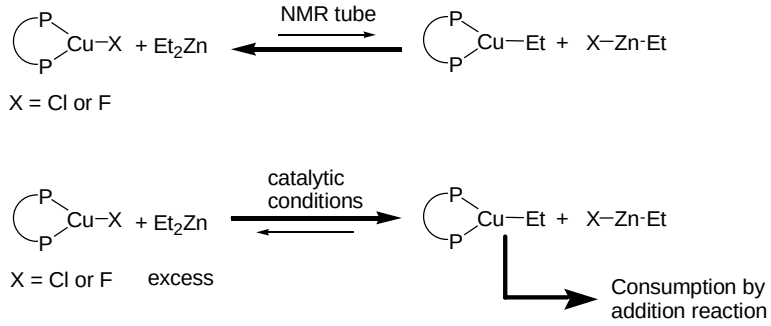
The combination of preformed copper(I) fluoride complex **158** and (*S*)-*p*-Tol-BINAP **166** does not lead to the complete displacement of triphenylphosphine by the bidentate ligand. An equilibrium between at least two species, an achiral copper(I) fluoride complex and a chiral complex, is taking place. Since the copper(I) fluoride complex **158** can catalyze the production of racemic adducts, the presence of several copper species will result in an achiral and a chiral pathways leading to an erosion of the overall enantioselectivity. This could explain the difference in enantiomeric excesses obtained with the pre-formed copper(I) fluoride **158** and the combination of copper(I) chloride and TBAT **130** in the presence of the same chiral ligand (*e. g.*: 45% ee *vs.* 75% ee with (*R*)-BINAP). NMR spectroscopy after addition of $Et_2Zn$ (2+8 equivalents) did only reveal the deprotonation of ethanol included in the starting complex. Decomposition of the sample after the addition of a total of 10 equivalents of $Et_2Zn$ was witnessed during the time of the NMR analysis.

Both "copper fluoride" catalysts, the copper(I) fluoride complex **158** and the copper(I) chloride-TBAT combination, decompose in the presence of an excess of $Et_2Zn$ during the NMR analysis of the samples (around one hour). This is in contradiction with the lack of catalyst's decomposition observed under catalytic conditions during the first 4 to 6 hours. The aldehyde seems to stabilize some catalytic intermediates.

## 9.8. Mechanism Proposals

How do our three mechanisms proposed at the beginning of this chapter (Scheme 111) fare when confronted to the literature data on related systems, the specific reactions performed and NMR spectroscopic data that we collected?

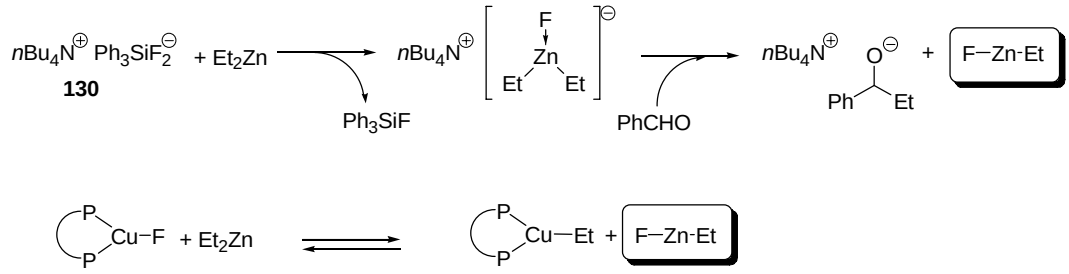
We have seen that a copper(I) chloride in the presence of a diorganozinc is known to produce an organocopper species (Scheme 112). Such a transmetallation reaction is an equilibrium which, in the NMR conditions applied, is certainly not shifted towards the organocopper. Nothing or only traces corresponding to a new M-Et moiety have been observed through $^1H$ NMR (Figure 25 & Figure 28). However, under catalytic conditions, such an equilibrium can be driven by the concomitant consumption of the organocopper and the excess of $Et_2Zn$. The mechanism proposals 1 & 2 can therefore be discarded since they do not involve an organocopper (Scheme 123).




**Scheme 123**

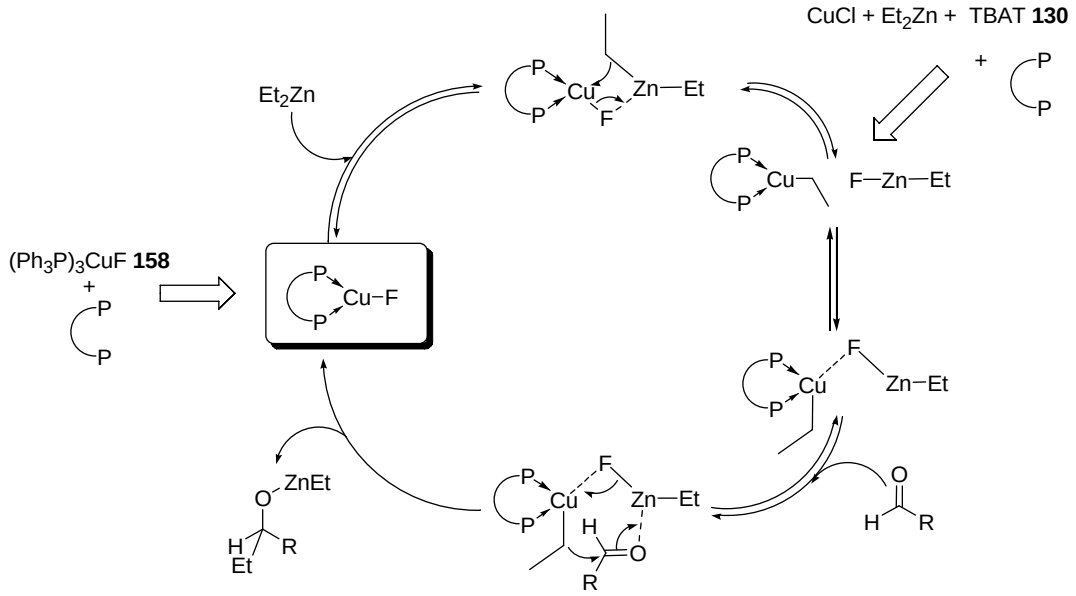
From the literature, it seems that a fluoride counterion is not required for the formation of an organocopper. Whichever copper(I) salt capable of forming an organocopper species in the presence of diorganozinc should be an appropriate precursor to enter the third mechanism proposed (Scheme 111). This is puzzling since we have observed a strong difference in catalytic properties between $(Ph_3P)_3CuCl$ and $(Ph_3P)_3CuF$ **158** (Chart 4, page 103) or "Copper salts-BINAP" and "Copper salts-BINAP-fluoride source" combinations (Chart 13, page 120). We are therefore convinced that in both catalytic systems the fluoride anion is involved throughout the entire catalytic system.

We have been surprised by the absence of formation of a copper(I) fluoride species upon mixing CuCl, TBAT and a diphosphine. Through which pathway does the fluoride anion penetrate the catalytic cycle? The fluoride anion that is added under the form of TBAT **130** or KF enters the catalytic cycle by first forming an organozincate ($[Ph_3SiF_2]^-$ decomposes upon addition of $Et_2Zn$, see Figure 26). We have shown early on that the resulting species, probably a zincate, is nucleophilic enough for the ethyl fragment to add on the aldehyde (Table 9, page 64). This should lead to a racemic alkoxide and ethylzinc fluoride. This last compound should also result from the transmetallation of a preformed copper(I) fluoride complex (Scheme 124).




**Scheme 124**

Inspired by the mechanism proposed by Noyori for the Michael addition of $Et_2Zn$ to enone catalyzed by copper salts and sulfonamide **111**, we propose that ethylzinc fluoride interacts with a chiral organocopper moiety to form an ambifunctional bimetallic active species. Coordination of the benzaldehyde on the zinc of the bimetallic species should result in the addition reaction through a six-membered ring transition state. A zinc alkoxide is produced and a copper-fluoride species is regenerated (Scheme 125).




**Scheme 125**

The large difference in reaction rate observed between a copper(I) chloride system or a "copper fluoride" catalyst would result from an acceleration of the transmetallation step by the formation of an ate complex between the fluoride counterion and the dialkylzinc compound. This mechanism not only works for the preformed copper fluoride complex **158** but it also allows access to the catalytic cycle from a combination of copper(I) chloride, diphosphine, TBAT **130** and $Et_2Zn$.

# Chapter 10

# Catalysis by Copper Diketonate Complexes

## 10.1. Introduction

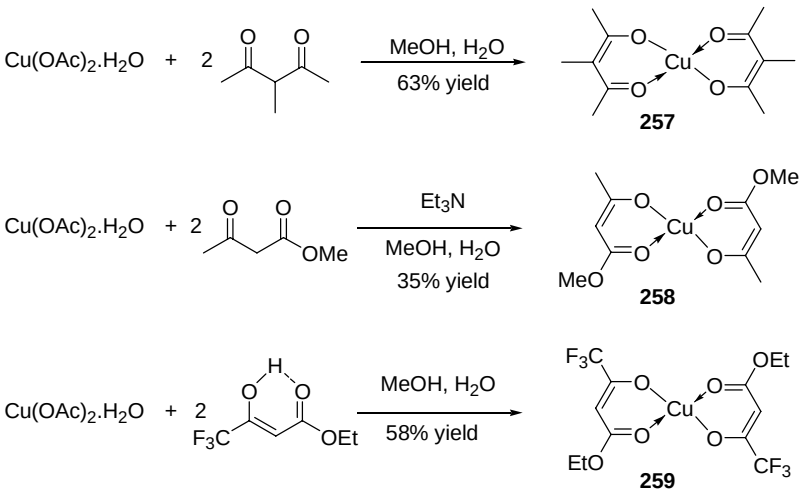
In the preceding chapter, we have discussed the probable role of the fluoride anion in the chain of catalytic events of the addition of diethylzinc to aldehydes in the presence of copper and a chiral diphosphine. It appeared to us that the fluoride anion was involved throughout the catalytic cycle and not just in the preparation of the active species. Alexakis *et al.* improved the enantioselectivity of Michael addition of dialkylzinc based on the choice of the copper source (Table 22)[380]. This further convinced us of the importance of the copper's counterion in our reaction.

We decided to test a range of copper salts, mostly complexed to oxygenated anions such as carboxylate or diketonate. As for the oxidation state of copper, both copper(I) and copper(II) species are available, but copper(II) species were privileged since they are easier to handle, synthesize and cheaper if commercially available. Moreover, it is known that dialkylzinc compounds reduce *in situ* any copper(II) to the catalytic active copper(I) species[401,380,148].

## 10.2. Achiral Copper Complexes

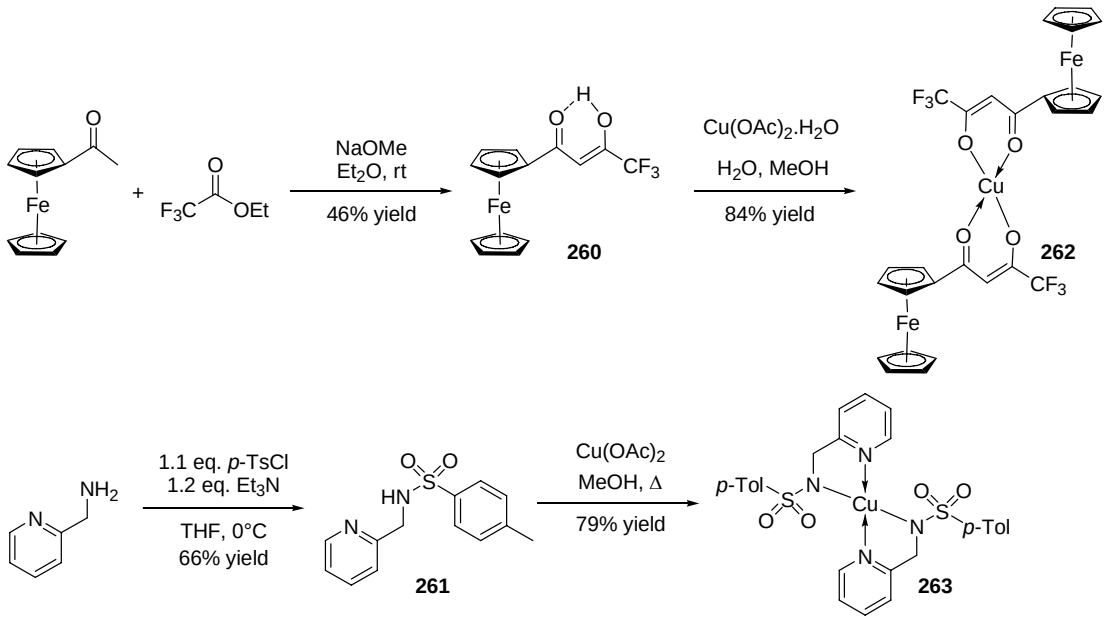
### 10.2.1. Access to Copper Complexes

A few copper(II) carboxylates and diketonates are commercially-available. However, the generation of such copper(II) diketonate complexes and analogs is extraordinarily simple and relies on a ligand exchange driven by precipitation of the product. Thus, deprotonation of 1,3-diketones and 1,3-ketoesters by the acetate anion of the commercially available copper(II) acetate or by an additional base yielded a variety of copper(II) complexes (Scheme 126).



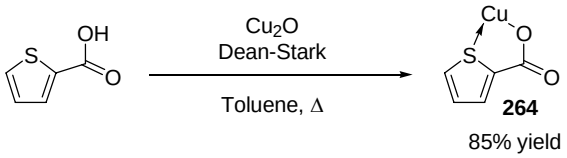

**Scheme 126**

Some ligands were commercially available. Others, **260**[402] and **261**[403], were prepared by known methods and then complexed to copper(II)(Scheme 127).




**Scheme 127**

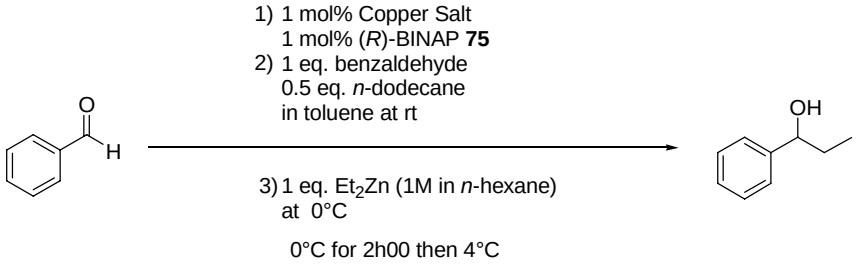
Copper(I) 2-thiophenecarboxylate **264** was obtained by reacting 2-thiophenecarboxylic acid with copper(I) oxide under Dean-Stark conditions as described by Liebeskind[404] (Scheme 128). We are grateful to Prof. O. Riant for samples of complexes **265** and **266**.




**Scheme 128**

## 10.2.2. Screening of Achiral Copper Complexes

The copper complexes were assessed in the model reaction of diethylzinc with benzaldehyde with (*R*)-BINAP **75** as chiral source (see General Procedure P).




**Scheme 129**

Copper(II) sulfate was even less active than copper(II) triflate. Copper(II) acetate monohydrate and copper(I) 2-thiophenecarboxylate **264** were quite efficient but gave moderate enantioselectivities. The replacement of an acetate ligand by a more electronegative ligand such as trifluoroacetate led to a decrease in reactivity and enantioselectivity. (Chart 26)

With the symmetric copper(II) *bis*(acetylacetonate) complex **267**, $Cu(acac)_2$, the conversion was almost quantitative with only one equivalent of $Et_2Zn$ and the reaction proceeded with high facial discrimination. Again, the substitution of the methyl groups by trifluoromethyl groups in the copper(II) *bis*(hexafluoroacetylacetonate) monohydrate **268**, $Cu(hfacac)_2.H_2O$, resulted in a substantial decrease of the reaction rate but had no effect on the facial selectivity. However the replacement of a single methyl substituent by a trifluoromethyl group as in copper(II) *bis*(trifluoroacetylacetonate) **269**, $Cu(tfacac)_2$, did not significantly decrease the reaction rates and even slightly improved the facial selectivities (Chart 26).

Complex **257** incorporating a 3-methyl acetylacetonate ligand led to lower conversion and enantioselectivity (77% ee) as compared to the acetylacetonate complex **267**. The presence of bulkier *t*-butyl substituents as in complex **265** did not improve the enantioselectivity of the reaction. The electronically and sterically non-symmetrical copper(II)$(fod)_2$ **270** essentially gave the same ee than $Cu(tfacac)_2$ **269**. In contrast, the ferrocene-derived diketonate copper complex **262** gave the adduct with lower conversion and slightly lower ee as compared to the simpler trifluoroacetylacetonate complex **269** (**Chart 27**).

Copper complexes of 1,3-ketoesters were also tested and provided high conversion levels comparable to those of the diketonate complexes. Higher levels of

enantioselectivity were obtained with the trifluoromethyl ketoester complex **259** as compared to the methyl-substituted complex **258**.

Two copper complexes with *N,O*- and *N,N*-ligands were also tested. Both sulfonamidopyridine complex **263** and hemisalen complex **266** led to reasonable conversions but enantiomeric excesses in the low seventies.

**Chart 26**: Screening of achiral copper salts in the presence of (*R*)-BINAP for the $Et_2Zn$ addition on benzaldehyde after 2 hours following **General Procedure P**

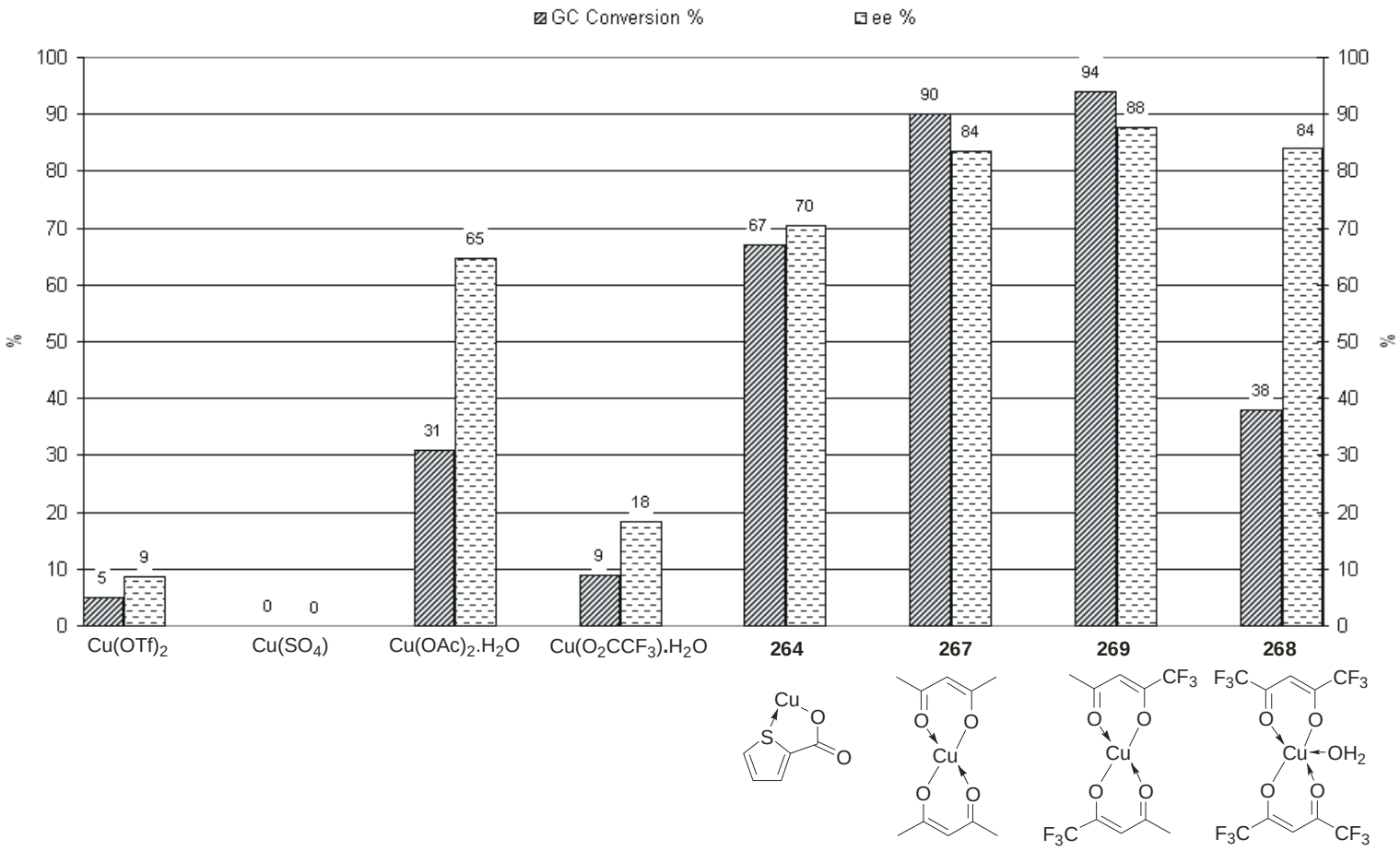
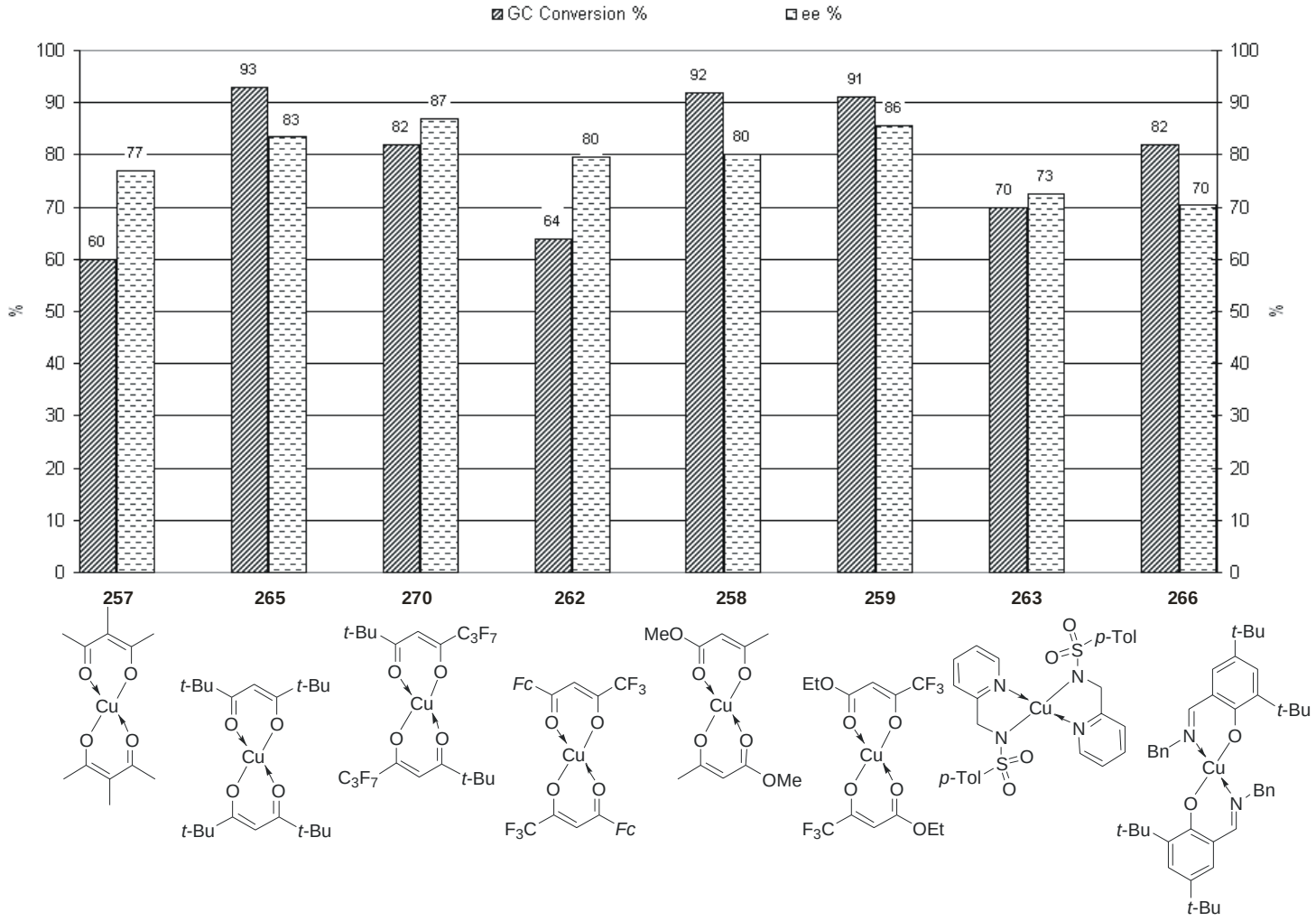


**Chart 27** : Screening of achiral copper salts in the presence of (*R*)-BINAP for the $Et_2Zn$ addition on benzaldehyde after 2 hours following **General Procedure P**



This screening revealed very promising results: copper(II) complexes bearing non-symmetrical chelates such as $Cu(tfacac)_2$ **269**, $Cu(fod)_2$ **270** and copper(II)trifluoromethylketoester **259** gave high conversions (82 to 94%) and enantioselectivities (~87% ee) with only one equivalent of diethylzinc. The facial selectivities are still less satisfactory than those obtained with some 1,2-amino alcohols and related ligands[38,22]. Instead of screening a range of chiral diphosphine ligands as we had done rather unsuccessfully for the copper-fluoride complexes, we considered the introduction of a second source of chiral information by using chiral copper(II) diketonates in addition to the chiral diphosphine.

# 10.3. Chiral Copper Complexes

## 10.3.1. Introduction

In 1970, chiral camphor-based diketonates europium(III) complex **271** were introduced by Whitesides as chiral shift reagents for the determination of enantiomeric compositions by NMR spectroscopy[405,406]. Goering[407,408] and Fraser[409] improved the chiral recognition of a larger range of substrates by using europium(III) diketonates **272** and **273**.

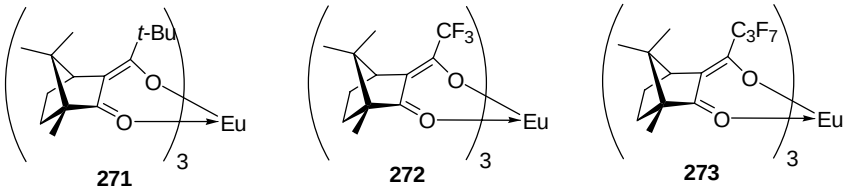
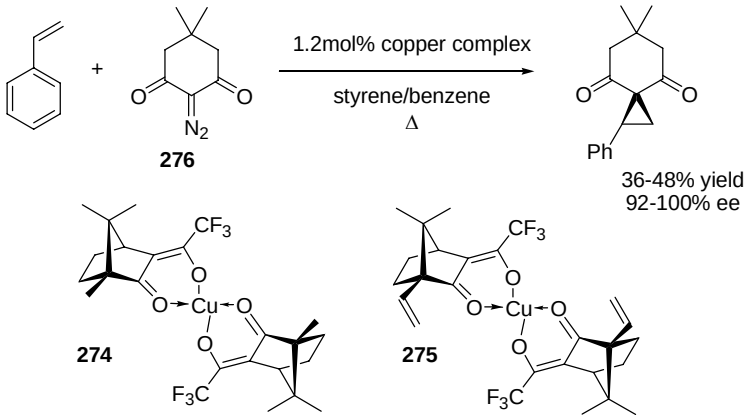



**Figure 29**

The copper complexes of camphor-based diketonate have been used as catalysts for the asymmetric cyclopropanation of olefins with diazo compounds[410-412]. Excellent facial discriminations were obtained with copper(II) *bis*(3-trifluoroacetyl-(+)-camphor) **274** and copper(II)*bis*(10-methylene-3-trifluoroacetyl-(+)-camphor) **275** as catalysts for the cyclopropanation of styrene by diazo compound **276** (Scheme 130).

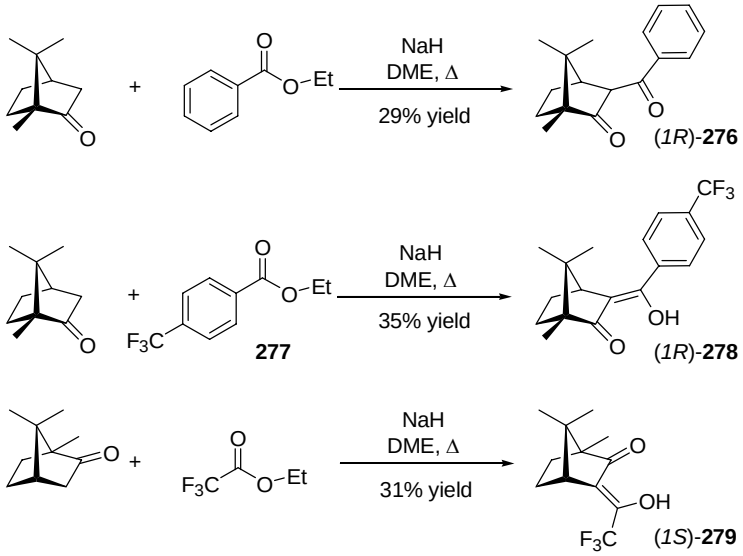



**Scheme 130**

We thus considered appropriate to use camphor-based diketonate ligands as additional sources of chirality in our copper catalysts.

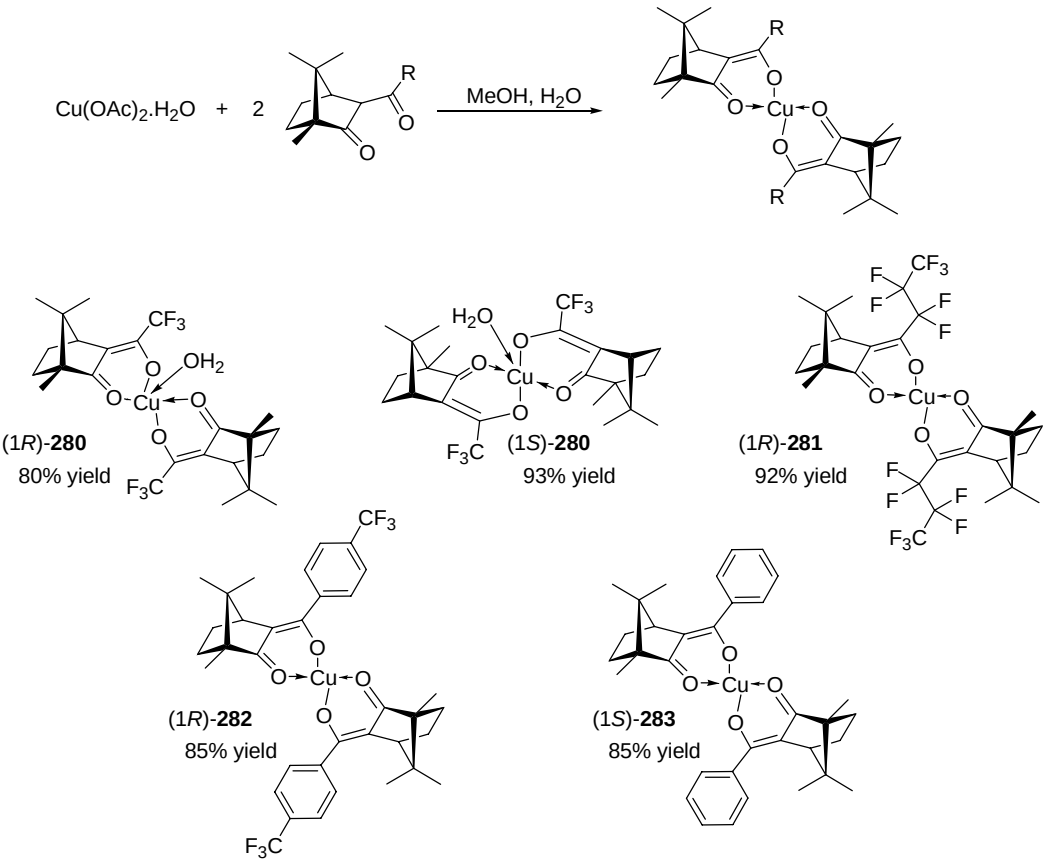
## 10.3.2. Synthesis of chiral diketones and their copper complexes

A few chiral camphor-based diketones were commercially available. The synthesis of additional diketones was carried out by deprotonation of camphor with sodium hydride followed by condensation with an appropriate ester following described procedures[413-415]. Both enantiomers of camphor are naturally-occurring and commercially available. The (*1S*)-**279** enantiomer derived from the less common (-)-camphor was also synthesized.



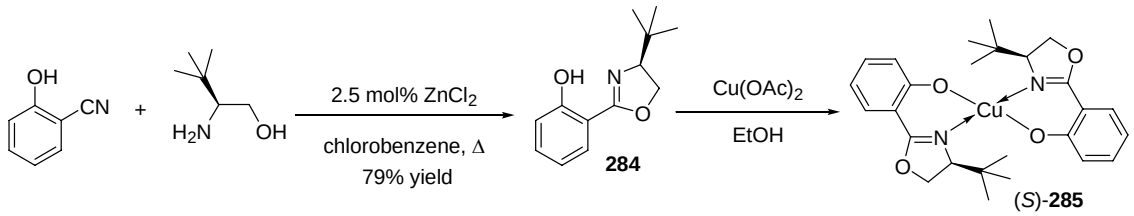

**Scheme 131**

The copper(II) complexes of these ligands were obtained in good to excellent yield by mixing the ligands with copper(II) acetate monohydrate. Most complexes were obtained under their anhydrous form after drying at *ca.* 90°C under vacuum in an horizontal distillation apparatus. However, the trifluoroacetylcamphor complexes **280** were obtained as monohydrates. The previous brief descriptions of this complex only mentioned it under its anhydrous form[416,417,410,412,411]. In our hands, heating the bright green powder obtained after complexation at *ca.* 90°C under vacuum led to a dark green powder. When left in the air, this powder recovered its bright green color apparently capturing atmospheric moisture. Complexes **280** were used as such.




**Scheme 132**

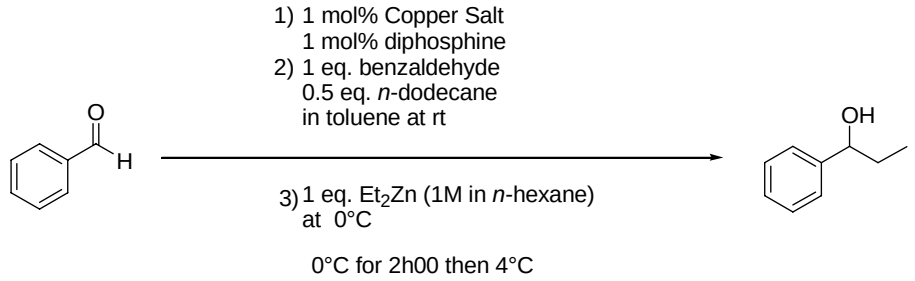
We also synthesized the (*S*)-enantiomer of **284** which forms a copper complex **285** already used by Bolm for catalytic enantioselective Baeyer-Villiger type reactions[418-420] (Scheme 133).




**Scheme 133**

## 10.3.3. Screening of chiral copper complexes

These chiral copper(II) complexes were then tested for the catalyzed addition of diethylzinc on benzaldehyde (Scheme 134, General Procedure P)




**Scheme 134**

In the presence of 1 mol% of copper(II) *bis*[(1*R*)-3-trifluoroacetyl-(+)-camphor] monohydrate **280** and in the absence of any diphosphine, the addition of diethylzinc to benzaldehyde did not take place and catalyst degradation was observed. However, upon addition of 1 mol% of (*R*)-BINAP, the adduct was obtained with a high conversion level and an improved enantioselectivity (91% ee *vs* 88% ee for the achiral copper(II) *bis*(trifluoroacetylacetate) (see Chart 26). The possibility for matched and mismatched combinations was explored. With (*S*)-BINAP, the addition product of opposite configuration was formed with a lower conversion and with a lower ee. In the presence of an achiral diphosphine such as dppf **171**, a small asymmetric induction was observed showing that the phosphine ligand is the main player in the stereofacial differentiation. We also tested the two enantiomers of copper(II) *bis*(trifluoroacetylcamphor] **280** in the presence of (*S*)-*p*-TolBINAP **166.** Results were almost identical to those obtained with BINAP **75** (Chart 28).

The other camphor-based copper complexes were also tested in the presence of each enantiomer of BINAP **75**. Copper(II) *bis*[(1*R*)-heptafluorobutyryl-(+)-camphor] **281** provided essentially the same results than **280**. Benzoylcamphor complexes (1*R*)-**283** and (1*R*)-**282** also combined favorably with the (*R*)-BINAP enantiomer although providing lower enantioselectivities than with the trifluoroacetyl (1*R*)-**280** copper complex. However, the differences in enantioselective catalysis between the matched and mismatched chiral inductors are less marked for the benzoylated derivatives (1*R*)-**283** and (1*R*)-**282** in combination with BINAP.

The *bis*oxazolinephenol copper complex (*S*)-**285** did provide the adduct with 66% ee to 68% ee with either enantiomer of BINAP. Achiral dppf only provided 2% ee and no clear match-mismatch pairing, from the point of view of enantioselectivity or reactivity, was observed with either enantiomer of BINAP. Also, the results of the chiral *bis*oxazolinephenol copper complex (*S*)-**285** with chiral BINAP are similar to the ones obtained with the achiral salicyldimine copper complex **266** (compare entries in Chart 27 and Chart 29). It therefore seems, that in the case of chiral complex (*S*)-**285**, the induction of chirality is solely provided by the diphosphine.

**Chart 28** : Screening of chiral copper salts in the presence of diphosphines for the $Et_2Zn$ addition on benzaldehyde after 2 hours following **General Procedure P**

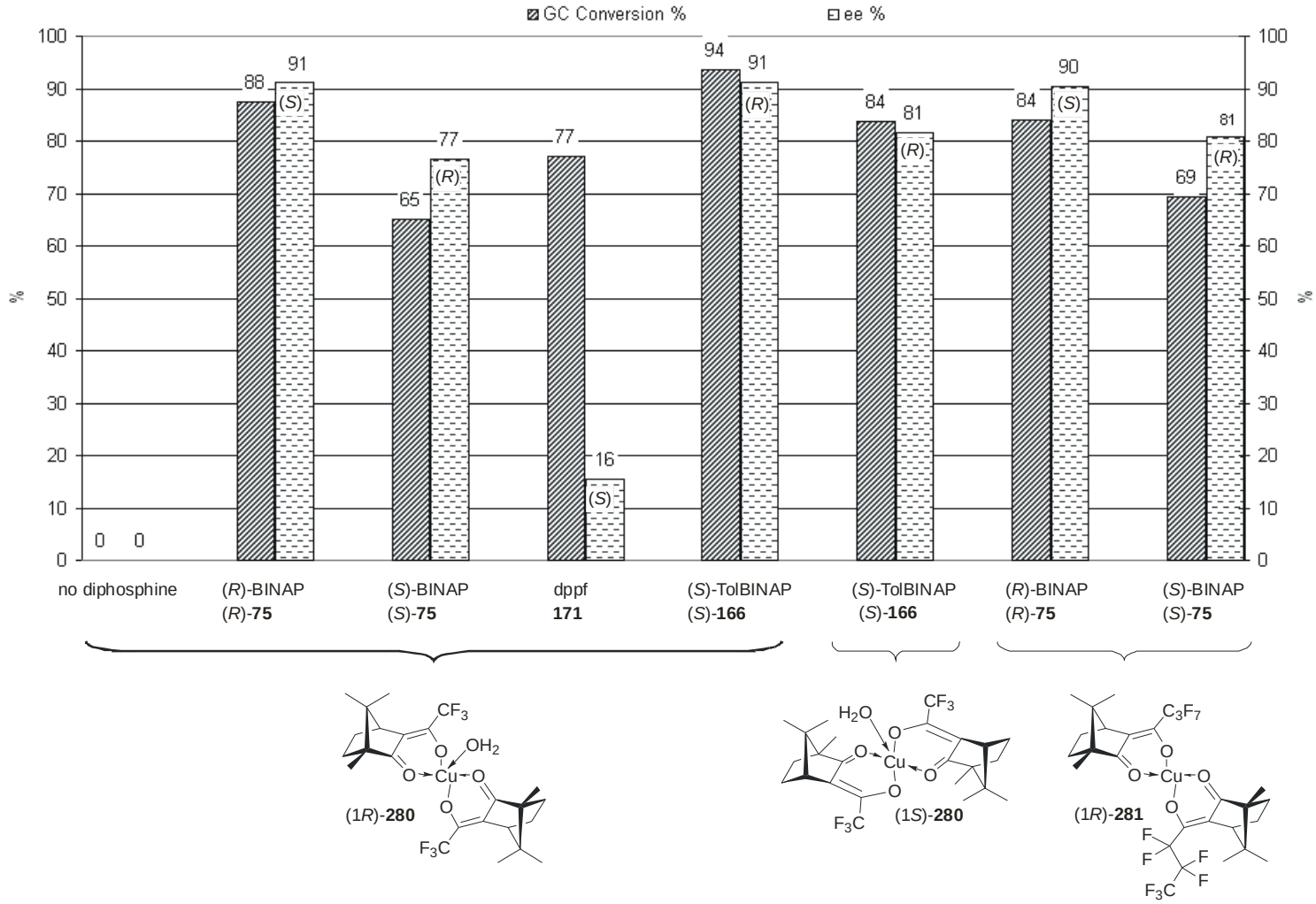
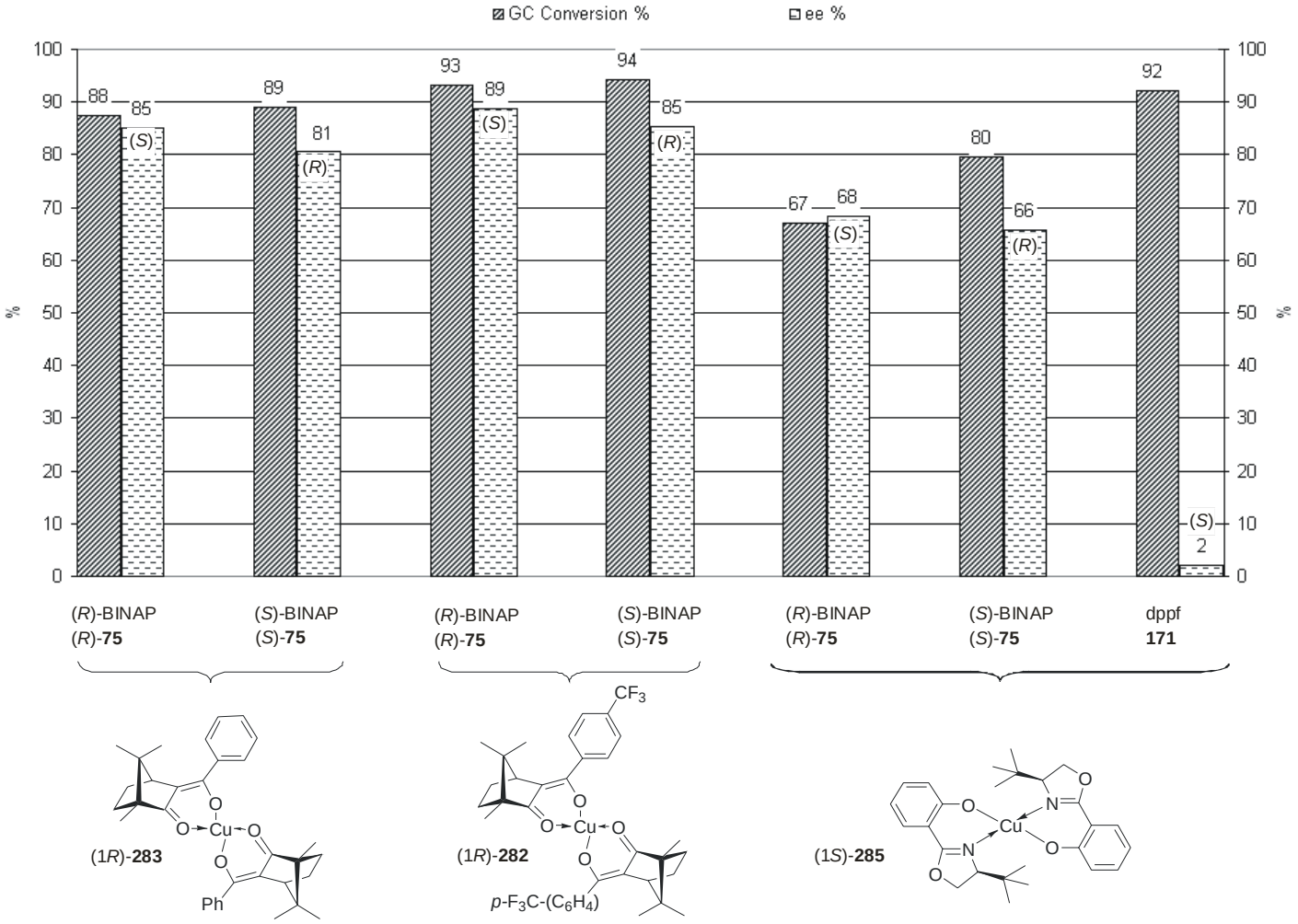


**Chart 29 :** Screening of chiral copper salts in the presence of diphosphines for the $Et_2Zn$ addition on benzaldehyde after 2 hours following **General Procedure P**

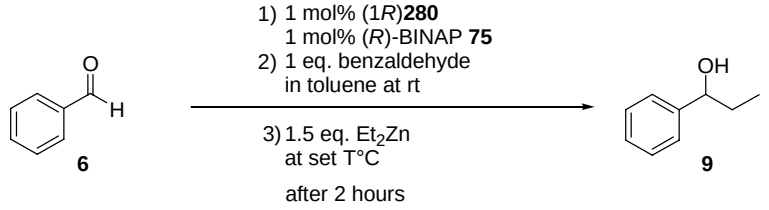


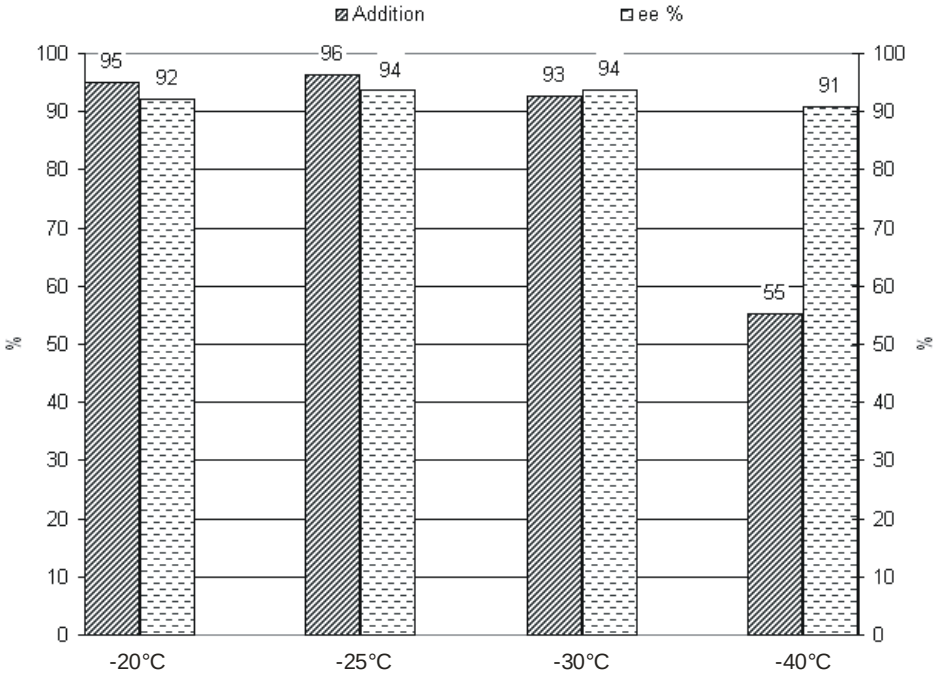
## 10.3.4. Generalization

The combination of copper(II) *bis*[(1*R*)-trifluoroacetyl-(+)-camphor] **280** and (*R*)-BINAP **75** was deemed sufficiently effective to be tested over a range of substrates.

Our goal was to maximize the yields in optically active products in a reasonable reaction time. The influence of the temperature was quickly assessed by chiral gas chromatography. By decreasing the reaction's temperature to -30°C and using 1.5 eq. of nucleophile, the addition product could be obtained with 94% ee while still maintaining almost complete conversion after 2 hours.

**Chart 30** : Influence of the temperature on the conversion level after 2 hours of the addition of $Et_2Zn$ on benzaldehyde in the presence of 1mol% of (1*R*)-**280** and 1mol% of (*R*)-BINAP (see General Procedure Q at 4.1mmol scale)

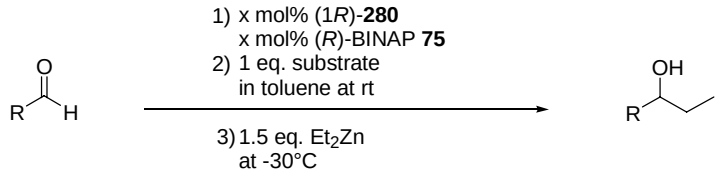



The impact of the loading of the catalyst's precursors was investigated at -30°C (Table 25, entries 1-4). The reaction proceeded to completion with loadings as low as 0.5mol% when 1.5 eq. of diethylzinc was used. And it could even be lowered to 0.1mol% by using 2 eq. of diethylzinc. In these conditions, a simple extraction without any further purification led to the pure ($^1$H NMR and GC) addition compound **9** with quantitative yield. However, lowering the catalyst's loading lengthened the reaction time and led to some erosion of the enantioselectivity. A

loading of 0.5mol% seemed a good compromise and was applied to a range of aldehydes.

**Table 25** : $Et_2Zn$ addition to various aldehydes catalyzed by copper(II) *bis*[(1*R*)-trifluoroacetyl-(+)-camphor] **280** and (*R*)-BINAP under conditions from General Procedure Q




| Entry | R | loading | time[a] | Yield[b] | ee[c] (*config.*)[d] |
|---|---|---|---|---|---|
| 1 | Ph | 2mol% | 2h | 83% | 94% (*S*) |
| 2 | Ph | 1mol% | 4h | 88% | 95% (*S*) |
| 3 | Ph | 0.5mol% | 12h | 91% | 93% (*S*) |
| 4[e] | Ph | 0.1mol% | 48h | 99%[f] | 90% (*S*) |
| 5 | *p*-$ClC_6H_4$ | 0.5mol% | 19h | 87% | 95% (*S*) |
| 6 | *p*-$MeOC_6H_4$ | 0.5mol% | 24h | 68% | 95% (*S*) |
| 7 | *o*-$MeOC_6H_4$ | 0.5mol% | 19h | 81% | 93% (*S*) |
| 8 | 1-naphtyl | 0.5mol% | 24h | 75% | 87%[g] (*S*) |
| 9 | 2-furyl | 0.5mol% | 24h | 48% | 73%[g] (*S*) |
| 10[e] | 4-pyridyl | 0.5mol% | 24h | 43% | 77% (*S*) |
| 11 | $PhCH_2CH_2$ | 0.5mol% | 48h | 69% | 24% |
| 12 | *c*-$C_6H_{11}$ | 0.5mol% | 48h | 44% | 12%[h] |

[a] reactions followed by GC until complete conversion or until no more noticeable evolution, [b] isolated yields, [c] ee measured on crude, [d] based on the order of elution and comparison to samples of known configuration, [e] 2 eq. $Et_2Zn$, [f] yield after a simple extraction of GC and $^1H$ NMR analytically pure adduct, [g] ee on purified compound, [h] ee of benzoylated product

The reaction was quite general for aromatic aldehydes; yields were moderate to excellent and enantiomeric excesses ranged between 73% and 95% with the same absolute configuration (Table 25, entries 1-10). Mono-substitution in *ortho* or *para* position of the aryl has little influence on the yields or the enantioselectivities (entries 5-8). Heterocyclic aldehydes, 2-furyl- and 4-pyridyl-carboxaldehydes, underwent asymmetric addition both with 73% ee and 77% ee respectively (entries 9 & 10). In the case of alkyl aldehydes, the addition products were obtained in moderate to good yields but with poor enantioselectivities (entries 11-12).

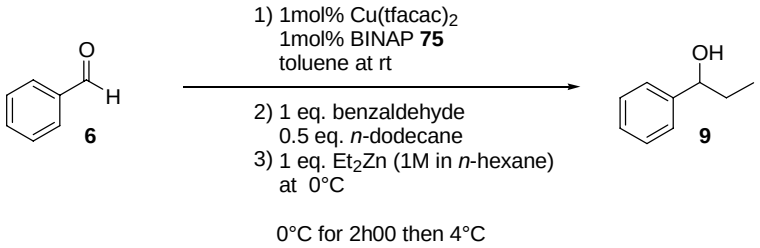
# 10.4. Mechanistic Proposal

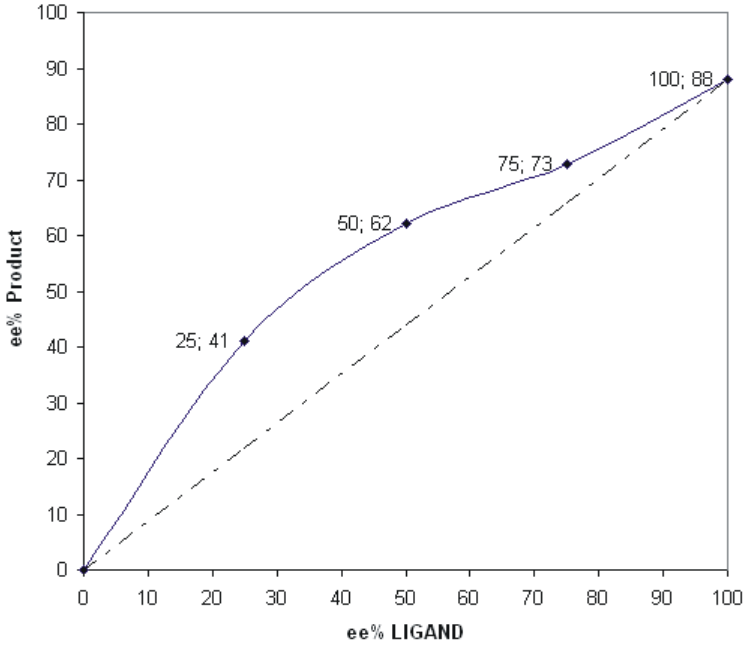
## 10.4.1. Non-Linear Effects

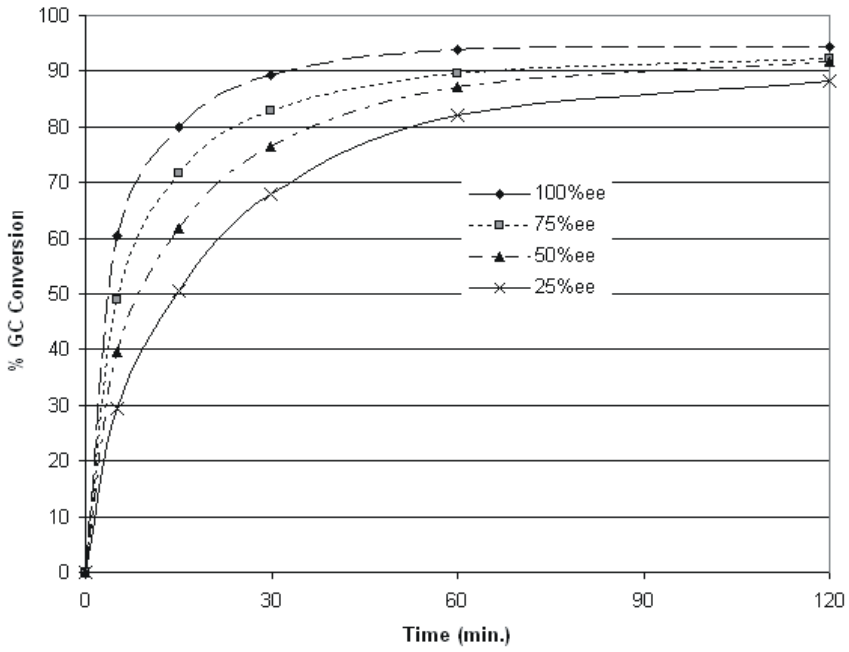
An investigation of the occurrence of non-linear effect in the reaction catalyzed by copper(II) diketonate was carried out. We decided to study the impact of scalemic BINAP **75** in the presence of achiral $Cu(tfacac)_2$ **269**. The plot of the enantiomeric excess of the diphosphine against the resulting enantiomeric excess of the addition product **9** yielded a slightly positive non-linear relationship. The use of partially resolved ligand **75** also has an impact on the conversion rates of the reaction. A slight decrease in reactivity parallels the decrease of the enantiomeric purity of (*R*)-BINAP **75** (Chart 31).

Both these indicate that diastereomeric species are generated in the reaction media. By comparing our curve with theoretical curves derived from models proposed by Kagan[387], it appears that diasteromeric species bearing two chirality inducers are involved. Yet, our results are insufficient to determine if the diastereomeric species are involved in the catalytic cycle or if they are spectators at its periphery. In light of the weak non-linear effect, we did not take into account such diastereomeric species in our mechanistic reasoning (Scheme 136).

**Chart 31** : Influence of BINAP's optical activity on the enantioselectivity and reactivity of the $Cu(tfacac)_2$ catalyzed addition of $Et_2Zn$ to benzaldehyde (General Procedure P)



## 10.4.2. Involvement of the Anion in the Catalytic Cycle

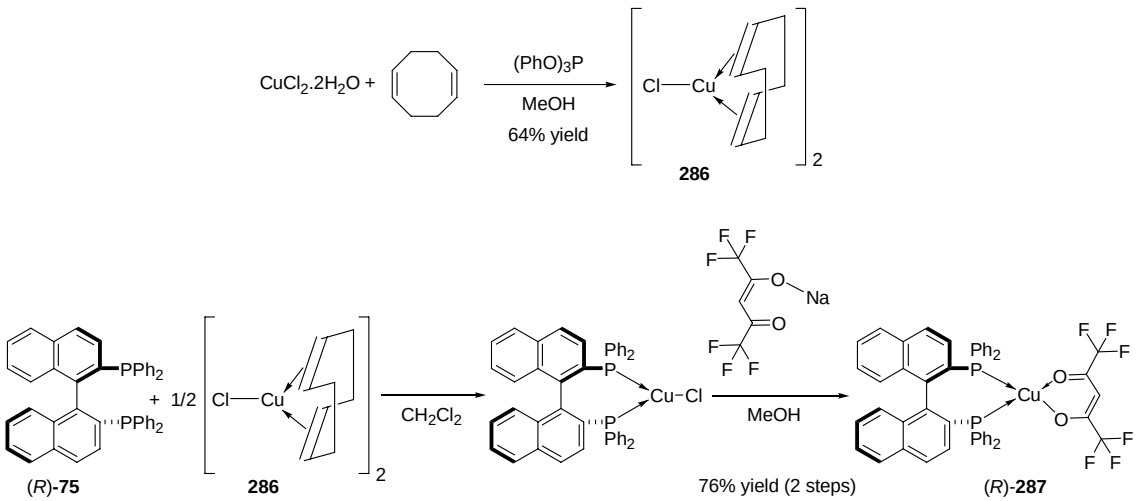
The results obtained with the chiral copper(II) diketonates open a window on the mechanism of the diorganozinc addition of aldehyde. Indeed, the matched mismatched pairing between a chiral diketonate such as (1*R*)**-280** and either enantiomer of chiral diphosphine point towards the involvement of the diketonate counterion in the catalytic cycle. This is further confirmed by the small asymmetric induction (16% ee) obtained in the presence of achiral diphosphine dppf **171** and optically active (1*R*)-**280**. Copper counterions such as 1,3-diketonates are involved in the stereodetermining step of the catalytic cycle.

## 10.4.3. A Copper(I) Active Species

Diorganozinc compounds are known to reduce copper(II) species to copper(I) [401,380,148,174,384]. In our case, a rapid color-change from blue-green to yellow is observed when $Et_2Zn$ is added to copper(II) precursors. This seems to confirm the *in situ* reduction since copper(I) chloride complexed by BINAP also produces a yellow solution. The *in situ* reduction of a copper(II) *bis*diketonate by $Et_2Zn$ in the presence of a diphosphine to form a copper(I) active species will produce unknown side-products. The intervention of these side-products in the catalytic cycle could not be ruled out.

A copper(I) complex bearing both a chiral BINAP unit and a diketonate ligand was synthesized to look into the matter. The dimer **286** was easily synthesized by reduction of copper(II) chloride dihydrate by triphenylphosphite in the presence of 1,5-cyclooctadiene[421§§§§]. The addition of (*R*)-BINAP **75** to a suspension of 1,5-cyclooctadiene copper(I) chloride lead to a yellow solution of (*R*)-BINAP·copper(I)chloride. After changing solvents, the chloride anion was exchanged by anion metathesis[422,423] with sodium hexafluoroacetylacetonate over the course of several days affording a orange-red solid in good yield. We later found out that a racemic version of complex **287** had been recently synthesized through another pathway for a spectroscopic study of diphosphine (hexafluoroacetylacetonato)copper(I) complexes[424] (Scheme 135).

§§§§ Complex **286** is relatively more stable than copper(I) chloride and was found to be more convenient for the isolation of pure complexes.




**Scheme 135**

The resulting (*R*)-BINAP copper(I) hexafluoroacetylacetonate **287** afforded crystals which where analyzed by X-ray diffraction. In the solid crystalline phase, (*R*)-**287** is a monomer with a tetrahedral arrangement around the copper(I) center (Figure 30).

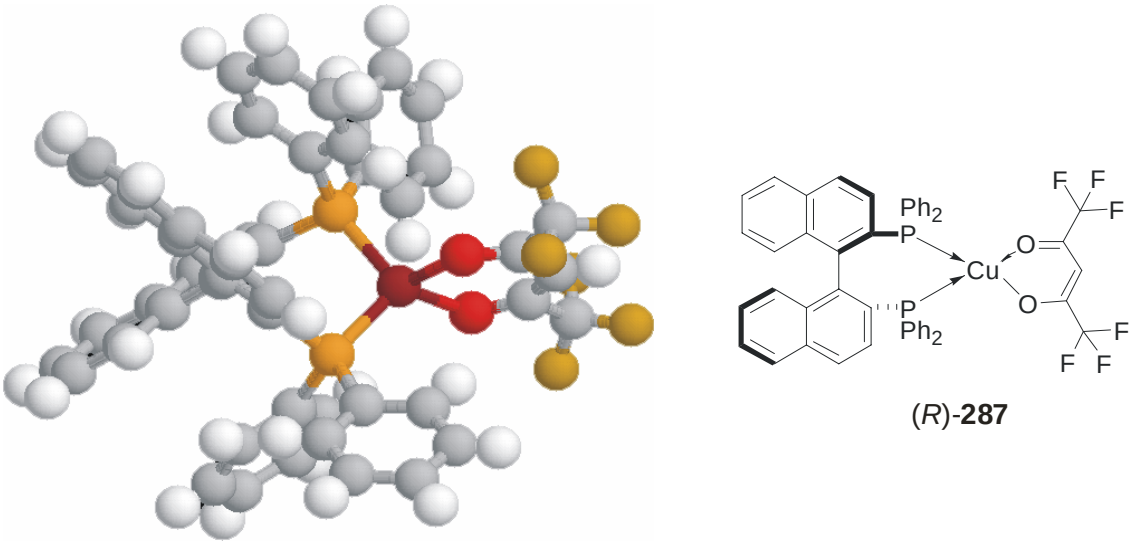
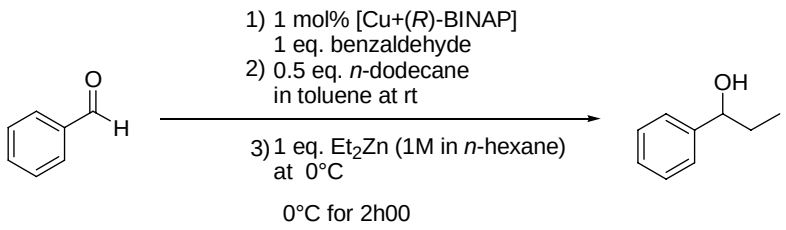



**Figure 30**

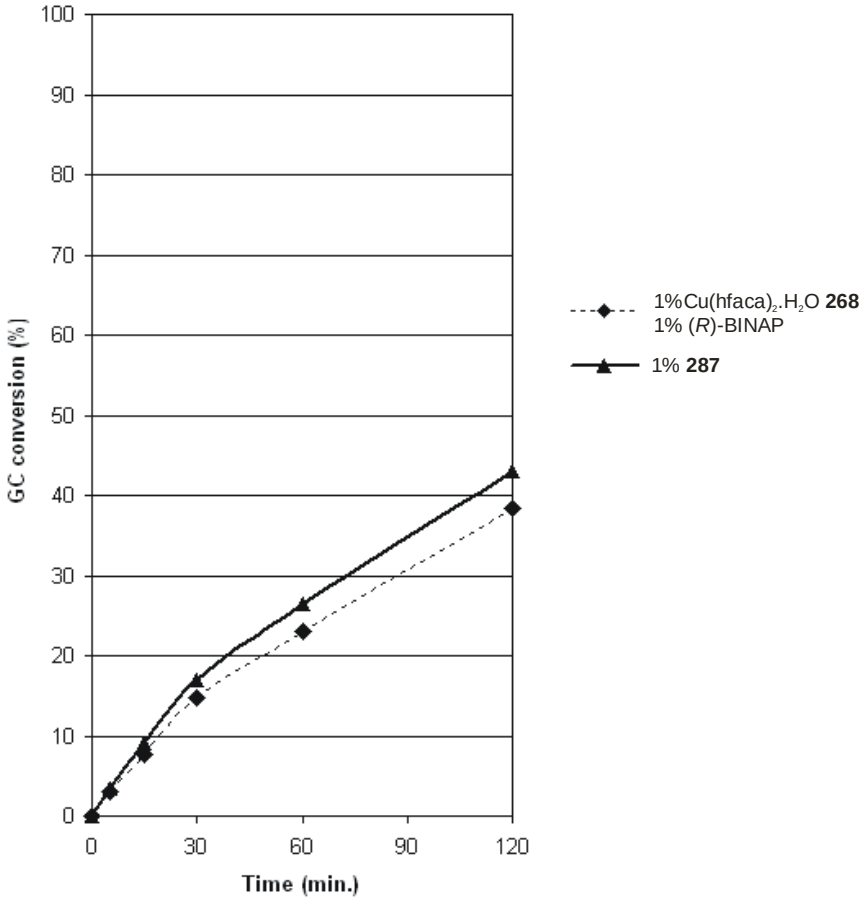
The catalytic properties of complex **287** were compared with the ones of $Cu(hfacac)_2.H_2O$ and (*R*)-BINAP under identical reaction conditions. The enantioselectivities provided by both catalyst's precursors are identical (Table 26). The reaction profiles are similar (Chart 32). These results therefore confirm that $Et_2Zn$ reduces *in situ* copper(II) species to copper(I) species. We can conclude that the side-products resulting from the initial reduction and traces of water have no impact of the enantioselective addition of $Et_2Zn$ to aldehydes.

**Table 26** : Comparison of copper-hexafluoroacetylacetonate based catalysts (General Procedure P)




| Entry | [Cu+(*R*)-BINAP] | | Time | GC Conversion | ee% |
|---|---|---|---|---|---|
| 1 | 1mol% $Cu(hfacac)_2.H_2O$ **268** | 1mol% (*R*)-BINAP | 2h | 38% | 84% ee |
| 2 | 1mol% (*R*)-**287** | | 2h | 43% | 84% ee |

**Chart 32** : Comparison of reaction profiles of copper-hexafluoroacetylacetonate based catalysts.



## 10.4.4. Electronic Structure and Catalytic Activity

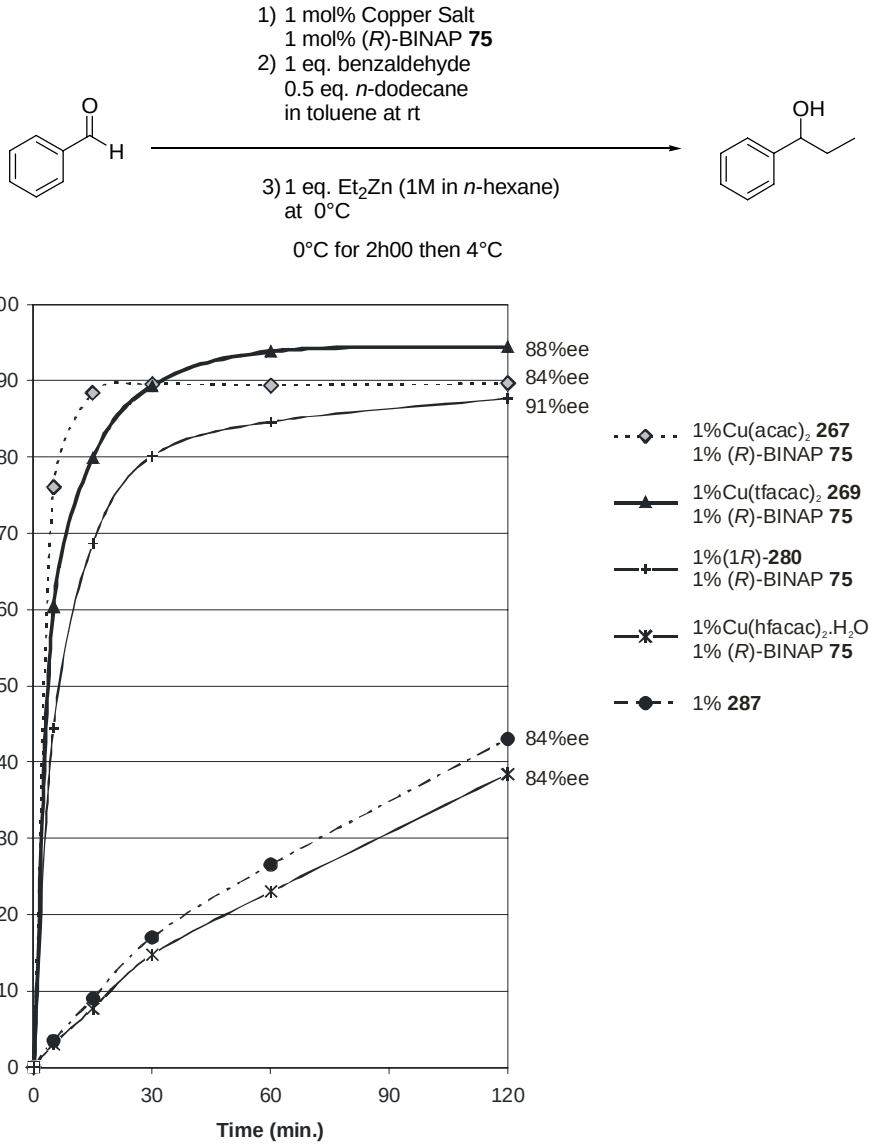
A strong difference in catalytic activity between copper diketonates as a function of their structure was noticed. In the presence of chiral (*R*)-BINAP, $Cu(acac)_2$ **267** , $Cu(tfacac)_2$ **269** and copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** lead to almost reaction completion in 15-30 minutes. While for $Cu(hfacac)_2.H_2O$ **268**, the reaction only attains around 40% conversion after 2 hours (Chart 33). Yet it is not a problem of catalyst's degradation since 88% conversion is attained after 24 hours with $Cu(hfacac)_2.H_2O$ **268**. Differences in the ease of reduction of a copper(I) species can be pushed aside since the use of hexafluoroacetylacetonate copper(I) complex **287** is as slow as a combination of $Cu(hfacac)_2.H_2O$ **268** and (*R*)-BINAP **75**.

Along the same lines, $Cu(OAc)_2.H_2O$ is also more active than $Cu(O_2CCF_3)_2.H_2O$ (Chart 26).[*****]

A methyl group and a trifluoromethyl group are sterically equivalent and steric effects cannot be responsible for the reactivity differences. However, the methyl and trifluoromethyl groups are not electronically equivalent since the fluorine atom is the element with the highest electronegativity. Electronically-depleted anions, trifluoroacetate and hexafluoroacetylacetonate (hfacac), on the copper do not lead to efficient catalysis. A diketonate counterion (acac and tfacac) with at least one electronically-undepleted oxygen is required for a high turnover frequency.

[*****] Alexakis *et al.* observed similar catalytic activity for $Cu(OAc)_2$, $Cu(OAc)_2.H_2O$ and $Cu(O_2CCF_3)_2$ for the Michael addition of diethylzinc in the presence of a chiral phosphoramidite(**Table 22**).

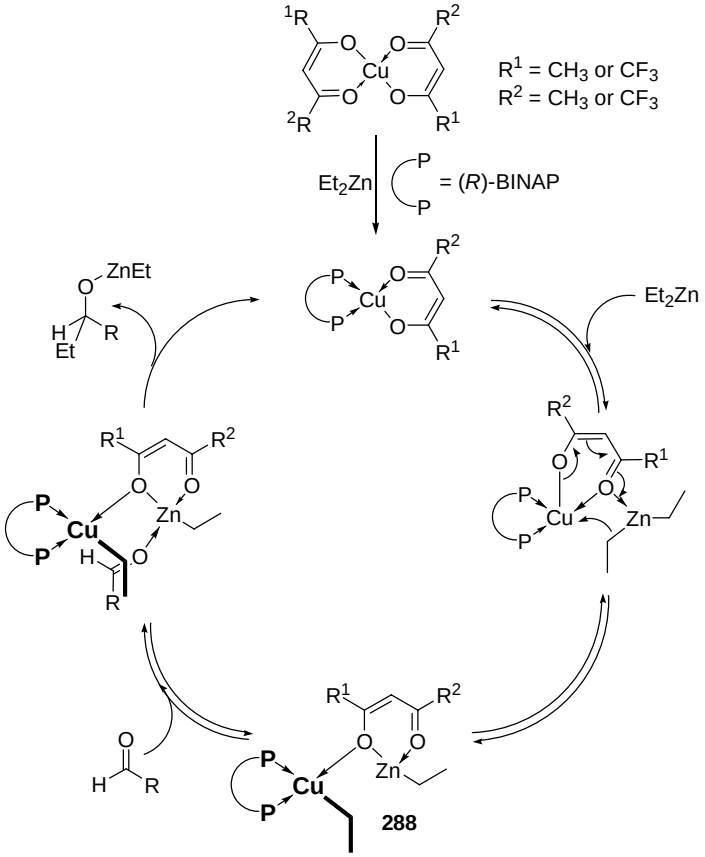
**Chart 33 :** Influence of the diketonate's nature on the reactivity (General Procedure P)




## 10.4.5. Mechanism Proposal

A mechanism is proposed to account for the experimental data exposed in this chapter. The catalyst precursors, a copper(II) diketonate and a chiral diphosphine, produce a diphosphine copper(I) diketonate upon addition of $Et_2Zn$. The formation of an ate complex between the diethylzinc and an oxygen atom of the diketonate is followed by a transmetallation step. The softer alkyl group is transferred to the softer copper(I) atom in exchange for a harder oxygen atom from the diketonate. A bimetallic species **288** is formed where the copper and zinc centers are held together by an oxygen atom from the diketonate. The bimetallic species **288** is considered as the nucleophilic species. Coordination of the benzaldehyde on the zinc should result in the addition reaction through a six-membered ring. A zinc alkoxide is generated as well as the starting copper(I) diketonate diphosphine complex (Scheme 136).

We propose that the transmetallation step could be the rate-determining step. This would explain the differences in turnover frequency observed between $Cu(acac)_2$ **267**, $Cu(tfacac)_2$ **269**, and $Cu(hfacac)_2.H_2O$ **268**. The presence of at least one electronically-undepleted oxygen on the diketonate ($R^1 \neq CF_3$) facilitates the formation of the zincate leading to a decrease of the activation energy for the transmetallation step and an overall acceleration of the catalytic activity. Kinetics experiments are needed to establish this.




**Scheme 136**

The diketonate-bridged bimetallic species that we postulated was supported by recently published X-ray structures of bismuth(III)-first row divalent transition metals (*i.e.*: $Zn^{2+}$) hexafluoroacetylacetonate complexes bridged through oxygen atoms of the diketonate[425] (Figure 31).

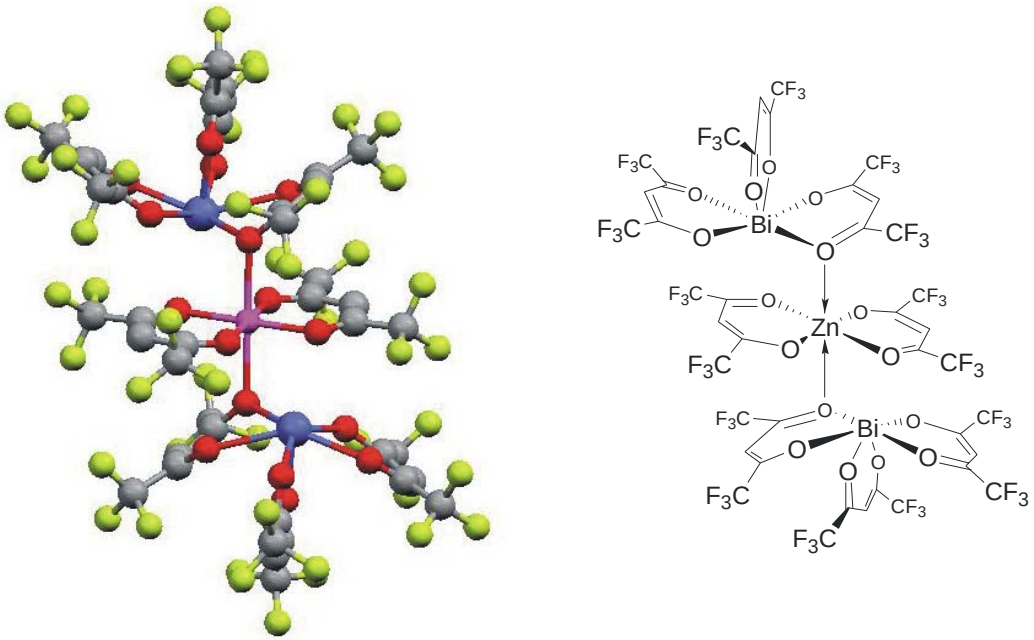



**Figure 31**

## 10.5. Conclusions

After our investigation into the influence of the fluoride anion in the copper catalyzed diorganozinc addition to benzaldehyde, we investigated the catalytic properties of copper complexes bearing various counterions. Copper(II) diketonates **267** and **269**, combined with (*R*)-BINAP **75**, were singled out as the most promising candidates providing respectively 84% ee and 88% ee with fast reaction rates.

The use of optically active copper(II) diketonate (1*R*)-**280** in combination with the (*R*)-BINAP **75** enantiomer improved further the enantioselectivity (91% ee). After a brief optimization, loadings in catalysts precursors (1*R*)-**280** and (1*R*)-BINAP between 0.1mol% and 0.5mol% were applied to obtain the adducts of aromatic aldehydes in good yields and enantiomeric excesses (73-95% ee).

The observation of matched-mismatched pairing between the chiral diphosphine and the chiral diketone is the proof of the involvement of the diketonate anion in the catalytic cycle. A mechanism involving a heterobimetallic active species has been proposed based on our experimental observations.

# Chapter 11

# Conclusions & Perspectives

## 11.1. Summary of Results

Our initial goal was the search for new catalysts to control the enantioselective addition of diorganozinc to carbon-oxygen and carbon-nitrogen double bonds. The catalytic properties of several systems were appraised.

1) First, several chiral sulfonamido alcohols were generated by grafting sulfonyl groups with various electronic and steric properties on (*S*)-leucinol and (1*S*)-3-aminoisoborneol. These were tested in stoichiometric quantities to direct the diethylzinc addition to benzaldehyde-derived *N*-phenylsulfonyl imine **3** and *N*-diphenylphosphinoyl imine **41**. None of the chiral sulfonamide alcohols could deliver the addition products in sensible yields (7-27%) and enantioselectivity (0-14% ee). However, the addition of diethylzinc on to benzaldehyde led to addition product with up to 47% ee with only 10mol% of sulfonamido alcohol **96**.

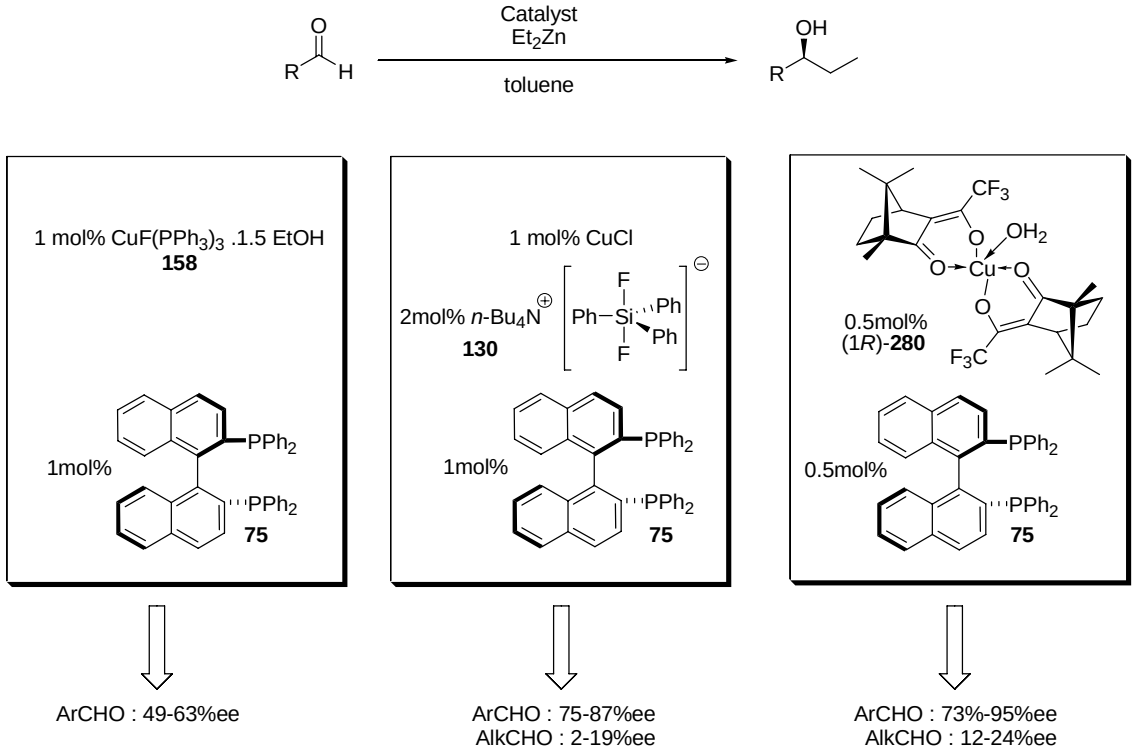
   Collecting results from the addition to imines was highly labor intensive since it required isolation and purification of the products. However, the addition to aldehydes lent itself to fast appraisal of the catalyst activity. By taking samples from the reaction media at regular intervals and analyzing them by gas chromatography on a chiral phase in the presence of an internal standard, the conversion rates, chemoselectivity and enantioselectivity were readily available. The addition of diethylzinc on benzaldehyde was therefore used as model reaction throughout the rest of our study.

2) The use of fluoride anions to catalyze the addition of diorganozinc towards aldehydes was explored. The use of stoichiometric amounts of cesium fluoride, tetrabutylammonium triphenyldifluorosilicate TBAT **130** and its tin derivative **131** which are anhydrous fluoride sources led to significant rate enhancement of the addition reaction of $Et_2Zn$ to benzaldehyde. An inorganic fluoride salt (KF) in conjunction with substoichiometric amounts of a phase transfer catalyst, crown ether 18-C-6 **138**, provided a fast acceleration of the reaction. Asymmetric versions of this system were not considered. Our results show that fluoride anion is capable of increasing the nucleophilicity of diorganozinc compounds towards aldehydes probably through the formation of an ate complex.

3) Metal fluoride complexes were investigated as potential catalysts for the diorganozinc addition to aldehydes. The copper(I)fluoride complex **158**, $[(Ph_3P)_3CuF].1.5EtOH$ led to high catalytic activity for the $Et_2Zn$ addition to benzaldehyde. A ligand screening showed that species generated by adding catalytic amounts of chiral diphosphines and complex **158** led to some enantiocontrol. The best ligand, BINAP **75**, gave the adducts to aromatic aldehydes in good to very good yields (77-89%) and modest to good enantioselectivities (49-63% ee) with a catalyst loading of 1mol% (Scheme 137).

4) An improved copper-fluoride based catalyst was developed by combining a copper salt, a fluoride source and a chiral diphosphine ligand. Several parameters were investigated : copper salt, fluoride source, chiral ligand, relative stoichiometry of catalyst's precursors, the catalyst loading, solvent, reaction temperature. The

optimized catalyst (1mol% CuCl + 1mol% (*R*)-BINAP + 2mol% TBAT **130**) was then applied to the addition of $Et_2Zn$ to a range of aldehydes. Very good enantioselectivities were obtained for the aromatic aldehydes (75-87% ee). The enantiocontrol of the addition on aliphatic aldehydes was weak (2-19% ee). Based on the literature and experimental observations, a mechanistic hypothesis was proposed (NMR, non-linear effects, 1,4-addition on cyclohexenone, copper alkoxide). Yet, we were unable to prove the involvement of the fluoride anion throughout the catalytic cycle (Scheme 137).




**Scheme 137**

5) We then examined the influence of the nature of the copper salts by combining chiral BINAP **75** and various copper complexes to catalyze the $Et_2Zn$ addition to benzaldehyde. Copper(II)diketonates, $Cu(acac)_2$ **267** & $Cu(tfacac)_2$ **269**, provided good enantiocontrol (up to 88% ee). This could be further improved (up to 91% ee) by using optically active a copper diketonate derived from camphor **280** with chiral BINAP **75**. This new system was applied to control the addition of $Et_2Zn$ to a range of aldehydes with a low catalyst loading (0.5mol%). Very good enantiocontrol was observed with aromatic aldehydes (73%-95% ee), modest enantiocontrol was obtained with alkylaldehydes (12-24% ee) (Scheme 137).

It was ascertained that the diketonate counterion was involved in the catalytic cycle through the influence of matched and mismatched combinations of chiral diphosphine and chiral diketonate on the level of enantiomeric excesses obtained. A mechanism, involving heterobimetallic active species **288**, has been proposed based on the literature and experimental observations.

Compared to the full range of chiral 1,2-aminoalcohols and related ligands[38,22]:

- We have still not matched the excellent enantioselectivities for the various aldehydes with our copper(II)diketonate-diphosphine system. Our system should allow for efficient optimization for particular substrates through *in situ*

generation of a range of catalysts by combining various copper(II) diketonates and chiral diphosphines.

- Our catalyst's loadings are comparatively low (0.5mol% *vs.* 2-3mol% for good *N,O*-ligands).

- Limited excess of $Et_2Zn$ have been shown to lead to complete conversions (1.5eq. *vs.* 2.0-2.2eq. generally for *N,O*-ligands).

We have shown that a copper catalyst bearing chiral diphosphine BINAP **75** and a diketonate was a highly successful catalytic system for the addition of diethylzinc to aromatic aldehydes. There is still need for improvement with alkylaldehydes, and the system has not been tested with ketones and imines. Also, the addition of functionalized alkyl compounds and aryl moieties has not been investigated.

# 11.2. Perspectives

## 11.2.1. Modifications of the Counterion

***Diketonate Bite Angle***

The bite angle of bidentate ligands has revealed itself a significant parameter during the optimization of catalytic systems, especially those involving diphosphines[426,427]. However, to the best of our knowledge, the influence of the bite angle of diketonate ligands has never been investigated in metal catalysts.

If the 1,3-diketone is part of a ring, varying the size of the ring will force the two oxygen atoms in specific positions around the metal. The bite angle of the diketonate will therefore be modified (considering that the metal-oxygen bond length cannot vary extensively). By way of consequence, the orbital electronic populations and energies should be modified. This could influence the properties of the catalytic complex (Figure 32).

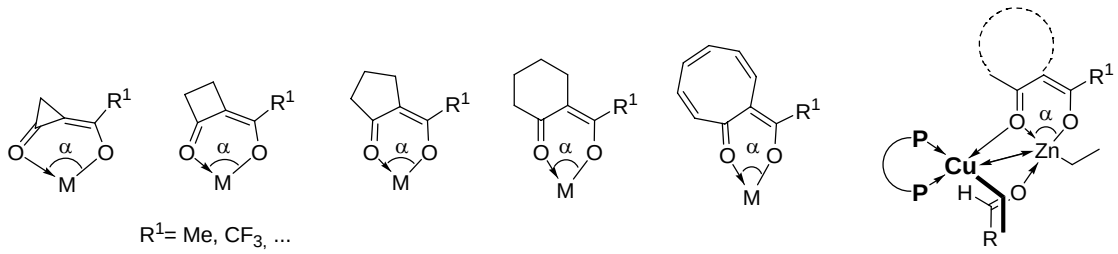



**Figure 32**

In the specific case of our reaction and if our mechanistic hypothesis of a bimetallic transition state holds true, modifying the bite angle of the diketonate ($\alpha$) will influence the relative position of the two metals. This should have repercussions on the relative positions of the carbonyl to the alkyl fragment to be transferred as well as the chiral skeleton of the diphosphine. Modifications of the bite angle of the diketonate are therefore expected to influence the transfer of the chiral information.

***Copper 1,3-Thiooxoketonate***

As we have seen, diketonates with two electronically differentiated oxygens lead to improved enantioselectivity. The replacement of one oxygen by an electron-rich sulfur atom should produce the same result (*e.g.* thiooxoketone **291**). Moreover, the softer sulfur should interact more strongly with the copper center influencing the transfer of the

chiral information from diphosphine to the prochiral aldehyde. The roles of the oxygen and the sulfur in the catalytic cycles could be differentiated even further by depleting the electronic population of the ketone with a perfluorinated group (*e.g.* **292**). In the case of chiral 1,3-thiooxoketones, switching the positions of sulfur and oxygen provides two different counterions from the same chiral starting material (*e.g.* **293** & **294**) (Figure 33).

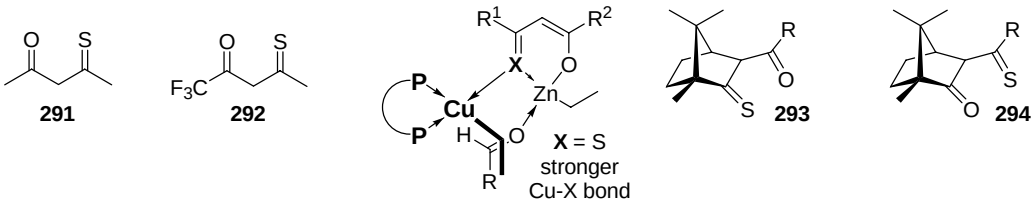
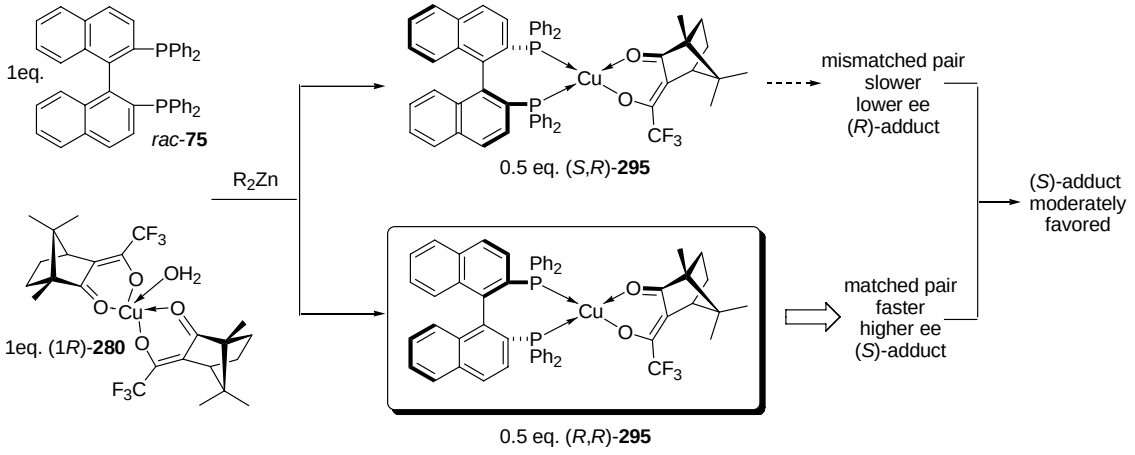



**Figure 33**

## 11.2.2. Optically Inactive Diphosphines

Our best system requires two sources of chiral information : the optically active diphosphine (*S*)-BINAP **75** and the chiral diketone (1*R*)-**280** However, without the diketone, the enantioselectivity only dropped slightly when using achiral $Cu(tfacac)_2$ **269** (88% ee *vs.* 91% ee for (1*R*)-**280**). Nevertheless the costliest source of chirality is the diphosphine. Avoiding the use of the enantiopure diphosphine would be economically interesting. Two pathways can be imagined to reach this goal : (1) resolving the racemic diphosphine in the reaction media, (2) evolving a chiral catalyst from an achiral diphosphine and a chiral activator.

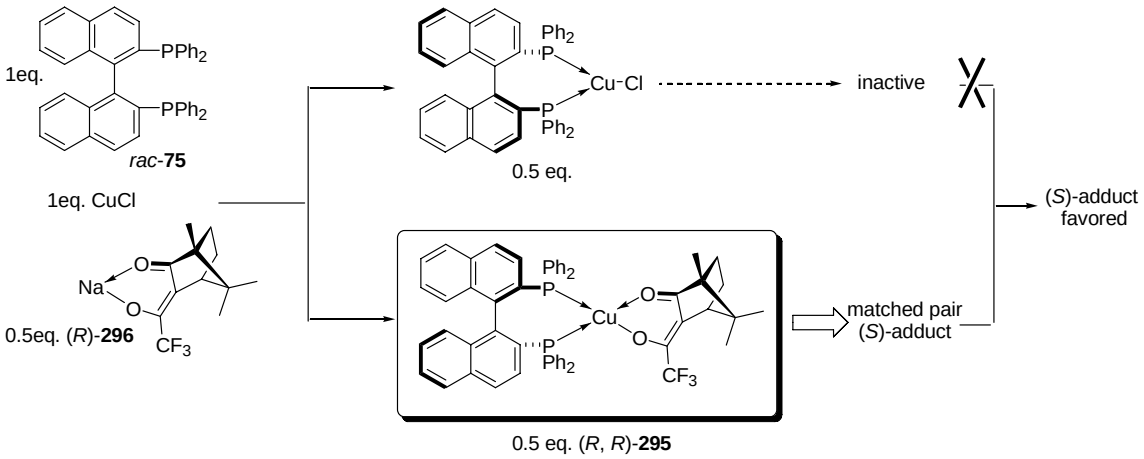
We have seen that the enantiopure camphor-derived copper(II) diketonate (1*R*)-**280** has to be combined with the correct enantiomer of BINAP **75** to reach high levels of enantioselectivity for the addition of diethylzinc to benzaldehyde. The mismatched pair also catalyzes the reaction but with lesser enantioselectivity and at a weaker rate. Therefore using racemic BINAP **75** and (1*R*)-**280** should favor the (*S*)-adduct. Yet, the overall enantioselectivity is not expected to be high due to the weak differences in rate between the matched and mismatched combination that we have already observed (see Chart 28, Chart 29) (Scheme 138).




**Scheme 138**

If the matched pair diphosphine copper(I) diketonate complex (*R,R*)-**295** is thermodynamically more stable than the mismatched (*S,R*)-**295**, putting together 1 equivalent of copper(I)chloride, 1 equivalent of racemic BINAP **75** and 0.5 equivalent of

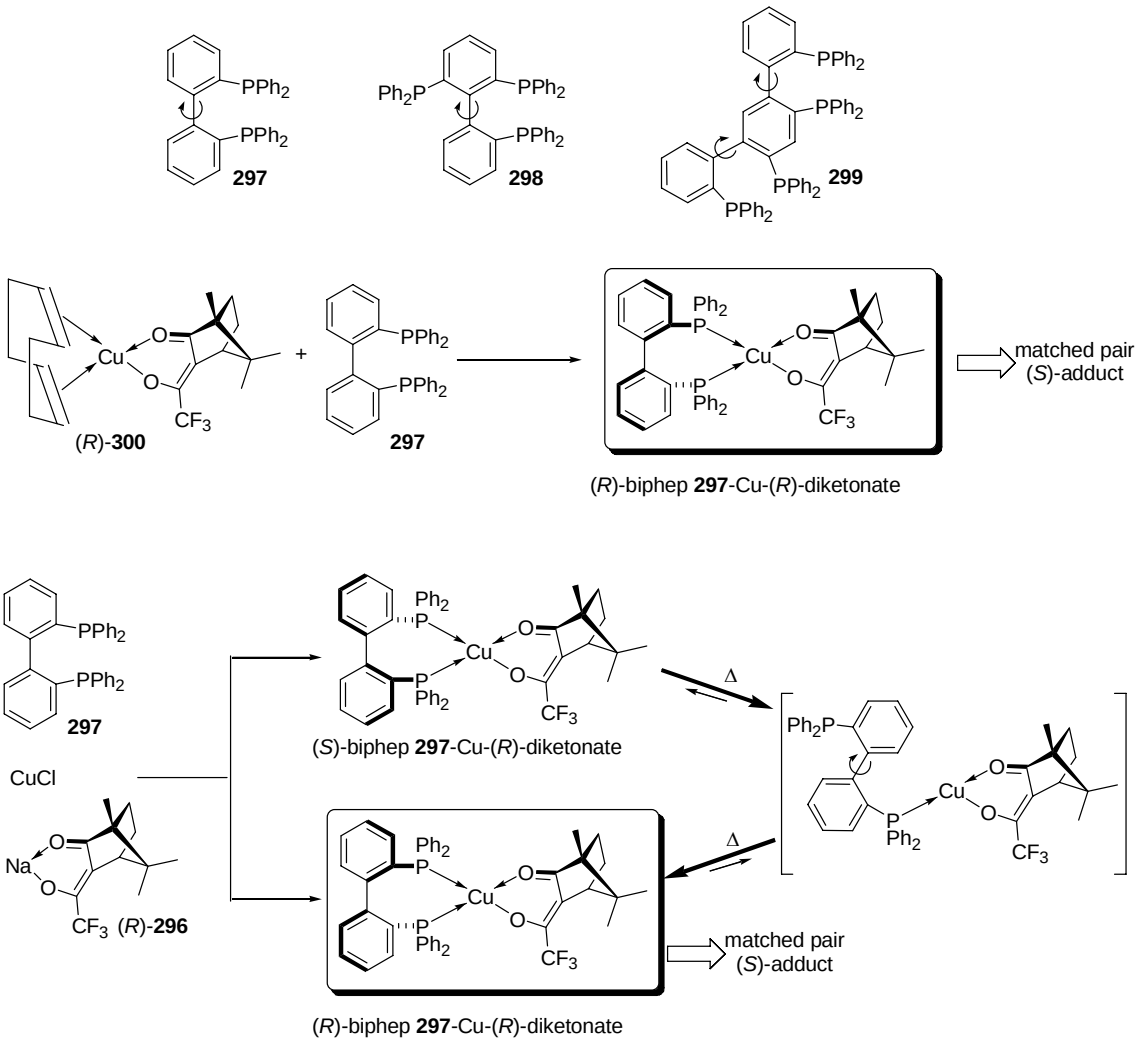
the optically active sodium diketonate (*R*)-**296** should produce preferentially the matched pair catalyst (*R,R*)**-295** and the inactive (*S*)-BINAP copper(I)chloride complex. The optically active sodium diketonate (*R*)-**296** is a chiral activator[428,429] leading to the production of the (*S*)-adduct[18] (Scheme 139).




**Scheme 139**

A more appealing approach is to use conformationally flexible and optically inactive phosphines such as biphep **297**, **298** and **299** developed by Mikami *et al.*[431-433]. The principle of these ligands is that the axial chirality is created upon complexation to the metal and controlled by an additional chiral ligand. In our case, the chiral complexes could be obtained through two strategies : (1) diastereoselective diphosphine complexation to enantiopure copper diketonate species (*R*)-**300**; (2) isomerization to the thermodynamically stable diasteroisomeric copper complex (hopefully the matched pair). Modifications of the chiral diketonate could be envisaged to influence the diastereoselection of the diphosphine-Cu-diketonate synthesis (Scheme 140).

[18] Simultaneous chiral activation and chiral deactivation should also be investigated, but an adequate chiral poison has to be found[430] Faller, J. W.; Lavoie, A. R.; Parr, J. *Chem. Rev.* **2003**, *103*, 3345-3367..




**Scheme 140**

## 11.2.3. A Building Block Approach to Catalyst

The copper catalysts we have started to develop for aromatic aldehydes could possibly be applied to other substrates such as alkyl aldehydes, ketones or imines. Optimization of the copper counterion and the chiral diphosphine will probably be necessary for each specific nucleophile-electrophile couple of interest. High-throughput screening would probably the way to go to speed up and ease such optimization of homogeneous catalysts[434,435].

Our system is ideally suited for optimization through parallel synthesis and testing of a range of complexes. Two points of diversity are available in the copper catalyst : the chiral diphosphine and the chiral diketonate (or related). The synthesis of these various catalysts can take place by simply stirring together a copper(I)salt, a sodium diketonate (or related) salt and a chiral diphosphine. This method has already been used to synthesize (*R*)-BINAP copper(I) hexafluoroacetylacetonate **287** and should suit automated parallel synthesis techniques. The various complexes could be directly applied to the reaction of interest without any tedious purification (Figure 34).

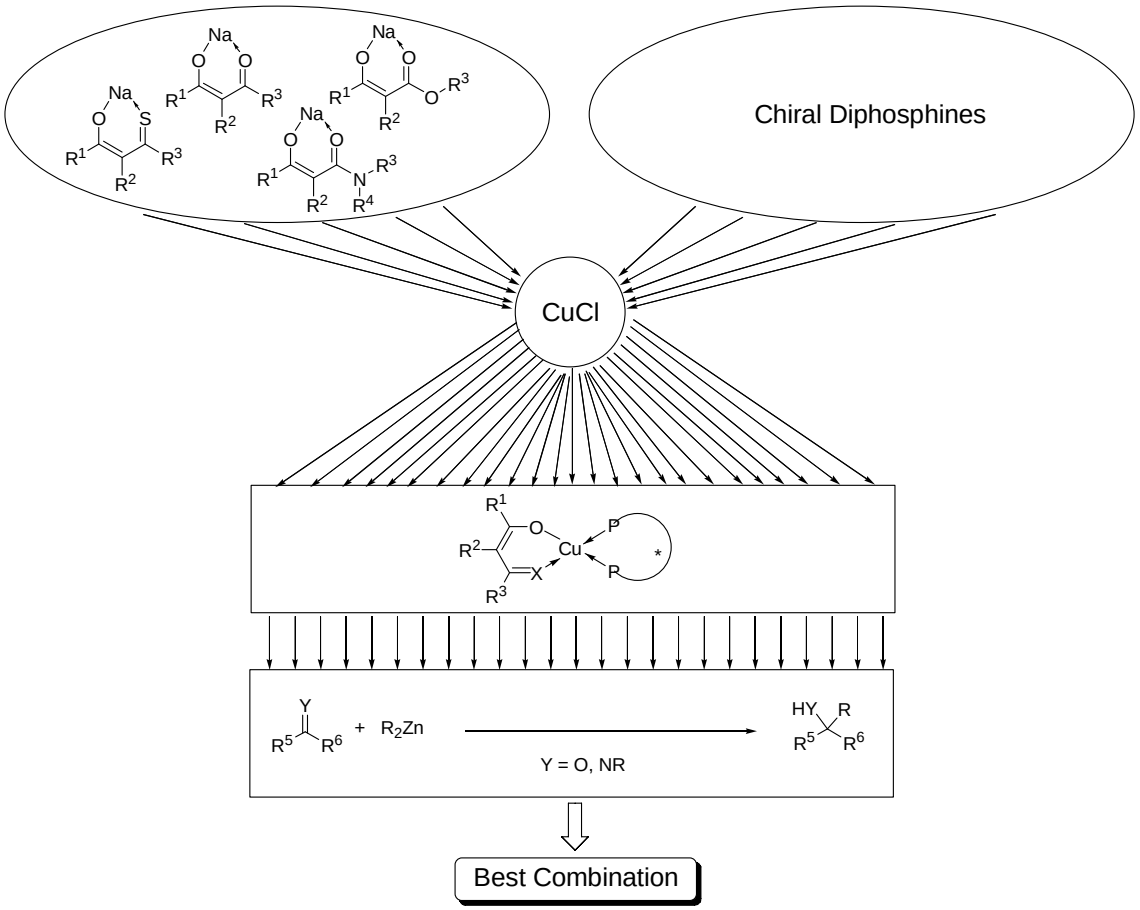



**Figure 34**

# Experimental Part

# Generalities

## 11.3. Equipment

Unless otherwise specified

- Infrared spectra were recorded on a Bio-Rad FTS-135 spectrometer.

- NMR experiments were carried out at room temperature unless otherwise stated. Chemical shifts are reported in ppm ($\delta$). Multiplicities are indicated as: s (singlet), d (doublet), t(triplet), q (quartet), quint (quintet), hept (heptet), mult (multiplet), m (massif), br (broad) and exch ($D_2O$ exchangeable). The coupling constants are reported in Hertz (Hz); integration is provided for $^{1}H$, $^{19}F$ and $^{31}P$ NMR. Data is presented in the form: chemical shift (multiplicity, J=coupling constant, integration, assignments when relevant).

- $^{1}H$ NMR spectra were recorded at 200 or 300 MHz on a Varian Gemini 200, VXR 200 or Gemini 300BB in a deuterated solvent with tetramethylsilane (TMS) as internal standard (TMS, $\delta$=0.00 for $^{1}H$).

- $^{13}C$ NMR spectra were recorded at 50 or 75 MHz on a Varian Gemini 200, VXR 200 or Gemini 300 in a deuterated solvent used as internal standard ($CDCl_3$: 77 ppm; MeOD-$d_4$: 49 ppm; DMSO-$d_6$: 39.5 ppm). Chemical shifts are given in ppm; coupling constants are given in Hz. Irradiation sequence is mentionned. When attached proton test (APT) sequence is used, chemical shifts of quaternary and secondary carbons are marked with a star (*)

- $^{19}F$ NMR spectra were recorded at 288.5 MHz on a Varian Gemini 300 spectrometer with an internal standard such as trichlorofluoromethane (0 ppm) or hexafluorobenzene (-163 ppm). Chemical shifts are given in ppm; coupling constants are given in Hz.

- Mass spectra were recorded on a Varian MAT-44 or a FINNIGAN MAT TSQ 70 spectrometer in the laboratory of Professors de Hoffmann and Habib-Jiwan. Data is reported in the form *m/z* (intensity relative to base 100%)

- Elemental analyses were realized in the laboratory of Dr Stone at University College, London

- GC analyses were performed on a CE Instruments GC 8000 with a Merck-Hitachi D-2500 Chromato Integrator on a Cp-Sil 8 CB WCOT Fused Silica (30 m x 0.25 mm – 0.25 µm) column; chiral GC analyses were done on a CE Instruments HRGC 5300 with a Merck-Hitachi D-2500 Chromato Integrator on a Chirasil Dex (25 m x 0.25 mm – 0.25 µm) column. Temperature programs are given as follows: (initial temperature (°C) / initial time (min) / ramp (°C/min) / final temperature (°C) / final time (min)) or (initial temperature (°C) / initial time (min) / ramp (°C/min) /

intermediate temperature (°C) / ramp (°C/min) / final temperature (°C) / final time (min)).

- HPLC analyses were performed with Waters 600 Controller and Pump and Waters 996 Photodiode array detector. The specific stationary phase is mentioned for each analysis. Elution programs are given in the following format: column type, solvent1/solvent2, solvents'volumic proportions, eluant flow, temperature, wavelength of integration.

- Optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter. Concentrations are given in g/100 ml.

- Bulb-to-bulb distillations were performed with a Büchi GKR 50 or GKR 51.

## 11.4. Techniques

All reactions were realized under argon atmosphere unless otherwise stated. All the glassware, except the reaction tubes of the Radley's carrousel, was flame-dried under vacuum and cooled under an argon atmosphere unless otherwise stated.

For reactions at 0°C flasks were placed in an ice bath; for reactions at -78°C flasks were placed in a dry-ice / *iso*-propanol bath; intermediate temperatures were realized by adding the desired quantity of dry-ice to *iso*-propanol; for longer reactions times flasks were placed in an ethanol bath cooled by a Haake EK90 cryostat.

Evaporation of solvents was performed at ±35°C with a rotary evaporator connected to a water pump (~16 mmHg) unless otherwise stated.

Flash chromatographies were performed on silica gel "60 Merck 40-63 µm". Solvents used were of technical grade and distilled prior to use. $R_f$ values were determined on silicagel plates Merck 60 $F_{254}$ on aluminum support. Spots were visualized using UV light ($\lambda$ = 254 mm) or revealed using an aqueous potassium permanganate solution.

$CH_2Cl_2$, 1,2-dichloroethane and benzene were dried over $CaH_2$ and distilled.

THF, diethyl ether, *tert*-butylmethylether, dimethoxyethane were dried over Na / benzophenone and distilled.

1,4-dioxane and toluene were distilled over sodium

*n*-hexane, DMF, chlorobenzene was dried over flame-dried molecular sieves (4Å) for minimum a night

Triethylamine was dried over $CaH_2$ and distilled.

Enones, sulfonyl chlorides were distilled prior to use.

Copper(II) triflate, zinc(II) chloride, and, when specified, potassium fluoride were dried by heating overnight at 150°C under reduced pressure.

Degassed solvents were prepared by the "freeze and thaw" method in a Schlenck flask

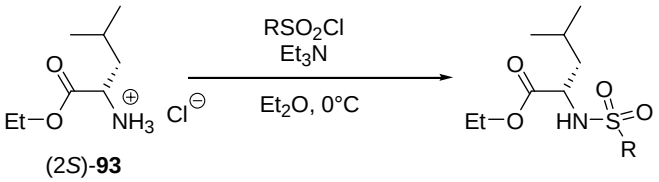
# Chapter 12

# Sulfonamido Alcohols

## 12.1. Synthesis of (2*S*)-Leucine based Sulfonamido Alcohols

### 12.1.1. Sulfonylation of Hydrochloride Salt of Aminoester (2*S*)-93

***General Procedure A***




(2*S*)-**93**

In a two-necked round-bottomed flask fitted with a septum and an argon inlet, aminoester **93** is dissolved in dry triethylamine and dry diethylether. The mixture is cooled at 0°C with an ice bath. The corresponding sulfonyl chloride is added in fractions by syringe. After one or several day(s), the reaction mixture is concentrated under vacuum.

The oil is dissolved in dichloromethane placed in an extraction funnel and washed successively with an aqueous solution of HCl (1 M), with an aqueous solution of NaOH (1M) and with water. The organic fraction is dried over $MgSO_4$, filtered and concentrated under vacuum.

***(2S)-Leucine Ethylester Phenylsulfonylamide***

**Operating Procedure** : see General Procedure A
**Reaction time:** 3 days

**Quantities Engaged** :

(2*S*)-Leucine ethylester hydrochloride: 3.00 g, 15.3 mmol, 1 eq.

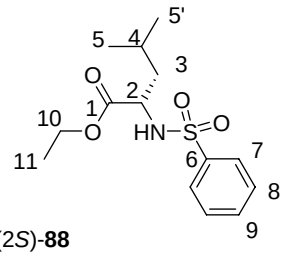
Phenylsulfonyl chloride : 2.55 ml, 3.52 g, 1.3 eq.

Triethylamine : 7.05 ml, 5.13 g, 3.3 eq.

Diethylether : 40 ml, 28.3 g, 25 eq.

**Purification** : The product is purified by flash chromatography on silica gel (cyclohexane/AcOEt/$Et_3N$, 60/35/5, $R_f$=0.40). 4.37 g of a white solid are obtained

**Name** : (2*S*)-2-Benzenesulfonylamino-4-methyl-pentanoic acid ethyl ester



(2*S*)-**88**

**M.F.** : $C_{14}H_{21}NO_4S$ **M.W.** : 299.39

**Yield** : 4.37 g (95.2%)

**Physical Property** : white solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.84 (d, $^3J_{7,8}$=8.4, 2H, $H^7$), 7.57-7.47 (m., 3H, $H^{8,9}$), 5.01 (bd, $^3J_{NH,2}$=9.9, 1H, N*H*), 3.97-3.89 (m, 1H, $H^2$), 3.85 (q, $^3J_{10,11}$=7.1, 2H, $H^{10}$), 1.81 (hept, *J*= 7.1, 1H, $H^4$), 1.48 (t, $^3J_{3,4}$ = $^3J_{2,3}$ =7.2, 2H, $H^3$), 1.07 (t, $^3J_{10,11}$ = 7.1, 3H, $H^{11}$), 0.91 (dd, *J*=3.9, $^3J_{4,5}$=6.6, 6H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 172.1* ($C^1$), 139.6* ($C^6$), 132.7 ($C^9$), 129.0 ($C^8$), 127.3 ($C^7$), 61.4* ($C^{10)}$), 54.5 ($C^2$), 42.5* ($C^3$), 24.3 ($C^4$), 22.7, 21.4 ($C^{5,5'}$), 13.9 ($C^{11}$)

**IR** (solid deposit, $cm^{-1}$) : 3296 (br, N-H); 2960 (C-H); 1739 (C=O); 1641 ($C_{ar}$=$C_{ar}$); 1448 ($CH_3$ or $CH_2$); 1338 (S=O); 1196; 1164; 1091; 1012

**Mass** (EI, 70eV) : 300.1 ($[M+1]^+$,0.3%); 299.1 ($[M]^{\cdot+}$, 0.3%); 254 ($[M-OEt]^+$,0.1%); 243.0 ($[M-(C_4H_8)]^{\cdot+}$, 1.5%); 226.1 ($[M-(CO_2Et)]^+$, 100%); 140.9 ($[SO_2Ph]^+$, 7.3%); 77.0 ($[C_6H_5]^+$, 2.0%)

***(2S)-Leucine Ethylester Methylsulfonylamide***

**Operating Procedure** : see General Procedure A

**Reaction time** : overnight

**Quantities Engaged** :

(2*S*)-Leucine ethylester : 3.68 g, 18.84 mmol, 1 eq.

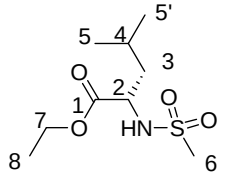
Methylsulfonyl chloride : 1.8 ml, 2.66 g, 1.2 eq.

Triethylamine : 8.5 ml, 6.2 g, 3.3 eq.

Diethylether : 40 ml, 28.2 g, 20 eq.

**Purification** : The product is purified by flash chromatography on silica gel (cyclohexane/AcOEt/$Et_3N$, 65/30/5, $R_f$=0.35). 4.12 g of colorless oil are obtained

**Name** : (2*S*)-2-Methylsulfonylamino-4-methyl-pentanoic acid ethyl ester



(2*S*)-**91**

**CAS-RN** : 36724-94-4

**M.F.** : $C_9H_{19}NO_4S$ **M.W.** : 237.32

**Yield** : 4.12 g (93.7%)

Physical Property : colorless oil

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 5.00 (bd, $^3J_{NH,2}$=9.6, 1H, N*H*), 4.24 (q, $^3J_{7,8}$=7.1, 2H, $H^7$), 4.11 (m, 1H, $H^2$), 2.95 (s, 3H, $H^6$), 1.85 (m, 1H, $H^4$), 1.59 (m, 2H, $H^3$), 1.31 (t, $^3J_{7,8}$=7.1, 3H, $H^8$), 0.96 (dd, *J*=4.8, $^3J_{4,5}$=6.6, 6H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 173.0* ($C^1$), 61.8* ($C^7$), 54.5 ($C^2$), 42.1* ($C^3$), 41.2 ($C^6$), 24.3, 22.7, 21.3 ($C^{4,5,5'}$), 14.1 ($C^8$)

**IR** (solid deposit, $cm^{-1}$) : 3282 (br, N-H); 2961, 2873 (C-H); 1746 (C=O); 1468 ($CH_3$ or $CH_2$); 1370 (S=O)

**Mass** (EI, 70eV) : 238.1 ($[M+1]^+$, 0.9%); 180.0 ($[M-(C_4H_8)]^+$, 2.6%); 164.0 ($[M-(CO_2Et)]^+$, 100%); 121.9 ($[M-(CO_2Et)-(C_3H_7)]^+$, 11.3%); 107.9 ($[M-(CO_2Et)-(C_4H_8)]^+$, 16.3%)

***(2S)-Leucine Ethylester pentafluorophenylsulfonylamide 92***

**Operating Procedure** : see General Procedure A

**Reaction time** : overnight

**Quantities Engaged** :

(2*S*)-Leucine ethylester : 0.36 g, 1.83 mmol, 1 eq.

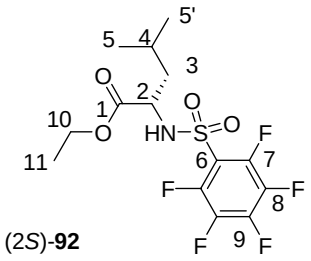
Pentafluorophenylsulfonyl chloride : 0.73 g, 1.5 eq.

Triethylamine : 0.69 ml, 0.050 g, 2.7 eq.

Diethylether : 10 ml, 7.1 g, 52 eq.

**Purification** : The product is purified by flash chromatography on silica gel (hexane/AcOEt, 95/5, $R_f$=0.17). 0.26 g of brown oil is obtained

**Name** : (2*S*)- 4-Methyl-2-pentafluorobenzenesulfonylamino-pentanoic acid ethyl ester




(2*S*)-**92**

**M.F.** : $C_{14}H_{16}F_5NO_4S$ **M.W.** : 389,34

**Yield** : 0.26 g (37%)

**Physical Property** : brown oil

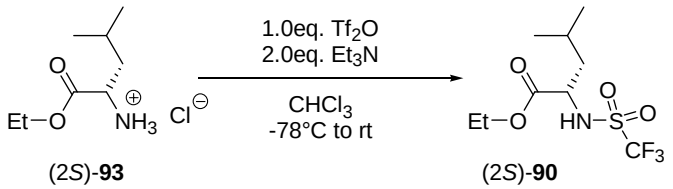
**$^1$H NMR** ($CDCl_3$, 300 MHz) : 5.54 (bd, $^3J_{NH,2}$=8.7, 1H, N*H*), 4.23 (m, 1H, $H^2$), 4.06 (q, $^3J_{10,11}$=7.0, 2H, $H^{10}$), 1.80 (m, 1H, $H^4$), 1.61 (m, 2H, $H^3$), 1.20 (t, $^3J_{10,11}$=7.0, 3H, $H^{11}$), 0.98 (d, $^3J_{4,5}$=4.8, 3H, $H^5$), 0.96 (d, $^3J_{4,5'}$=4.8, 3H, $H^{5'}$)

**$^{13}$C NMR** ($CDCl_3$, 62.9 MHz) : 171.6* ($C^1$), 144.5* (dm, $^2J_{CF}$=257.9, $C^7$), 143.8* (dm, $^2J_{CF}$=261.4, $C^9$), 137.7* (dm, $^2J_{CF}$=247.5, $C^8$), 116.5* (m, $C^6$), 62.0* ($C^{10}$), 55.1 ($C^2$), 41.9* ($C^3$), 24.4, 22.7 & 21.8 ($C^{4,5\&5'}$), 13.9 ($C^{11}$)

**Mass** (CI, $CH_4$ / $N_2O$) : 418.2 ($[M+(C_2H_5)]^+$, 12%) 390.1 ($[M+1]^+$, 100.0%); 316.1 ($[M-(CO_2Et)]^+$, 54.0%); 308.1 (58.1%); 276.0 (19.2%); 234.2 (24.3%); 144.2 (72.9%); 130.2 (40.9%)

***(2S)-Leucine Ethylester Trifluoromethylsulfonylamide 90***

**Operating Procedure** :




(2*S*)-**93** (2*S*)-**90**

In a two-necked round-bottomed flask fitted with a septum, an argon inlet and a magnetic stirrer, aminoester **93** is dissolved in dry triethylamine and dry dichloromethane. The mixture is cooled at -78°C. Triflic anhydride ($Tf_2O$) is added in fractions by syringe in 30 minutes. The reaction temperature is brought back to room temperature. After an hour at room temperature, the reaction mixture is concentrated under vacuum. The oil is extracted three times with diethylether (3x70 ml). The ethereal phase is washed with a portion of brine and dried over $MgSO_4$. 14.5 g of an oil is recovered after evaporation under vacuum

**Quantities Engaged** :

(2*S*)-Leucine ethylester : 10.0 g, 51.1 mmol, 1 eq.

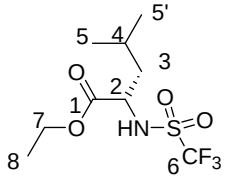
Triflic anhydride : 8.6 ml, 14.4 g, 1.0 eq.

Triethylamine : 14.2 ml, 10.3 g, 2.0 eq.

Chloroform : 100 ml, 148.9 g, 24.4 eq.

**Purification** : The product is purified by bulb-to-bulb distillation under vacuum (*ca*. 75°C at $7x10^{-3}$mbar). 10.15 g of colorless oil are recovered.

**Name** : (2*S*)-4-Methyl-2-trifluoromethanesulfonylamino-pentanoic acid ethyl ester




(2*S*)-**90**

**M.F.** : $C_9H_{16}F_3NO_4S$ **M.W.** : 291,29

**Yield** : 10.15 g (68.2%)

**Physical Property** : colorless oil

**$^1$H NMR** ($CDCl_3$, 200 MHz) : 4.5-5.0 (bs, 1H, N*H*), 4.23 (apparent quint, $^3J_{2,3}$= 6,9 & $^3J_{7,8}$=7.2, 3H, $H^{2\&7}$), 1.78 (m, 1H, $H^4$), 1.62 (m, 2H, $H^3$), 1.31 (t, $^3J_{7,8}$=7.1, 3H, $H^8$), 0.97 (dd, *J*=1.9, $^3J_{4,5}$=6.4, 6H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 171.7* ($C^1$), 119.4* (q, $^1J_{C,F}$=320.5, $C^6$), 62.3* ($C^7$), 55.8 ($C^2$), 42.4* ($C^3$), 24.2, 22.6, 21.3 ($C^{4,5,5'}$), 13.9 ($C^8$)

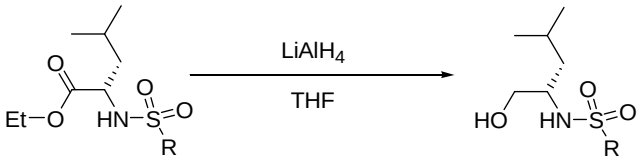
**$^{19}$F NMR** ($CDCl_3$, 282.2MHz) : -78.0 (s)

**IR** (solid deposit, $cm^{-1}$) : 3277 (br, N-H); 2.965, 2877 (C-H); 1731 (C=O); 1466 ($CH_3$ or $CH_2$); 1382 (S=O); 1233; 1197; 1148; 1086; 1025

**Mass** (EI, 70eV) : 292.0 ($[M+1]^+$, 4.6%); 246.0 ($[M-(OEt)]^+$, 1.2%); 235.0 ($[M-(C_4H_8)]^+$, 5.0%); 218.0 ($[M-(CO_2Et)]^+$, 100%); 175.9 ($[M-(CO_2Et)-(C_3H_7)]^+$, 5.0%); 161.9 ($[M-(CO_2Et)-(C_4H_8)]^+$, 11.5%)

## 12.1.2. Reduction of Sulfonamido esters

***General Procedure B***




In a flame-dried two-necked round-bottomed flask fitted with a septum, an argon inlet and a magnetic stirring bar, lithium aluminum hydride ($LiAlH_4$) is weighted and suspended in dry THF (half the total volume). This flask is cooled at 0°C in an ice-bath. In a flame-dried two-necked round-bottomed flask fitted with a septum and an argon inlet, the sulfonamide ester is weighted and dissolved in dry THF (half the total volume). This solution is added to the hydride suspension in fractions over 5 minutes via a syringe.

After a few hours at 0°C, the reaction is mixture is quenched by adding cautiously and successively calculated amounts of water, 15% solution of sodium hydroxide and water (*n* g of $LiAlH_4$ requires *n* ml of water, *n* ml of NaOH (15%) and 3*n* ml of water) (See the following reference[436]).

***(2S)-Leucinol Phenylsulfonylamide 89***

**Operating Procedure** : see General Procedure B

**Reaction time** : 2 hours

**Quantities Engaged** :

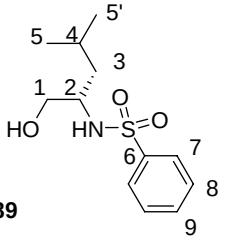
(2*S*)-Leucine ethylester phenylsulfonylamide **88**: 2.33 g, 7.79 mmol, 1 eq.

Lithium Aluminum hydride : 0.888 g, 3.0 eq.

Dry THF : 115 ml, 102 g, 182 eq.

**Purification** : After quenching, the reaction mixture is filtered over Celite. Unfortunately, the filtration is difficult and only ±0.8 g of matter is recovered after concentration under vacuum. The Celite and precipitate are extracted with large volumes of warm $Et_2O$. After filtration and evaporation, the presence of inorganic salts required the solubilization of the product in dichloromethane and washing with a $H_2SO_4$ solution (±20%) followed by NaOH (2M) and water. After drying and concentration under vacuum, the product was purified by flash chromatography on silica gel (cyclohexane/AcOEt/$Et_3N$, 25/70/5, $R_f$=0.27). 1.44 g of a white solid is obtained.

**Name** : (2*S*)-*N*-(1-Hydroxymethyl-3-methyl-butyl)-benzenesulfonamide




(2*S*)-**89**

**M.F.** : $C_{12}H_{19}NO_3S$ **M.W.** : 257.35

**Yield** : 1.44 g (72%)

**Physical Property** : white solid

$[\alpha]_D^{30}$ =-29.0 (*c*0.5, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.92 (d, $^3J_{7,8}$=6.9, 2H, $H^7$), 7.65-7.48 (m., 3H, $H^{8,9}$), 4.77 (bd, $^3J_{NH,2}$=8.0, 1H, N*H*), 3.57 (m, $^2J_{AB}$=23,3, 1H, $H^{1A}$), 3.49 (m, $^2J_{AB}$=23,2, 1H, $H^{1B}$), 3.31 (m, 1H, $H^2$), 2.1 (bs, 1H, O*H*), 1.42 (hept, *J*= 7.1, 1H, $H^4$), 1.24 (apparent t, $^3J_{3,4}$ & $^3J_{2,3}$ =6.8 & 7.9, 2H, $H^3$), 0.69 (dd, *J*=46.0, $^3J_{4,5}$=6.5, 6H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 140.5* ($C^6$), 132.7 ($C^9$), 129.1 ($C^8$), 127,1 ($C^7$), 65.2* ($C^1$), 53.8 ($C^2$), 40.9* ($C^3$), 24.9 ($C^4$), 22.7, 21.8 ($C^{5,5'}$)

**Mass** (EI, 70eV) : 258.2 ($[M+1]^+$,0.5%); 227.2 ($[M-(CH_2O)]^{\cdot+}$, 12.9%); 226.1 ($[M-(CH_2OH)]^+$, 100%); 184.1 ($[M-(CH_2OH)-(C_3H_7)]^+$, 6.1%); 170.1 ($[M-(CH_2OH)-(C_4H_9)]^+$, 20%); 141.0 ($[SO_2Ph]^+$, 29.2%); 77.1 ($[C_6H_5]^+$, 12.6%)

**Elemental Analysis** :

| | | | | |
|---|---|---|---|---|
| Calculated: | C 56.01% | H 7.44% | N 5.44% | S 12.46% |
| Found: | C 55.75% | H 7.20% | N 5.37% | S 12.27% |

***(2S)-Leucinol Methylsulfonylamide 94***

**Operating Procedure** : see General Procedure B

**Reaction time** : 2 hours

**Quantities Engaged** :

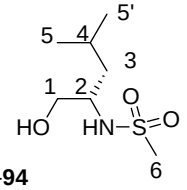
(2*S*)-Leucine ethylester methylsulfonylamide **91**: 2.50 g, 10.53 mmol, 1 eq.

Lithium Aluminumhydride : 0.60 g, 1.5 eq.

Dry THF : 100 ml, 89 g, 117 eq.

**Purification** : After quenching, the reaction mixture is acidified with HCl (1 M) and extracted with several portions of dichloromethane. The combined organic phases are washed successively with saturated $NaHCO_3$ and water. After drying over $MgSO_4$ and concentration under vacuum, the product is purified by flash chromatography on silica gel ($AcOEt/Et_3N$ , 95/5, $R_f$=0.26, ninhydrine). 2.04 g of a slightly yellow oil are obtained

**Name** : (2*S*)-*N*-(1-Hydroxymethyl-3-methyl-butyl)-methanesulfonamide




(2*S*)-**94**

**M.F.** : $C_7H_{17}NO_3S$ **M.W.** : 195.28

**Yield** : 2.04 g (99%)

**Physical Property** : yellowish oil

$[\alpha]_D^{30}$ =-26.6 (*c*1.0, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 5.31 (bd, $^3J_{NH,2}$=8.0, 1H, N*H*), 3.72 (mult, 1H, $H^2$), 3.44-3.56 (m, 2H, $H^1$), 3.23 (bs, 1H, O*H*), 3.04 (s, 3H, $H^6$), 1.75-1.82 (m, 1H, $H^4$), 1.25-1.45 (m, 2H, $H^3$), 0.94 (d, $^3J_{4,5}$=6.5, 6H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 65.3* ($C^1$), 54.2 ($C^2$), 41.7 ($C^6$), 41.1* ($C^3$), 24.4 ($C^4$), 22.8 & 22.0 ($C^{5\&5'}$)

**IR** (solid deposit, $cm^{-1}$) : 3495 (br, O-H); 3286 (br, N-H); 2957, 2871 (C-H); 1470, 1414 ($CH_3$ or $CH_2$); 1309 (S=O); 1143; 1073; 988

**Mass** (EI, 70eV) : 196.2 ($[M+1]^+$, 1.1%); 165.1 ($[M-(CH_2O)]^{\cdot+}$, 7.5%); 164.1 ($[M-(CH_2OH)]^+$, 100%); 122.0 ($[M-(CH_2OH)-(C_3H_7)]^+$, 18.5%); 108.0 ($[M-(CH_2OH)-(C_4H_9)]^+$, 29.1%); 79.0 ($[SO_2Me]^+$, 24.7%)

**Elemental Analysis** :

| | | | |
|---|---|---|---|
| Calculated: | C 43.06% | H 8.77% | N 7.17% |
| Found: | C 42.75% | H 8.57% | N 6.97% |

***(2S)-Leucinol Trifluoromethylsulfonylamide 95***

**Operating Procedure** : see General Procedure B

**Reaction time** : 2 hours

**Quantities Engaged** :

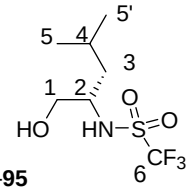
(2*S*)-Leucine Ethylester Trifluoromethylsulfonylamide **90**:5.00 g, 17.16 mmol, 1 eq.

Lithium aluminum hydride : 0.977 g, 1.5 eq.

Dry THF : 175 ml, 155 g, 126 eq.

**Purification** : After quenching, the reaction mixture is acidified with HCl (1 M), neutralized with NaOH (15%) and saturated $NH_4Cl$. After stirring overnight, the mixture is filtered over Celite then extracted with several portions of dichloromethane (4x50 ml). The combined organic phases are washed successively with saturated $NaHCO_3$ and water. After drying over $MgSO_4$ and concentration under vacuum, a slightly yellow powder (3.82 g) is obtained with sufficient purity. The product has a strong characteristic odor of rancid butter.

**Name** : (2*S*)-*C,C,C*-Trifluoro-*N*-(1-hydroxymethyl-3-methyl-butyl)-methane sulfonamide




(2*S*)-**95**

**M.F.** : $C_7H_{14}F_3NO_3S$ **M.W.** : 249.25

**Yield** : 3.82 g (89%)

**Physical Property** : yellowish solid

$[\alpha]_D^{30}$ =-26.4 (*c*0.5, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 5.2-5.3 (bs, 1H, N*H*), 3.75-3.85 (m, 1H, $H^2$), 3.6-3.75 (m, 2H, $H^1$), 1.8 (bs, 1H, O*H*), 1.69 (m, 1H, $H^4$), 1.49 (m, 2H, $H^3$), 0.95 (d, 6H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 119.5* (q, $^1J_{C,F}$=320.5, $C^6$), 64.7* ($C^1$), 55.5 ($C^2$), 41.0* ($C^3$), 24.4 ($C^4$), 22.5 ($C^5$), 22.1 ($C^{5'}$)

**$^{19}$F NMR** ($CDCl_3$, 282.2MHz) : -78.2 (s)

**Mass** (EI, 70eV) : 219.1 ($[M-(CH_2O)]^{\cdot+}$, 5.2%); 218.0 ($[M-(CH_2OH)]^+$, 100%); 191.9 (7.2%); 175.9 ($[M-(CH_2OH)-(C_3H_7)]^+$, 6.0%); 161.9 ($[M-(CH_2OH)-(C_4H_9)]^+$, 10.7%); 69.0 ($[CF_3]^+$, 9.9%); 43.0 ($[C_3H_7]^+$, 61%)

**Elemental Analysis** :

| | | | | |
|---|---|---|---|---|
| Calculated: | C 33.73% | H 5.66% | N 5.62% | S 12.86% |
| Found: | C 33.95% | H 5.68% | N 5.50% | S 12.84% |

***Attempted Reduction of Ethylester pentafluorophenylsulfonylamide 92***

**Operating Procedure** : see General Procedure B

**Reaction time** : 1 hour

**Quantities Engaged** :

(2*S*)-Leucine ethylester pentafluorohenylsulfonylamide **92**: 0.267 g, 0.69 mmol, 1 eq.

Lithium Aluminumhydride : 0.0850 g, 3.0 eq.

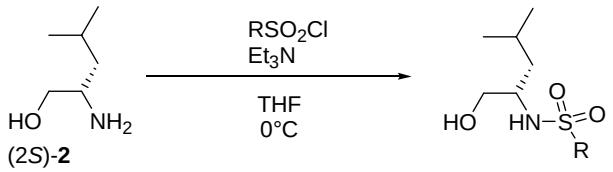
Dry THF : 20 ml, 17.8 g, 360 eq.

**Purification** : After quenching, the reaction mixture is filtered over Celite.

Note : A drop of yellowish oil is obtained and analyzed by $^1$H NMR. A complex mixture is obtained in which the signals of the reagent are not recognized and which contains signals characteristic of aromatic protons. The reaction is abandoned.

## 12.1.3. Direct Sulfonylation of (2*S*)-Leucinol

***General Procedure C***




A flame-dried two-necked round-bottomed flask fitted with a septum , an argon inlet and a magnetic stirring bar is charged with (2*S*)-Leucinol **2**, THF and triethylamine. After cooling the reaction mixture in an ice-bath, the corresponding sulfonyl chloride is added via syringe. The temperature is slowly brought back to room temperature. After some defined time, the reaction media is concentrated under vacuum and purified.

***(2S)-Leucinol Phenylsulfonylamide 89***

**Operating Procedure** : see General Procedure C

**Reaction time** : 4 hours

**Quantities Engaged** :

(2*S*)-Leucinol **2**: 2.18 ml, 2.00 g, 16.90 mmol, 1 eq.

Phenylsulfonyl chloride : 2.18 ml, 3.01 g, 1.0 eq.

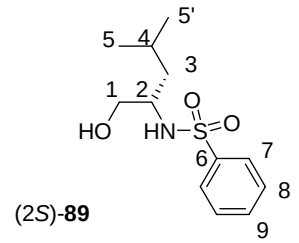
Triethylamine : 4.70 ml, 3.41 g, 2.0 eq.

Dry THF : 21.8 ml, 19.3 g, 16 eq.

**Purification** : The mixture is extracted with several portions of ether. The combined ethereal phases are transferred to an extraction funnel and washed successively with HCl (1 M), saturated $NaHCO_3$ and brine. After drying over $MgSO_4$ and concentration under vacuum, the product is purified by flash chromatography

on silica gel (cyclohexane/AcOEt/$Et_3N$, 25/70/5, $R_f$=0.27). 3.65 g of a white solid are obtained

**Name** : (2*S*)-*N*-(1-Hydroxymethyl-3-methyl-butyl)-benzenesulfonamide




(2*S*)-**89**

**M.F.** : $C_{12}H_{19}NO_3S$ **M.W.** : 257.35

**Yield** : 3.65 g (84%)

**Physical Property** : white solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

***(2S)-Leucinol Methylsulfonylamide 94***

**Operating Procedure** : see General Procedure C

**Reaction time** : 4 hours

**Quantities Engaged** :

(2*S*)-Leucinol **2**: 2.18 ml, 2.00 g, 16.90 mmol, 1 eq.

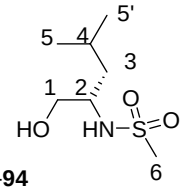
Methylsulfonyl chloride : 1.32 ml, 1.95 g, 1.0 eq.

Triethylamine : 4.70 ml, 3.41 g, 2.0 eq.

Dry THF : 21.8 ml, 19.3 g, 16 eq.

**Purification** : The mixture is extracted with several portions of ether. The combined ethereal phases are transferred to an extraction funnel and washed successively with water and brine. After drying over $MgSO_4$ and concentration under vacuum, the product was purified by flash chromatography on silica gel (AcOEt/$Et_3N$, 95/5, $R_f$=0.26, ninhydrine). 1.62 g of a slightly yellow oil is obtained

**Name** : (2*S*)-*N*-(1-Hydroxymethyl-3-methyl-butyl)-methanesulfonamide




(2*S*)-**94**

**M.F.** : $C_7H_{17}NO_3S$ **M.W.** : 195.28

**Yield** : 1.62 g (49%)

**Physical Property** : yellowish oil

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

***(2S)-Leucinol Pentafluorophenylsulfonylamide 96***

**Operating Procedure** : see General Procedure C

**Reaction time** : 4hours

**Quantities Engaged** :

(2*S*)-Leucinol **2**: 0.5 ml, 0.459 g, 3.87 mmol, 1 eq.

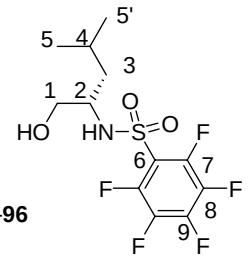
Pentafluorophenylsulfonyl chloride : 0.58 ml, 1.04 g, 1.0 eq.

Triethylamine : 0.54 ml, 0.39 g, 1.0 eq.

Dry THF : 5.0 ml, 4.44 g, 16 eq.

**Purification** : The mixture is extracted with several portions of ether. The combined ethereal phases are transferred to an extraction funnel and washed successively with HCl (1 M), saturated $NaHCO_3$ and brine. After drying over $MgSO_4$ and concentration under vacuum, the product is purified by flash chromatography on silica gel (cyclohexane/AcOEt/$Et_3N$, 40/55/5, $R_f$=0.38). 0.57 g of a white solid is obtained

**Name** : (2*S*)-2,3,4,5,6-Pentafluoro-*N*-(1-hydroxymethyl-3-methyl-butyl)-benzenesulfonamide




(2*S*)-**96**

**M.F.** : $C_{12}H_{14}F_5NO_3S$ **M.W.** : 347.30

**Yield** : 0.57 g (42%)

**Physical Property** : white solid

$[\alpha]_D^{30}$ =+3.8 (*c*0.5, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 5.70 (bd, $^3J_{NH,2}$=8.3, 1H, N*H*), 3.62 (m, 2H, $H^1$), 3.51 (m, 1H, $H^2$), 2.23 (bdd, $^3J_{OH,1a}$=4.9, $^3J_{OH,1b}$=5.3, 1H, O*H*), 1.61 (hept, *J*= 6.5, 1H, $H^4$), 1.28-1.45 (m, 2H, $H^3$), 0.87 (dd, *J*=27.0, $^3J_{4,5}$=6.6, 6H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 144.3* (dm, $^1J_{C,F}$=258, $C^7$), 143.6* (dm, $^1J_{C,F}$=264, $C^9$), 137.9* (dm, $^1J_{C,F}$=279, $C^8$), 117.6* (m, $C^6$), 65.0* ($C^1$), 55.0 ($C^2$), 40.6* ($C^3$), 24.4 ($C^4$), 22.7 ($C^5$), 21.8 ($C^{5'}$)

**$^{19}$F NMR** ($CDCl_3$, 282.2MHz) : -137.3 (dmult, *J*=20.9, $F^9$), -147.0 (apparent tt, *J*=21, *J*=6.2, $F^{7or8}$), -150.9 (m, $F^{7or8}$)

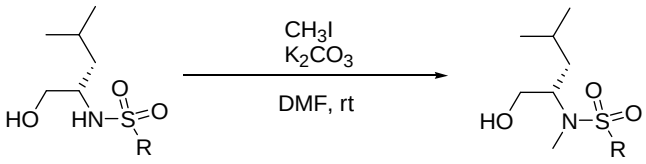
**Mass** (EI, 70eV) : 330.0 ($[M-(OH)]^+$, 0.7%); 316.0 ($[M-(CH_2O)]^+$, 100%); 274.0 ($[M-(CH_2OH)-(C_3H_7)]^+$, 22.0%); 260.0 ($[M-(CH_2OH)-(C_4H_9)]^+$, 30.6%); 231.0 ($[SO_2C_6F_5]^+$, 20.7%); 167.0 ($[C_6F_5]^+$, 5.6%)

**Elemental Analysis** :

| | | | | |
|---|---|---|---|---|
| Calculated: | C 41.50% | H 4.06% | N 4.03% | S 9.23% |
| Found: | C 41.84% | H 3.90% | N 3.99% | S 9.12% |

## 12.1.4. Methylation of Sulfonamido alcohol (2*S*)-Leucinol Derivatives

***General Procedure D***




This procedure is based on a published procedure[437]

A one-necked round-bottomed flask, fitted with a magnetic stirring bar, is charged with the sulfonamido alcohol, potassium carbonate and *N,N*-dimethyl formamide (DMF). The methyl iodide is added at once to the suspension which is stirred at room temperature. The reactions are followed by thin layer chromatography.

***(2S)-N-methylated Leucinol Phenylsulfonylamide 97***

**Operating Procedure** : see General Procedure D

**Reaction time** : 2 hours

**Quantities Engaged** :

(2*S*)-**89**: 0.413 g, 1.60 mmol, 1 eq.

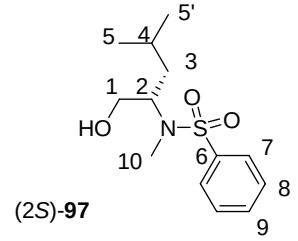
Methyl iodide : 0.30 ml, 0.68 g, 3 eq.

Potassium carbonate : 1.33 g, 6 eq.

DMF : 5.0 ml, 4.7 g, 40 eq.

**Purification** : After 2 hours, 20 ml of water (4 x volume of DMF) are added to the reaction mixture which is then extracted with 3 portions of diethylether. The combined organic phases are washed successively with HCl (1M) and brine. After drying over $MgSO_4$ and concentration under vacuum, the product is purified by flash chromatography on silica gel (cyclohexane/AcOEt/$Et_3N$, 50/45/5, $R_f$=0.38). The product is recrystallized in a minimum of dichloromethane and n-hexane. 0.38 g of a white solid is obtained.

**Name** : (2*S*)-*N*-(1-Hydroxymethyl-3-methyl-butyl)-*N*-methyl-benzenesulfonamide




(2*S*)-**97**

**M.F.** : $C_{13}H_{21}NO_3S$ **M.W.** : 271.38

**Yield** : 0.38 g (88%)

**Physical Property** : white solid

$[\alpha]_D^{30}$ =-11.6 (*c*0.95, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.86, (d, $^3J_{7,8}$=8.4, 2H, $H^7$), 7.50-7.58 (m, 3H, $H^{8,9}$), 4.05 (mult., 1H, $H^2$), 3.42-3.58 (m, 2H, $H^1$), 2.76 (s, 3H, $H^{10}$), 1.97 (bs, O*H*), 1.39 (hept, *J*= 6.7, 1H, $H^4$), 1.13 (m, 2H, $H^3$), 0.81 (dd, *J*=4.4, $^3J_{4,5}$=6.6, 6H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 62.9 MHz) : 139.9 ($C^6$), 132.5 ($C^9$), 129.0 & 127.2 ($C^{7\&8}$), 62.5 ($C^1$), 57.2 ($C^2$), 37.4 ($C^3$), 28.2 ($C^{10}$), 24.6 ($C^4$), 22.8 & 22.4 ($C^{5\&5'}$)

**Mass** (EI, 70eV) : 271.4 ($[M]^{\cdot+}$, traces); 241.6 (19%); 240.2 ($[M-(CH_2OH)]^+$, 100%); 77.3 ($[C_6H_5]^+$, 43.9%)

**Elemental Analysis** :

| | | | | |
|---|---|---|---|---|
| Calculated: | C 57.54% | H 7.80% | N 5.16% | S 11.82% |
| Found: | C 57.36% | H 7.89% | N 5.27% | S 11.51% |

***(2S)-N-methylated Leucinol Pentafluorophenylsulfonylamide 98***

**Operating Procedure** : see General Procedure D

**Reaction time** : 4h30

**Quantities Engaged** :

(2*S*)-**96** : 1.023 g, 2.95 mmol, 1 eq.

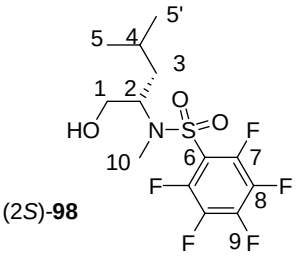
Methyl iodide : 0.55 ml, 1.25 g, 3 eq.

Potassium carbonate : 2.44 g, 6 eq.

DMF : 10.0 ml, 9.45 g, 44 eq.

**Purification** : After 4h30, 40 ml of water (4 x volume of DMF) are added to the reaction mixture which is extracted with 3 portions of diethylether (40 ml). The combined organic phase are washed successively with HCl (1 M) and brine. After drying over $MgSO_4$ and concentration under vacuum, the product is purified by flash chromatography on silica gel (cyclohexane/AcOEt/$Et_3N$, 70/25/5, $R_f$=0.22). The residues of solvents are removed from the thick oil by heating it at 50°C under vacuum in a horizontal distillation apparatus.

**Name** : (2*S*)-*N*-(1-Hydroxymethyl-3-methyl-butyl)-*N*-methyl-benzenesulfonamide




(2*S*)-**98**

**M.F.** : $C_{13}H_{16}F_5NO_3S$ **M.W.** : 361.33

**Yield** : 0.91 g (86%)

**Physical Property** : slightly yellow oil

$[\alpha]_D^{30}$ =-1.3 (*c*1.1, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 4.15 (m, 1H, $H^2$), 3.61 (dd, $^2J_{AB}$=11.5, $^3J_{1,2}$=4.4, 1H, $H^{1A}$), 3.52 (dd, $^2J_{AB}$=11.5, $^3J_{1,2}$=9.4, 1H, $H^{1B}$), 2.92 (t, *J*=1.6, 3H, $H^{10}$), 1.60 (heptt, *J*=6.7, *J*=1.7, 1H, $H^4$), 1.46-1.28 (bs, 1H, O*H*), 1.35 (ddd, $^2J_{AB}$=14.1, *J*=8.8, *J*=5.4, 1H, $H^{3A}$), 1.18 (ddd, $^2J_{AB}$=14.1, *J*=8.4, *J*=5.6, 1H, $H^{3B}$), 0.93 & 0.92(dd, $^3J_{4,5}$=$^3J_{4,5'}$=6.5, 2x3H, $H^{5\&5'}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 144.6* (dm, $^1J_{C,F}$=263.4, $C^7$), 143.4* (dm, $^1J_{C,F}$=261, $C^9$), 137.6* (dm, $^1J_{C,F}$=254, $C^8$), 116.5* (m, $C^6$), 62.1* ($C^1$), 57.8 ($C^2$), 37.4* ($C^3$), 28.0 ($C^{10}$), 24.4 ($C^4$), 22.9 ($C^5$), 21.9 ($C^{5'}$)

**$^{19}$F NMR** ($CDCl_3$, 282.2MHz) : -134.1 (dmult, *J*=21.2, $F^9$), -147.0 (apparent tt, *J*=21.1, *J*=6.0, $F^{7or8}$), -159.3 (tmult, *J*=16.5, $F^{7or8}$)

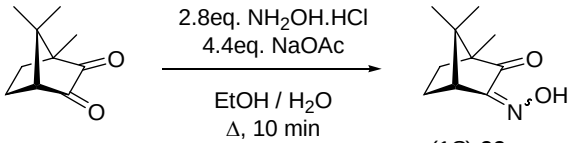
**Mass** (EI, 70eV) : 330.1 ($[M-(CH_2O)]^+$, 100%); 288.1 ($[M-(CH_2OH)-(C_3H_7)]^+$, 21.0%); 274.0 ($[M-(CH_2OH)-(C_4H_9)]^+$, 18.6%); 231.0 ($[SO_2C_6F_5]^+$, 7.5%); 167.1 ($[C_6F_5]^+$, 3.3%)

**Elemental Analysis** :

| | | | |
|---|---|---|---|
| Calculated: | C 43.21% | H 4.46% | N 3.88% |
| Found: | C 42.81% | H 4.54% | N 3.34% |

## 12.2. Synthesis of (1*S*)-Camphorquinone-based Sulfonamido alcohols

***(1S,4R)-1,7,7-Trimethyl-bicyclo[2.2.1]heptane-2,3-dione 3-oxime***




(1*S*)-**99**

**Ref.** : operating procedure and spectral data[185]

**Operating Procedure** : see [185]

**Quantities Engaged** :

(1*S*)-camphorquinone : 11.14 g, 66.4 mmol, 1 eq.

Hydroxylamine hydrochloride : 13.37 g, 2.8 eq.

Sodium Acetate : 24.33 g, 4.4 eq.

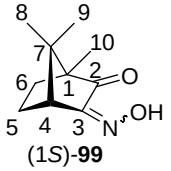
Ethanol : 180 ml, 141.3 g, 46.2 eq.

Water : 90 ml, 90 g, 75.3 eq.

**TLC** : cyclohexane/AcOEt (50/50) $R_f$=0.25 (product), 0.44 (camphorquinone)

**Purification** : The product is used without further purification than the one specified in the literature's operating procedure. 11.48 g of a white solid are obtained. The solid contains the *syn* and *anti* oxime isomers in a 13:87 ratio as measured by $^1$H NMR (without knowledge of the respective assignment).

**Name** : (1*S,*4*R*)-1,7,7-Trimethyl-bicyclo[2.2.1]heptane-2,3-dione 3-oxime




(1*S*)-**99**

**CAS-RN** : 251645-83-7

**M.F.** : $C_{10}H_{15}NO_2$ **M.W.** : 181.23

**Yield** : 11.48 g (94%)

**Physical Property** : off-white solid

**Melting point** : 134-138°C (lit: 142-143°C after recrystallization)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 10.5-8.5 (broad hump, 1H, O*H*), 3.26 & 2.72 (2 d, 0,83H et 0,17H, *J*= 4.3 et *J*= 3.8, $H^4$ of *anti* & *syn* isomers), 2.2-1.35 (m, 4H, $H^{5,6}$), 1.03 & 1.02 & 1.00 & 0.93 & 0,88 (5s, 9H, $H^{8\text{-}9\text{-}10}$).

**$^{13}$C NMR** ($CDCl_3$, 50.2 MHz) :

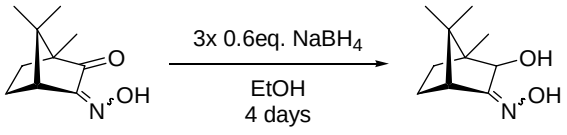
Major isomer : 204.5* ($C^2$) ; 159.6* ($C^3$) ; 58.5* ($C^1$) ; 46.6* ($C^4$) ; 44.9* ($C^7$), 30.7* ($C^6$) ; 23.7* ($C^5$) ; 20.6 & 17.6 (2C, $C^{8\text{-}9}$) ; 8.9 ($C^{10}$)

Minor isomer : 204.7* ($C^2$) ; 156.1* ($C^3$), 59.5* ($C^1$), 49.6* ($C^4$), 46.9* ($C^7$), 29.9* ($C^6$), 25.5* ($C^5$), 20.6 & 18.0 (2C, $C^{8\text{-}9}$), 8.4 ($C^{10}$)

**IR** ($CHCl_3$, $cm^{-1}$) : 3565 (O-H, *anti* isomer), 3500-3100 (br, O-H···O, *syn* isomer), 3000-2840 (C-H), 1748 (C=O), 1653 (C=N)

**Mass** (EI, 70eV) : 181.2 ($[M]^{\cdot+}$, 51%); 136.2 (100%); 109.2 (23%); 95.2 (17%); 94.2 (15.5%)

## ***(1S,2R,4R)-3-Hydroxy-4,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one oxime***




(1*S*)-**99** (1*S*)-**100**

94% yield

**Ref.** : operating procedure and spectral data[185]

**Operating Procedure** : see [185]

Note : Additional sodium borohydride had to be added for full conversion (TLC monitoring) since it was an old flask.

**Quantities Engaged** :

(1*S*)-ketooxime **99**: 11.42 g, 62.99 mmol, 1 eq.

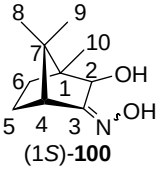
Sodium borohydride : 1.37 g, 0.57 eq. (3 x)

Ethanol : 73 ml, 57.3 g, 19.8 eq.

**TLC** : cyclohexane/AcOEt (50/50) $R_f$=0.22 (product)

**Purification** : The product is used without further purification than the one specified in the literature's operating procedure. 10.73 g of a white solid are obtained. The solid contains the *syn* and *anti* oxime isomers in a 19:81 ratio as measured by $^1$H NMR (without knowledge of the respective assignment).

**Name** : (1*S*,2*R*,4*R*)-3-Hydroxy-4,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one oxime




(1*S*)-**100**

**CAS-RN** : 162425-97-0

**M.F.** : $C_{10}H_{17}NO_2$ **M.W.** : 183.25

**Yield** : 10.75 g (93%)

**Physical Property** : white solid

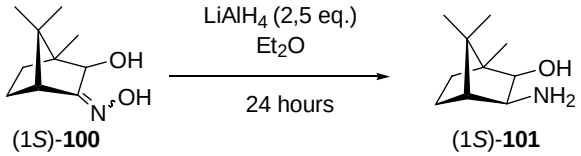
**Melting point** : 139-142°C (lit: 116-118°C)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 8.4-8.8 (br double hump, 1H, O*H* or NO*H*), 4.26 & 3.94 (2 s, 0,1H et 0,9H, $H^2$), 4.8 (br double hump, 1H, O*H* or NO*H*), 3.05 & 2.33 (2d, $^3J_{4,5exo}$=4.4 & $^3J_{4,5exo}$=4.1, 0.9H & 0,1 H respectively, $H^4$), 1.96-1.05 (m, 4H, $H^{5,6}$), 1.05, 0.99, 0.94, 0.93, 0.88, 0.84 (6s, 9H, $H^{8,9,10}$)

**$^{13}$C NMR** ($CDCl_3$, 50.2 MHz) : Major isomer of the isomer mixture: 170.3* ($C^3$), 78.0 ($C^2$), 49.6* ($C^{1or7}$), 47.6 ($C^4$), 47.5*($C^{1or7}$), 33.7* ($C^6$), 22.9* ($C^5$), 21.3, 19.0 & 10.7 ($C^{8,9\&10}$).

**Mass** (EI, 70eV) : 183.2 ($[M]^{\bullet+}$, 6.3%); 166.2 ($[M-(OH)]^+$, 100%); 136.2 (37.9%) ; 125.2 (22.1%) ; 110.1 (38.7%) ; 95.2 (25.6%) ; 84.1 (21.3%)

## ***(1S,2R,3S,4R)-3-Amino-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol 101***




(1*S*)-**100** (1*S*)-**101**

**Ref.** : operating procedure[186]

spectral data[185]

**Operating Procedure** : In a flame-dried two-necked round-bottomed 1000 ml flask fitted with a septum and an argon inlet and a magnetic stirring bar, lithium aluminum hydride ($LiAlH_4$) is weighted and suspended in dry THF (half the total solvent volume). This flask is cooled at 0°C in an ice-bath. In a flame-dried two-necked round-bottomed flask fitted with a septum and an argon inlet, the alcohol oxime **100** is weighted and dissolved in dry THF (half the total volume). This solution is added to the hydride suspension in fractions over 2 hours via an addition funnel. Once the addition is finished, the addition funnel is replaced by a water condensator and the reaction is heated at reflux for 30 minutes. Once the reaction cools down, it is quenched.

**Quantities Engaged** :

(1*S*)-oximealcohol **100** : 8.38 g, 45.75 mmol, 1 eq.

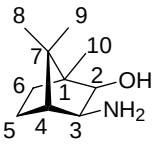
Lithium aluminum hydride : 4.41 g, 2.5 eq.

Diethylether : 754 ml, 534 g, 158 eq.

**Purification** : The reaction is mixture is quenched by adding cautiously and successively calculated amounts of water, 15% solution of sodium hydroxide and water (*n* g of $LiAlH_4$ requires *n* ml of water, *n* ml of NaOH (15%) and 3*n* ml of water) (See the following reference :[436]). The mixture is stirred vigorously for 20 minutes before being filtered over Celite. The solid is washed with methanol and the organic phase is concentrated under vacuum. The remaining aqueous phase is extracted with three portions of dichloromethane. The combined organic phases are dried over $MgSO_4$, filtered and evaporated under vacuum.

The resulting solid is then sublimated under vacuum (100°C, $5x10^{-2}$ mbar). 4.97 g of an off-white solid are obtained together with some impurities (observed by $^1$H NMR). The product is used as such in the following reactions.

**Name** : (1*S*,2*R*,3*S*,4*R*)-3-Amino-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol



(1*S*)-**101**

**CAS-RN** : 246029-30-1

**M.F.** : $C_{10}H_{19}NO$ **M.W.** : 169.26

**Yield** : 4.97 g (64%)

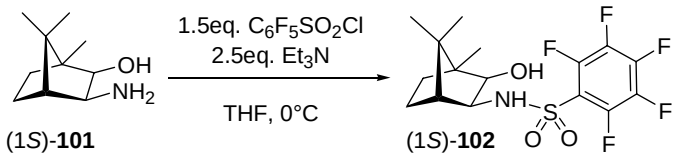
**Physical Property** : off-white solid

$[\alpha]_D^{30}$ =- 17.4(*c*1.45, $CHCl_3$)

**Melting point** : 175-182°C (lit: 190-194°C)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 3.39 (d, $^3J$= 7.2 Hz, 1H, $H^2$), 3.05 (d, J= 7.2 Hz, 1H, $H^3$), 2.0-2.8 (broad hump, 3H, N$H_2$ & O*H*), 1.55 (d, J= 4.5 Hz, 1H, $H^4$), 1.1-1.8 (m, 4H, $H^{5,6}$), 1.07 (s, 3H, $H^{10}$), 0.92 & 0.76 (2s, 6H, $H^{8,9}$).

***(1S,2R,3S,4R)-2,3,4,5,6-Pentafluoro-N-(3-hydroxy-4,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-benzenesulfonamide 102***



(1*S*)-**101** (1*S*)-**102**

**Operating Procedure** : A flame-dried two-necked round-bottomed flask fitted with a septum and an argon inlet and a magnetic stirring bar is charged with (1*S*)-**101**, THF and triethylamine. After cooling the reaction mixture in an ice-bath, the pentafluorophenylsulfonyl chloride is added *via* syringe. After 10 minutes, the temperature is brought back to room temperature. After 2h30, the reaction media is purified.

**Quantities Engaged** :

(1*S*)-aminoisoborneol **101**: 1.00 g, 5.85 mmol, 1 eq.

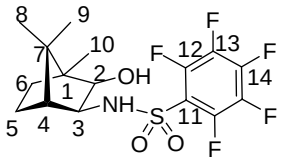
Pentafluorophenylsulfonyl chloride : 1.32 ml, 2.36 g, 1.5 eq.

Triethylamine : 2.00 ml, 1.48 g, 2.5 eq.

Dry THF : 15.0 ml, 13.3 g, 32 eq.

**Purification** : The solid is filtered over sintered glass and rinsed with ether. The combinate filtrates are washed successively with a saturated sodium bicarbonate solution and brine. After drying over $MgSO_4$ and concentration under vacuum, the product is purified by flash chromatography on silica gel (cyclohexane/AcOEt/$Et_3N$, 80/15/5, $R_f$=0.22). 0.986 g of a white solid is obtained.

**Name** : (1*S,*2*R*,3*S*,4*R*)-2,3,4,5,6-Pentafluoro-*N*-(3-hydroxy-4,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-benzenesulfonamide



(1*S*)-**102**

**M.F.** : $C_{16}H_{18}F_5NO_3S$ **M.W.** : 399.38

**Yield** : 0.986 g (42%)

**Physical Property** : white solid

**Melting point** : 109°C

$[\alpha]_D^{30}$ =+8.5 (*c*1.0, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 500 MHz) : 5.7-6.4 (broad hump, 1H, O*H* or N*H*), 3.70 (d, $^3J_{2,3}$=8.0, 1H, $H^2$), 3.43 (d, $^3J_{2,3}$=8.0, 1H, $H^3$), 2.0-2.6 (broad hump, 1H, or N*H*), 1.90 (d, $^3J_{4,5exo}$=4.5, 1H, $H^4$), 1.72 (apparent tt, dddd, $^2J_{AB}$=$^3J_{5exo,6exo}$=12.5, $^3J_{4,5exo}$=$^3J_{5exo,6endo}$=4.5, 1H, $H^{5exo}$), 1.50 (apparent td, ddd, $^2J_{AB}$=$^3J_{5exo,6exo}$=12.3, $^3J_{5endo,6exo}$=3.0, 1H, $H^{6exo}$), 0.95-1.10 (m, 2H, $H^{5endo\ \&\ 6endo}$), 1.06 , 0.92, 0.81 (3s, 3x3H, $H^{8,9,10}$)

**$^{13}$C NMR** ($CDCl_3$, 125.7 MHz) : 144.4 (dm, $^2J_{C,F}$=248, $C^{12or13}$), 143.7 (dm, $^2J_{C,F}$=261, $C^{14}$), 137.8 (dm, $^2J_{C,F}$=261, $C^{12or13}$), 116.4 (m, $C^{11}$), 78.9 ($C^2$), 60.3 ($C^3$), 50.7 ($C^4$), 49.1 & 46.8 ($C^{1\&7}$), 32.7 ($C^6$), 25.9 ($C^5$), 21.5 & 20.7 ($C^{8\&9}$), 11.0 ($C^{10}$)

**$^{19}$F NMR** ($CDCl_3$, 235.4MHz) : -137.2 (s, $F^{12or13}$), -146.8 (s, $F^{14}$), -159.1 (s, $F^{12or13}$)

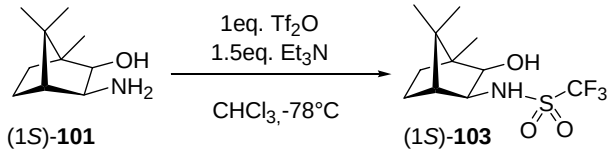
**IR** (KBr, $cm^{-1}$) : 3524 (O-H), 3280 (N-H), 2982-2880 (C-H), 1646 (C=$C_{ar}$), 1521, 1491, 1395, 1363 (S=O), 1332, 1295, 1167, 1102, 987

**Mass** (EI, 70eV) : 399.2 ($[M]^{\cdot+}$, trace); 231.0 ($[SO_2C_6F_5]^+$, 17.9%); 168.1 ($[M-(SO_2C_6F_5)]^+$, 100%); 167.0 ($[C_6F_5]^+$, 23.0%); 123.2 (14.0%); 95.1 (28.2%)

**Elemental Analysis** :

| | | | | |
|---|---|---|---|---|
| Calculated: | C 48.12% | H 4.54% | N 3.51% | S 8.03% |
| Found: | C 48.39% | H 4.44% | N 3.46% | S 8.08% |

***(1S,2R,3S,4R)-C,C,C-Trifluoro-N-(3-hydroxy-4,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-methanesulfonamide 103***




(1*S*)-**101** (1*S*)-**103**

49% yield

**Operating Procedure** : A flame-dried two-necked round-bottomed flask fitted with a septum and an argon inlet and a magnetic stirring bar is charged with (1*S*)-**101**, chloroform (8.4 ml) and triethylamine. In another flame-dried two-necked round-bottomed flask fitted with a septum and an argon inlet, triflic anhydride is dissolved in the rest of chloroform. After cooling the substrate mixture in a dry ice-isopropanol bath, the triflic anhydride solution is added slowly via syringe. After one hour, the temperature is brought back slowly to room temperature. The reaction media is concentrated under vacuum then purified.

**Quantities Engaged** :

(1*S*)-aminoisoborneol **101**: 070 g, 4.05 mmol, 1 eq.

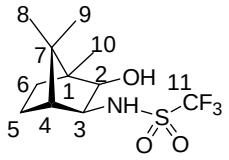
Triflic anhydride : 0.68 ml, 1.14 g, 1 eq.

Triethylamine : 0.85 ml, 0.62 g, 1.5 eq.

Dry $CHCl_3$ : 13.6 ml, 20.2 g, 41.7 eq.

**Purification** : The oil is dissolved in diethylether. The resulting solution is washed successively with a saturated sodium bicarbonate solution (3 times), water and brine. After drying over $MgSO_4$ and concentration under vacuum, the product is purified by flash chromatography on silica gel (cyclohexane/AcOEt, 75/25, $R_f$=0.43). 0.599 g of a white solid is obtained

**Name** : (1*S,*2*R*,3*S*,4*R*)-*C,C,C*-Trifluoro-*N*-(3-hydroxy-4,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl)-methanesulfonamide




(1*S*)-**103**

**M.F.** : $C_{11}H_{18}F_3NO_3S$ **M.W.** : 301.33

**Yield** : 0.599 g (49%)

**Physical Property** : white solid

$[\alpha]_D^{30}$ =+11.7 (*c*1.0, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 500 MHz) : 5.75 (bs, 1H, O*H* or N*H*), 3.82 (d, $^3J_{2,3}$=8.0, 1H, $H^2$), 3.68 (d, $^3J_{2,3}$=8.0, 1H, $H^3$), 2.4 (bs, 1H, O*H* or N*H*), 1.93 (d, $^3J_{4,5exo}$=5.0, 1H, $H^4$), 1.74 (apparent tt, dddd, $^2J_{AB}$=$^3J_{5exo,6exo}$=12.3, $^3J_{4,5exo}$=4.3, 1H, $H^{5exo}$), 1.52 (apparent td, ddd, $^2J_{AB}$=$^3J_{5exo,6exo}$=12.1, $^3J_{5endo,6exo}$=3.2, 1H, $H^{6exo}$), 0.8-1.1 (m, 2H, $H^{5endo\ \&\ 6endo}$), 1.05 (s, 3H, $H^{8or9}$), 0.95 (s, 3H, $H^{10}$), 0.84 (s, 3H, $H^{8or9}$)

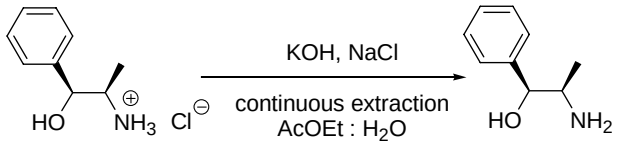
**$^{13}$C NMR** ($CDCl_3$, 125.7MHz) : 119.7 (q, $^2J_{C,F}$=321.5, $C^{11}$), 78.8 ($C^2$), 61.0 ($C^3$), 51.1 ($C^4$), 49.1 & 46.8 ($C^{1\&7}$), 32.6 ($C^6$), 25.9 ($C^5$), 21.5 & 20.7 ($C^{8\&9}$), 11.1 ($C^{10}$)

**$^{19}$F NMR** ($CDCl_3$, 282.2MHz) : -77.3 (s)

**Mass** (EI, 70eV) : 301.1 ($[M]^{\cdot+}$, 25.2%); 286.1 ($[M\text{-}CH_3]^+$, 100%); 270.1 ($[M\text{-}CH_3\text{-}CH_3]^+$, 29.5%); 268.1 ($[M\text{-}CH_3\text{-}H_2O]^+$, 51.8%); 243.0 (36.4%); 240.0 ($[M\text{-}CH_3\text{-}H_2O\text{-}C_2H_4]^+$,42.4%); 230.1 (21.0%); 215.1 ($[M\text{-}CH_3\text{-}H_2O\text{-}C_2H_4\text{-}C_2H_4]^{\cdot+}$, 33.4%); 168.1 ($[M\text{-}SO_2CF_3]^+$, 13.2%)

## 12.3. Soai's Dibutylnorephedrine ligand 13

***(1S,2R)-Norephedrine***




(1*S*,2*R*)-**104** · HCl (1*S*,2*R*)-**104**

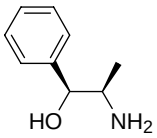
**Operating Procedure** : The commercial (1*S*,2*R*)-norephedrine chlorhydrate salt is dissolved in brine solution containing potassium hydroxide. This solution is placed in a continuous liquid-liquid extractor. The extractor is charged with ethyl acetate and left to run overnight. The organic phase is dried over $MgSO_4$, filtered and concentrated under vacuum. The norephedrine is recovered and used as such in the following alkylation reaction.

**Quantities Engaged** :

(1*S*,2*R*)-norephedrine chlorhydrate: 8.55 g, 45.6 mmol, 1 eq.

Potassium hydroxide : 2.56 g, 1 eq.

**Name** : (1*S*,2*R*)-2-Amino-1-phenyl-propan-1-ol




(1*S*,2*R*)-**104**

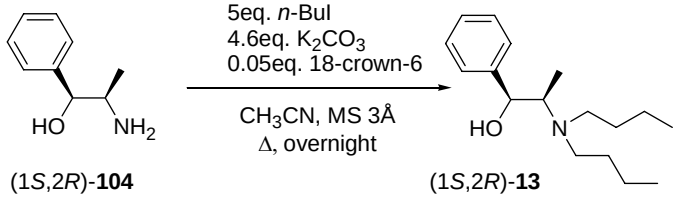
**CAS-RN** : 37577-28-9

**M.F.** : $C_9H_{13}NO$ **M.W.** : 151.21

**Yield** : 6.46 g (94%)

**Physical Property** : colorless oil

***(1S,2R)-2-(N,N-dibutylamino)-1-phenyl-propan-1-ol 13***




(1*S*,2*R*)-**104** (1*S*,2*R*)-**13**

**Ref. :** see [187]

**Operating Procedure :** Norephedrine, potassium carbonate, 18-C-6 crown ether and acetonitrile are charged into a one-necked round-bottomed flask fitted with a magnetic stirring bar, a water condensator and an argon inlet. The butyl iodide is then added at once and the flask is heated at reflux overnight. After cooling, the reaction media is filtered over Celite and concentrated under vacuum.

**Quantities Engaged** :

(1*S*,2*R*)-Norephedrine**104**: 6.30 g, 41.7 mmol, 1 eq.

*n*-Butyl iodide : 23.7 ml, 38.32 g, 5 eq.

Potassium carbonate : 26.38 g, 4.6 eq.

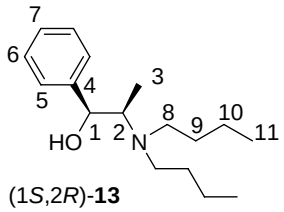
18-C-6 crown ether : 0.55 g, 0.05 eq.

Molecular Sieves 3Å : 1.5 g

Dry $CH_3CN$ : 100.0 ml, 78.1 g, 47 eq.

**Purification** : The product was purified by flash chromatography on neutral alumina (AcOEt $R_f$=0.82) followed by a bulb-to-bulb distillation under vacuum (±140°C at $2x10^{-2}$ mbar)

**Name** : (1*S*,2*R*)-2-(*N,N*-dibutylamino)-1-phenyl-propan-1-ol




(1*S*,2*R*)-**13**

**CAS-RN** : 114389-70-7

**M.F.** : $C_{17}H_{29}NO$ **M.W.** : 263.42

**Yield** : 8.44 g (77%)

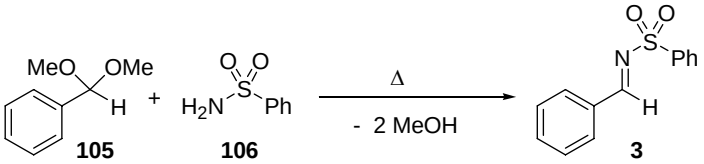
**Physical Property** : slightly yellow oil

**$^1$H NMR** ($CDCl_3$, 200 MHz) : 7.1-7.4 (m, 5H, $H^{5,6,7}$), 4.66 (d, $^3J_{1,2}$=5.0, 1H, $H^1$), 4.1-4.35 (br, 1H, O*H*), 2.9-3.1 (m, 1H, $H^2$), 2.2-2.4 (m, 4H, $H^8$), 1.1-1.55 (m, 8H, $H^{9,10}$), 0.8-1.0 (m, 9H, $H^{3\&11}$)

# 12.4. Imines, racemic adducts and secondary products

## 12.4.1. Imines 3 and 41

***N-Benzylidene-benzenesulfonamide 3***




**Ref** : Operating Procedure[188]

**Operating Procedure** : A one-necked round-bottomed flask fitted with a short distillation apparatus and a magnetic stirring bar is charged with benzaldehyde dimethylacetal **105** and benzenesulfonamide **106**. The reagents are heated to 160-170°C (melting occurs towards 140°C). The produced methanol is distilled during 3 hours. Once the distillation stops, the flask is submitted to water-aspirator vacuum at 160°C-170°C for 30 minutes. The mixture solidifies when cooled to room temperature.

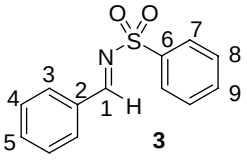
**Quantities Engaged** :

Benzenesulfonamide : 14.42 g, 89.9 mmol, 1 eq.

Benzaldehyde dimethylacetal : 15.0 ml, 14.42 g, 1.1 eq.

**Purification** : The product is recrystallized in warm toluene. The solid is filtered and washed with ether. The mother liquors and the filtrates are concentrated under vacuum and recrystallized. 17.47 g (total) of white solid are recovered.

**Name** :*N*-Benzylidene-benzenesulfonamide




**CAS-RN** : 13909-34-7

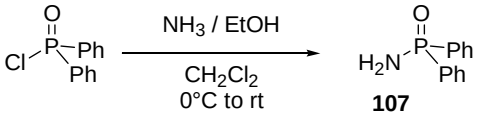
**M.F.** : $C_{13}H_{11}NO_2S$ **M.W.** : 245.30

**Yield** : 17.47 g (79%)

Physical Property : white solid

**$^1$H NMR** ($CDCl_3$, 200 MHz) : 9.07 (s, 1H, $H^1$), 7.85-8.1 (m, 4H, $H^{3\&7}$), 7.4-7.7 (m, 6H, $H^{4,5,8\&9}$)

***P,P-diphenylphoshinic amide 107***




**Operating Procedure** : See [189]

**Quantities Engaged** :

Diphenylphosphinic chloride : 20.16 g, 103.5 mmol, 1 eq.

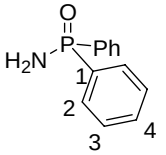
Gazeous ammonia : saturated ethanol

Ethanol : 267.5 ml, 210 g, 44 eq

Dichloromethane : 45.2 ml, 60 g, 6.8 eq.

**Purification** : 19.7 g of white solid are recovered after recrystallization in toluene

**Name** : *P,P*-diphenylphoshinic amide




**CAS-RN** : 5994-87-6

**M.F.** : $C_{12}H_{12}NOP$ **M.W.** : 217.20

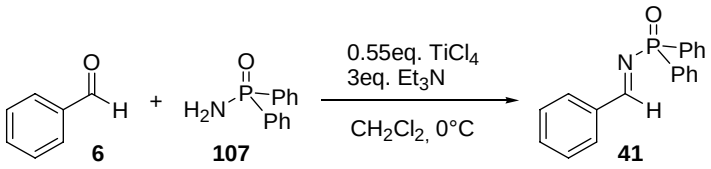
**Yield** : 19.7 g (87.6%)

**Physical Property** : white solid

**$^1$H NMR** ($CDCl_3$, 200 MHz) : 7.85-8.05 (m, 4H, $H^{ar}$), 7.35-7.6 (m, 6H, $H^{ar}$), 3.1 (bs, 2H, N*H*)

**Mass** (EI, 70eV) : 218.1 ($[M+1]^+$, 12.7%); 217.1 ($[M]^{\cdot+}$, 53.8%); 216.1 (100%), 199.1 (62.3%); 140.1 ($[M-[C_6H_5)]^+$, 15.6%)

***N-Benzylidene-P,P-diphenylphosphinic amide 41***




**Operating Procedure** : As described in [189]

**Quantities Engaged** :

Benzaldehyde : 17.7 ml, 18.48 g, 174.5 mmol, 1 eq.

*P,P*-Diphenylphoshinic amide: 37.90 g, 1 eq.

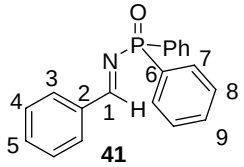
Titanium(IV) chloride : 10.5 ml, 18.12 g, 0.55 eq.

Triethylamine : 73.1, 53.22 g, 3 eq.

Dichloromethane : 900 ml, 1192.5 g, 80.5 eq.

**Purification** : The product issued from the described purification contained traces of *P,P*-diphenylphoshinic amide **107** due either to incomplete reaction or hydrolysis during the purification. Pure imine **41** was obtained by selectively extracting it with warm *n*-hexane in a Soxhlet apparatus (Soxhlet apparatus isolated with aluminum foil). 25.1 g of white solid were recovered and stocked under argon with a $P_2O_5$ trap.

**Name** : *N*-Benzylidene-*P,P*-diphenylphosphinic amide




**41**

**CAS-RN** : 67764-52-7

**M.F.** : $C_{19}H_{16}NOP$ **M.W.** : 305.31

**Yield** : 25.1 g (47%)

Physical Property : white solid

**$^1$H NMR** ($CDCl_3$, 200 MHz) : 9.33 (d, $^4J_{1,P}$=31.8, 1H, $H^1$), 7.9-8.08 (m, 6H, $H^{ar}$), 7.4-7.7 (m, 9H, $H^{5\&ar}$)

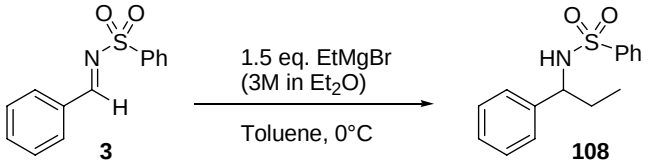
**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 173.7 (d, $^2J_{1,P}$=7.7, $C^1$), 135.8* (d, $^3J_{2,P}$=25.2, $C^2$), 132.9* (d, $^1J_{6,P}$=127.1, $C^6$), 133.6, 131.8 (d), 131.6, 131.5, 130.2, 128.9, 128.5 & 128.4 (coupling constants not determined, $C^{3,4,5,7,8\&9}$)

**IR** ($CH_2Cl_2$, $cm^{-1}$) : 1624 (C=N), 1579, 1439, 1201 (P=O)

**Mass** (EI, 70eV) : 306.2 (23.6%); 305.1 ($[M]^{\cdot+}$, 93.0%); 304.2 (21.8%); 203.1 (12.2%); 202.1 (95.4%); 201.1 ($[POPh_2]^+$, 100%); 180 (14.3%); 77.1 ($[C_6H_5]^+$, 17.5%)

## 12.4.2. Racemic Adducts of Imines 3 and 41

***racemic N-(1-Phenyl-propyl)-benzenesulfonamide 108***




**3** **108**

**Operating Procedure** : A flame-dried two-necked round-bottomed flask, fitted with a septum a magnetic stirring bar and an argon inlet is charged with imine **3** and toluene. The flask is cooled in an ice-bath prior to the addition of ethylmagnesium bromide (*ca* 3.0M in $Et_2O$). The reaction is followed by thin layer chromatography. After 2h30, the mixture is quenched by addition of an aqueous sodium hydroxide solution (1.0M).

**Quantities Engaged** :

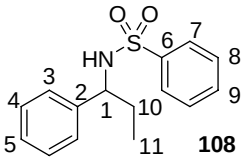
*N*-Benzylidene-benzenesulfonamide: 0.5 g, 89.9 mmol, 1 eq.

Ethylmagnesium bromide (3.0M in $Et_2O$): 15.0 ml, 1.1 eq.

Toluene : 10.0 ml, 8.65 g, 46 eq.

**Purification** : The mixture is filtered over Celite and the salts are rinsed with dichloromethane. The aqueous phase is extracted once with dichloromethane. The united organic phases are washed three times with sodium bicarbonate then dried over $MgSO_4$. After concentration, the oil is purified by column chromatography over silica gel (cyclohexane/AcOEt/$Et_3N$, 65/30/5, $R_f$=0.4). 0.40 g of white solid is recovered.

**Name** : *N*-(1-Phenyl-propyl)-benzenesulfonamide




**108**

**M.F.** : $C_{15}H_{17}NO_2S$ **M.W.** : 275.37

**Yield** : 0.40 g (71%)

**Physical Property** : white solid

**Melting point** : 77-81°C

**Chiral HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 95/5, 1.2 ml/min., 25°C, 220nm )

$t_R$= 10.51 min

$t_R$= 14.90 min

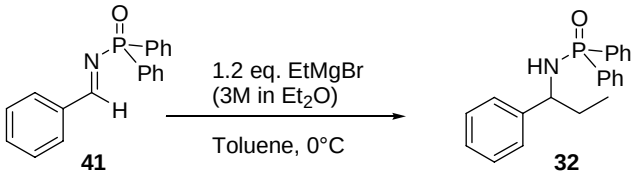
**$^1$H NMR** ($CDCl_3$, 200 MHz) : 6.97-7.66 (m, 10H, $H^{ar}$), 5.15 (d, $^3J_{1,NH}$=7.5, 1H, N*H*), 4.22 (apparent q, dt, $^3J_{1,NH}$=$^3J_{1,10}$=7.5, 1H, $H^1$), 1.61-1.91 (mult., *J*=7.5, 2H, $H^{10}$), 0.80 (t, $^3J_{10,11}$=7.5, 3H, $H^{11}$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 140.7* & 140.5* ($C^{2\&6}$), 132.0 ($C^9$), 128.6, 128.3, 127.2, 126.9 & 126.5 ($C^{3,4,5,7\&8}$), 59.9 ($C^1$), 30.6* ($C^{10}$), 10.4 ($C^{11}$)

**IR** ($CH_2Cl_2$, $cm^{-1}$) : 3380-3275 (N-H), 1448 (C-H), 1410 (C-H), 1326 (S=O), 1163(S=O), 1093, 909, 688

**Mass** (EI, 70eV) : 274.5 ($[M]^{\cdot+}$, traces), 247.3 (11.0%), 246.1 ($[M-(C_2H_5)]^+$, 100%), 141.0 ($[SO_2Ph]^+$, 13.0%), 77.0 ($[C_6H_5]^+$, 8.7%)

***racemic N-(1-Phenyl-propyl)-P,P-diphenylphosphinic amide 32***




**41** **32**

**Operating Procedure** : A flame-dried two-necked round-bottomed flask, fitted with a septum a magnetic stirring bar and an argon inlet is charged with imine **41** and dry toluene. The flask is cooled in an ice-bath prior to the drop-by-drop addition of ethylmagnesium bromide (*ca* 3.0M in $Et_2O$) over 5 minutes. The stirring is pursued overnight at room temperature then the mixture is quenched by adding a saturated ammonium chloride solution.

**Quantities Engaged** :

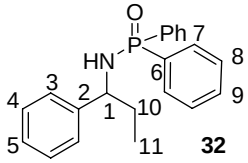
*N*-Benzylidene-*P,P*-diphenylphosphinic amide: 0.37 g, 1.2 mmol, 1 eq.

Ethylmagnesium bromide (3.0M in $Et_2O$): 0.48 ml, 1.2 eq.

Dry toluene : 20 ml, 17.3 g, 156 eq.

**Purification** : The reaction mixture is extracted three times with dichloromethane. The united organic phases are washed once with water and dried over $MgSO_4$. After concentration, the oil is purified by column chromatography over silica gel with an eluent of varying polarity (cyclohexane/AcOEt/$Et_3N$, 50/45/5 to 25/70/5, $R_f$=0.31). 0.244 g of white solid is recovered.

**Name** : *N*-(1-Phenyl-propyl)-*P,P*-diphenylphosphinic amide




**32**

**CAS-RN** :154675-31-7

**M.F.** : $C_{21}H_{22}NOP$ **M.W.** : 335.38

**Yield** : 0.244 g (61%)

Physical Property : white solid

**Chiral HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 90/10, 1.0 ml/min., 25°C, 220nm )

$t_R$= 6.12 min

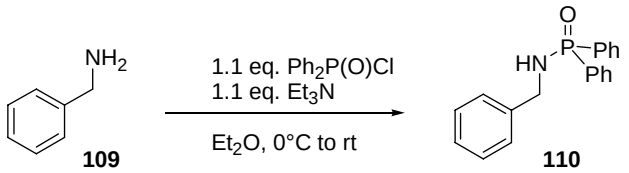
$t_R$= 7.72 min

**$^1$H NMR** ($CDCl_3$, 200 MHz) : identical to published spectrum[100]

## 12.4.3. Synthesis of Side Products 110 and 111

**N-*Benzyl*-P,P-*diphenylphosphinic amide***

**Ref.** : spectral data[438]




**109** **110**

**Operating Procedure** : A flame dried one-necked round-bottomed flask is charged with benzylamine, triethylamine and dry ether, closed with an argon inlet then placed in a ice-bath. The diphenylphosphinic chloride is added slowly. The mixture is brought back slowly to room temperature and is stirred over three days.

**Quantities Engaged** :

Benzylamine **109** : 0.50 ml, 0.49 g, 4.58 mmol, 1 eq.

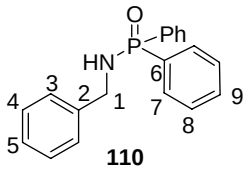
Diphenylphosphinic chloride : 1.00 ml, 1.24 g, 1.1 eq.

Triethylamine : 0.71 ml, 0.52 g, 1.1 eq.

Dry ether : 8.0 ml, 5.66 g, 16.7 eq.

**Purification** : The resulting mixture is filtered and the solids are washed with additional diethyl ether. The combined ethereal phases are concentrated under vacuum. The resulting oil is purified by flash chromatography on silica gel (AcOEt/$Et_3N$, 95/5, $R_f$=0.3). 0.45 g of a white solid is obtained

**Name** : *N*-Benzyl-*P,P*-diphenylphosphinic amide




**110**

**CAS-RN :** 27127-08-8

**M.F.** : $C_{19}H_{18}NOP$ **M.W.** : 307.33

**Yield** : 0.45 g (32%)

Physical Property : white solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.8-8.1 (m, 4H, $H^{7or8}$), 7.2-7.6 (m, 11H, $H^{3,4,5\&9+7or8}$), 4.15 (apparent t, dd, $^3J_{1,NH}$=$^3J_{1,P}$=7.3, $H^1$), 3.13 (bm, 1H, N*H*)

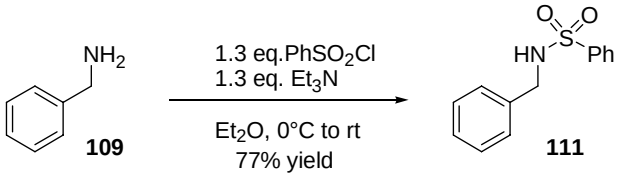
**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 139.5* (d, $^3J_{2,P}$=8.2, $C^2$), 132.1* (d, $^3J_{2,P}$=128.8, $C^6$), 132.1, 132.0, 131.9, 128.6, 128.4, 127.6, 127.2, 44.6* ($C^1$)

**IR** ($CH_2Cl_2$, $cm^{-1}$) : 3390 (br, N-H), 1496, 1439, 1403, 1198 (P=O), 1124, 1194, 1068

**Mass** (EI, 70eV) : 308.2 (16.8%), 307.0 ($[M]^{\cdot+}$, 100%), 201.0 ($[POPh_2]^+$, 50.1%), 155.0 (14.2%), 106.0 ($[M-(POPh_2)]^+$, 51.3%), 77.0 ($[C_6H_5]^+$, 13.7%)

## N-*Benzyl-benzenesulfonamide 111*

**Ref.** : spectral data[439]




**109** **111**

**Operating Procedure** : A flame dried one-necked round-bottomed flask is charged with benzylamine, triethylamine and dry ether, closed with an argon inlet then placed in a ice-bath. The phenylsulfonyl chloride is added slowly. The mixture is brought back slowly to room temperature and is stirred overnight.

**Quantities Engaged** :

Benzylamine **109** : 1.0 ml, 0.98 g, 9.15mmol, 1 eq.

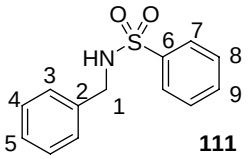
Phenylsulfonyl chloride : 1.5 ml, 2.08 g, 1.3 eq.

Triethylamine : 1.7 ml, 1.24 g, 1.3 eq.

Dry ether : 16.0 ml, 11.3 g, 16.7 eq.

**Purification** : The reaction media is concentrated under vacuum and dissolved in $CH_2Cl_2$. The mixture is washed successively with a NaOH (1 M) solution and water. The organic phase is dried over $MgSO_4$ and concentrated under vacuum. The resulting oil is purified by flash chromatography over silica gel (cyclohexane/AcOEt/$Et_3N$, 65/30/5, $R_f$=0.29). 1.75 g of a white solid is obtained

**Name** : *N*-Benzyl-benzenesulfonamide




**111**

**CAS-RN** : 837-18-3

**M.F.** : $C_{13}H_{13}NO_2S$ **M.W.** : 247.31

**Yield** :1.75 g (77%)

**Physical Property** : white solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.87 (m, 2H, $H^7$), 7.48-7.62 (m, 3H, $H^{8\&9}$), 7.15-7.30 (5H, $H^{1,2\&3}$), 4.74 (bm, 1H, N*H*), 4.15 (d, $^3J_{1,NH}$=9.3, 2H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 139.9*, 136.2* ($C^{2\&6}$), 132.7, 129.1, 129.7, 127.9, 127.9, 127.1 ($C^{3,4,5,7,8\&9}$), 47.2* ($C^1$)

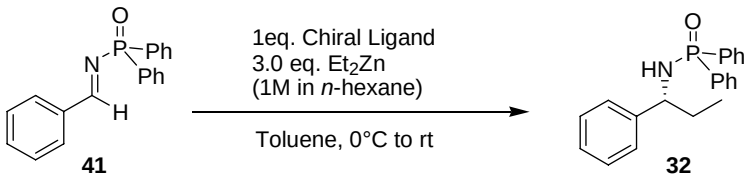
**IR** ($CH_2Cl_2$, $cm^{-1}$) : 3377.4 (N-H), 1447.8 (C-H), 1409.3 (C-H), 1332.1 (S=O), 1274.1, 1256.7, 1164.4 (S=O), 1094.1

**Mass** (EI, 70eV) : 247.1 ($[M]^{\cdot+}$, 2.6%); 141.0 ($[SO_2Ph]^+$, 7.1%); 106.1 ([M-(SO2Ph)]$^+$, 38.5%); 77.1 ($[C_6H_5]^+$, 26.3%)

# 12.5. Addition to Imines

## 12.5.1. Addition to *N*-Phosphinoyl Imine 41

***General Procedure E***




**41** **32**

In a flame-dried round-bottomed two-necked flask (25 ml) fitted with a septum and an argon inlet, *N*-diphenylphosphinoyl imine **41** and the ligand are suspended in dry toluene. After a few minutes, the reaction mixture is cooled in an ice-bath. A freshly prepared solution of diethylzinc in *n*-hexane (*ca* 1M) is added in one fraction. After the organometallic addition, the reaction is brought back to room temperature and left to run for the desired length of time.

***Directed by Soai's DBNE 13***

**Ref.** : see[89]

**Operating Procedure** : see General Procedure E

**Reaction time**: 3 days.

**Quantities Engaged** :

*N*-Benzylidene-*P,P*-diphenylphosphinic amide: 0.305 g, 1.0 mmol, 1 eq.

(1*S*,2*R*)-dibutyl-*N,N*-norephedrine **13**: 0.263 g, 1.0 mmol, 1 eq.

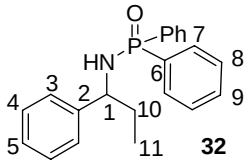
Diethylzinc: 3.0 ml, 3.0 mmol, 3.0 eq.

Toluene : 6.0 ml, 5.19 g, 56.4 eq

Substrate Concentration : *ca.* 0.11M

**Purification** : After 3 days, a NaOH (*ca* 1M) aqueous solution is added and the mixture stirred for 2 extra hours. The reaction media is neutralized with HCl (*ca* 1M) and extracted with dichloromethane. The combined organic phases are washed with a saturated $NH_4Cl$ solution and dried over $MgSO_4$. The oil obtained after evaporation under vacuum is purified by column chromatography over silica gel (cyclohexane/AcOEt/$Et_3N$, 70/25/5 to 20/75/5, $R_f$=0.66 for **13**, $R_f$=0.14 for adduct **32** with 50/45/5). 0.18 g of a yellowish oil identified as **13** is first collected (67%) ; 0.29 g of a white solid identified as **32** is collected in a second fraction.

**Name** : *N*-(1-Phenyl-propyl)-*P,P*-diphenylphosphinic amide




**32**

**M.F.** : $C_{21}H_{22}NOP$ **M.W.** : 335.38

**Yield** : 0.29 g (60%)

**Physical Property** : white solid

**Chiral HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 90/10, 1.0 ml/min., 25°C, 220nm )

$t_R$= 5.41 min (*R*)

$t_R$= 6.82 min (*S*)

**Enantiomeric Excess** : 84.3% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 200 MHz) : identical to racemic sample

***Directed by (2S)-Leucinol 2***

**Operating Procedure** : see General Procedure E

**Reaction time** : 3 days.

**Quantities Engaged** :

*N*-Benzylidene-*P,P*-diphenylphosphinic amide: 0.305 g, 1.0 mmol, 1 eq.

(2*S*)-Leucinol **2**: 0.12 g, 1.0 mmol, 1 eq.

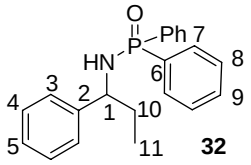
Diethylzinc (*ca* 1M in *n*-hexane): 3.0 ml, 3.0 mmol, 3.0 eq.

Toluene : 6.0 ml, 5.19 g, 56.4 eq

**Substrate Concentration** : *ca.* 0.11M

**Purification** : After 3 days, a NaOH (*ca* 1M) aqueous solution is added and the mixture stirred for 2 extra hours. The reaction media is neutralized with a minimum of HCl (*ca* 1M) and a saturated $NH_4Cl$ solution before being extracted with dichloromethane. The combined organic phases are washed with a saturated $NH_4Cl$ solution and dried over $MgSO_4$. The oil obtained after evaporation under vacuum is purified by column chromatography over silica gel (AcOEt/$Et_3N$, 95/5 $R_f$=0.35).

**Name** : *N*-(1-Phenyl-propyl)-*P,P*-diphenylphosphinic amide




**32**

**CAS-RN** :154675-31-7

**M.F.** : $C_{21}H_{22}NOP$ **M.W.** : 335.38

**Yield** : 0.050 g (15%)

Physical Property : white solid

**Chiral HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 90/10, 1.0 ml/min., 25°C, 220nm )

$t_R$= 10.69 min (*R*)

$t_R$= 13.63 min (*S*)

Enantiomeric Excess : 66% ee (*R*)

**$^1$H NMR** ($CDCl_3$, 200 MHz) : identical to racemic sample

***<u>In the Absence of Ligand</u>***

**Operating Procedure** : see General Procedure E

**Reaction time** : 24 hours.

**Quantities Engaged** :

*N*-Benzylidene-*P,P*-diphenylphosphinic amide: 0.305 g, 1.0 mmol, 1 eq.

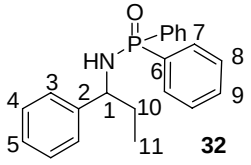
Diethylzinc: 3.0 ml, 3.0 mmol, 3.0 eq.

Toluene : 6.0 ml, 5.19 g, 56.4 eq

**Substrate Concentration** : *ca.* 0.11M

**Purification** : After 24 hours, a NaOH (*ca* 1M) aqueous solution is added and the mixture stirred overnight. The reaction media is neutralized with a minimum of HCl (*ca* 1M) and a saturated $NH_4Cl$ solution before being extracted with dichloromethane. The combined organic phases are dried over $MgSO_4$. The oil obtained after evaporation under vacuum is purified by column chromatography over silica gel (cyclohexane/AcOEt/$Et_3N$, 25/70/5). Two fractions are obtained. The first fraction is identified as the adduct **32** (0.146 g, 43% yield). The second one is the reduction product **110** (0.034 g, 11% yield).

**Name** : *N*-(1-Phenyl-propyl)-*P,P*-diphenylphosphinic amide




**32**

**CAS-RN** :154675-31-7

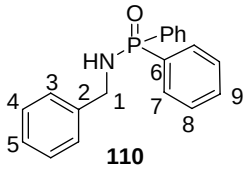
**M.F.** : $C_{21}H_{22}NOP$ **M.W.** : 335.38

**Yield** : 0.146 g (43%)

Physical Property : white solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to racemic sample

**Name** : *N*-Benzyl-*P,P*-diphenylphosphinic amide




**110**

**CAS-RN** : 27127-08-8

**M.F.** : $C_{19}H_{18}NOP$ **M.W.** : 307.33

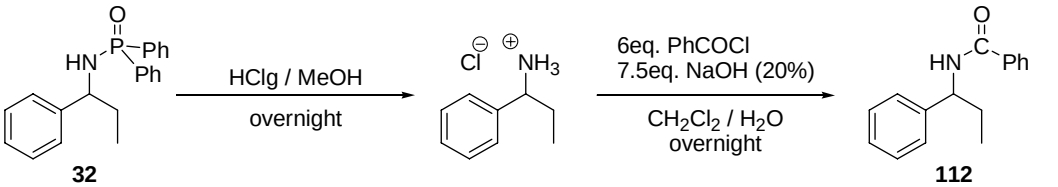
**Yield** : 0.034 g (11%)

**Physical Property** : white solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

***Deprotection and Benzoylation of 32***

**Ref** : deprotection[100]




**32** **112**

92%-100% yield

**Operating Procedure** : **32** is dissolved in methanol saturated by gaseous HCl (freshly prepared solution) in a round-bottomed flask isolated from the atmosphere by an oil-bubbler. After a minimum of 12 hours, the methanol is evaporated and the resulting oil is dissolved in HCl (*ca* 1M). The media is washed with 3 portions of AcOEt. The organic phase contains the ligand while the aqueous phase contains the amine under its ammonium form.

The aqueous phase is basified by addition of solid sodium hydroxide then extracted with 3 portions of dichloromethane. The combined organic phases a re dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting oil is dissolved in dichloromethane and a sodium hydroxide solution (20%). After cooling this biphasic mixture in an ice-bath, benzoyl chloride is added at once and the reaction is stirred at room temperature overnight.

**Quantities Engaged** :

*N*-(1-Phenyl-propyl)-*P,P*-diphenylphosphinic amide **32**: 1.00 g, 2.98 mmol, 1 eq.

Methanol saturated with $HCl_g$ : 60.0 ml

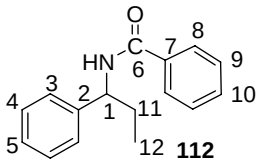
Benzoyl chloride : 2.10 ml, 2.54 g, 6 eq.

Dichloromethane : 25.0 ml, 33.1 g, 131 eq.

Aqueous NaOH (20%) : 4.5 ml, *ca* 7.5 eq.

**Purification** : The reaction media is decanted and extracted with 3 fractions of dichloromethane. The combined organic phases are dried over $MgSO_4$ and concentrated under vacuum. The product is purified by column chromatography over silica gel (cyclohexane/AcOEt/$Et_3N$, 70/25/5). 0.66 g of a white solid is recovered.

**Name** : *N*-(1-Phenyl-propyl)-benzamide



**112**

**CAS-RN :** 2698-80-8 (racemic)

**M.F.** : $C_{16}H_{17}NO$ **M.W.** : 239.31

**Yield** : 0.66 g (92%)

**Physical Property** : white solid

**Chiral HPLC** : (Chiracel AD, *n*-hexane/isopropanol, 85/15, 1.0 ml/min., 25°C, 220nm )

$t_R$= 7.58 min

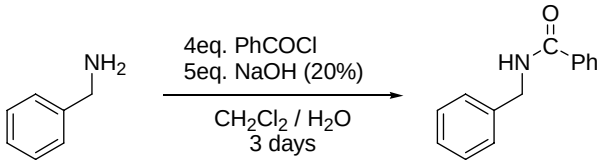
$t_R$= 11.56 min

**$^1$H NMR** ($CDCl_3$, 200 MHz) : 7.75-7.79 (mult., 2H, $H^8$), 7.20-7.52 (m, 8H, $^{H3,4,5,9,10}$), 6.3-6.6 (bs, 1H, N*H*), 5.09 (apparent q, td, $^3J_{1,11}$=7.7, $^3J_{1,NH}$=7.4, 1H, $H^1$), 1.94 (mult, 2H, $H^{11}$), 0.95 (t, $^3J_{11,12}$=7.3, 3H, $H^{12}$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 166.7* ($C^6$), 142.2* ($C^2$), 134.9* ($C^7$), 131.3 ($C^{10}$), 129.6, 128.5, 127.3, 126.9 & 126.7 ($C^{3,4,5,\ 8\&9}$), 55.4 ($C^1$), 29.2* ($C^{11}$), 10.7 ($C^{12}$)

**Mass** (EI, 70eV) : 240.2 (10.5%); 239.1 ($[M]^{\cdot+}$, 76.7%); 211.2 (12.1%); 210.1 ($[M-(C_2H_5)]^+$, 100.0%); 105.0 ($[PhCO]^+$, 17.3%); 77.0 ($[C_6H_5]^+$ 2.9%)

***Benzoylation of Benzylamine***



**113**

**Operating Procedure** : A one-necked round-bottomed flask is charged with benzylamine, dichloromethane and a sodium hydroxide solution (20%). After cooling the biphasic mixture in an ice-bath, benzoyl chloride is added. Stirring is pursued at room temperature.

**Quantities Engaged** :

Benzylamine: 0.50 ml, 0.49 g, 4.58 mmol, 1 eq.

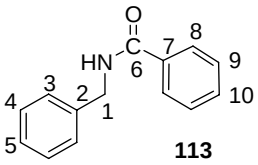
Benzoyl chloride : 2.15 ml, 2.60 g, 4 eq.

Dichloromethane : 5.4 ml, 7.1 g, 18.3 eq.

Aqueous NaOH (20%) : 4.6 ml, *ca* 5.0 eq.

**Purification** : After 3 days, the reaction media is decanted and extracted with 3 fractions of dichloromethane. The combined organic phases are dried over $MgSO_4$, filtered and concentrated under vacuum. The product is purified by column chromatography over silica gel (cyclohexane/AcOEt/$Et_3N$, 70/25/5, $R_f$=0.25). 0.91 g of a white solid is recovered.

**Name** : *N*-Benzyl-benzamide



**113**

**CAS-RN :** 1485-70-7

**M.F.** : $C_{14}H_{13}NO$ **M.W.** : 211.26

**Yield** : 0.91 g (94%)

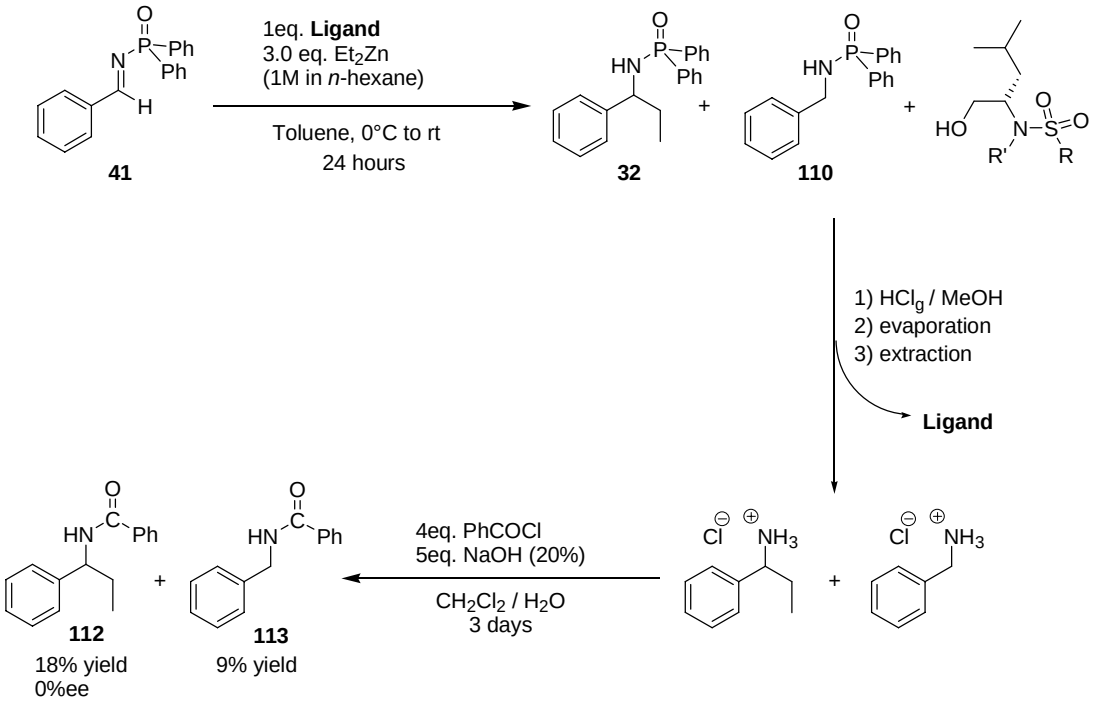
**Physical Property** : white solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.75-7.81 (mult., 2H, $H^8$), 7.30-7.55 (m, 8H, $H^{3,4,5,9,10}$), 6.35-6.55 (bs, 1H, N*H*), 4.65 (d, $^3J_{1,NH}$=5.6, 2H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 167.4* ($C^6$), 138. 2* ($C^2$), 134.3* ($C^7$), 131.5 ($C^{10}$), 128.7, 128.5, 127.8, 127.5 & 126.9 ($C^{3,4,5,8\&9}$), 44.0*($C^1$)

**Mass** (EI, 70eV) : 212.2 (10.8%); 211.0 ($[M]^{\cdot+}$, 100%); 210.0 ($[M-(H)]^+$, 29.2%); 104.9 ($[PhCO]^+$, 36.6%); 77.0 ($[C_6H_5]^+$, 12.7%)

***Directed by Sulfonamido alcohols derived from (2S)-Leucinol : General Procedure F***




**Operating Procedure** : A flame-dried round-bottomed two-necked flask (25 ml) fitted with a septum and an argon inlet is charged with the ligand and dry toluene (2 ml). The flask is cooled in an ice-bath. A freshly prepared solution of diethylzinc in *n*-hexane (3 ml, *ca* 1M) is added in one fraction. The mixture is stirred at 0°C for 15 minutes.

In a second flame-dried round-bottomed two-necked flask (25 ml) fitted with a septum and an argon inlet, *N*-diphenylphosphinoyl imine **41** is suspended in dry

toluene (5 ml). After a few minutes, the reaction mixture is cooled in an ice-bath. The diethylzinc-sulfonamido alcohol mixture is added *via* syringe onto the substrate suspension.

After the organometallic addition, the reaction is brought back to room temperature and left to run 24 hours.

**Purification** : After 24 hours, a NaOH (*ca* 1M) aqueous solution is added and the mixture stirred overnight. The reaction media is neutralized with a minimum of HCl (*ca* 1M) and a saturated $NH_4Cl$ solution before being extracted with dichloromethane. The combined organic phases are dried over $MgSO_4$.

**Deprotection and Benzoylation** : The crude oil is dissolved in methanol saturated by gaseous HCl (freshly prepared solution) in round-bottomed flask isolated from the atmosphere by an oil-bubbler. After a minimum of 12 hours, the methanol is evaporated and the resulting oil is dissolved in HCl (*ca* 1M). The media is washed with 3 portions (10 ml) of AcOEt. The organic phase contains the ligand while the aqueous phase contains the products of the reaction under their ammonium form.

The aqueous phase is basified by adding solid sodium hydroxide then is extracted with 3 portions of dichloromethane. This organic phase is dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting oil is dissolved in 5 ml of dichloromethane and sodium hydroxide solution (20%). After cooling this biphasic mixture in an ice-bath, benzoyl chloride is added at once. Stirring is pursued at room temperature overnight. The reaction media is then decanted and extracted with 3 fractions of dichloromethane (10 ml). The combined organic phases are dried over $MgSO_4$, filtered and concentrated under vacuum. The products are separated and purified by column chromatography over silica gel (cyclohexane/AcOEt/$Et_3N$, 60/35/5). Fractions containing a mixture of both products were separated by a second column chromatography over silica gel.

**Quantities Engaged** :

*N*-Benzylidene-*P,P*-diphenylphosphinic amide: 0.305 g, 1.0 mmol, 1 eq.

(2*S*)-sulfonamido alcohol ligand: 1.0 mmol, 1 eq.

Diethylzinc (*ca* 1M in *n*-hexane): 3.0 ml, 3.0 mmol, 3.0 eq.

Toluene : 7.0 ml, 6.1 g, 65.8 eq

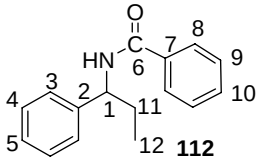
Methanol saturated with $HCl_g$ : 30.0 ml

Benzoyl chloride : 0.47 ml, 0.57 g, 4 eq.

Dichloromethane : 5.0 ml, 6.63 g, 78.1 eq.

Aqueous NaOH (20%) : 1.0 ml, *ca* 5 eq.

**Name** : *N*-(1-Phenyl-propyl)-benzamide




**112**

**CAS-RN :** 2698-80-8

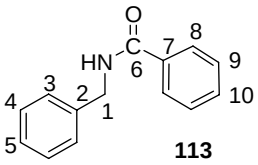
**M.F.** : $C_{16}H_{17}NO$ **M.W.** : 239.31

**Physical Property** : white solid

**Chiral HPLC** : see page 241 for conditions

**$^1$H NMR** ( $CDCl_3$) : identical to previous sample

**Name** : *N*-Benzyl-benzamide




**113**

**CAS-RN :** 1485-70-7

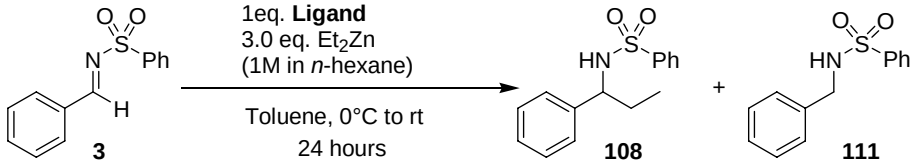
**M.F.** : $C_{14}H_{13}NO$ **M.W.** : 211.26

**Physical Property** : white solid

**$^1$H NMR** ($CDCl_3$) : identical to previous sample

## 12.5.2. Addition to *N*-Sulfonyl Imine 3

***General Procedure G***




**3** **108** **111**

**Operating Procedure** : A flame-dried round-bottomed two-necked flask (25 ml) fitted with a septum and an argon inlet is charged with the ligand and dry toluene (2 ml). The flask is cooled in an ice-bath. A freshly prepared solution of diethylzinc in *n*-hexane (3 ml, *ca* 1M) is added in one fraction. The mixture is stirred at 0°C for 15 minutes.

In a second flame-dried round-bottomed two-necked flask (25 ml) fitted with a septum and an argon inlet, *N*-phenylsulfonyl imine **3** is suspended in dry toluene (2 ml). After a few minutes, the reaction mixture is cooled in an ice-bath. The diethylzinc-sulfonamido alcohol mixture is added *via* syringe onto the substrate suspension.

After the organometallic addition, the reaction is left for one hour in the ice-bath and then brought back to room temperature and left to run for a total of 24 hours.

**Quantities Engaged** :

*N*-Benzylidene-benzenesulfonamide: 0.245 g, 1.0 mmol, 1 eq.

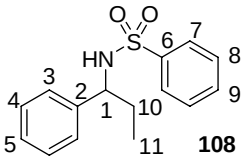
Sulfonamido alcohol ligand: 1.0 mmol, 1 eq.

Diethylzinc (*ca* 1M in *n*-hexane): 3.0 ml, 3.0 mmol, 3.0 eq.

Toluene : 4.0 ml, 3.46 g, 37.6 eq

**Purification** : After 24 hours, the reaction is quenched with a saturated $NH_4Cl$ aqueous solution and stirred for 24 hours. The mixture is extracted 3 times with dichloromethane. The united organic phases are washed once with water and dried over $MgSO_4$. After concentration, the resulting oil is purified by column chromatography over silica gel (cyclohexane/AcOEt/$Et_3N$, 65/30/5, $R_f$=0.4 for adduct **108** and $R_f$=0.32 for reduction product **111**)

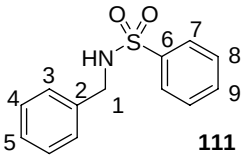
**Name** : *N*-(1-Phenyl-propyl)-benzenesulfonamide



**108**

**M.F.** : $C_{15}H_{17}NO_2S$ **M.W.** : 275.37
**Physical Property** : white solid
**Melting point** : 77-81°C
**Chiral HPLC** : see page 234 for conditions
**$^1$H NMR** ($CDCl_3$) : identical to previous sample

**Name** : *N*-Benzyl-benzenesulfonamide



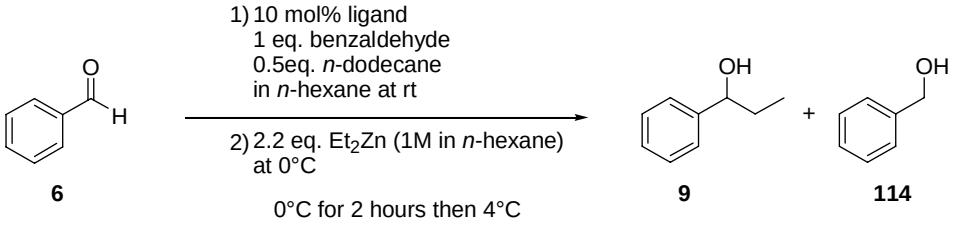
**111**

**CAS-RN** : 837-18-3
**M.F.** : $C_{13}H_{13}NO_2S$ **M.W.** : 247.31
**Physical Property** : white solid
**$^1$H NMR** ($CDCl_3$) : identical to previous sample

# 12.6. Addition to Benzaldehyde

## 12.6.1. Addition Reaction

***General Procedure H***




**6** **9** **114**

**Operating Procedure** : A flame-dried round-bottomed two-necked flask (25 ml) fitted with a septum and an argon inlet is charged with the ligand (0.1 mmol, 0.1 eq.). A solution of benzaldehyde (0.5 M) and dodecane (0.25 M) in *n*-hexane is prepared in a flame-dried graduated Schlenck flask. 2 ml of the prepared solution (0.102 ml, 0.106 g, 1 mmol, 1 eq. of benzaldehyde and 0.113 ml, 0.085 g, 0.5 mmol, 0.5 eq. of *n*-dodecane) are engaged in the two-necked flask. After 20 to 30 minutes, the mixture is cooled to 0°C in an ice bath.

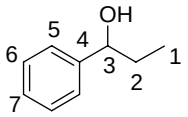
A diethylzinc solution (1 M) in dry *n*-hexane is prepared from commercially available pure diethylzinc in a flame-dried graduated Schlenck flask. 2.2 ml of the diorganozinc solution (2.2 ml, 2.2 mmol, 2.2 eq.) is added at once on the substrate-catalyst mixture. The reaction is left at 0°C for two hours, after what the reaction vessel is moved to a cool room at 4°C.

Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. Sampling is realized at least after 5 min, 15 min, 30 min, 1 hour, 2 hours and 24 hours. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

**Quantities Engaged** :

Benzaldehyde: 0.102 ml, 0.106 g, 1 mmol, 1 eq.
n-Dodecane: 0.113 ml, 0.085 g, 0.5 mmol, 0.5 eq.
Sulfonamido alcohol ligand: 0.1 mmol, 0.1 eq.
Diethylzinc (ca 1M in n-hexane): 2.2 ml, 2.2. mmol, 2.2 eq.
Dry *n*-hexane : 2.0 ml, 1.32 g, 15.2 eq

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Chiral GC** (120) :

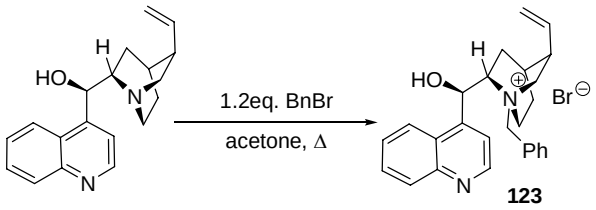
$t_R$= 15.22 min (*R*)
$t_R$= 15.95 min (*S*)

# Chapter 13

# Fluoride Anion Activation

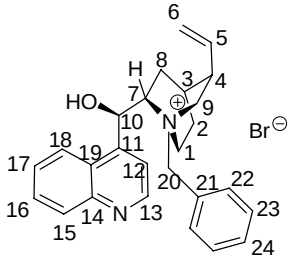
## 13.1. Synthesis of *O*-allyl-*N*-benzylcinchonidium fluoride

### 13.1.1. Reaction of *N*-Benzylcinchonidine with Benzyl Bromide




**Operating Procedure** : In a three-necked 250 ml round-bottom flask fitted with a septum, a magnetic stirring bar and a reflux condenser, cinchonidine (9.20 g, 31.2 mmol, 1 eq.) is suspended in acetone (160 ml). The mixture is heated to reflux and benzyl bromide is added by fractions via syringe. After 4 hours at reflux, the reaction media is cooled and filtered. The white powder is dried under vacuum prior to being recrystallized in a mixture of water (400 ml) and ethanol (60 ml). After one night, the solid is filtered and washed with acetone. The mother liquors and the washes are concentrated by rotatory evaporation and filtered. The crystals are dried under vacuum in the presence of $P_2O_5$. 10.6 g of off-white crystalline solid are recovered.

**Name** : *N*-benzylcinchonidium bromide




**CAS-RN** : 118089-84-2

**M.F.** : $C_{26}H_{29}BrN_2O$ **M.W.** : 465.43

**Yield** : 10.6 g (73%)

**Physical Property** : Off-white solid

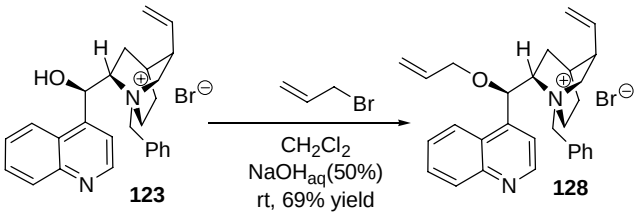
**$^1$H NMR** ($CDCl_3$, 300 MHz) : similar to commercial *N*-benzylcinchonidium chloride

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 149.3 ($C^{13}$); 147.0*($C^{14}$); 144.5*($C^{11}$); 136.0 ($C^5$); 134.0 ($C^{15}$); 129.9, 129.4, 128.6, 128.4, 127.3 ($C^{16,17,22,23,24}$); 126.8*($C^{21}$); 123.5*($C^{19}$); 122.8 ($C^{18}$); 119.7 ($C^{12}$); 117.7*($C^6$); 66.9; 64.9 ($C^{7,10}$); 62.0*, 59.9* ($C^{1 \text{ or } 9, 20}$); 50.2* ($C^{1 \text{ or } 9}$); 37.7 ($C^3$); 26.4 ($C^4$); 25.0*, 22.2* ($C^{2,8}$)

**Mass** (FAB, eV) : 386.1 ($[M\text{-}Br+1]^+$, 22.1%); 385.1 ($[M\text{-}Br]^{\cdot+}$, 100%), 153.9 (42.2%); 135.9 (38.3%)

## 13.1.2. Reaction of *N*-Benzylcinchonidinium with Allyl Bromide

**Ref :** operating procedure and spectral data[198]




**Operating Procedure** : In a one-necked 250 ml round-bottom flask fitted a magnetic stirring bar, *N*-benzylcinchonidium bromide (6.34 g, 13.3 mmol, 1 eq.) is dissolved in dichloromethane (115 ml). Benzyl bromide (3.5 ml, 4.89 g, 3 eq.) is added at once followed by a 50% sodium hydroxide aqueous solution (2 eq.).

After 4 hours at room temperature, 5 ml of water are added. The phases are decanted and the aqueous phase is extracted with dichloromethane (2 x 20 ml). The combined organic phases are finally washed with water (2 x 20 ml), dried over $MgSO_4$, filtered and evaporated under vacuum.

The product is purified by two sequential flash chromatographies over silica gel ($CH_2Cl_2$ / MeOH, 90 : 10, $R_f$=0.35)

**Name** : *O*-allyl-*N*-benzylcinchonidium bromide

**CAS-RN** : 158195-40-5

**M.F.** : $C_{29}H_{33}BrN_2O$ **M.W.** : 505.49

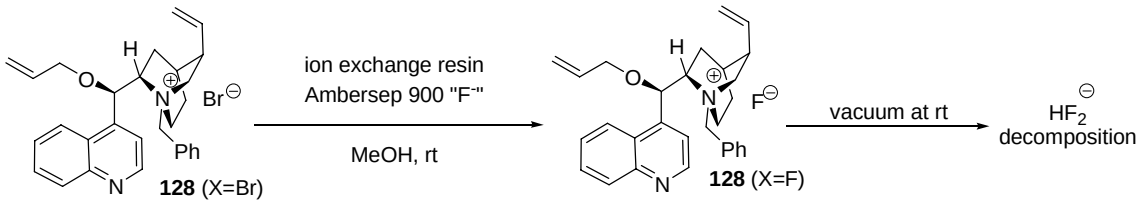
**Yield** : 4.64 g (69%)

**Physical Property** : yellowish solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to described spectrum[198]

**Mass** (FAB, eV) : 426.5 ($[M\text{-}Br+1]^+$, 22.8%); 425.3 ($[M\text{-}Br]^{\cdot+}$, 100%)

## 13.1.3. Transhalogenation Attempt to Obtain *O*-Allyl-*N*-Benzylcinchonidium Fluoride




**Operating Procedure** : 2.6 g of wet Ambersep 900-OH resin (hydroxide form) are placed in a capped plastic vial and suspended in a $NH_4F$ (1 M) aqueous solution. The resin is stirred by orbital movement during 40 minutes. The resin is filtered, rinsed successively with water and methanol then it is briefly (a few seconds) submitted to vacuum.

The *O*-allyl-*N*-benzylcinchonidium bromide salt **128** is dissolved in 10 ml of methanol in a capped plastic vial to which the resin is added. The reaction media is stirred by orbital movement during 50 minutes. The reaction media is filtered and the resin washed with methanol. The organic phase is concentrated by rotatory evaporation (no heat). The resulting oil is briefly submitted to pump vacuum to remove residual solvents.

The $^1$H NMR spectrum ($CDCl_3$) is highly similar to the starting material. The $^{19}$F NMR spectrum ($CDCl_3$) is characterized by two signals :-121.3 ppm (86%, $F^-$), -150.0 ppm (14%, $HF_2^-$).

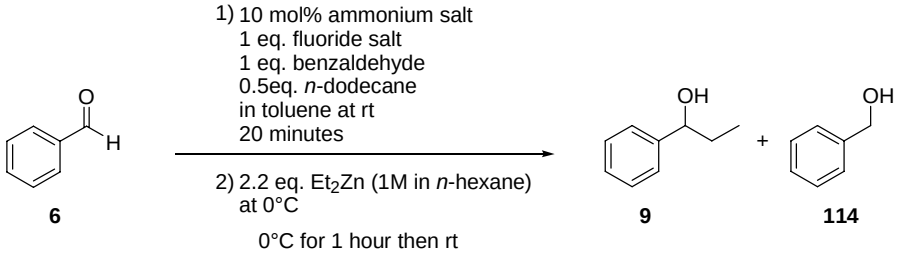
The sample is submitted to vacuum during several hours and analyzed. The $^{19}F$ NMR spectrum ($CDCl_3$) is characterized by one signal : -149.8 ppm ($HF_2^-$)

**Name** : *O*-allyl-*N*-benzylcinchonidium fluoride

**M.F.** : $C_{29}H_{32}FN_2O$ **M.W.** : 443.58

# 13.2. Alkylation of Benzaldehyde Catalyzed by Fluoride Sources

## 13.2.1. General Procedure I




**Operating Procedure** : A flame-dried round-bottomed two-necked flask (25 ml) fitted with a septum and an argon inlet is charged with the catalyst precursors. A solution of benzaldehyde (0.5 M) and dodecane (0.25 M) in toluene is prepared in a flame-dried graduated Schlenck flask. 2 ml of the prepared solution (0.102 ml, 0.106 g, 1 mmol, 1 eq. of benzaldehyde and 0.113 ml, 0.085 g, 0.5 mmol, 0.5 eq. of *n*-dodecane) are engaged in the two-necked flask. After 20 minutes, the mixture is cooled to 0°C in an ice bath.

A diethylzinc solution (1 M) in dry *n*-hexane is prepared from commercially available pure diethylzinc in a flame-dried graduated Schlenck flask. 2.2 ml of the diorganozinc solution (2.2 ml, 2.2 mmol, 2.2 eq.) is added at once on the substrate-catalyst mixture. The reaction is left at 0°C for one hour, after what the reaction is brought to room temperature.

Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. Sampling is realized at least after 5 min, 15 min, 30 min, 1 hour, 2 hours and 24 hours. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

**Quantities Engaged** :

Benzaldehyde: 0.102 ml, 0.106 g, 1 mmol, 1 eq.

n-Dodecane: 0.113 ml, 0.085 g, 0.5 mmol, 0.5 eq.

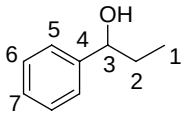
Ammonium salt or crown ether : 0.1 mmol, 0.1 eq.

Inorganic fluoride salt : 1 mmol, 1 eq.

Diethylzinc (ca 1M in *n*-hexane): 2.2 ml, 2.2. mmol, 2.2 eq.

Dry toluene : 2.0 ml, 1.73 g, 18.7 eq

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 93-54-9

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Chiral GC** (100/0/2/140) :

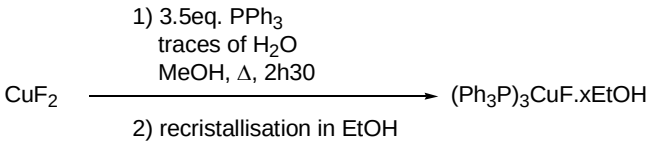
$t_R$= 17.49 min (*R*)

$t_R$= 17.91 min (*S*)

# Chapter 14

# First Generation Copper Fluoride

## 14.1. Synthesis of *tris*(triphenylphosphine)copper(I) fluoride 158

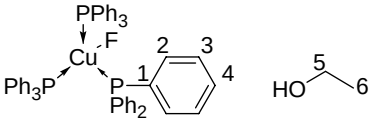



**Ref.** : operating procedure and analytical data[254]

**Operating Procedure** : In a one-necked 250 ml round-bottom flask fitted with a magnetic stirring bar, a reflux condenser and an argon inlet, copper (II) fluoride (1.03 g, 10 mmol, 1 eq.) and triphenylphosphine (9.18 g, 35 mmol, 3.5 eq.) are suspended in methanol (100 ml, analytical grade). A drop of water is added (monohydrated copper fluoride is used in the literature). The mixture is heated at reflux for 2h40 before being filtered warm on sintered glass. The solution is concentrated under vacuum to *ca.* 40 ml. After a night in the fridge, the solid is recovered by filtration on sintered glass. The mother liquors are concentrated under vacuum. The resulting solid is dissolved in methanol (30 ml), left overnight in the fridge and the solid is recovered. The mother liquors are once more concentrated under vacuum and dissolved in methanol (20 ml). After one night in the fridge, additional solid is recovered. 6.10 g (total) of white crystalline solid are recovered.

The solid is recrystallized twice in 30 ml portions of absolute ethanol after what 3.42 g of white crystalline solid are recovered.

**Name** : *tris*(triphenylphosphine)copper(I) fluoride.ethanol




**158**

**CAS-RN** : 80558-33-4

**M.F.** : $C_{54}H_{45}CuFP_3.xC_2H_6O$ (1.5<x<2) **M.W.** : 869.41 + x 46.07

**Yield** : 3.42 g (35% if x=2)

**Note** : Two molecules of ethanol were considered to be part of the complex for the calculations of the quantities of reagents engaged.

**Physical Property** : White crystalline solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.30 (m, 45H, $H^{ar}$), 3.71 (q, $^3J_{HH}$=7.2, 3H (x=1.5), $H^5$); 1.5 (bs, 1.5H (x=1.5), -O*H*), 1.24 (t, $^3J_{HH}$=7.2, 4.5H (x=1.5), $H^6$)

**Comment** : the number of ethanol molecules complexed to the copper(I) fluoride species varies with the preparation. Levanson *et al.* mention that x ranges between 1 and 2. In our hands, x varied from 1.5 to 2. However removing all the ethanol molecules from the complex requires high vacuum ($1.33x10^{-5}$bar) and heating (70°C) for four hours[254].

**$^{13}$C NMR** ($CDCl_3$, 125.7 MHz) : 135.4 (d, $^1J_{CP}$=5.4, $C^1$); 133.8 (d, $^2J_{CP}$=17.3, $C^2$); 128.9 (s, $C^4$); 128.3 (d,$^3J_{CP}$=7.8, $C^3$); 58,0 (s, $C^5$); 18,0 (s, $C^6$)

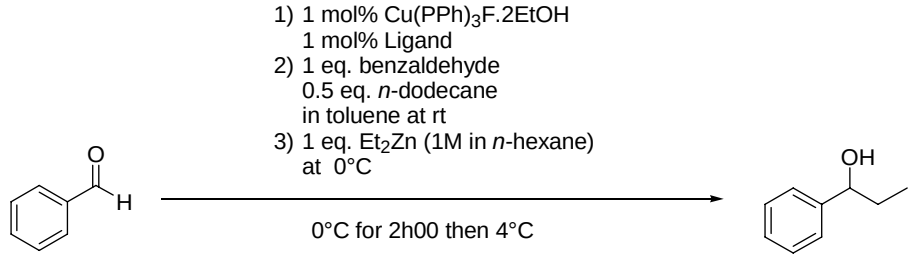
**$^{19}$F NMR** ($CDCl_3$, 282.2 MHz) : -204.2 (s)

**$^{31}$P NMR** ($CDCl_3$, 202.4 MHz) : 1.4 (s), -4.0 (s)

**IR** (solid deposit on NaCl, $cm^{-1}$) : 3438 (br, O–H), 3050 (=C-$H_{ar}$), 1647 (C=$C_{ar}$), 1585 (C=$C_{ar}$), 1480, 1434, 1091 ($CH_2$-O)

## 14.2. Alkylation of Benzaldehyde Catalyzed by Complex 158

### 14.2.1. General Procedure J



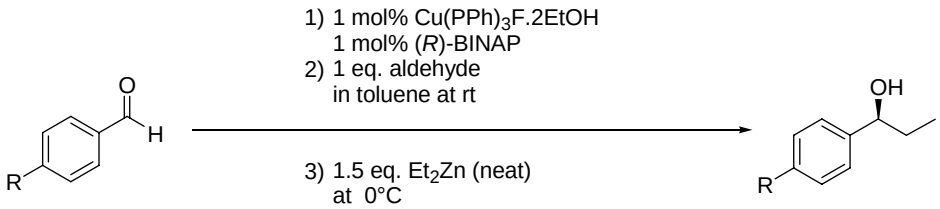

Copper (I) fluoride **158** (19.4 mg, $2x10^{-2}$ mmol, 0.01 eq.) and ligand (2 $x10^{-2}$ mmol, 0.01 eq.) are placed in a two-necked flame-dried round-bottom flask fitted with a rubber septum and an argon inlet. A solution of benzaldehyde (0.5 M) and dodecane (0.25 M) in dry toluene is prepared in a flame-dried graduated Schlenck flask. 4 ml of the prepared solution (0.213 g, 2 mmol, 1 eq. of benzaldehyde & 0.171 g, 1 mmol, 0.5 eq. of *n*-dodecane) is engaged in the two-necked flask. After 20 to 30 minutes, the mixture is cooled to 0°C in an ice bath.

A 1M diethylzinc solution in dry *n*-hexane is prepared from commercially available pure diethylzinc in a flame-dried graduated Schlenck flask. 2 ml of the diorganozinc solution are added at once on the substrate-catalyst mixture. The reaction is left at 0°C for two hours, after what the reaction vessel is moved to a cool room at 4°C.

Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. Sampling is realized at least after 5 min, 15 min, 30 min, 1 hour, 2 hours and 24 hours. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

## 14.3. Asymmetric Alkylation of Aldehydes Catalyzed by Complex 158 and (*R*)-BINAP 75

### 14.3.1. General Procedure K




The following reactions are carried out in a 12 test tubes Radley's carrousel. The test tube and the stirring bar are dried overnight in an oven and cooled under argon once set up in the carrousel. Copper(I) fluoride **158** (92.7 mg, 9.6 x $10^{-2}$ mmol, 0.01 eq.) and

(*R*)-BINAP **75** (59.4 mg, 9.6 x $10^{-2}$ mmol, 0.01 eq.) are introduced in the tube which is then subjected to three vacuum-argon cycles.

In a flame-dried round-bottom 25 ml flask, the aldehyde (1 eq.) is dissolved in 10 ml of dry toluene. This solution is added to the catalyst precursor. The solution immediately turns yellow. The mixture is stirred for 10 minutes at room temperature before being cooled in ice-bath. The diethylzinc (1.5 ml, 1.77 g, 14.3 mmol, 1.5 eq.) is added in one portion.

The reaction is followed by GC. Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. Sampling is realized at least after 30 min, 1 hour and every hour after that. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

Once the reaction is complete, 3 ml of methanol are added and the white suspension is stirred vigorously.

## 14.3.2. Addition to Benzaldehyde

**Ref.** : Optical activity[440]

**Operating Procedure** : General Procedure K

**Reaction time**: 30 min.

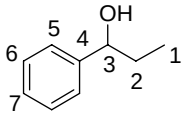
**Quantities Engaged** : Benzaldehyde: 0.97 ml, 1.01 g, 9.55 mmol, 1 eq.

**Substrate Concentration** : *ca.* 0.8M

**Purification** : An aqueous solution of HCl (1 M) is added until the white suspension disappears. The mixture is extracted with three portions of ether. The combined organic extracts are washed with brine and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 1.114 g of a colorless oil is obtained.

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Yield** : 1.114 g (85%)

**Physical Property** : colorless oil

$[\alpha]_D^{30}$ =-19.3 (*c*1.025, toluene)

**GC** (100/4/1/110/5) : $t_R$=4.18 min for benzaldehyde
$t_R$=8.60 min for 1-phenyl-1-propanol

**Chiral GC** (100/7/4/140/7) : $t_R$= 21.36 min (minor)
$t_R$= 21.67 min (major)

**Enantiomeric Excess** : 49.1% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.26 (m, 5H, $H^{ar}$); 4.45 (t, $^3J_{2,3}$=6.6, 1H, $H^3$), 2.73 (bs, 1H, O*H*); 1.70 (mult., 2H, $H^2$); 0.84 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 144.6* ($C^4$); 128.2 ($C^{ar}$), 127.2 ($C^{ar}$), 125.9 ($C^{ar}$), 76.4 ($C^3$), 31.7* ($C^2$), 9.9 ($C^1$)

**Mass** (EI, eV) : 137.0 ($[M+1]^+$,1.4%); 136.0 ($[M]^{\cdot+}$, 12.9%); 118.9 ($[M-OH]^+$, 32.4%); 107.0 ($[M-(C_2H_5)]^+$, 84.5%); 78.9 ($[C_6H_7]^+$, 100%); 76.9 ($[C_6H_5]^+$, 42.5%)

## 14.3.3. Addition to *p*-Chlorobenzaldehyde

**Operating Procedure** : General Procedure K

**Reaction time**: less than 30 min..

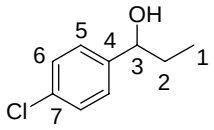
**Quantities Engaged** : *p*-Chlorobenzaldehyde: 1.343 g, 9.55 mmol, 1 eq.

**Substrate Concentration** : *ca.* 0.8 M

**Purification** : An aqueous solution of HCl (1 M) is added until the white suspension disappears. The mixture is extracted with three portions of ether. The combined organic extracts are washed with brine and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 1.384 g of a colorless oil is obtained.

**Name** : 1-(4'-chorophenyl)-1-propanol




**CAS-RN** : 73890-73-0 (*S* enantiomer)

**M.F.** : $C_9H_{11}ClO$ **M.W.** : 170.63

**Yield** : 1.384 g (85%)

**Physical Property** : colorless oil

**GC** ( 100/4/1/110/5) : $t_R$=7.80 min for *p*-chlorobenzaldehyde
$t_R$=17.5 min for 1-(4'-chlorophenyl)-1-propanol

**Chiral GC** (100/7/4/140/30) : $t_R$= 39.29 min (minor)
$t_R$= 41.45 min (major)

**Enantiomeric Excess** : 55.8% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.26 (d, $^3J_{HH}$=8.7, 2H, $H^{ar}$); 7.17 (d, $^3J_{HH}$=8.7, 2H, $H^{ar}$); 4.45 (t, $^3J_{2,3}$=6.3, 1H, $H^3$); 2.97 (bs, 1H, O*H*); 1.67 (mult., 2H, $H^2$); 0.83 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 142.9* ($C^4$); 132.9* ($C^7$); 128.3 ($C^{ar}$); 127.3 ($C^{ar}$); 75.0 ($C^3$); 31.7* ($C^2$), 9.8 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3362 (br, O-H); 2966 (C-H); 2934 (C-H); 2877 (C-H); 1597 ($C_{ar}$=$C_{ar}$); 1492 ($C_{ar}$=$C_{ar}$); 1463($C_{ar}$=$C_{ar}$); 1409 (O-H); 1091 ($C_{ar}$-*p*-Cl); 1044 (CH-O); 1014 (CH-O); 824 (=C-H)

**Mass** (EI, eV) : 171.6 ($[M+1]^+$,3.5%); 169.9 ($[M]^{\cdot+}$, 8.1%); 152.9 ($[M-OH]^+$, 4.2%); 140.9 ($[M-(C_2H_5)]^+$, 72.4%), 76.9 ($[C_6H_5]^+$, 100%)

## 14.3.4. Addition to *p*-Tolylaldehyde

**Operating Procedure** : General Procedure K

**Reaction time**: less than 1 hour.

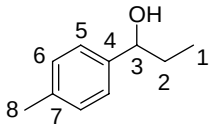
**Quantities Engaged** : *p*-Tolylaldehyde: 1.13 ml, 1.148 g, 9.55 mmol, 1 eq.

**Substrate Concentration** : *ca.* 0.8 M

**Purification** : An aqueous solution of HCl (1 M) is added until the white suspension disappears. The mixture is extracted with three portions of ether. The combined organic extracts are washed with brine and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 1.104 g of a colorless oil is obtained.

**Name** : 1-(4'-methylphenyl)-1-propanol




**CAS-RN** : 73854-03-2 (*S* enantiomer)

**M.F.** : $C_{10}H_{14}O$ **M.W.** : 150.22

**Yield** : 1.104 g (77%)

**Physical Property** : colorless oil

**GC** (100/4/1/110/5) : $t_R$= 6.50 min for *p*-tolylaldehyde

$t_R$= 13.40 min for 1-(4'-methylphenyl)-1-propanol

**Chiral GC** (100/7/4/140/30) : $t_R$= 24.16 min (minor)

$t_R$= 24.89 min (major)

**Enantiomeric Excess** : 57.9% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.14 (d, $^3J_{HH}$=8.1, 2H, $H^{ar}$); 7.08 (d, $^3J_{HH}$=8.1, 2H, $H^{ar}$); 4.40 (t, $^3J_{2,3}$=6.6, 1H, $H^3$); 2.76 (bs, 1H, O*H*); 2.30 (s, 3H, $H^8$); 1.68 (mult., 2H, $H^2$); 0.83 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 141.6* ($C^4$); 136.7* ($C^7$); 128.8 ($C^{ar}$); 125.8 ($C^{ar}$); 75.5 ($C^3$); 31.6* ($C^2$); 20.9 ($C^8$); 10.0 ($C^1$)

**IR** (solid deposit, $cm^{-1}$) : 3373 (br, O-H); 3021 ($C_{ar}$-H); 2964 (C-H); 2930 (C-H); 2876 (C-H); 1514 ($C_{ar}$=$C_{ar}$); 1456 (O-H); 1098; 1043 (CH-O); 1012 (CH-O); 973 (=C-H); 816 (=C-H)

**Mass** (EI, eV) : 151.1 ($[M+1]^+$,1.6%);149.9 ($[M]^{\cdot+}$, 11.9%); 132.9 ($[M\text{-}OH]^+$, 8.6%); 120.9 ($[M\text{-}(C_2H_5)]^+$, 100%); 92.8 (72.0%); 90.9 ($[C_7H_7]^+$, 69.4%); 76.9 ($[C_6H_5]^+$, 53.5%)

## 14.3.5. Addition to *p*-Anisaldehyde

**Ref.** : optical activity[440]

absolute configuration[42]

**Operating Procedure** : General Procedure K

**Reaction time**: more than 3 hours.

**Quantities Engaged** : *p*-Anisaldehyde: 1.16 ml, 1.301 g, 9.55 mmol, 1 eq.

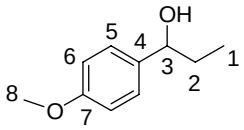
**Substrate Concentration** : *ca.* 0.8M

**Purification** : The white suspension is extracted with three portions of dichloromethane. The combined organic extracts are washed successively with a saturated aqueous solution of $NH_4Cl$, a saturated aqueous solution of $Na_2CO_3$ and brine before drying on $MgSO_4$. Some grains of solid $Na_2CO_3$ are added to the solution. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 1.407 g of a colorless oil is obtained.

**Note** : Addition of solid $Na_2CO_3$ during the concentration and bulb-to-bulb distillation provided the addition product cleanly without the elimination product.

**Name** : 1-(4'-methoxyphenyl)-1-propanol




**CAS-RN** : 5349-60-0 (*S* enantiomer)

**M.F.** : $C_{10}H_{14}O_2$ **M.W.** : 166.21

**Yield** : 1.407 g (88.6%)

**Physical Property** : colorless oil

**[α]** $^{30}_{D}$ =-21.4 (*c*1.04, toluene)

**GC** (100/4/1/25) : $t_R$= 13.42 min for *p*-anisaldehyde

$t_R$= 24.25 min for 1-(4'-methoxphenyl)-1-propanol

**Chiral GC** (100/8/4/150/15) : $t_R$= 31.87 min (minor)

$t_R$= 32.45 min (major)

**Enantiomeric Excess** : 63.4% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.18 (d, $^3J_{HH}$=8.4, 2H, $H^5$); 6.81 (d, $^3J_{HH}$=8.7, 2H, $H^6$); 4.42 (td, $^3J_{2,3}$=6.6, $^3J_{OH,3}$=3, 1H, $H^3$); 3.73 (s, 3H, $H^8$); 2.83 ($^3J_{3,OH}$=3, 1H, $H^{OH}$); 1.69 (mult., 2H, $H^2$); 0.83 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 158.8* ($C^4$); 136.8* ($C^7$); 127.0 ($C^5$); 113.6 ($C^6$); 75.2 ($C^3$); 55.0 ($C^8$); 31.6* ($C^2$); 9.9 ($C^1$)

**Mass** (EI, eV) : 167.0 ($[M+1]^+$, 1.5%); 165.9 ($[M]^{\cdot+}$, 14.8%); 148.9 ($[M-OH]^+$, 2.72%); 136.9 ($[M-(C_2H_5)^+]^+$, 100%]; 108.9 ($[M-(C_3H_5O)^+]^+$, 28.8); 93.9 ($[C_6H_5O]^+$, 34.2); 90.9 ($[C_7H_7]^+$, 4.8%); 76.9 (28.7%)

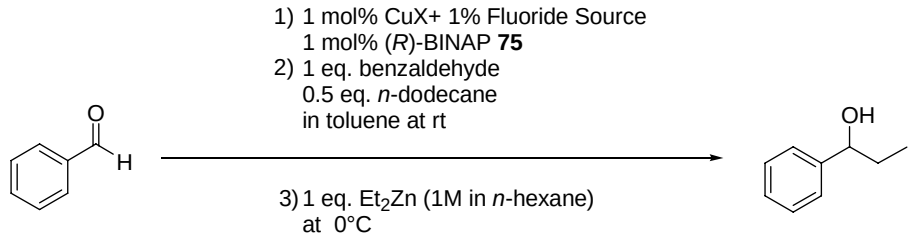
151.1 ($[M+1]^+$,1.6%);149.9 ($[M]^{\cdot+}$, 11.9%); 132.9 ($[M-OH]^+$, 8.6%); 120.9 ($[M-(C_2H_5)]^+$, 100%]; 92.8 (72.0%); 90.9 ($[C_7H_7]^+$, 69.4%); 76.9 ($[C_6H_5]^+$, 53.5%)

# Chapter 15

# Second Generation Copper Fluoride

## 15.1. Copper Salt Catalyst Investigation

### 15.1.1. General Procedure L

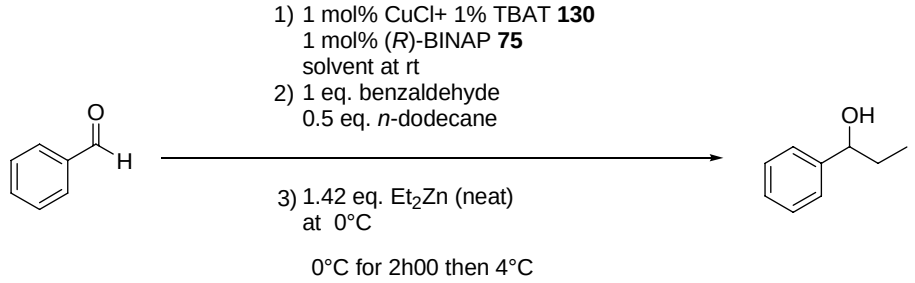



Copper(I) salt ($2x10^{-2}$ mmol, 0.01 eq.), (*R*)-BINAP **75** (12.7 mg, 2 $x10^{-2}$ mmol, 0.01 eq.) and a fluoride source ($2x10^{-2}$ mmol, 0.01 eq., when mentioned) are placed in a two-necked flame-dried round-bottom flask fitted with a rubber septum and an argon inlet. A solution of benzaldehyde (0.5 M) and dodecane (0.25 M) in dry toluene is prepared in a flame-dried graduated Schlenck flask. 4 ml of the prepared solution (0.213 g, 2 mmol, 1 eq. of benzaldehyde and 0.171 g, 1 mmol, 0.5 eq. of *n*-dodecane) are engaged in the two-necked flask. After 20 to 30 minutes, the mixture is cooled to 0°C in an ice bath.

A diethylzinc solution (1 M) in dry *n*-hexane is prepared from commercially available pure diethylzinc in a flame-dried graduated Schlenck flask. 2 ml of the diorganozinc solution are added at once on the substrate-catalyst mixture. The reaction is left at 0°C for two hours, after what the reaction vessel is moved to a cool room at 4°C.

Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. Sampling is realized at least after 5 min, 15 min, 30 min, 1 hour, 2 hours and 24 hours. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

## 15.1.2. General Procedure M

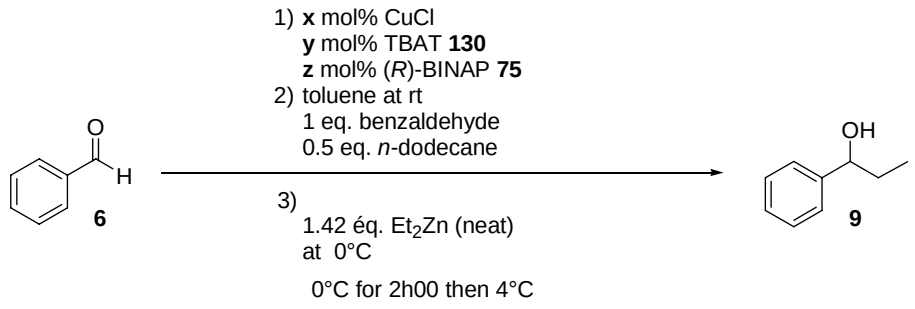



The following reactions are carried out in a 12 test tubes Radley's carrousel. The test tube and the stirring bar are dried beforehand overnight in an oven and cooled under argon once set up in the carrousel. Copper(I) chloride (2.0 mg, 2.0 x $10^{-2}$ mmol, 0.01 eq.), tetrabutylammonium triphenyldifluorosilicate (TBAT) **130** (10.9 mg, 2.0 x $10^{-2}$ mmol, 0.01 eq.) and (*R*)-BINAP **75** (12.7 mg, 2.0 x $10^{-2}$ mmol, 0.01 eq.) are introduced in the tube which is then subjected to three vacuum-argon cycles. Solvent (5 ml) is then introduced.

In a flame-dried round-bottom 25 ml flask, a mixture of benzaldehyde (2 ml, 2.088 g, 19.68 mmol) and *n*-dodecane (2.24 ml, 1.675 g, 9.84 mmol) is prepared. 0.435 ml of this mixture (corresponding to 0.206 ml, 0.215 g, 2.0 mmol, 1 eq. of benzaldehyde and 0.230 ml, 0.172 g, 1.0 mmol, 0.5 eq of *n*-dodecane) is introduced on the catalyst precursor. The mixture is stirred for 20-30 minutes at room temperature before being cooled in an ice-bath. Neat diethylzinc (0.3 ml, 0.354 g, 2.87 mmol, 1.42 eq.) is added in one portion. The reaction is left at 0°C for two hours, after what the reaction vessel is moved to a cool room at 4°C.

Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. Sampling is realized at least after 5 min, 15 min, 30 min, 1 hour, 2 hours and 24 hours. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

## 15.1.3. General Procedure N



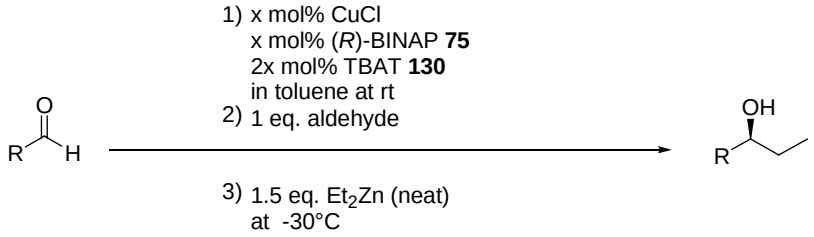

The following reactions are carried out in a 12 test tubes Radley's carrousel. The test tube and the stirring bar are dried beforehand overnight in an oven and cooled under argon once set up in the carrousel. Copper(I) chloride, tetrabutylammonium triphenyldifluorosilicate (TBAT) **130** and (*R*)-BINAP **75** are introduced in the corresponding amounts in the tube which is then subjected to three vacuum-argon cycles. Dry toluene (5 ml) is then introduced.

In a flame-dried round-bottom 25 ml flask, a mixture of benzaldehyde (2 ml, 2.088 g, 19.68 mmol) and *n*-dodecane (2.24 ml, 1.675 g, 9.84 mmol) is prepared. 0.435 ml of this mixture (corresponding to 0.206 ml, 0.215 g, 2.0 mmol, 1 eq. of benzaldehyde and 0.230 ml, 0.172 g, 1.0 mmol, 0.5 eq of *n*-dodecane) is introduced on the catalyst precursor. The mixture is stirred for 20-30 minutes at room temperature before being cooled in an ice-bath. Neat diethylzinc (0.3 ml, 0.354 g, 2.87 mmol, 1.42 eq.) is added in one portion. The reaction is left at 0°C for two hours, after what the reaction vessel is moved to a cool room at 4°C.

Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. Sampling is realized at least after 5 min, 15 min, 30 min, 1 hour, 2 hours and 24 hours. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

## 15.2. Asymmetric Alkylation of Several Aldehydes Catalyzed by Copper(I) Chloride, TBAT 130 and (*R*)-BINAP 75

### 15.2.1. General Procedure O




In a flame dried two-necked round-bottom 50 ml flask equipped with a magnetic stirring bar, a septum and an argon-inlet, copper(I) chloride (0.01 eq.), tetrabutylammonium triphenyldifluorosilicate **130** (0.02 eq.) and (*R*)-BINAP **75** (0.01 eq.) are introduced in the flask which is then subjected to three vacuum-argon cycles. 20 ml of dry toluene are then added. The solution immediately turns yellow.

The aldehyde (1 eq.) is added to the catalyst precursor. The mixture is stirred for 30 minutes at room temperature before being cooled to -30°C in an isopropanol bath cooled by a cryostat. The diethylzinc (1.5 eq.) is added portionwise over 5 minutes.

The reaction is monitored by GC to estimate the reaction time. Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

After 24 hours, 3 ml of methanol are added to the cool reaction media and the white suspension is stirred vigorously.

## 15.2.2. Addition to Benzaldehyde (1mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: > 3 hours.

**Quantities Engaged** :

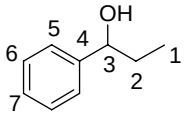
Benzaldehyde: 0.813 ml, 848.9 g, 8 mmol, 1 eq.
Copper(I) chloride: 7.9 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 86.4 mg, 16.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 50.3 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 1.256 ml, 1.48 g, 12.0 mmol, 1.5 eq.
Toluene : 20 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.903 g of a colorless oil is obtained.

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Yield** : 0.903 g (83%)

**Physical Property** : colorless oil

**GC** (100/4/1/110/5) : $t_R$=4.98 min for benzaldehyde
$t_R$=8.56 min for 1-phenyl-1-propanol

**Chiral GC** (105/5/4/130/13) : $t_R$= 22.92 min (*R*)
$t_R$= 23.49 min (*S*)

**Enantiomeric Excess** : 80.7% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 15.2.3. Addition to Benzaldehyde (0.5mol% loading)

**Ref.** : Optical activity[440]

**Operating Procedure** : see General Procedure O

**Reaction time**: 17 hours.

**Quantities Engaged** :

Benzaldehyde: 0.61 ml, 0.637 g, 6 mmol, 1 eq.
Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.

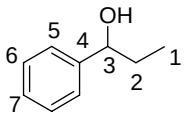
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.689 g of a colorless oil is obtained.

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Yield** : 0.689 g (84%)

**Physical Property** : colorless oil

$[\alpha]_D^{30}$ =-41.5 (*c*1.06, toluene)

**GC** (100/4/1/110/5) : $t_R$=4.47 min for benzaldehyde

$t_R$= 7.65 min for 1-phenyl-1-propanol

**Chiral GC** (110/4/4/135/12) : $t_R$= 21.18 min (minor)

$t_R$= 21.52 min (major)

**Enantiomeric Excess** : 80.6% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 15.2.4. Addition to Benzaldehyde (0.1mol% loading, 1.5 eq. $Et_2Zn$)

**Ref.** : Optical activity[440]

**Operating Procedure** : see General Procedure O

**Reaction time**: 48 hours (reaction is incomplete)

**Quantities Engaged** :

Benzaldehyde: 0.61 ml, 0.637 g, 6 mmol, 1 eq.

Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.

(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.

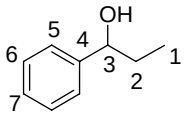
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash chromatography on silica gel. (cyclohexane/AcOEt, 75/25 $R_f$= 0.25, $KMnO_4$). 0.346 g of a colorless oil is obtained.

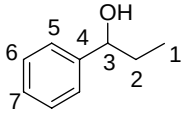
**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)
**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19
**Yield** : 0.346 g (42%)
**Physical Property** : colorless oil
**[α]** $^{30}_{D}$ =-47.4 (*c*0.99, toluene)
**GC** (100/4/1/110/5) : $t_R$=4.47 min for benzaldehyde
$t_R$= 7.65 min for 1-phenyl-1-propanol
**Chiral GC** (110/4/4/135/12) : $t_R$= 21.88 min (minor)
$t_R$= 22.38 min (major)
**Enantiomeric Excess** : 78.4% ee (*S*)
**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 15.2.5. Addition to Benzaldehyde (0.1mol% loading, 2 eq. $Et_2Zn$)

**Operating Procedure** : see General Procedure O
**Reaction time**: 24 hours (reaction is incomplete)
**Quantities Engaged** :
Benzaldehyde: 1.22 ml, 1.273 g, 12 mmol, 1 eq.
Copper(I) chloride: 11 mg, 12.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 129 mg, 24.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 75.0 mg, 12.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 2.51 ml, 2.964 g, 24.0 mmol, 2 eq.
Toluene : 30 ml
**Substrate Concentration** : *ca.* 0.36M
**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, 0.836 g colorless oil is obtained.
The oil is purified by flash chromatography on silica gel. (cyclohexane/AcOEt, 75/25 $R_f$= 0.25, $KMnO_4$). 0.696 g of a colorless oil is obtained.
**Name** : 1-phenyl-1-propanol

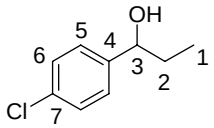



**CAS-RN** : 613-87-6 (*S* enantiomer)
**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19
**Yield** : 0.696 g (42.6%)
**Physical Property** : colorless oil

**GC** (100/4/1/110/5) : $t_R$=4.47 min for benzaldehyde
$t_R$= 7.65 min for 1-phenyl-1-propanol
**Chiral GC** (110/4/4/135/12) : $t_R$= 21.57 min (minor)
$t_R$= 22.06 min (major)
**Enantiomeric Excess** : 74.8% ee (*S*)
**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 15.2.6. Addition to p-Chlorobenzaldehyde

**Ref.** : Optical activity[40]
**Operating Procedure** : see General Procedure O
**Reaction time**: < 1 hour
**Quantities Engaged** :
*p*-Chlorobenzaldehyde: 0.843 g, 6 mmol, 1 eq.
Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.
Toluene : 15 ml
**Substrate Concentration** : *ca.* 0.36M
**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.
The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.942 g of a colorless oil is obtained.
**Name** : 1-(4'-chorophenyl)-1-propanol




**CAS-RN** : 73890-73-0 (*S* enantiomer)
**M.F.** : $C_9H_{11}ClO$ **M.W.** : 170.63
**Yield** : 0.942 g (92%)
**Physical Property** : colorless oil
$[\alpha]_D^{30}$ =-27.2 (*c*0.85, benzene)
**GC** (100/5/10/290) : $t_R$=13.98 min for 1-(4'-chlorophenyl)-1-propanol
**Chiral GC** (110/5/4/135/30) : $t_R$= 35.46 min (minor)
$t_R$= 37.36 min (major)
**Enantiomeric Excess** : 84.5% ee
**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 15.2.7. Addition to p-Tolylaldehyde

**Ref.** : Optical activity[193]

**Operating Procedure** : see General Procedure O

**Reaction time**: less than 8 hours

**Quantities Engaged** :

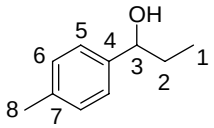
*p*-Tolylaldehyde: 0.729 ml, 0.743 g; 6 mmol, 1 eq.
Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.844 g of a colorless oil is obtained.

**Name** : 1-(4'-methylphenyl)-1-propanol




**CAS-RN** : 73854-03-2 (*S* enantiomer)

**M.F.** : $C_{10}H_{14}O$ **M.W.** : 150.22

**Yield** : 0.844 g (94%)

**Physical Property** : colorless oil

$[\alpha]_D^{30}$ =-31.7 (*c*1.20, benzene)

**GC** (100/5/10/290) : $t_R$= 8.96 min for *p*-tolylaldehyde
$t_R$= 12.24 min for 1-(4'-methylphenyl)-1-propanol

**Chiral GC** (110/5/4/135/10) : $t_R$= 18.37 min (minor)
$t_R$= 19.12 min (major)

**Enantiomeric Excess** : 85.1% ee

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 15.2.8. Addition to p-Cyanobenzaldehyde

**Ref.** : Optical activity[441]

**Operating Procedure** : see General Procedure O

**Reaction time**: > 8 hours.

**Quantities Engaged** :

*p*-cyanobenzaldehyde: 1.049 g, 8 mmol, 1 eq.
Copper(I) chloride: 7.9 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.

TBAT **130**: 86.4 mg, 16.0 x $10^{-2}$ mmol, 0.02 eq.

(*R*)-BINAP **75**: 50.3 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc: 1.256 ml, 1.48 g, 12.0 mmol, 1.5 eq.

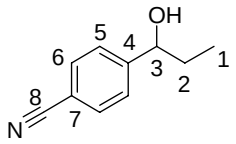
Toluene : 20 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 1.028 g of a colorless oil is obtained.

**Name** : 1-(4'-cyanophenyl)-1-propanol




**CAS-RN** : 184777-47-7 (*S* enantiomer)

**M.F.** : $C_{10}H_{11}NO$ **M.W.** : 161,20

**Yield** : 1.028 g (80%)

**Physical Property** : colorless oil

$[\alpha]_D^{30}$ =-38.6 (*c*0.80, $CHCl_3$)

**GC** (100/5/10/290) : $t_R$= 10.32 min for *p*-cyanobenzaldehyde

$t_R$= 14.97 min for 1-(4'-cyanophenyl)-1-propanol

**Chiral GC** (105/5/4/180/15) : $t_R$= 35.20 min (minor)

$t_R$= 36.09 min (major)

**Enantiomeric Excess** : 81.1% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.57 (d, $^3J_{HH}$=8.1, 2H, $H^{ar}$); 7.43 (d, $^3J_{HH}$=8.1, 2H, $H^{ar}$); 4.63 (t, $^3J_{2,3}$=6.3, 1H, $H^3$); 3.63 (bs, 1H, O*H*); 1.73 (mult., 2H, $H^2$); 0.89 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 150.0* ($C^4$); 131.6 ($C^{ar}$); 126.3 ($C^{ar}$); 118.5* ($C^8$); 110.0* ($C^7$); 74.3 ($C^3$); 31.6* ($C^2$); 9.6 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3343 (br, O-H); 2971 (C-H); 2932 (C-H); 2874 (C-H); 2228 (C≡N); 1603 ($C_{ar}$=$C_{ar}$); 1501 ($C_{ar}$=$C_{ar}$); 1458 ($CH_3$ or $CH_2$); 1410 (O-H); 1200; 1091; 968 (=C-H); 851 (=C-H)

**Mass** (EI, eV) : 162.0 ($[M+1]^+$,3.5%); 160.8 ($[M]^{\cdot+}$, 6.5%); 131.9 ($[M-(C_2H_5)]^+$, 100%); 104.9 ($[M-(C_2H_5)-(CN)]^+$, 8.4%); 103.9 ($[M-(C_2H_5)-(HCN)]^{\cdot+}$, 97.2%); 90.9 ($[C_7H_7]^+$, 15.1%); 76.9 ($[C_6H_5]^+$, 36.9%)

## 15.2.9. Addition to o-Tolylaldehyde

**Ref.** : Optical activity[442]

**Operating Procedure** : see General Procedure O

**Reaction time**: more than 19 hours.

**Quantities Engaged** :

*o*-Tolylaldehyde : 0.925 ml, 0.961 g, 8 mmol, 1 eq.

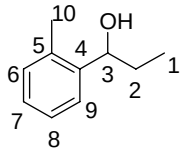
Copper(I) chloride : 7.9 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130** : 86.4 mg, 16.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75** : 50.3 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc : 1.256 ml, 1.48 g, 12.0 mmol, 1.5 eq.
Toluene : 20 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.950 g of a colorless oil is obtained.

**Name** : 1-(2'-methylphenyl)-1-propanol




**CAS-RN** : 117409-10-6 (*S* enantiomer)

**M.F.** : $C_{10}H_{14}O$ **M.W.** : 150,22

**Yield** : 0.950 g (79%)

**Physical Property** : colorless oil

$[\alpha]_D^{30}$ =-57.3 (*c*1.15, benzene)

**GC** (100/5/10/290) : $t_R$= 6.86 min for *o*-tolylaldehyde
$t_R$= 10.7 min for 1-(2'-methylphenyl)-1-propanol

**Chiral GC** (105/5/4/180) : $t_R$= 20.96 min (minor)
$t_R$= 21.30 min (major)

**Enantiomeric Excess** : 80.4% ee (*S*)

**$^1$H NMR** ( $CDCl_3$, 300 MHz) : 7.46 (d, $^3J_{HH}$=1.2, 1H, $H^{ar}$); 7.15 (m, 3H, $H^{ar}$); 4.77 (t, $^3J_{2,3}$=6.0, 1H, $H^3$); 2.29 (bs, 1H, O*H*); 2.28 (s, 3H, $H^{10}$); 1.69 (quint, *J*=7.2, 2H, $H^2$); 0.92 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) : 142.6* ($C^4$); 134.3* ($C^5$); 130.0 ($C^6$); 126.8 ($C^{ar}$); 126.0 ($C^{ar}$); 125.0 ($C^{ar}$); 71.8 ($C^3$); 30.8* ($C^2$); 19.0 ($C^{10}$); 10.3 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3343 (br, O-H); 3065 (=$C_{ar}$-H); 3024 (=$C_{ar}$-H); 2964 (C-H); 2933 (C-H); 2874 (C-H); 1605 ($C_{ar}$=$C_{ar}$); 1487; 1461 ($CH_3$ or $CH_2$); 1379; 1091 (C-O; 1052; 1041; 1008; 973 (=C-H); 835 (=C-H); 751 ($C_{ar}$=$C_{ar}$)

**Mass** (EI, eV) : 151.0 ($[M+1]^+$,2%); 149.9 ($[M]^{\cdot+}$, 14.7%); 133.0 ($[M-OH]^+$, 31.3%); 120.9 ($[M-(C_2H_5)]^+$, 100%); 92.8 (74.1%); 90.9 ($[C_7H_7]^+$, 72.6%); 76.9 ($[C_6H_5]^+$, 46.8%)

## 15.2.10. Addition to o-Anisaldehyde

**Ref.** : Optical activity[440]
Absolute configuration[42]

**Operating Procedure** : see General Procedure O

**Reaction time**: 3 hours.

**Quantities Engaged** :

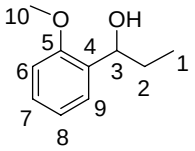
*o*-Anisaldehyde: 0.747 ml, 0.842 g, 6 mmol, 1 eq.
Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $Na_2CO_3$ and water prior to being dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.922 g of a colorless oil is obtained.

**Name** : 1-(2-Methoxy-phenyl)-propan-1-ol




**CAS-RN** : 114389-71-8 (*S* enantiomer)

**M.F.** : $C_{10}H_{14}O_2$ **M.W.** : 166,22

**Yield** : 0.922 g (92%)

**Physical Property** : colorless oil

$[\alpha]_D^{30}$ =-48.11 (*c*1.06, toluene)

**GC** (100/5/10/290) : $t_R$= 11.14 min for *o*-anisaldehyde
$t_R$= 13.39 min for 1-(2-Methoxy-phenyl)-propan-1-ol

**Chiral GC** (140/10/5/180) : $t_R$= 16.45 min (major)
$t_R$= 17.68 min (minor)

**Enantiomeric Excess** : 82.6% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.21-7.31 (mult, 2H, $H^{7\ \&\ 9}$); 6.95 (dd, $^3J_{7,8}$ & $^3J_{8,9}$=6.8 & 8.1, 1H, $H^8$); 6.88 (d, $^3J_{6,7}$=8.1, 1H, $H^6$); 4.78 (q, $^3J_{2,3}$=$^3J_{2,OH}$=6.6, 1H, $H^3$), 3.85 (s, 3H, $H^{10}$); 2.57 (d, $^3J_{2,3}$=6.6, 1H, $H^{OH}$); 1.82 (mult.; 2H, $H^2$); 0.95 (t, $^3J_{1,2}$=7.2; 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 156.6* ($C^5$); 132.5* ($C^4$); 128.1 & 127.0 ($C^{7\ \&\ 9}$); 120.7 ($C^8$); 110.5 ($C^6$); 72.1 ($C^3$); 55.2 ($C^{10}$); 30.2* ($C^2$); 10.3 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3403 (br, O-H); 3071 (=$C_{ar}$-H); 2964 (C-H); 2935 (C-H); 2876 (C-H); 2837 (C-H); 2030 (overtones); 1904 (overtones); 1786 (overtones); 1601 ($C_{ar}$=$C_{ar}$); 1588 ($C_{ar}$=$C_{ar}$); 1491;1464; 1439; 1239 ($C_{ar}$-O); 1190 ($C_{ar}$-O); 1174 (C-O); 1089 (C-O); 1028; 754

**Mass** (CI, $CH_4$-$N_2O$) : 167.0 ($[M+1]^+$, 1.2%); 166 ($[M]^{\cdot+}$, 5.3%); 149.0 ($[M\text{-}OH]^+$, 100%); 137.0 ($[M\text{-}(C_2H_5)]^+$, 44.4%); 121 (6.5%); 120.9 (20.7%); 107.0 ($[M\text{-}(C_3H_7O)]^+$, 6.0%)

## 15.2.11. Addition to 1-naphtaldehyde

**Ref.** : Optical activity and absolute configuration[42]

**Operating Procedure** : see General Procedure O

**Reaction time**: more than 24 hours.

**Quantities Engaged** :

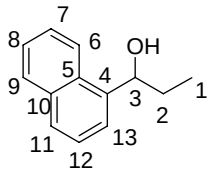
1-Naphtaldehyde: 0.84 ml, 0.966 g, 6 mmol, 1 eq.
Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $Na_2CO_3$ and water prior to being dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is first purified by flash-chromatography on silica-gel (*n*-pentane/ diethylether, 75/25, $R_f$=0.29). Then it is purified by bulb-to-bulb distillation by heating under controlled vacuum. 0.814 g of a colorless oil is obtained.

**Name** : 1-Naphthalen-1-yl-propan-1-ol




**CAS-RN** : 135818-31-4 (*S* enantiomer)

**M.F.** : $C_{13}H_{14}O$ **M.W.** : 186,25

**Yield** : 0.814 g (73%)

**Physical Property** : colorless oil

$[\alpha]_D^{30}$ =-40.6 (*c*2.4, $CHCl_3$)

**GC** (100/5/10/290) : $t_R$= 15.75 min for 1-naphtaldehyde
$t_R$= 18.37 min for 1-Naphthalen-1-yl-propan-1-ol

**HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 90/10, 1 ml/min., 25°C, 220nm )
$t_R$= 15.18 min (major)
$t_R$= 27.22 min (minor)

**Enantiomeric Excess** : 75% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 8.12 (d, $^3J_{6,7}$=4.4, 1H, $H^6$); 7.88 (d, $^3J_{8,9}$=8.1, 1H, $H^9$); 7.78 (d, $^3J_{11,12}$=8.4, 1H, $H^{11}$); 7.64 (d, $^3J_{12,13}$=7.2, 1H, $H^{13}$); 7.44-7.56 (m.; 3H, $H^{7,8\ \&\ 12}$); 5.41 (apparent quint., $^3J_{2,3}$=$^3J_{3,OH}$=3.9, 1H, $H^3$); 1.8-2.1 (m, 2H, $H^2$); 1.94 (d, $^3J_{2,3}$ =3.9, 1H, O*H*); 1.04 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 140.2* ($C^4$); 133.8* ($C^{10}$); 130.5* ($C^5$); 128.8 ($C^9$); 127.8 ($C^{11}$); 125.8, 125.4 & 125.3 ($C^{7,8\ \&\ 12}$); 123.2 & 122.9 ($C^{6\ \&\ 13}$); 72.5 ($C^3$); 31.0* ($C^2$); 10.4 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3384 (br, O-H); 3049 (=$C_{ar}$-H); 2965 (C-H); 2933 (C-H); 2875 (C-H); 1597 ($C_{ar}$=$C_{ar}$); 1559 ($C_{ar}$=$C_{ar}$); 1540; 1510; 1457; 1385; 1377; 1168; 1114; 1095; 1045; 1029 (C-O); 969; 799; 777

**Mass** (CI, $CH_4$-$N_2O$) : 187 ($[M+1]^+$, 3.8%); 185.9 ($[M]^{\cdot+}$, 17.1%); 168.9 ($[M-OH]^+$, 100%); 156.9 ($[M-(C_2H_5)]^+$, 27.2%); 128.9 ($[C_{10}H_8]^{\cdot+}$, 26.6%); 127.6 ($[C_{10}H_7]^{\cdot+}$, 3.3%)

## 15.2.12. Addition to 2-Furfuraldehyde

**Ref.** : Optical activity and absolute configuration[351]

**Operating Procedure** : see General Procedure O

**Reaction time**: 5 hours.

**Quantities Engaged** :

2-Furfuraldehyde: 0.683 ml, 0.792 g, 8 mmol, 1 eq.
Copper(I) chloride: 7.9 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 86.4 mg, 16.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 50.3 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 1.256 ml, 1.48 g, 12.0 mmol, 1.5 eq.
Toluene : 20 ml

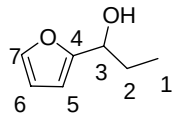
**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed with water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash-chromatography on silica gel (cyclohexane/AcOEt, 75/25 $R_f$= 0.25, $KMnO_4$). 0.649 g of a colorless oil is obtained.

**Note**: Care is to be taken during solvents evaporation since the product is volatile

**Name** : 1-furan-2-yl-propan-1-ol




**CAS-RN** : 127418-31-9 (*S* enantiomer)

**M.F.** : $C_7H_{10}O_2$ **M.W.** : 126,15

**Yield** : 0.649 g (64%)

**Physical Property** : colorless oil

$[\alpha]_D^{30}$ =-19.4 (*c* 2.06, $CHCl_3$)

**GC** (100/5/10/290) : $t_R$= 4.89 min for *2*-furfuraldehyde
$t_R$= 8.03 min for 1-furan-2-yl-propan-1-ol

**HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 98/2, 1.2 ml/min., 25°C, 220nm )
$t_R$= 13.06 min
$t_R$= 14.35 min

**Enantiomeric Excess** : 80.5% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 200 MHz) : 7.34 (mult., 1H, $H^7$); 6.31 (m, 1H, $H^6$); 6.21 (d, $^3J_{5,6}$=3.2, 1H, $H^5$); 4.55 (t, $^3J_{2,3}$=6.8, 1H, $H^3$); 2.55 (bd, $^3J_{3,OH}$=9.5, 1H, O*H*); 1.85 (mult., 2H, $H^2$); 0.92 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 156.8* ($C^4$); 141.7 ($C^7$); 110.0 ($C^6$); 105.7 ($C^5$); 69.1 ($C^3$); 28.6* ($C^2$); 9.7 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3373 (br, O-H); 3119 (=C-H); 2967 (C-H); 2936 (C-H); 2878 (C-H); 1599 (C=C); 1505 (C=C); 1463 (C=C); 1380; 1225; 1150 (C-O); 1108 (C-O); 1071 (C-O); 1044 (C-O); 1008; 881 (=C-H); 811 (=C-H); 734 (=C-H)

**Mass** (CI, $CH_4$-$N_2O$) : 127.0 ($[M+1]^+$,6.0%); 125.9 ($[M]^{\cdot+}$, 9.8%); 108.9 ($[M-OH]^+$, 100%); 96.9 ($[M-(C_2H_5)]^+$ or $[M-(CHO)]^+$, 15.7%)

## 15.2.13. Addition to 2-pyridinecarboxaldehyde

**Operating Procedure** : see General Procedure O

**Reaction time**: 3 hours.

**Quantities Engaged** :

2-Pyridinecarboxaldehyde: 0.588 ml; 0.663 g, 6 mmol, 1 eq.

Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.

(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.

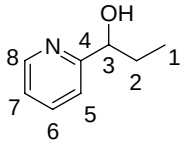
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with an aqueous saturated solution of $Na_2CO_3$, water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.584 g of a colorless oil is obtained.

**Name** : 1-Pyridin-2-yl-propan-1-ol




**CAS-RN** : 3616-83-9 (racemic)
**M.F.** : $C_8H_{11}NO$ **M.W.** : 137,18

**Yield** : 0.584 g (71%)

**Physical Property** : colorless oil

**GC** (100/5/10/290) : $t_R$= 4.77 min for 2-pyridinecarboxaldehyde
$t_R$= 8.67 min for 1-Pyridin-2-yl-propan-1-ol

**HPLC** : (Chiracel OD-H, *n*-hexane/diethylamine/isopropanol, 99.4/0.1/0.5, 1.3 ml/min., 10°C, 260nm )
$t_R$= 39.35 min.
$t_R$= 43.43 min.

**Enantiomeric Excess** : 2.2% ee

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 8.55 (d, $^3J_{7,8}$=4.8, 1H, $H^8$); 7.68 (apparent td, *J*= 7.5, *J*=1.5, 1H, $H^6$); 7.25 (d, $^3J_{5,6}$=8.7, 1H, $H^5$); 7.20 (apparent dd, *J*=6.15, *J*=6.4, 1H, $H^7$); 4.70 (dd, *J*=7.2, *J*= 4.8, 1H, $H^3$); 4.3 (bs, 1H, O*H*); 1.95-1.83 (m, 1H, $H^{2a}$); 1.74 (mult., 1H, $H^{2b}$); 0.947 (t, $^3J_{1,2}$=7.8, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 162.3* ($C^4$); 148.1 ($C^8$); 136.4 ($C^6$), 122.0 & 120.3 ($C^5$ & $C^7$); 74.0 ($C^3$); 31.2* ($C^2$); 9.3 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3373 (br, O-H); 3014 (=$C_{ar}$-H); 2966 (C-H); 2933 (C-H); 2876 (C-H); 1596 ($C_{ar}$=$C_{ar}$); 1572($C_{ar}$=$C_{ar}$); 1474 (C-H); 1436 (C-H); 1328; 1124. 1096; 1048; 982; 907; 837

**Mass** (CI, $CH_4$-$N_2O$) : 275.0 ([2M+1]$^+$, 3.2%); 139.1 ([M+2]$^{\cdot+}$, 16.6%); 137.9 ([M+1]$^+$, 100%); 119.9 ([M-(OH)]$^+$, 64.1); 109.1 ([M-($C_2H_4$)]$^{\cdot+}$, 5.5%); 107.9 ([M-($C_2H_5$)]$^+$, 9.6%)

## 15.2.14. Addition to 4-pyridinecarboxaldehyde

**Ref.** : optical activity

**Operating Procedure** : see General Procedure O

**Reaction time**: 24 hours, reaction is incomplete.

**Quantities Engaged** :

4-Pyridinecarboxaldehyde: 0.591 ml; 0.663 g, 6 mmol, 1 eq.

Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.

(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.

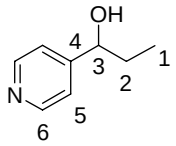
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with an aqueous saturated solution of $Na_2CO_3$, water and dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash chromatography on silica gel. (AcOEt/$CH_2Cl_2$/$Et_3N$, 60/35/5 $R_f$= 0.25, $KMnO_4$). 0.553 g of a yellow-brown low melting point solid is obtained.

**Name** : 1-Pyridin-4-yl-propan-1-ol




**CAS-RN** : 157371-07-8 (*S* enantiomer)

**M.F.** : $C_8H_{11}NO$ **M.W.** : 137,18

**Yield** : 0.553 g (67%)

**Physical Property** : low melting point yellow-brown solid

$[\alpha]_D^{30}$ =-39.5 (*c*2.33, MeOH)

**GC** (100/5/10/290) : $t_R$= 4.62min for 4-pyridinecarboxaldehyde

$t_R$= 9.62min for 1-pyridin-4-yl-propan-1-ol

**HPLC** : (Chiracel AS, *n*-hexane/ isopropanol, 90/10, 1 ml/min., 25°C, 260nm )

$t_R$= 11.91min (minor)

$t_R$= 16.12min. (major)

**Enantiomeric Excess** : 81% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 8.52 (dd, $^3J_{5,6}$=4.2, *J*=2.1, 2H, $H^6$); 7.27 (dd, $^3J_{5,6}$=4.2, *J*=2.1, 2H, $H^5$); 4.64 (t, $^3J_{2,3}$=6.6, 1H, $H^3$); 2.69 (bs, 1H, *O*H); 1.77 (apparent quint, $^3J_{2,3}$=$^3J_{1,2}$=7.2, 2H, $H^2$); 0.95 (t, $^3J_{1,2}$=7.2, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 154.0* ($C^4$), 149.4 ($C^6$), 121.0 ($C^5$), 74.0 ($C^3$), 31.7* ($C^2$), 9.7 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3217 (br, O-H); 2967 (C-H); 2934 (C-H); 2876 (C-H); 1605 ($C_{ar}$=$C_{ar}$); 1560 ($C_{ar}$=$C_{ar}$); 1457 (C-H); 1414 (C-H); 1120; 1049; 1003; 983; 844; 817

**Mass** (CI, $CH_4$-$N_2O$) : 139.0 ($[M+2]^{\cdot+}$, 9.2%); 137.9 ($[M+1]^+$, 100%); 121.2 ($[M-(OH)+2]^+$, 2.9%); 119.9 ($[M-(OH)]^+$, 27.0%); 107.9 ($[M-(C_2H_5)]^+$, 7.3%)

## 15.2.15. Addition to ferrocenecarboxaldehyde

**Ref.** : Analytical data[443]

Optical activity[42]

**Operating Procedure** : see General Procedure O

Reaction temperature modified to 0°C to solubilize substrate

Reaction monitored by $^1$H NMR

**Reaction time**: less than 3 hours.

**Quantities Engaged** :

Ferrocenecarboxaldehyde: 1.324 g, 6 mmol, 1 eq.

Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.

(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.

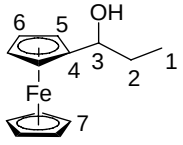
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36 M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with an aqueous saturated solution of $Na_2CO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation in the presence of solid $Na_2CO_3$, a brown oil is obtained.

The oil is purified by flash chromatography on silica gel. (cyclohexane/AcOEt, 80/20 $R_f$= 0.31, visible, UV & $KMnO_4$). 1.352 g of a red-brown solid is obtained.

**Name** : 1-ferrocenyl-propan-1-ol




**CAS-RN** : 106818-34-2 (*S* enantiomer)

**M.F.** : $C_{13}H_{16}FeO$ **M.W.** : 244,11

**Yield** : 1.352 g (92%)

**Physical Property** : red-brow solid

$[\alpha]_D^{30}$ =+29.2 (*c*1.13, benzene)

**HPLC** : (Chiracel AD, *n*-hexane /isopropanol, 90/10, 1.0 ml/min., 25°C, 254nm )

$t_R$= 9.77 min.

$t_R$= 17.71 min.

**Enantiomeric Excess** : 65.3% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 4.25-4.10 (m., 10H, $H^{5,6,7}$ et $H^3$); 1.93 (d, $^3J_{3,OH}$=3.3, 1H, O*H*); 1.68 (mult., 2H, $H^2$); 0.943 (t, $^3J_{1,2}$=7.5, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 94.2* ($C^4$); 71.0, 68.2, 67.8, 67.6; 67.2 & 65.1 ($C^{5,6,7\ \&\ 3}$); 30.9* ($C^2$); 10.3 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3429 (br, O-H); 3093 ($C_{Fc}$-H); 2963 (C-H); 2931 (C-H); 2875 (C-H); 1653; 1463 (C-H); 1411 (C-H); 1384; 1105 (C-O); 1089 (C-O); 1035; 1001; 968; 879; 817

**Mass** (CI, $CH_4$-$N_2O$) : 245 ($[M+1]^+$, 15.7%); 243.9 ($[M]^{\cdot+}$, 100%); 226.9 ($[M-(OH)]^+$, 23.4%); 225.9 ($[M-(H_2O)]^+$, 18.4%); 185.8 ($[M-(C_3H_6O)]^{\cdot+}$, 14.3%); 160.8 (15.7%); 137.8 (34.4%); 120.8 (17.8%)

## 15.2.16. Addition to 3-phenylpropionaldehyde

**Operating Procedure** : see General Procedure O

**Reaction time**: more than 24 hours.

**Quantities Engaged** :

3-Phenylpropionaldehyde: 0.82 ml, 0.830 g, 6 mmol, 1 eq.

Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.

(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.

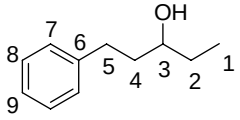
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $Na_2CO_3$ and water prior to being dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash-chromatography on silica-gel (cyclohexane/AcOEt, 80/20, $R_f$=0.26). 0.808 g of a colorless oil is obtained.

**Name** : 1-Phenyl-pentan-3-ol




**CAS-RN** : 1992-50-3 (racemic)

**M.F.** : $C_{11}H_{16}O$ **M.W.** : 164,24

**Yield** : 0.808 g (82.0%)

**Physical Property** : colorless oil

**GC** (100/5/10/290) : $t_R$= 9.71 min for 3-phenylpropionaldehyde
$t_R$= 13.45 min for 1-phenyl-pentan-3-ol

**HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 95/5, 1 ml/min., 25°C, 210nm )
$t_R$= 10.14 min
$t_R$= 14.48 min

**Enantiomeric Excess** : 2% ee

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.15-7.32 (m., 5H, $H^{ar}$); 3.55 (m, 1H, $H^4$); 2.60-2.86 (mult.; 2H, $H^5$); 1.43-1.86 (m, 4H, $H^{4\ \&\ 2}$); 1.41 (bd, 1H, O*H*); 0.94 (t, $^3J_{1,2}$=7.8, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 142.2* ($C^6$); 128.3 ($C^{7\ \&\ 8}$); 125.7 ($C^9$); 72.6 ($C^3$); 38.5* ($C^4$); 32.0* & 30.2* ($C^{2\ \&\ 5}$); 9.7 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3362 (br, O-H); 3085 (=$C_{ar}$-H); 3062 (=$C_{ar}$-H); 3026 (=$C_{ar}$-H); 2962 (C-H); 2933 (C-H); 2876 (C-H); 1944 (overtone); 1873 (overtone); 1801 (overtone); 1604 ($C_{ar}$=$C_{ar}$); 1496 (C-H); 1455 (C-H); 1120; 1056; 1029 (C-O); 989 (=C-H); 968 (=C-H); 933 (=C-H); 745; 699

**Mass** (CI, $CH_4$-$N_2O$) : 164.9 ($[M+1]^+$, 7.3%); 163.6 ($[M]^{\cdot+}$, 9.0%); 148.1 ($[M-OH]^{\cdot+}$, 9.3%); 146.7 ($[M-H_2O]^+$, 100%); 119.0 ($[C_9H_9]^+$, 11.2%); 105.1 ($[C_8H_9]^+$, 11.5%); 91.1 ($[C_7H_7]^+$, 25.6%)

## 15.2.17. Addition to cyclohexylcarboxaldehyde

**Operating Procedure** : see General Procedure O

**Reaction time**: more than 24 hours.

**Quantities Engaged** :

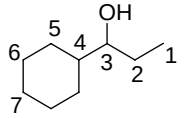
Cyclohexycarboxaldehyde: 0.75 ml, 0.694 g, 6 mmol, 1 eq.
Copper(I) chloride: 5.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 64.7 mg, 12.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 37.7 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.94 ml, 1.112 g, 9.0 mmol, 1.5 eq.
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.36M

**Purification** : An aqueous saturated solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $Na_2CO_3$ and water prior to being dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash-chromatography on silica-gel (cyclohexane/AcOEt, 75/25, $R_f$=0.34). 0.568 g of a colorless oil is obtained.

**Name** : 1-Cyclohexyl-propan-1-ol




**CAS-RN** : 17264-02-7 (racemic)

**M.F.** : $C_9H_{18}O$ **M.W.** : 142,24

**Yield** : 0.568 g (66.6%)

**Physical Property** : colorless oil

**GC** (110/5/10/290) : $t_R$= 4.73 min for cyclohexylcarboxaldehyde

$t_R$= 8.79 min for 1-cyclohexyl-propan-1-ol

**Enantiomeric Excess** : 19.2% ee (after benzoylation, see page 277)

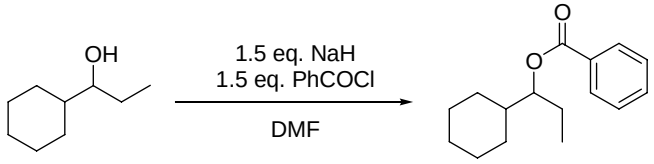
**$^1$H NMR** ($CDCl_3$, 300 MHz) : 3.28 (apparent quint., *J*=4.8 & *J*=3.9, 1H, $H^3$); 0.95-1.86 (m, 14H, $H^{2,4,5,6,7\ \&\ OH}$), 0.95 (t, $^3J_{1,2}$=7.8, 3H, $H^1$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 75.8 ($C^3$); 42.7 ($C^4$); 28.8*, 27.2*, 26.3*, 26.0*, 25.8* & 25.7* ($C^{5ax}$, $C^{5eq}$, $C^{6ax}$, $C^{6eq}$, $C^{7ax}$ & $C^{7eq}$); 9.6 ($C^1$)

**IR** (deposit on NaCl, $cm^{-1}$) : 3373 (br, O-H); 2937 (C-H); 2853 (C-H); 1450 (C-H); 1124 (C-O); 1103 (C-O); 1068; 1053; 971; 908; 893; 734

**Mass** (CI, $CH_4$-$N_2O$) : 142.3 ($[M]^{\cdot+}$, 2.1%); 125.0 ($[M\text{-}OH]^+$, 100%); 112.9 ($[M\text{-}((C_2H_4)]^+$, 8.7%); 82.9 ($[C_6H_{11}]^+$, 8.0%); 69.0 (8.0%); 58.7 (6.9%)

***Benzoylation of 1-cyclohexyl-propan-1-ol***

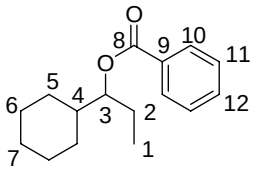



**Operating Procedure** : In a 10 ml round-bottom flask, 1-cyclohexyl-propan-1-ol (75 mg, 0.53 mmol, 1 eq.) is solubilizied in 2 ml of DMF and cooled to 0°C. A 60% dispersion of sodium hydride in mineral oil (31.6 mg, 0.79 mmol; 1.5 eq.) is added to the substrate solution at 0°C and agitated for one hour at room temperature. A solution of benzoyl chloride ($9.2x10^{-2}$ ml, 0.111 g, 0.79 mmol, 1.5 eq.) in 1 ml of DMF is added. The mixture is heated for 5 minutes at 70°C.

After one night, 2 ml of water are added carefully (!!!).The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NH_4Cl$ and water prior to being dried on $MgSO_4$. After concentration by rotatory evaporation, a brown oil is obtained.

**Purification** : The oil is purified by flash-chromatography on silica-gel with a gradient of eluents to eliminate the mineral oil (start with *n*-hexane, end with *n*-hexane/diethylether 99/1 ($R_f$=0.18)). 14 mg of a colorless oil are obtained.

**Name** : Benzoic acid 1-cyclohexyl-propyl ester




**CAS-RN** : 166031-54-5 (*R* enantiomer)

**M.F.** : $C_{16}H_{22}O_2$ **M.W.** : 246,34

**Yield** : 0.014 g (10.8%)

**Physical Property** : colorless oil

**HPLC** : (Chiracel AS, *n*-hexane, 0.5 ml/min., 20°C, 254nm )

$t_R$= 12.01 min

$t_R$= 13.03 min

**Enantiomeric Excess** : 19.2% ee

**$^{1}$H NMR** ($CDCl_3$, 300 MHz) : 8.06 (d, $^{3}J_{10,11}$=8.0, 2H, $H^{10}$); 7.55 (t, $^{3}J_{11,12}$=7.1, 1H, $H^{12}$), 7.44 (dd, $^{3}J_{10,11}$=7.8, $^{3}J_{11,12}$=7.1, 2H, $H^{11}$), 4.95 (apparent q., $J$=5.1 & 5.7, 1H, $H^{3}$), 1.58-1.84 (m, 8H, $H^{2\ \&\ 4}$, $H^{5,6\ and/or7}$), 1.0-1.33 (m, 5H, $H^{5,6\ and/or7}$), 0.93 (t, $^{3}J_{1,2}$=7.2, 3H, $H^{1}$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 166.4* ($C^{8}$); 132.6 ($C^{12}$); 131* ($C^{9}$); 129.6, 128.3 ($C^{10\ \&\ 11}$); 79.9 ($C^{3}$); 41.1 ($C^{4}$); 29.3*, 28.2*, 26.5*, 26.2*, 24.3* ($C^{2,5,6\ \&\ 7}$); 9.8 ($C^{1}$)

**IR** ($CH_2Cl_2$, $cm^{-1}$) : 3056 ($C_{ar}$-H); 2971 (C-H); 2932 (C-H); 2855 (C-H); 1709 (C=O); 1451 ($CH_2$); 1315; 1274 (C-O); 1251; 1177; 1117 (C-O); 1070; 1026; 935

**Mass** (CI, $CH_4$-$N_2O$) : 246.9 ($[M+1]^+$, 6%); 245.0 ($[M]^{\cdot+}$, 6.5%); 124.9 ([M-PhCO-OH]$^+$, 100%); 123.9 ([M-PhCO-$H_2O$]$^{\cdot+}$, 17.0%); 104.9 ($[PhCO]^+$, 27.7%); 76.9 ($[C_6H_5]^+$, 2.3%)

## 15.2.18. Addition to pivalaldehyde

**Operating Procedure** : see General Procedure O

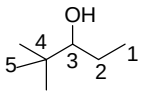
**Reaction time**: 24 hours.

**Quantities Engaged** :

Pivaladehyde: 0.896 ml, 0.710 g, 8 mmol, 1 eq.
Copper(I) chloride: 7.9 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 86.4 mg, 16.0 x $10^{-2}$ mmol, 0.02 eq.
(*R*)-BINAP **75**: 50.3 mg, 8.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 1.256 ml, 1.48 g, 12.0 mmol, 1.5 eq.
Toluene : 20 ml

**Substrate Concentration** : *ca.* 0.36M

**Name** : 2,2-Dimethyl-pentan-3-ol




**CAS-RN** : 3970-62-5 (racemic)

**M.F.** : $C_7H_{16}O$ **M.W.** : 116.20

**Yield** : no isolation (0%)

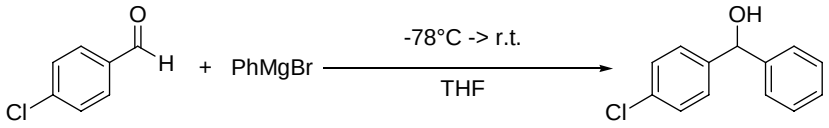
**Physical Property** : colorless oil

**Chiral GC** (40/5/4/70) : $t_R$= 4.69 min for pivalaldehyde
$t_R$= 10.58 to 11.55 min for toluene

# 15.3. Phenyl addition to *p*-Chlorobenzaldehyde

The following operating procedures correspond to the work presented in 8.3.3 on pages 138 and following.

## 15.3.1. Phenylmagnesium bromide addition




**Ref.** : For order of elution in chiral HPLC and absolute configuration[60]

**Operating Procedure** : In three-necked flask fitted with an argon inlet, a septum, a glass stopper and a magnetic stirring bar, 4-chlorobenzaldehyde is placed in an inert atmosphere and dissolved in dry THF. The mixture is cooled in dry ice-isopropanol bath (*ca* -78°C) prior to the slow addition of phenylmagnesium bromide *via* syringe. The temperature is left to increase slowly.

**Quantities Engaged** :

4-Chlorobenzaldehyde: 0.703 g, 5 mmol, 1 eq.

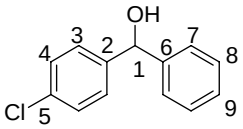
PhMgBr (1M in THF): 6 ml, 6 mmol, 1.2 eq.

THF: 12 ml

**Purification** : After 5 hours, 15 ml of an aqueous solution of HCl (*ca.* 1M) is added carefully. The mixture is placed in a separation funnel and decanted. The aqueous phase is extracted with dichloromethane. The combined organic extracts are washed successively with an aqueous saturated solution of $NaHCO_3$ and saturated NaCl prior to drying over $MgSO_4$. The organic phase is filtered and concentrated under vacuum.

The oil is purified by flash chromatography on silica gel (cyclohexane/AcOEt, 95:5 $R_f$= 0.1). 0.97 g of a colorless oil is obtained

**Name** : (4-Chloro-phenyl)-phenyl-methanol




**CAS-RN** : 119-56-2 (racemic)

**M.F.** : $C_{13}H_{11}ClO$ **M.W.** : 218.68

**Yield** : 0.97 g (88.7%)

**Physical Property** : colorless oil

**HPLC** : (Chiracel OB-H, *n*-hexane/ isopropanol, 80/20, 1 ml/min., 25°C, 220nm )

$t_R$= 8.75min (*R*)

$t_R$= 11.85min. (*S*)

**Enantiomeric Excess** : 0.08% ee

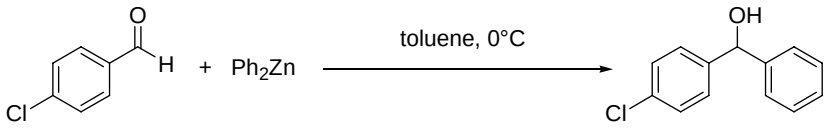
**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.25-7.35 (mult., 9H, $H^{ar}$); 5.79 (bs, 1H, $H^1$); 2.28 (bs, 1H, *O*H)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 143.4*& 142.2* ($C^{2\ \&\ 6}$), 133.2* ($C^5$), 128.5, 127.9, 127.8, 126.5 ($C^{3,4,7,8\ \&\ 9}$), 75.5 ($C^1$)

**IR** ($CH_2Cl_2$, $cm^{-1}$) : 3595 (O-H); 1603 ($C_{ar}$-$C_{ar}$); 1490 ($C_{ar}$-$C_{ar}$); 1278 (C-O); 1090 ($C_{ar}$-Cl); 1014

**Mass** (EI, 70eV) : 183.1 ($[M-H]^+$, 2.5%); 166.1 ($[M-H_2O-Cl]^+$, 5.7%); 141.0 (8.5%); 139.0 ($[C_7H_4ClO]^+$, 20.9%); 105.9 (4.4%); 104.9 ($[C_7H_5O]^+$, 47.7%); 79.0 ($[C_6H_9]^+$, 14.9%); 78.0 ($[C_6H_6]^{\cdot+}$, 10.3%); 76.9 ($[C_6H_5]^{\cdot+}$, 27.1%); 75.9 ($[C_6H_4]^+$, 1.3%); 43.8 (100%)

## 15.3.2. $Ph_2Zn$ addition with no catalyst




**Operating Procedure** : Inside a glovebox, diphenylzinc (STREM, sealed flask opened inside the glove box) is weighed and placed in a Radley's Carrousel test tube, dried in an oven and cooled under argon beforehand. The diphenylzinc is dissolved in 2 ml of dry toluene. *p*-Chlorobenzaldehyde is dissolved in 2 ml of dry toluene in a septum capped dried flask. The two solutions are cooled to 0°C by an ice bath. The aldehyde is added *via* syringe onto the organometallic compound.

Samples are taken *via* syringe, quenched in methanol then injected in GC. The reaction is complete in less than one hour (first sample).

**Quantities Engaged** :

4-Chlorobenzaldehyde: 0.070 g, 0.5 mmol, 1 eq.

$Ph_2Zn$:0.143 g, 0.65 mmol, 1.3 eq.

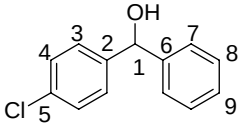
Toluene: 4 ml

**Substrate Concentration** : *ca.* 0.125M

**Purification** : 2 ml of MeOH are added followed by a saturated aqueous solution of $NH_4Cl$ (*ca.* 1 M). The mixture is placed in a separation funnel and decanted. The aqueous phase is extracted three times with dichloromethane. The combined organic extracts are washed with water prior to drying over $MgSO_4$. The organic phase is filtered then concentrated under vacuum.

The oil is purified by flash chromatography on silica gel. (*n*-pentane/$Et_2O$, 75:25 $R_f$= 0.3). 0.097 g of a colorless oil is obtained.

**Name** : (4-Chloro-phenyl)-phenyl-methanol




**CAS-RN** : 119-56-2 (racemic)

**M.F.** : $C_{13}H_{11}ClO$ **M.W.** : 218.68

**Yield** : 0.097 g (88.7%)

**GC** (140/5/10/290) : $t_R$= 5.08 min for *p*-chlorobenzaldehyde

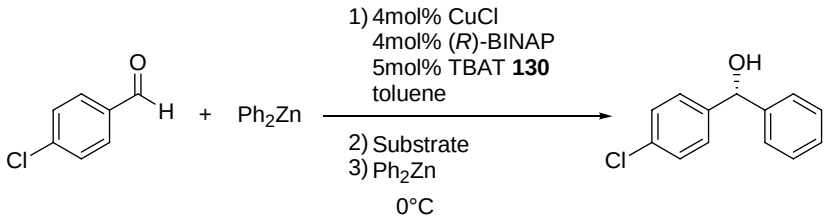
$t_R$= 15.9 min for (4-Chloro-phenyl)-phenyl-methanol

**Physical Property** : colorless oil

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 15.3.3. $Ph_2Zn$ addition in the presence of CuCl, (*R*)-BINAP and TBAT

**Ref.** : For order of elution in chiral HPLC and absolute configuration[60]




**Operating Procedure** : Inside a glovebox, diphenylzinc (STREM, sealed flask opened inside the glove box) is weighed and placed in a Radley's Carrousel test tube, dried in an oven and cooled under argon beforehand. The diphenylzinc is dissolved in 2 ml of dry toluene. Copper(I) chloride (0.04 eq.), tetrabutylammonium triphenyldifluorosilicate **130** (0.05 eq.) and (*R*)-BINAP **75** (0.04 eq.) are introduced in a flamed dried-flask and dissolved in 2 ml of dry toluene under an argon atmosphere (yellow solution). The flask is quickly opened to add the solid *p*-chlorobenzaldehyde. The catalyst substrate mixture is stirred 30 minutes at room temperature.

The two solutions are cooled to 0°C by an ice bath. The aldehyde / catalyst solution is added *via* syringe onto the organometallic compound.

Samples are taken *via* syringe, quenched in methanol then injected in GC. The reaction is complete in less than one hour (first sample).

**Quantities Engaged** :

4-Chlorobenzaldehyde: 0.070 g, 0.5 mmol, 1 eq.

$Ph_2Zn$:0.143 g, 0.65 mmol, 1.3 eq.

Copper(I) chloride: 1.9 mg, 2.0 x $10^{-2}$ mmol, 0.04 eq.

TBAT **130**: 13.4 mg, 2.5 x $10^{-2}$ mmol, 0.05 eq.

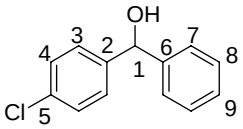
(*R*)-BINAP **75**: 12.5 mg, 2.0 x $10^{-2}$ mmol, 0.04 eq.

Toluene: 4 ml

**Substrate Concentration** : *ca.* 0.125M

**Purification** : : same purification procedure as above furnishing 0.098 g of a colorless oil

**Name** : (4-Chloro-phenyl)-phenyl-methanol




**CAS-RN** : 123535-85-3 (*R* enantiomer)

**M.F.** : $C_{13}H_{11}ClO$ **M.W.** : 218.68

**Yield** : 0.098 g (89.6%)

**GC** (140/5/10/290) : $t_R$= 5.08 min for *p*-chlorobenzaldehyde

$t_R$= 16.01min for (4-Chloro-phenyl)-phenyl-methanol

**Physical Property** : colorless oil

**HPLC** : (Chiracel OB-H, *n*-hexane/ isopropanol, 80/20, 1 ml/min., 25°C, 220nm )

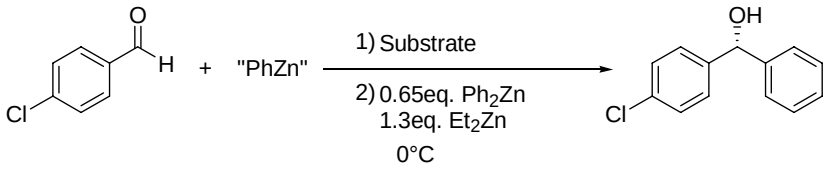
$t_R$= 8.71min (*R*, major)

$t_R$= 11.82min. (*S*)

**Enantiomeric Excess** : 3 % ee (*R*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 15.3.4. $Ph_2Zn/Et_2Zn$ addition in the absence of any catalyst




**Ref.** : $Ph_2Zn$ and $Et_2Zn$ mixture[68]

For order of elution in chiral HPLC and absolute configuration[60]

**Operating Procedure** : Inside a glovebox, diphenylzinc (STREM, sealed flask opened inside the glove box) is weighed and placed in a Radley's Carrousel test tube, dried in an oven and cooled under argon beforehand. The diphenylzinc is dissolved in 4 ml of dry toluene. This solution is cooled in an ice bath before pure diethylzinc is added. This solution is stirred at 0°C for 30 minutes.

4 ml of dry toluene are introduced in a flamed dried-flask under an argon atmosphere (yellow solution). The flask is quickly opened to add the solid *p*-chlorobenzaldehyde. The substrate solution is stirred 30 minutes at room temperature.

The two solutions are cooled to 0°C by an ice bath. The aldehyde solution is added *via* syringe onto the organometallic compounds.

Samples are taken *via* syringe, quenched in methanol then injected in GC. The reaction is almost complete in 6 hours (next sample: 24 hours and total completion).

**Quantities Engaged** :

4-Chlorobenzaldehyde: 0.141 g, 1.0 mmol, 1 eq.

$Ph_2Zn$: 0.143 g, 0.65 mmol, 0.65eq

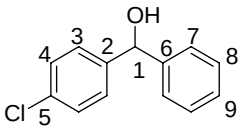
$Et_2Zn$: 0.135 ml, 0.161 g, 1.3 mmol, 1.3 eq.

Toluene: 8 ml

**Substrate Concentration** : *ca.* 0.125M

**Purification** : same purification procedure as above furnishing 0.191 g of a colorless oil

**Name** : (4-Chloro-phenyl)-phenyl-methanol




**CAS-RN** : 119-56-2 (racemic)

**M.F.** : $C_{13}H_{11}ClO$ **M.W.** : 218.68

**Yield** : 0.191 g (87.3%)

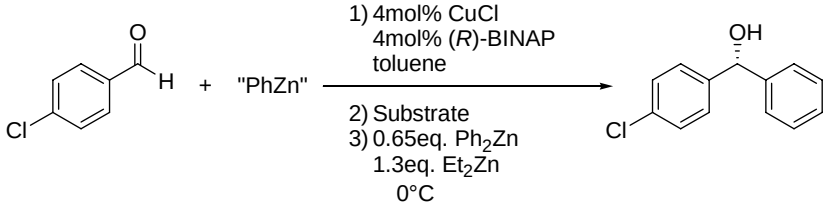
**GC** (140/5/10/290) : $t_R$= 5.08 min for *p*-chlorobenzaldehyde

$t_R$= 15.92min for (4-Chloro-phenyl)-phenyl-methanol

**Physical Property** : colorless oil

**$^1$H NMR** ( $CDCl_3$,300 MHz) : identical to previous sample

## 15.3.5. $Ph_2Zn/Et_2Zn$ addition in the presence of CuCl and (*R*)-BINAP




**Ref.** : $Ph_2Zn$ & $Et_2Zn$ mixture[68]

For order of elution in chiral HPLC and absolute configuration[60]

**Operating Procedure** : Inside a glovebox, diphenylzinc (STREM, sealed flask opened inside the glove box) is weighed and placed in a Radley's Carrousel test tube, dried in an oven and cooled under argon beforehand. The diphenylzinc is dissolved in 4 ml of dry toluene. This solution is cooled in an ice bath before pure diethylzinc is added. This solution is stirred at 0°C for 30 minutes

Copper(I) chloride (0.04 eq.) and (*R*)-BINAP **75** (0.04 eq.) are introduced in a flamed dried-flask and dissolved in 4 ml of dry toluene under an argon atmosphere (yellow solution). The flask is quickly opened to add the solid *p*-chlorobenzaldehyde. The catalyst substrate mixture is stirred 30 minutes at room temperature.

The two solutions are cooled to 0°C by an ice bath. The aldehyde / catalyst solution is added *via* syringe onto the organometallic compound.

Samples are taken *via* syringe, quenched in methanol then injected in GC. The reaction is almost complete in 6 hours (next sample: 24 hours and total completion).

**Quantities Engaged** :

4-Chlorobenzaldehyde: 0.141 g, 1.0 mmol, 1 eq.

$Ph_2Zn$: 0.143 g, 0.65 mmol, 0.65eq

$Et_2Zn$: 0.135 ml, 0.161 g, 1.3 mmol, 1.3 eq.

Copper(I) chloride: 3.9 mg, 4.0 x $10^{-2}$ mmol, 0.04 eq.

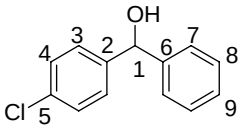
(*R*)-BINAP **75**: 25.1 mg, 4.0 x $10^{-2}$ mmol, 0.04 eq.

Toluene: 8 ml

**Substrate Concentration** : *ca.* 0.125M

**Purification** : : same purification procedure as above furnishing 0.193 g of a colorless oil

**Name** : (4-Chloro-phenyl)-phenyl-methanol




**CAS-RN** : 123535-85-3 (*R* enantiomer)

**M.F.** : $C_{13}H_{11}ClO$ **M.W.** : 218.68

**Yield** : 0.193 g (88.3%)

**GC** (140/5/10/290) : $t_R$= 5.08 min for *p*-chlorobenzaldehyde

$t_R$= 15.92min for (4-Chloro-phenyl)-phenyl-methanol

**Physical Property** : colorless oil

**HPLC** : (Chiracel OB-H, *n*-hexane/ isopropanol, 80/20, 1 ml/min., 25°C, 220nm )

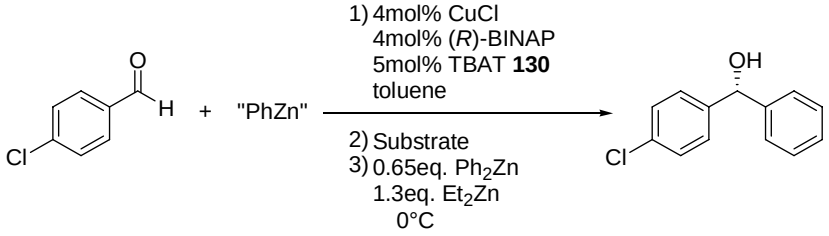
$t_R$= 11.98min (*R*, major)

$t_R$= 16.06min. (*S*)

**Enantiomeric Excess** : 2.5 % ee (*R*)

**$^1$H NMR** ($CDCl_3$,300 MHz) : identical to previous sample

## 15.3.6. $Ph_2Zn/Et_2Zn$ addition in the presence of CuCl, (*R*)-BINAP and TBAT




**Ref.** : $Ph_2Zn$ and $Et_2Zn$ mixture[68]

For order of elution in chiral HPLC and absolute configuration[60]

**Operating Procedure** : Inside a glovebox, diphenylzinc (STREM, sealed flask opened inside the glove box) is weighed and placed in a Radley's Carrousel test tube, dried in an oven and cooled under argon beforehand. The diphenylzinc is dissolved in 4 ml of dry toluene. This solution is cooled in an ice bath before pure diethylzinc is added. This solution is stirred at 0°C for 30 minutes

Copper(I) chloride (0.04 eq.), tetrabutylammonium triphenyldifluorosilicate **130** (0.05 eq.) and (*R*)-BINAP **75** (0.04 eq.) are introduced in a flamed dried-flask and dissolved in 4 ml of dry toluene under an argon atmosphere (yellow solution). The flask is quickly opened to add the solid *p*-chlorobenzaldehyde. The catalyst substrate mixture is stirred 30 minutes at room temperature.

The two solutions are cooled to 0°C by an ice bath. The aldehyde / catalyst solution is added *via* syringe onto the organometallic compounds.

Samples are taken *via* syringe and quenched in methanol. The samples are then injected in GC. The reaction is complete in 6hours.

**Quantities Engaged** :

4-Chlorobenzaldehyde: 0.141 g, 1.0 mmol, 1 eq.

$Ph_2Zn$: 0.143 g, 0.65 mmol, 0.65eq

$Et_2Zn$: 0.135 ml, 0.161 g, 1.3 mmol, 1.3 eq.

Copper(I) chloride: 3.9 mg, 4.0 x $10^{-2}$ mmol, 0.04 eq.

TBAT **130**: 26.9 mg, 5.0 x $10^{-2}$ mmol, 0.05 eq.

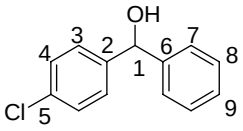
(*R*)-BINAP **75**: 25.1 mg, 4.0 x $10^{-2}$ mmol, 0.04 eq.

Toluene: 8 ml

**Substrate Concentration** : *ca.* 0.125M

**Purification** : same purification procedure as above furnishing 0.187 g of a colorless oil

**Name** : (4-Chloro-phenyl)-phenyl-methanol




**CAS-RN** : 123535-85-3 (*R* enantiomer)

**M.F.** : $C_{13}H_{11}ClO$ **M.W.** : 218.68

**Yield** : 0.187 g (85.5%)

**GC** (140/5/10/290) : $t_R$= 5.00 min for *p*-chlorobenzaldehyde

$t_R$= 16.03min for (4-Chloro-phenyl)-phenyl-methanol

**Physical Property** : colorless oil

**HPLC** : (Chiracel OB-H, *n*-hexane/ isopropanol, 80/20, 1 ml/min., 25°C, 220nm )

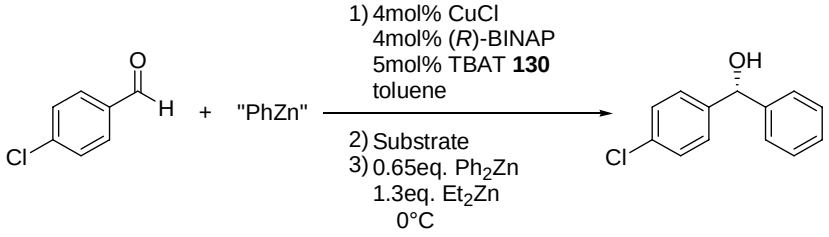
$t_R$= 8.69min (*R*, major)

$t_R$= 11.74min. (*S*)

**Enantiomeric Excess** : 5 % ee

**$^1$H NMR** ($CDCl_3$,300 MHz) : identical to previous sample

## 15.3.7. $Ph_2Zn/Et_2Zn$ addition in the presence of CuCl, (*R*)-BINAP and TBAT




**Ref.** : $Ph_2Zn$ and $Et_2Zn$ mixture[68]

For order of elution in chiral HPLC and absolute configuration[60]

**Operating Procedure** : Identical operating procedure than 15.3.6 above except that diphenylzinc was supplied by Aldrich (5 g in glass bottle with screw cap).

The reaction is complete in more than 3 hours.

**Quantities Engaged** :

4-Chlorobenzaldehyde: 0.141 g, 1.0 mmol, 1 eq.

$Ph_2Zn$: 0.143 g, 0.65 mmol, 0.65eq

$Et_2Zn$: 0.135 ml, 0.161 g, 1.3 mmol, 1.3 eq.

Copper(I) chloride: 3.9 mg, 4.0 x $10^{-2}$ mmol, 0.04 eq.

TBAT **130**: 26.9 mg, 5.0 x $10^{-2}$ mmol, 0.05 eq.

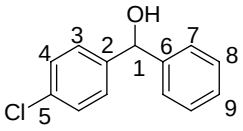
(*R*)-BINAP **75**: 25.1 mg, 4.0 x $10^{-2}$ mmol, 0.04 eq.

Toluene: 8 ml

**Substrate Concentration** : *ca.* 0.125M

**Purification** : same purification procedure as above furnishing 0.170 g of a colorless oil

**Name** : (4-Chloro-phenyl)-phenyl-methanol



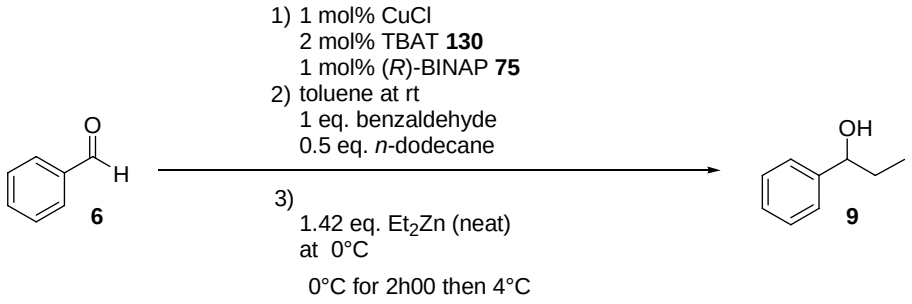

**CAS-RN** : 123535-85-3 (*R* enantiomer)
**M.F.** : $C_{13}H_{11}ClO$ **M.W.** : 218.68
**Yield** : 0.170 g (77.7%)
**GC** (140/5/10/290) : $t_R$= 6.80min for *p*-chlorobenzaldehyde
$t_R$= 15.30min for (4-Chloro-phenyl)-phenyl-methanol
**Physical Property** : colorless oil
**HPLC** : (Chiracel OB-H, *n*-hexane/ isopropanol, 80/20, 1 ml/min., 25°C, 220nm )
$t_R$= 8.49min (*R*, major)
$t_R$= 11.30min. (*S*)
**Enantiomeric Excess** : 8.3 % ee
**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

# Chapter 16

# Mechanistic Studies

## 16.1. Nonlinear effects

The influence of the optical purity of BINAP **75** on the enantioselectivity of the addition of diethylzinc to benzaldehyde catalyzed by copper(I) chloride and TBAT **130** was tested under reaction conditions of General Procedure N. The catalyst loading was of 1mol% in copper chloride and BINAP and 2mol% of TBAT. Mixture of enantiopure *(R)*-BINAP and racemic BINAP afforded BINAP ligand samples of various optical purities.




**Operating Procedure** : see General Procedure N

**Reaction time:** reaction followed over 24 hours, 98% to 100% complete after 2 hours.

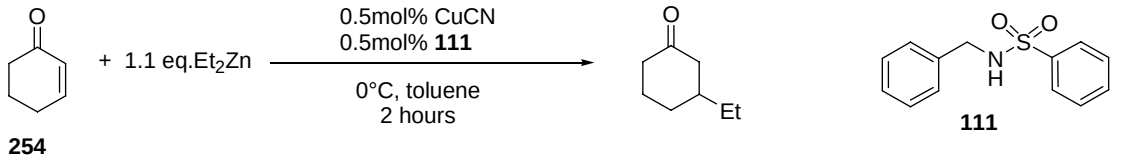
**Quantities Engaged** : Benzaldehyde: 0.206 ml, 0.215 g, 2.02 mmol, 1 eq.
Copper(I) chloride: 2.0mg, 2.0.0 x $10^{-2}$ mmol, 0.01 eq.
TBAT **130**: 21.8 mg, 4.0 x $10^{-2}$ mmol, 0.02 eq.
Scalemic BINAP **75**: 12.4 mg, 2.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.30 ml, 0.254 g, 2.87 mmol, 1.42 eq.
Toluene : 5 ml

**BINAP Mixtures** :

| ee% BINAP | 0% ee | 10% ee | 25% ee | 50% ee | 75% ee | 100% ee |
|---|---|---|---|---|---|---|
| **(*rac*)-BINAP (mg)** | 12.4 | 11.2 | 9.3 | 6.2 | 3.1 | 0.0 |
| **(*R*)-BINAP (mg)** | 0.0 | 1.2 | 3.1 | 6.2 | 9.3 | 12.4 |

# 16.2. Conjugated Addition to 2-Cyclohexenone

## 16.2.1. Synthesis of Racemic Sample of 3-Ethylcylohexanone




**254** **111**

**Ref.** : Operating procedure[310]

**Operating Procedure** : Copper(I) cyanide and *N*-benzylbenzenesulfonamide **111** are placed in a two-necked flame-dried round-bottom flask fitted with a rubber septum and an argon inlet. Dry toluene is introduced into the flask *via* syringe and the flask is cooled to 0°C in an ice bath. Neat diethylzinc is added and the reaction media is stirred for 10 minutes. 2-cyclohexenone is then added and the reaction is stirred a further 2 hours at 0°C.

**Quantities Engaged** : 2-Cyclohexenone **254**: 1.07 ml, 1.061 g, 11.04 mmol, 1 eq.

Copper(I)cyanide: 5.2 mg, 5.7 x $10^{-2}$ mmol, 0.0052 eq.

*N*-Benzylbenzenesulfonamide **111** : 14.2 mg, 5.7 x $10^{-2}$ mmol, 0.0052 eq.

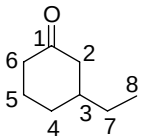
Diethylzinc: 2 ml, 1.5 g, 12.15 mmol, 1.1 eq.

Toluene : 3.2 ml

**Reaction time** : 2 hours.

**Purification** : The reaction is poured over 12 ml of a saturated solution of $NH_4Cl$. The mixture is placed in a separating funnel and the aqueous phase is extracted twice with $Et_2O$. The combined organic phases are washed once with water and once with brine, prior to drying over $MgSO_4$. The solution is concentrated under vacuum. The resulting oil is distilled by bulb-to-bulb distillation under controlled vacuum. 0.997 g of a colorless oil with a characteristic odor is obtained.

**Name** : 3-ethylcyclohexanone




**CAS-RN :** 22461-89-8 (racemic)

**M.F.** : $C_8H_{14}O$ **M.W.** : 126,20

**Yield** : 0.997 g (72%)

**Physical Property** : colorless oil

**GC** (95/4/1) : $t_R$= 3.87 min for 2-cyclohexenone

$t_R$= 7.22 min for 3-ethylcylohexanone

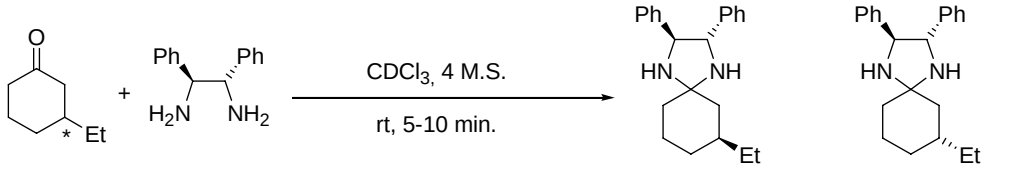
**$^1$H NMR** ($CDCl_3$, 300 MHz) : 2.20-2.46 (m, 3H); 1.88-2.08 (m, 3H), 1.58-1.72 (m, 2H); 1.26-1.42 (m, 3H); 0.91 (t, $^3J_{8,7}$=7.5, 3H, $H^8$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 211.7* ($C^1$); 47.8* ($C^2$); 41.4* ($C^6$); 40.7 ($C^3$); 30.9*, 29.2* ($C^{4\&7}$); 25.2* ($C^5$); 11.1 ($C^8$)

**IR** (oil deposit on NaCl, $cm^{-1}$) : 1716 (C=O)

**Mass** (CI, $CH_4/N_2O$) : 128.1 ($[M+2]^{\cdot+}$, 9.4%); 126.9 ($[M+1]^+$, 100%); 124.8 (11.6%); 108.9 (16.2%); 96.9 (16.2%)

## 16.2.2. Enantiomeric Excess Determination of 3-Ethylcyclo hexanone




(1*S*,2*S*)-**289** (2*S*,3*S*,*7S*)-**290** (2*S*,3*S*,*7R*)-**290**

**Ref.** : Operating procedure and $^{13}C$ NMR peak attributions[385]

**Operating Procedure** : In a small vial, 1 eq. of 3-ethylcyclohexanone is dissolved in approximately 0.75 ml of $CDCl_3$ (minimum solvent amount for NMR test tube) followed by a few beads of 4Å molecular sieves and 1.1 eq. of (1*S*,2*S*)-1,2-diphenylethylene diamine **289**. The vial is capped and hand-shaked for a few minutes. The solution contained in the vial is then placed in a NMR tube and a $^{13}C$ NMR proton decoupled spectra is acquired overnight.

**Quantities Engaged** :

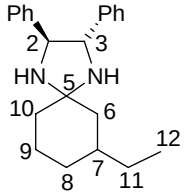
3-Ethylcyclohexanone : 35.0 mg, 0.28 mmol, 1 eq.

(1*S*,2*S*)-1,2-Diphenylethylene diamine **289**: 64.7 mg, 0.31 mmol, 1.1 eq.

A few beads of 4Å molecular sieves

$CDCl_3$: *ca.* 0.75 ml

**Name** : 7-Ethyl-2,3-diphenyl-1,4-diaza-spiro[4.5]decane




**CAS-RN** : 155324-77-9 (*R,R,R)* & 155250-11-6 (*S,R,R*)

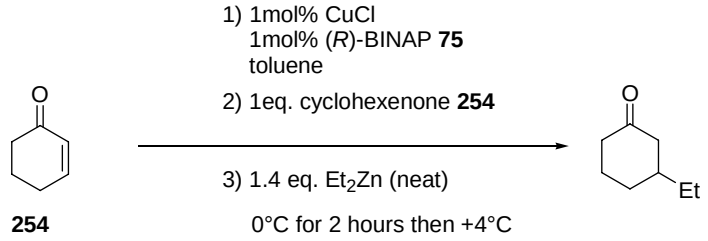
**M.F.** : $C_{22}H_{28}N_2$ **M.W.** : 320,47

**$^{13}C$ NMR** of diastereomeric mixture starting from racemic 3-ethylcyclohexanone ( $CDCl_3$, 50.3MHz) : 143.3, 141.0, 140.9, 140.8, 140.6, 128.3, 128.1, 127.3, 127.2, 127.0, 126.9, 126.8 ($C^{ar}$); 77.9 ($C^5$ of (2*S*,3*S*,7*R*)-**290**); 77.5 ($C^5$ of (2*S*,3*S*,7*S*)-**290**); 70.0 ($C^2$ of (2*S*,3*S*,7*S*) and (2*S*,3*S*,7*R*)-**290**); 69.3 ($C^3$ of (2*S*,3*S*,7*R*)-**290**); 69.2 ($C^3$ of (2*S*,3*S*,7*S*)-**290**); 46.7 ($C^6$ of (2*S*,3*S*,7*R*)-**290**); 45.8 ($C^6$ of (2*S*,3*S*,7*S*)-**290**); 40.3 ($C^{10}$ of (2*S*,3*S*,7*S*)-**290**); 39.0 ($C^{10}$ of (2*S*,3*S*,7*R*)-**290**); 37.3 ($C^7$ of (2*S*,3*S*,7*S*)-**290**); 36.5 ($C^7$ of (2*S*,3*S*,7*R*)-**290**); 31.8 ($C^9$ of (2*S*,3*S*,7*R*)-**290**); 31.7 ($C^9$ of (2*S*,3*S*,7*S*)-**290**); 29.7 ($C^{11}$ of (2*S*,3*S*,7*S*) and (2*S*,3*S*,7*R*)-**290**); 23.8 ($C^8$ of (2*S*,3*S*,7*R*)-**290**); 23.0 ($C^8$ of (2*S*,3*S*,7*S*)-**290**); 11.2 ($C^{12}$ of (2*S*,3*S*,7*S*) and (2*S*,3*S*,7*R*)-**290**)

**Diastereomeric Excess** can be measured following the procedure proposed by Alexakis[385] based on the integrals of pairs of $^{13}C$ NMR signals for the following carbons: $C^6$ (at 46.7 and 45.8ppm), $C^{10}$ (at 39.0 and 40.3 ppm) and $C^7$ (at 37.3 and 36.5ppm) and then averaging the three de's measured. The absolute configuration can be assigned based on the attributions proposed by Alexakis see $^{13}C$ NMR spectra description.

On the racemic sample, 2.3% ee were measured in favor of (2*S*,3*S*,7*S*)-**290**.

## 16.2.3. $Et_2Zn$ addition to cyclohexenone catalyzed by CuCl and *(R)*-BINAP




**254**

**Operating Procedure** : In a flame dried two-necked round-bottom 50 ml flask equipped with a magnetic stirring bar, a septum and an argon-inlet, copper(I) chloride (0.01 eq.) and (*R*)-BINAP **75** (0.01 eq.) are introduced. The flask is subjected to three vacuum-argon cycles then 15 ml of dry toluene are added. The solution immediately turns yellow.

The cyclohexenone (1 eq.) is added to the catalyst precursor. The mixture is stirred for 30 minutes at room temperature before being cooled to 0°C in an ice bath. The diethylzinc (1.42 eq.) is added at once.

The reaction is monitored by GC to estimate the reaction time. Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

After 19 hours, only a trace of cyclohexenone remains. 3 ml of methanol are added to the cool reaction media and the white suspension is stirred vigorously.

**Quantities Engaged** :

2-Cyclohexenone **254**: 0.59 ml, 0.584 g, 6.07 mmol, 1 eq.
Copper(I) chloride: 6.0 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
(*R*)-BINAP **75**: 38.1 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.90 ml, 1.062 g, 8.6 mmol, 1.42 eq.
Toluene : 15 ml

**Reaction time** : 19 hours.

**Purification** : A saturated solution of $NH_4Cl$ is added. The mixture is placed in a separating funnel and extracted three times with $CH_2Cl_2$. The combined organic phases are washed once with a saturated aqueous solution of $Na_2CO_3$ and water, prior to drying over $MgSO_4$. The solution is concentrated under vacuum. The resulting oil is purified by flash chromatography on silica gel (*n*-pentane/$Et_2O$, 80/20 $R_f$= 0.25). 0.400 g of an odorous colorless oil is obtained.

Yield is non-representative due to the volatility of the product under vacuum.

**Name** : 3-ethylcyclohexanone

**CAS-RN** : 74006-73-8 (*S* enantiomer)

**M.F.** : $C_8H_{14}O$ **M.W.** : 126,20

**Yield** : 0.400 g (52%)

**Physical Property** : colorless oil

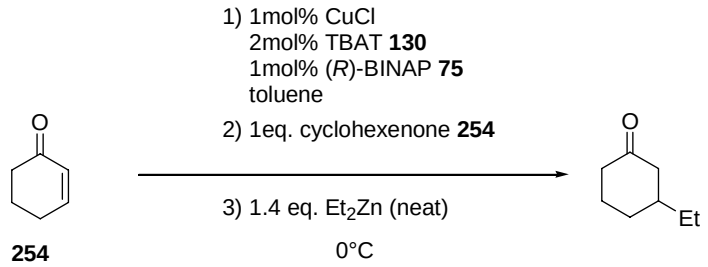
**GC** (95/4/1) : $t_R$= 3.87 min for 2-cyclohexenone

$t_R$= 7.22 min for 3-ethylcylohexanone

**$^1$H NMR** ($CDCl_3$, 200 MHz) : identical to previous sample

**Enantiomeric Excess** : 19.6% ee (*S*) based on diastereomeric excess by derivatization with (1*S*,2*S*)-1,2-diphenylethylene diamine **289**.

## 16.2.4. $Et_2Zn$ addition to cyclohexenone catalyzed by CuCl, TBAT and *(R)*-BINAP




**254**

**Operating Procedure** : Copper(I) chloride (0.01 eq.), TBAT **130** (0.02 eq.) and (*R*)-BINAP **75** (0.01 eq.) are introduced in a flame dried two-necked round-bottom 50 ml flask equipped with a magnetic stirring bar, a septum and an argon-inlet which is then subjected to three vacuum-argon cycles. 15 ml of dry toluene are added. The solution immediately turns yellow.

The cyclohexenone (1 eq.) is added to the catalyst precursor. The mixture is stirred for 30 minutes at room temperature before being cooled to 0°C in an ice bath. The diethylzinc (1.42 eq.) is added at once.

The reaction is monitored by GC to estimate the reaction time. Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

After 1 hour, no cyclohexenone remains. 3 ml of methanol are added to the cool reaction media and the white suspension is stirred vigorously.

**Quantities Engaged** :

2-Cyclohexenone **254**: 0.59 ml, 0.584 g, 6.07 mmol, 1 eq.

Copper(I)chloride: 6.0 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

TBAT **130**: 65.5 mg, 12.1 x $10^{-2}$ mmol, 0.02 eq.

(*R*)-BINAP **75**: 38.1 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc: 0.90 ml, 1.062 g, 8.6 mmol, 1.42 eq.

Toluene : 15 ml

**Reaction time** : 1 hour

**Purification** : A saturated solution of $NH_4Cl$ is added. The mixture is placed in a separating funnel and extracted three times with $CH_2Cl_2$. The combined organic

phases are washed once with a saturated aqueous solution of $Na_2CO_3$ and water, prior to drying over $MgSO_4$. The solution is concentrated under vacuum. The resulting oil is purified by flash chromatography on silica gel (*n*-pentane/$Et_2O$, 80/20 $R_f$= 0.25). 0.507 g of an odorous colorless oil is obtained.

Yield is non-representative due to the volatility of the product under vacuum.

**Name** : 3-ethylcyclohexanone

**CAS-RN** : 74006-73-8 (*S* enantiomer)

**M.F.** : $C_8H_{14}O$ **M.W.** : 126,20

**Yield** : 0.507 g (66.2%)

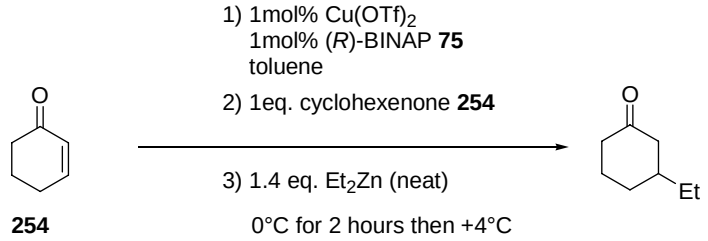
**Physical Property** : colorless oil

**GC** (95/4/1) : $t_R$= 3.72 min for 2-cyclohexenone

$t_R$= 6.04 min for 3-ethylcylohexanone

**Enantiomeric Excess** : 30.7% ee (*S*) based on diastereomeric excess by derivatization with (1*S*,2*S*)-1,2-diphenylethylene diamine **289**

## 16.2.5. $Et_2Zn$ addition to cyclohexenone catalyzed by $Cu(OTf)_2$ and *(R)*-BINAP




**254**

**Operating Procedure** : Copper(II) triflate (0.01 eq.) and (*R*)-BINAP **75** (0.01 eq.) are introduced in a flame dried two-necked round-bottom 50 ml flask equipped with a magnetic stirring bar, a septum and an argon-inlet which is then subjected to three vacuum-argon cycles. 15 ml of dry toluene are added.

The cyclohexenone (1 eq.) is added to the catalyst precursor. The mixture is stirred for 30 minutes at room temperature before being cooled to 0°C in an ice bath. The diethylzinc (1.42 eq.) is added at once.

The reaction is monitored by GC to estimate the reaction time. Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

After 19 hours only a trace of cyclohexenone remains. 3 ml of methanol are added to the cool reaction media and the white suspension is stirred vigorously.

**Quantities Engaged** :

2-Cyclohexenone **254**: 0.59 ml, 0.584 g, 6.07 mmol, 1 eq.
Copper(II)triflate: 21.9 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
(*R*)-BINAP **75**: 38.1 mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
Diethylzinc: 0.90 ml, 1.062 g, 8.6mmol, 1.42 eq.
Toluene : 15 ml

**Reaction time** : 2 hours.

**Purification** : A saturated solution of $NH_4Cl$ is added. The mixture is placed in a separating funnel and extracted three times with $CH_2Cl_2$. The combined organic phases are washed once with a saturated aqueous solution of $Na_2CO_3$ and water, prior to drying over $MgSO_4$. The solution is concentrated under vacuum. The resulting oil is purified by flash chromatography on silica gel (*n*-pentane/$Et_2O$, 80/20 $R_f$= 0.25). 0.427 g of an odorous colorless oil is obtained.

Yield is non-representative due to the volatility of the product under vacuum.

**Name** : 3-ethylcyclohexanone

**CAS-RN** : 74006-74-9 (*R* enantiomer)

**M.F.** : $C_8H_{14}O$ **M.W.** : 126,20

**Yield** : 0.427 g (56%)

**Physical Property** : colorless oil

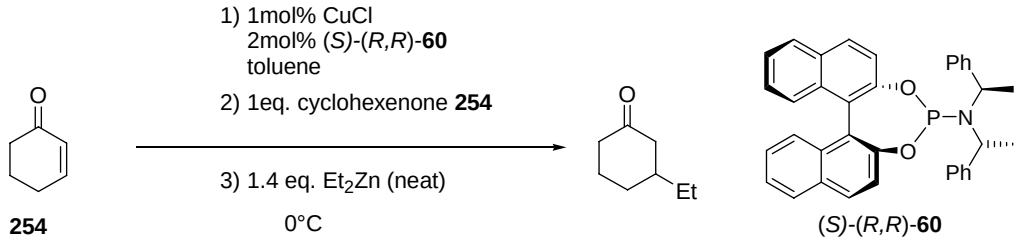
**GC** (100) : $t_R$= 3.95 min for 2-cyclohexenone

$t_R$= 6.46 min for 3-ethylcylohexanone

**$^1$H NMR** ($CDCl_3$, 200 MHz) : identical to previous sample

**Enantiomeric Excess** : 29.9% ee (*R*) based on diastereomeric excess by derivatization with (1*S*,2*S*)-1,2-diphenylethylene diamine **289**.

## 16.2.6. $Et_2Zn$ addition to cyclohexenone catalyzed by CuCl and Phosphoramidite (*S*)-(*R,R*)-60




**254** (*S*)-(*R*,*R*)-**60**

**Operating Procedure** : Copper(I)chloride (0.01 eq.) and (*S*)-(*R,R*) **60** (0.01 eq.) are introduced in a flame dried two-necked round-bottom 50 ml flask equipped with a magnetic stirring bar, a septum and an argon-inlet which is then subjected to three vacuum-argon cycles. 15 ml of dry toluene are added.

The cyclohexenone (1 eq.) is added to the catalyst precursor. The mixture is stirred for 30 minutes at room temperature before being cooled to 0°C in an ice bath. The diethylzinc (1.42 eq.) is added at once.

The reaction is monitored by GC to estimate the reaction time. Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

After 5 minutes, there is no more trace of 2-cyclohexenone. After 15 minutes, 5 ml of methanol are added to the cool reaction media and the white suspension is stirred vigorously.

**Quantities Engaged** :

2-Cyclohexenone **254**: 0.59 ml, 0.584 g, 6.07 mmol, 1 eq.

Copper(I)chloride: 6.0mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.

(*S*)-(*R,R*) **60**: 66.2 mg, 12.1 x $10^{-2}$ mmol, 0.02 eq.

Diethylzinc: 0.90 ml, 1.062 g, 8.6 mmol, 1.42 eq.
Toluene : 15 ml

**Reaction time** : >5 minutes.

**Purification** : A saturated solution of $NH_4Cl$ is added. The mixture is placed in a separating funnel and extracted three times with $CH_2Cl_2$. The combined organic phases are washed once with a saturated aqueous solution of $Na_2CO_3$ and water, prior to drying over $MgSO_4$. The solution is concentrated under vacuum. The resulting oil is purified by flash chromatography on silica gel (*n*-pentane/$Et_2O$, 80/20 $R_f$= 0.25). 0.510 g of an odorous colorless oil is obtained.

Yield is non-representative due to the volatility of the product under vacuum.

**Name** : 3-ethylcyclohexanone

**CAS-RN** : 74006-73-8 (*S* enantiomer)

**M.F.** : $C_8H_{14}O$ **M.W.** : 126,20

**Yield** : 0.510 g (67%)

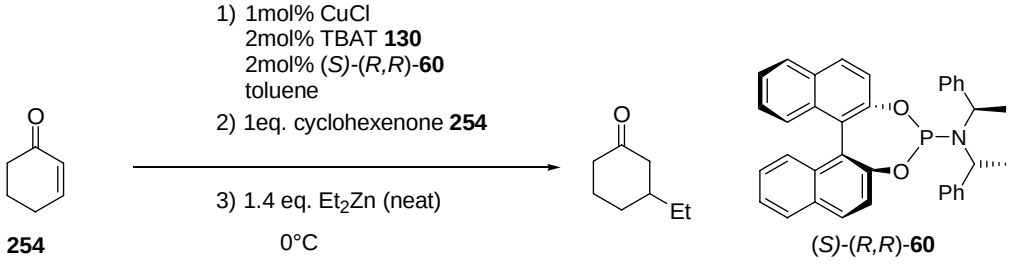
**Physical Property** : colorless oil

**GC** (95/4/1) : $t_R$= 3.93 min for 2-cyclohexenone
$t_R$= 6.42 min for 3-ethylcylohexanone

**$^1$H NMR** ($CDCl_3$, 200 MHz) : identical to previous sample

**Enantiomeric Excess** : 84.3% ee (*S*) based on diastereomeric excess by derivatization with (1*S*,2*S*)-1,2-diphenylethylene diamine **289.**

## 16.2.7. $Et_2Zn$ addition to cyclohexenone catalyzed by CuCl, TBAT and Phosphoramidite (*S*)-(*R,R*)-60




**254** (*S*)-(*R*,*R*)-**60**

**Operating Procedure** : Copper(I)chloride (0.01 eq.), TBAT **130** (0.02 eq.) and (*S*)-(*R,R*) **60** (0.01 eq.) are introduced in a flame dried two-necked round-bottom 50 ml flask equipped with a magnetic stirring bar, a septum and an argon-inlet which is then subjected to three vacuum-argon cycles. 15 ml of dry toluene are then added.

The cyclohexenone (1 eq.) is added to the catalyst precursor. The mixture is stirred for 30 minutes at room temperature before being cooled to 0°C in an ice bath. The diethylzinc (1.42 eq.) is added at once.

The reaction is followed by GC to estimate the reaction time. Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1 ml of methanol (analytical grade) in a capped glass-vial. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

After 1 hour, there is no more trace of 2-cyclohexenone. 5 ml of methanol are added to the cool reaction media and the white suspension is stirred vigorously.

**Quantities Engaged** :

2-Cyclohexenone **254**: 0.59 ml, 0.584 g, 6.07 mmol, 1 eq.
Copper(I)chloride: 6.0mg, 6.0 x $10^{-2}$ mmol, 0.01 eq.
(*S*)-(*R,R*) **60**: 66.2 mg, 12.1 x $10^{-2}$ mmol, 0.02 eq.
TBAT **130**: 65.5 mg, 12.1 x $10^{-2}$ mmol, 0.02 eq.
Diethylzinc: 0.90 ml, 1.062 g, 8.6mmol, 1.42 eq.
Toluene : 15 ml

**Reaction time** : >1 hour (first sample taken).

**Purification** : A saturated solution of $NH_4Cl$ is added. The mixture is placed in a separating funnel and extracted three times with $CH_2Cl_2$. The combined organic phases are washed once with a saturated aqueous solution of $Na_2CO_3$ and water, prior to drying over $MgSO_4$. The solution is concentrated under vacuum. The resulting oil is purified by bulb-to-bulb distillation under controlled vacuum. 0.378 g of a odorous colorless oil is obtained.

Yield is non-representative due to the volatility of the product under vacuum.

**Name** : 3-ethylcyclohexanone

**CAS-RN** : 74006-73-8 (*S* enantiomer)

**M.F.** : $C_8H_{14}O$ **M.W.** : 126,20

**Yield** : 0.378 g (49.3%)

**Physical Property** : colorless oil

**GC** (90/4/1) : $t_R$= 5.24 min for 2-cyclohexenone
$t_R$= 9.51 min for 3-ethylcylohexanone

**$^1$H NMR** ($CDCl_3$, 200 MHz) : identical to previous sample

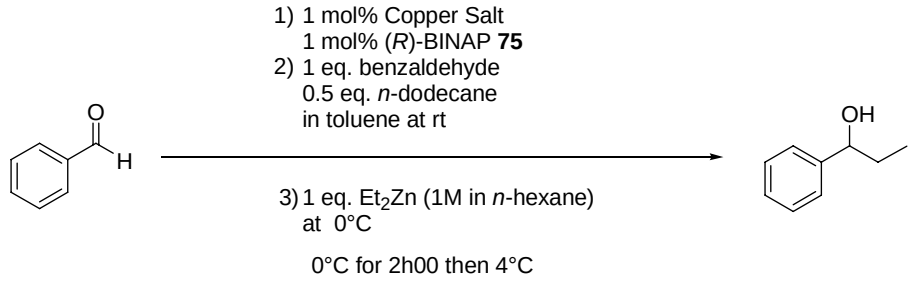
**Enantiomeric Excess** : 82.9% ee (*S*) based on diastereomeric excess by derivatization with (1*S*,2*S*)-1,2-diphenylethylene diamine **289**.

# Chapter 17

# Copper Diketonates

## 17.1. General Procedures

### 17.1.1. General Procedure P : Screening of Copper Complexes



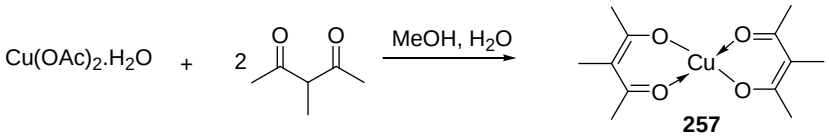

Copper(I) salt ($2x10^{-2}$ mmol, 0.01 eq.) and (*R*)-BINAP **75** (12.4 m g, 2 $x10^{-2}$ mmol, 0.01 eq.) are placed in a two-necked flame-dried round-bottom flask fitted with a rubber septum and an argon inlet. A solution of benzaldehyde (0.5 M) and dodecane (0.25 M) in dry toluene is prepared in a flame-dried graduated Schlenck flask. 4 ml of the prepared solution (0.204 g, 2 mmol, 1 eq. of benzaldehyde and 0.171 g, 1 mmol, 0.5 eq. of *n*-dodecane) are engaged in the two-necked flask. After 20 to 30 minutes, the mixture is cooled to 0°C in an ice bath.

A diethylzinc solution (1 M) in dry *n*-hexane is prepared from commercially available pure diethylzinc in a flame-dried graduated Schlenck flask. 2 ml of the diorganozinc solution is added at once on the substrate-catalyst mixture. The reaction is left at 0°C for two hours, after what the reaction vessel is moved to a cool room at 4°C.

Samples (± 0.1 ml) are taken with the help of a syringe and are directly quenched by *ca*. 1ml of methanol (analytical grade) in a capped glass-vial. Sampling is realized at least after 5 min, 15 min, 30 min, 1 hour, 2 hours and 24 hours. The salts in the sample are either filtered on Celite® or left to settle prior to the injection on the gas chromatography column.

# 17.2. Synthesis of Achiral Copper Complexes and Their Precursors

## 17.2.1. Synthesis of copper(II) *bis*(3-methylpentane-2,4-dionato) 257

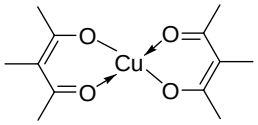



**257**

**Ref.** : Operating procedure and spectral data [444]

**Operating Procedure** : Copper(II) acetate monohydrate (0.866 g, 4.34 mmol, 1 eq.) is suspended in water (14ml) and methanol (1.4ml) in a 50ml one-necked round-bottomed flask. The reaction media is cooled in an ice bath prior to adding a solution of 3-methyl-2,4-pentanedione (1.02 ml, 1.00 g, 8.67 mmol, 2 eq.) in methanol (1 ml). The mixture is stirred during 3 hours. The solid is filtered, washed with water and dried under vacuum.

**Name** : *Bis*(3-methylpentane-2,4-dionato) copper(II)
*Bis*(3-methylacetylacetone)copper




**CAS-RN** : 14781-49-8

**M.F.** : $C_{12}H_{18}CuO_4$ **M.W.** : 289.81

**Yield** : 0.792 g (63.0%)

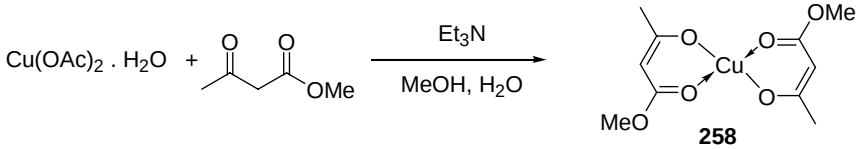
**Physical Property** : grey-bronze solid

**Melting Point** : over 235°C

**IR** (Nujol mull, $cm^{-1}$) : 1576.2 (C-O, C=C); 1291; 1169.0; 1016.7; 986.6; 724.2

**Mass** (APCI in MeOH) : 469.7 (17.4%); 468.1 (17.5%); 467.1 (82.8%); 466.2 (19.4%); 465.1 ($[Cu_2L_3]^+$, 100%); 293.1 (19.9%); 292.2 (17.9%); 291.1 (9.5%); 290.1 ($[M+1]^{\cdot+}$, 44.1%); 241.9 (11.4%); 239.8 (25.3%); 237.2 ($[M-L+2MeOH-1]^+$, 11.8%); 227.9 (8.1%); 225.8 ($[M-L+MeOH+H_2O-1]^{\cdot+}$, 15.1%); 210.0 (35.0%); 209.1 (17.4%); 208.0 ($[M-L+MeOH]^{\cdot+}$, 77.8%); 196.0 (8.0%); 195.0 (21.3%); 194.0 ($[M-L+H_2O]^{\cdot+}$,20.2%); 193.1 (23.9%)

## 17.2.2. Synthesis of copper(II) *bis*(methyl acetoacetato)




**258**

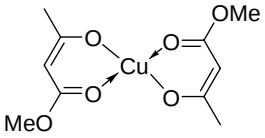
**Ref.** : Operating procedure and spectral data[445], spectral data[446]

**Operating Procedure** : Copper(II) acetate monohydrate (0.718 g, 3.60 mmol, 1 eq.) is suspended in 20 ml of water in a 50ml two-necked round bottomed flask fitted with a septum and a condenser. The suspension is heated lightly with a heat

gun until complete dissolution. A solution of methylacetoacetate (0.870 ml, 0.935 g, 7.97 mmol, 2.2 eq.) in methanol (6ml) is added to the blue copper solution which turns green.

A solution of triethylamine (1 ml, 0.728 g, 7.2 mmol, 2 eq.) in methanol (2ml) is added to the copper solution. The reaction media is stirred for one hour at room temperature while a green precipitate appears. The green solid is filtered on sintered glass, washed with diethylether. The solid is solubilized in chloroform under heating. A brown solid appears during heating and this hot solution is filtered. The organic phase is washed with water, dried on magnesium sulfate, filtered and concentrated under vacuum. The solid is dissolved in chloroform at room temperature and precipitated by cooling in an ice bath. The recovered solid is dried under vacuum.

**Name** : *Bis*(methyl acetoacetato)copper
*Bis*(methyl-3-oxobutanoato-O1',O3)-copper




**CAS-RN** : 15556-36-2

**M.F.** : $C_{10}H_{14}CuO_6$ **M.W.** : 293.76

**Yield** :0.375 g (35.5%)

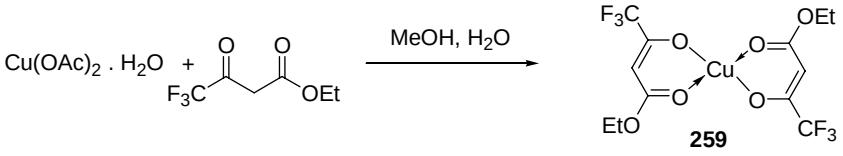
**Physical Property** : green solid

**Melting Point** : over 235°C

**IR** (Nujol mull, $cm^{-1}$) : 1601.6, 1558 & 1540 ($C=O_{ester}$, C=C and $C\text{-}O_{enolate}$); 1418.6; 1290.2; 1190.8 & 1175.9 ($C\text{-}O_{ester}$); 1068.0; 1009.9; 969.6; 923.7; 777.7

**Mass** (APCI in MeOH) : 473.0 (27%), 472.0 (7.4%); 470.9 ($[Cu_2L_3]^+$, 30.3%); 358.9 (12.7%); 357.0 ($[M+2MeOH]^+$, 8.7%); 298.9 (13.0%); 296.1 (42.0%); 295.1 (15.1%); 294.1 ( $[M+1]^{\cdot+}$, 100%); 293.1 ($[M]^+$, 14.5%);243.9 (10.9%); 242.0 (($[M\text{-}L+2MeOH]^{\cdot+}$, 27.9%); 213.0 (11.5%); 212.0 (31.6%); 211.0 (23.2%); 210.0 ($[M\text{-}L+MeOH]^{\cdot+}$, 56.4%); 196.0 (15.0%); 196.0 ( $[M\text{-}L+H_2O]^{\cdot+}$, 9.7%).

## 17.2.3. Synthesis of *Bis*(ethyl-4,4,4-trifluoro acetoacetato) copper




**259**

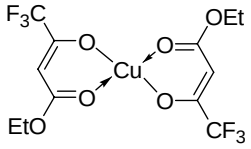
**Ref.** : IR spectroscopic data[447]

**Operating Procedure** : In a 50ml one-necked round-bottomed flask, copper(II) acetate monohydrate (0.421 g, 2.10 mmol, 1 eq.) is suspended in 10 ml of water and 1ml of methanol. The suspension is heated lightly with a heat gun until complete dissolution. A solution of ethyl-4,4,4-trifluoroacetoacetate (0.635 ml, 0.800 g, 4.21 mmol, 2.0 eq.) in methanol (2 ml) is added to the blue copper solution which turns green. The reaction media is stirred for 3 hours in an ice-bath.

The green solid is filtered on sintered glass, washed with water. The solid is dissolved in ethyl acetate (twice) and evaporated under reduced pressure. The solid is dissolved in toluene (three times) and then evaporated under reduced pressure.

The solid is dried by heating at *ca.* 90°C under reduced pressure with a horizontal distillation apparatus.

**Name** : *Bis*(ethyl-4,4,4-trifluoroacetoacetato)copper
*Bis*(ethyl-4,4,4-trifluoro-3-oxobutanoato-O1,O3)copper



**CAS-RN** : 2249-25-4

**M.F.** : $C_{12}H_{12}CuF_6O_6$ **M.W.** : 429,76

**Yield** :0.525 g (58%)

**Physical Property** : green solid

**Melting Point** : 181-182°C

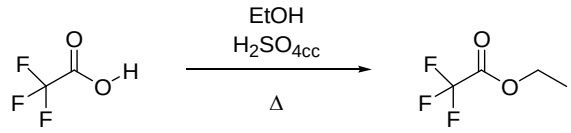
**IR** (Nujol mull, $cm^{-1}$) : 1637, 1612, 1562 ($C{=}O_{ester}$, C=C and $C\text{-}O_{enolate}$); 1370; 1311; 1245; 1186; 1153; 1091; 1013; 985; 923; 814; 755; 700

**Mass** (APCI in MeOH) : 678.5 (15%); 676.5 (8.8%); 676,5 ($[Cu_2L_3+1]^+$, 19.0%); 448.9 (20.1%); 448.0 (7.0%); 446.9 (46.6%, $[M+H_2O]^+$); 329.9 (41.5%); 329.1 (19.8%); 327.9 ($[M\text{-}L+2MeOH+H_20]^{\cdot+}$, 90.5%); 147.1 (49.2%); 145.1 (100%)

**Elemental Analysis** : Calculated: C 33.54% H 2.81%
Found: C 33.63% H 2.85%

## 17.2.4. Synthesis of *Bis*(1-ferrocenyl-4,4,4-trifluorobutane-1,3-dionate) copper(II)

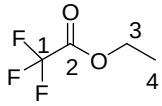
***Synthesis of ethyl 1,1,1-trifluoroacetate***




**Operating Procedure** : Trifluoroacetic acid (25.0 ml, 37.0 g, 0.324 mol, 1 eq.) is introduced in a 250 ml one-necked round bottom flask then cooled by an ice-bath while ethanol (23.0 ml, 18.05 g, 0.392 mol, 1.2 eq.) is added by fractions. Once heat has ceased evolving, concentrated sulfuric acid (37.2 ml, 66.92 g, 0.682 mol, 2.1 eq.) is added. The mixture is then heated to reflux for 30 minutes. The product is purified through distillation.

**Purification** : distillation with a short distillation column (b.p. 61°C)

**Name** : ethyl 1,1,1-trifluoroacetate



**CAS-RN** : 383-63-1

**M.F.** : $C_4H_5F_3O_2$ **M.W.** : 142.08

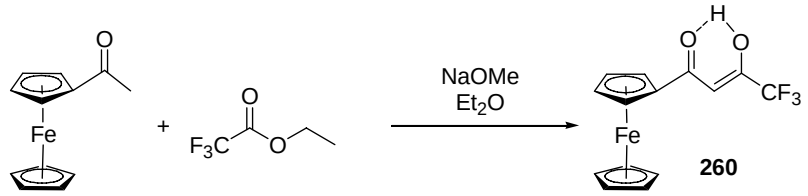
**Yield** : 39.61 g (86%)

**Physical Property** : colorless liquid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 4.42 (q, 2H, $^3J_{3,4}$=7.2, $H^3$), 1.40 (t, 3H, $^3J_{3,4}$=7.2, $H^4$)

**$^{19}$F NMR** ($CDCl_3$, 282.2 MHz) : -76,5 (s)

***Synthesis of 1-ferrocenyl-4,4,4-trifluorobutane-1,3-dione***

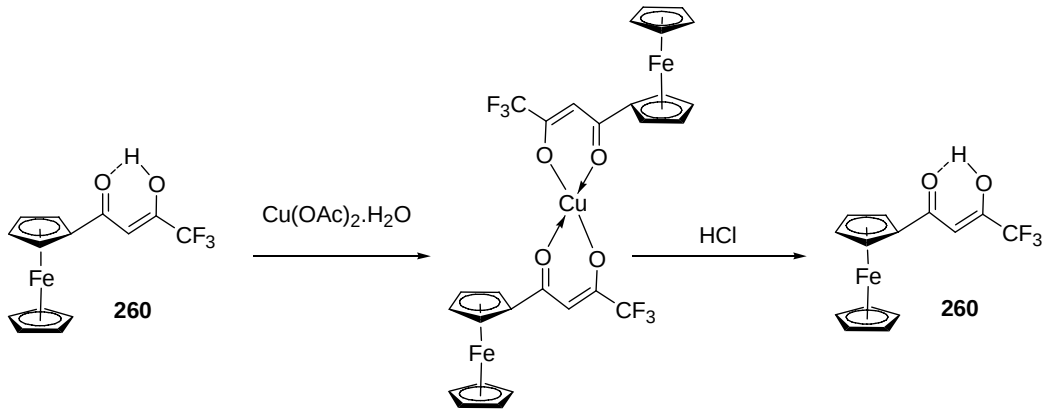



**Ref.** : Operating procedure, purification, spectroscopic data[402]

**Operating Procedure** : Sodium methoxide (0.500 g, 9.26 mmol, 2.11 eq.) is added to a solution of acetylferrocene (1.00 g, 4.38 mmol, 1 eq.) in dry ether (8 ml). After 15 minutes, ethyl trifluoroacetate (1.05 ml, 1.253 g, 8.82 mmol, 2.01 eq.) is added slowly. The mixture is stirred overnight.

The resulting precipitate is filtered and washed with dry ether. The solid is dissolved in lukewarm water (50-60°C), filtered and the aqueous phase is acidified to pH 2 with HCl. The aqueous phase is extracted with pentane. The organic phase is washed successively with an aqueous $NaHCO_3$ saturated solution and water, dried over $MgSO_4$, filtered and concentrated under vacuum. 1,00 g of a blood red solid is obtained.

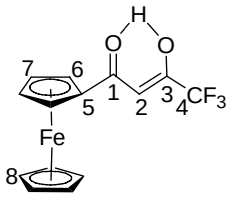
**Purification** :




1-ferrocenyl-4,4,4-trifluorobutane-1,3-dione (1.00 g, 3.09 mmol, 1 eq) is dissolved in acetone (2 ml). A solution of copper acetate monohydrate (1.11 g, 5.55 mmol, 1.8 eq.) in water (12 ml) is added. The mixture is stirred for 45 minutes prior to filtration, and washing with water. The solid is azeotropically dried with AcOEt and toluene under reduced pressure.

The complex is dissolved in chloroform and shacked with HCl 6 M (the aqueous phase is green), washed with HCl (1 M) and water, dried on $MgSO_4$ and concentrated under vacuum.

**Name** : 1-ferrocenyl-4,4,4-trifluorobutane-1,3-dione




**CAS-RN** : 162823-12-3

**M.F.** : $C_{14}H_{11}F_3FeO_2$ **M.W.** : 324.01

**Yield** : 0,648 g (46%)

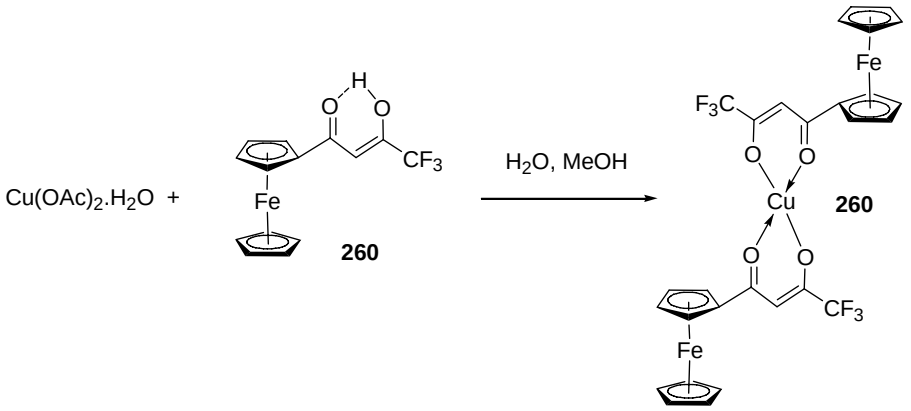
**Physical Property** : deep red solid

**Melting Point** : 100-102°C

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 15.2 (bs, 1H, O*H*); 6.09 (s, 1H, $H^2$); 4.87 (mult., 2H, $H^{6\text{ or }7}$); 4.68 (t, 2H, $^3J_{6,7}$=1.5, $H^{6\text{ or }7}$); 4.24 (t, 2H, $^3J_{6,7}$=1.5, $H^{6\text{ or }7}$), 4.24 (s, 5H, $H^8$)

**$^{19}$F NMR** ($CDCl_3$, 282.2 MHz) : -76,2 (s)

***Synthesis of Bis(1-ferrocenyl-4,4,4-trifluorobutane-1,3-dionate)copper(II)***

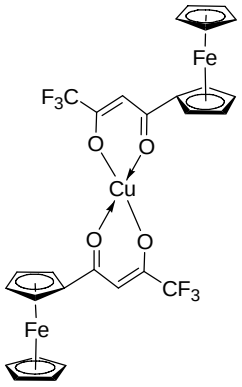



**Ref.** : Operating procedure, purification, spectroscopic data[402]

**Operating Procedure** : Copper(II)acetate monohydrate (0.421 g, 2.10 mmol, 1 eq.) is suspended in 10 ml of water and 1 ml of methanol in a 50 ml one-necked round-bottomed flask. The suspension is heated lightly with a heat gun until complete dissolution. A solution of ethyl-4,4,4-trifluoroacetoacetate (0.635 ml, 0.800 g, 4.21 mmol, 2.0 eq.) in methanol (2ml) is added to the blue copper solution which turns green. The reaction media is stirred for 3 hours in an ice-bath.

The red solid is filtered on sintered glass, washed with water. The solid is dissolved in ethyl acetate (twice) and evaporated under reduced pressure. The solid is dissolved in toluene (three times) and then evaporated under reduced pressure. The solid is dried by heating at *ca.* 90°C under reduced pressure with a horizontal distillation apparatus.

**Name** : *Bis*(1-ferrocenyl-4,4,4-trifluorobutane-1,3-dionato) copper




**CAS-RN** : 213037-40-2

**M.F.** : $C_{28}H_{20}CuF_6Fe_2O_4$ **M.W.** : 709,68

**Yield** : 0.366 g (83.6%)

**Physical Property** : deep red solid

**Melting Point** : 238°C (decomposition)

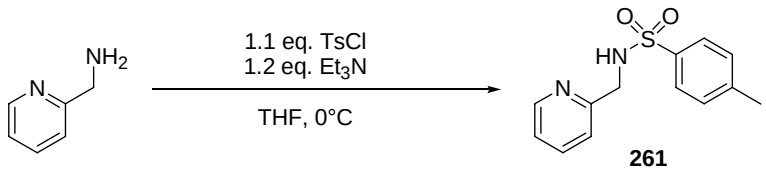
**IR** (Nujol mull, $cm^{-1}$) : 1602.8, 1587.9 (C-O and C=C); 1435.2; 1303.1; 1187.8; 1138.1; 948.9; 828.9; 797;5

**Mass** (APCI in MeOH) : 742.6 (2.5%); 741.9 (10.6%); 740.8 ($[M+MeOH]^+$, 14.6%); 712.5 (30.8%); 711.5 (54.8%); 710.4 (46.3%); 709.6 ($[M]^{\cdot+}$, 56.3%); 708.8 (17.8%); 420.9 (28.9%); 419.8 (55.0%); 419.1 (47.2%); 418.3 (27.0%); 417.7 ($[M-L+MeOH]^{\cdot+}$, 100%); 417.0 (27.0%); 406.7 (13.2%); 405.8 (27.0%); 405.0 ($[M-L+H_2O]$, 37.5%); 404.0 (27.1%); 403.5 (37.5%); 402.8 (16.5%); 325.1 ($[L+1]^+$, 73.2%)

**Elemental Analysis** : Calculated: C 47.39% H 2.84%
Found: C 47.29% H 2.86%

## 17.2.5. Synthesis of 263

***Synthesis of 4-Methyl-N-pyridin-2-ylmethyl-benzenesulfonamide 261***




**261**

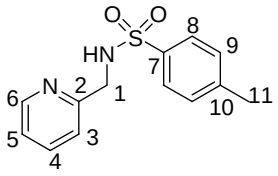
**Ref.** : Analytical data[403]

**Operating Procedure** : In a 50 ml one necked flask fitted with an argon inlet, 2-aminomethylpyridine (1.21 ml, 1.269 g, 11.62 mmol, 1 eq.) and distilled triethylamine (2 ml, 1.456 g, 14,38 mmol, 1.23 eq.) are dissolved in 15 ml of dry THF. The mixture is cooled at 0°C before adding at once *p*-toluenesulfonyl chloride (2.461 g, 12.78 mmol, 1.1 eq.).

After being stirred overnight at room temperature, the reaction mixture is dissolved in dichloromethane and washed with two portions of a saturated aqueous solution of $K_2CO_3$, followed by one portion of water. After drying on $MgSO_4$, the organic phase is concentrated under vacuum.

**Purification** : The solid is recrystallized in a mixture of *n*-hexane, ethyl acetate and dichloromethane and is used as such in the following reaction.

**Name** : 2-(*p*-toluenesulfonylaminomethyl)pyridine
*N*-(pyridyl-2-methyl)-*p*-toluenesulfonamide



**CAS-RN** : 75391-97-8

**M.F.** : $C_{13}H_{14}N_2O_2S$ **M.W.** : 262,33

**Yield** : 2.03 g (66.6%)

**Physical Property** : White solid

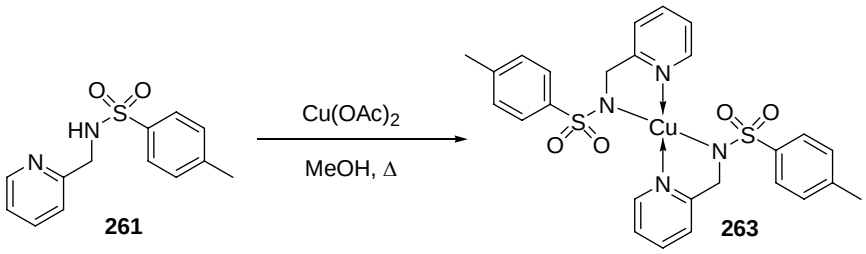
**Melting Point** : 87-88°C

**$^1$H NMR** ($CDCl_3$, 200 MHz) : 8.43 (d, $^3J_{5,6}$=3.2, 1H, $H^6$); 7.73 (d, $^3J_{8,9}$=8.3, 2H, $H^8$); 7.58 (mult, 1H, $H^4$); 7.15-7.30 (m, 4H, $H^{3,5\&9}$); 6.15 (bs, 1H, $H^{NH}$); 4.24 (d, $^3J_{1,NH}$=5.4, $H^1$); 2.38 (s, 3H, $H^{11}$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 156.0* ($C^2$); 148.9 ($C^6$); 143.2* ($C^{10}$); 136.8* ($C^7$); 136.7 ($C^4$); 129.5 & 127.2 ($C^{8-9}$); 122.5 & 121.9 ($C^{3-5}$); 47.5* ($C^1$); 21.4 ($C^{11}$)

**Mass** (CI, $CH_4$-$N_2O$) : 263.1 ($[M+1]^+$, 14%); 187 (8.4%); 146 (12.8%); 130 (36.1%); 117.8 (100%); 101.6 (59.4%); 100 (21.9%); 86 ($[C_6H_7N]^+$, 17.8%)

***Complexation of pyridinesulfonamide ligand 261 with copper(II) acetate***

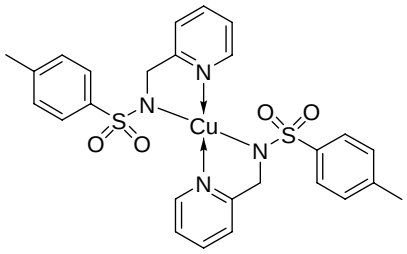



**261** **263**

**Ref.** : Operating procedure and analytical data[403]

**Operating Procedure** : In a 100 ml one-necked round-bottomed flask fitted with a condenser and an argon inlet, 2-(*p*-toluenesulfonylaminomethyl)pyridine **261** (1.04 g, 3.96 mmol, 2 eq.) and anhydrous copper(II) acetate (0.360 g, 1.98 mmol, 1 eq.) are suspended in 50 ml of methanol. The mixture is heated at reflux for 18 hours before being cooled at room temperature. The solid is left to settle before being filtered and washed with cool methanol.

**Name** : *bis*[4-methyl-*N*-[(2-pyridinyl-κ*N*)methyl]benzenesulfonamidato-κ*N*]-copper



**CAS-RN** : 353248-11-0

**M.F.** : $C_{26}H_{26}CuN_4O_4S_2$ **M.W.** : 586,19

**Yield** : 0.922 g (79.3%)

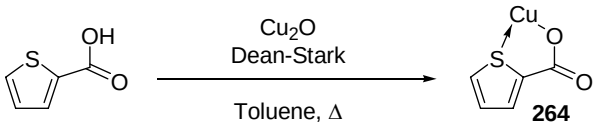
**Physical Property** : khaki solid

**Melting Point** : 195°C

**IR** (Nujol, $cm^{-1}$) : 1610 (C=C or C=N); 1276 (S=O); 1243; 1136 (S=O); 1084; 844; 814; 674; 556

**Mass** (APCI in MeOH) : 654.7 (19.1%); 653.8 (19.9%); 653.1 (24.6%); 652.1 (53.8%); 651.2 (55.2%); 650.3 ($[M+2MeOH+1]^{\cdot+}$,78.5%); 649.2 (66.6%); 648.1 (66.4%); 646.9 (22.6%); 646.0 (10.8%); 645.0 (12.9%); 593.3 (9.4%); 592.3 (13.3%); 591.2 (22.4%); 590.3 (23.8%); 589.2 (54.3%); 588.1 5 (83.5%); 587.0 (72.7%); 586.0 ($[M+1]^{\cdot+}$, 97.8%); 585.1 (14.6%); 584.1 (13.6%); 583.2 (10.2%); 582. 3 (11.7%); 581.5 (8.4%); 580.6 (12.5%); 358.0 (8.1%); 357.0 ($[M-L+MeOH+1]^{+}$, 8.8%); 355.6 (12.9%); 341.3 (($[M-L+H_2O+1]^{+}$, 10.7%); 263.1 ($[L+1]^{\cdot+}$, 100%)

## 17.2.6. Synthesis of copper(I) (2-thiophenecarboxylate)



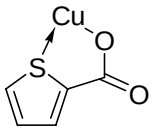

**264**

**Ref.** : Operating procedure and IR spectroscopic data[404]

**Operating Procedure** :. In a round-bottomed 25 ml flask fitted with a Dean-Stark apparatus, copper(I)oxide (2.21 g; 15.45mmol, 1 eq.) and 2-thiophenecarboxylic acid (8.00 g, 61.8 mmol, 4 eq.) are suspended in degassed toluene. The mixture is heated overnight before being cooled to 60°C. At which time, the solid is filtered and washed with methanol to remove the excess of acid and with ether until the eluant is colorless, then with small portions of hexane. The filtration and washings are effected under argon with an inverted funnel fitted with an argon inlet over the sintered glass filter.

**Note** : the product in solution or suspension is highly sensitive to oxygen, yet it is supposedly stable under solid dry form.

**Name** : copper(I) (2-thiophenecarboxylate)

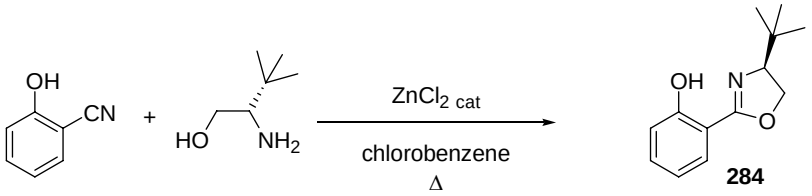


**CAS-RN** : 2249-25-4
**M.F.** : $C_5H_3CuO_2S$ **M.W.** : 190,69
**Yield** : 4.98 g (85%)
**Physical Property** : tan colored solid
**Mass** : FAB and APCI spectra were inconclusive

# 17.3. Synthesis of Chiral Copper Complexes and Their Precursors

## 17.3.1. Synthesis of 285

***Synthesis of (4S)-2-(4-tert-Butyl-4,5-dihydro-oxazol-2-yl)-phenol 284***

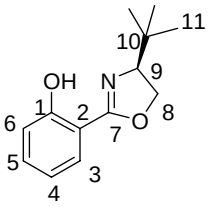



**Ref.** : Analytical data[418], operating procedure[419]

**Operating Procedure** : In a two-necked round-bottomed flask fitted with a condenser, a rubber septum and an argon inlet, zinc chloride (9.6m g, 71 µ mol, 0.025 eq.) is heated with a heat gun under vacuum until melted. Chlorobenzene (dried over 4Å molecular sieves), 2-cyanophenol (0.339 g, 2.84 mmol, 1 eq.) and (*S*)-*tert*-leucinol (0.500 g, 4.27 mmol, 1.5 eq.) are successively. The reaction media is heated at reflux for 24 hours. Once cool, the solvents are removed under vacuum. The oil is dissolved in dichloromethane and washed with three portions of water. The combined aqueous phases are extracted once with dichloromethane. The combined organic phases are dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting oil tends to crystallize.

**Purification** : The crude product is purified by flash chromatography on silica gel (cyclohexane/AcOEt, 95/5, $R_f$=0.38). 0.490 g of an off-white low melting point solid is obtained.

**Name** : (4*S*)-*2*-(4-*tert*-Butyl-4,5-dihydro-oxazol-2-yl)-phenol




**CAS-RN** : 135772-60-0
**M.F.** : $C_{13}H_{17}NO_2$ **M.W.** : 219.28
**Yield** : 0.490 g (78.7%)

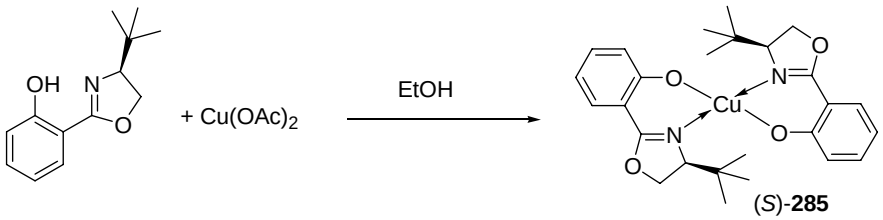
**Physical Property** : off-white solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 12,40 (bs, 1H, O*H*); 7.63 (d, $^3J_{3,4}$=8.1, 1H, $H^3$); 7.37 (mult., 1H, $H^5$); 7.01 (d, $^3J_{5,6}$=8.4, 1H, $H^6$); 6.86 (dd, $^3J_{3,4}$=$^3J_{4,5}$=8.1, 1H, $H^4$); 4,35 (dd, $^3J_{8a,9}$=8.7, $^{AB}J_{8a,8b}$=9.9, 1H, $H^{8a}$); 4.22 (*pseudo* t, *J*=7.8 & 8.7, 1H, $H^9$); 4.12 (dd, $^3J_{8b,9}$=7.8, $^{AB}J_{8a,8b}$=9.9, 1H, $H^{8b}$); 0.94 (s, 9H, $H^{11}$)

**$^{13}$C NMR** ($CDCl_3$, 50.3 MHz) : 165.1* ($C^7$); 160.1* ($C^1$); 133.2, 128.0 ($C^{3\&5}$); 118.4, 116.7 ($C^{4\&6}$); 110.7* ($C^2$); 75.1 ($C^8$); 68.0 ($C^9$); 33.7* ($C^{10}$); 25.7 ($C^{11}$).

**Mass** (CI, $CH_4$-$N_2O$) : 220.0 ($[M+1]^+$, 11.9%); 219.0 ($[M]^{\cdot+}$, 70.4%); 163 ($[M-(C_4H_8)]^{\cdot+}$; 12.9%); 161.9 $[M-(C_4H_9)]^+$; 100%); 133.9 (30.1%); 120.5 ($[C_7H_4O_2]^+$, 20.4%); 106.9 (25.0%); 92.9 ($[C_6H_5O]^+$, 2.5%); 91.5 (10.3%)

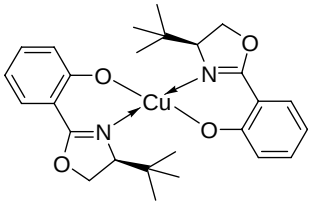
***Complexation of oxazolinephenol ligand 284 with copper(II)acetate***




**Ref.** : Analytical data and operating procedure[418]

**Operating Procedure** : In a 100 ml one-necked flask, oxazolinephenol ligand (*S*)-**284** (0.220 g, 1.00mmol; 2 eq.) is solubilized in 30 ml of ethanol. To this solution, a solution of copper(II) acetate (91 mg, 0.5 mmol, 1 eq.) in 10 ml of ethanol is added at room temperature. The reaction media is agitated over 15 days before being filtered. The solid is washed with some cold ethanol. The mother liquors and the washes are then concentrated under vacuum. The resulting solid is solubilized in 10 ml of ethanol, stirred over 15 days. The resulting solid is filtered and washed with some cold ethanol. A total of 133 mg of dark green solid is recovered.

**Name** : (*S*)-bis[2-[4-(1,1-dimethylethyl)-4,5-dihydro-2-oxazolyl]phenolato]-copper




**CAS-RN** : 135772-60-0

**M.F.** : $C_{26}H_{32}CuN_2O_4$ **M.W.** : 500,09

**Yield** : 133 mg (53.1%)

**Physical Property** : dark green solid

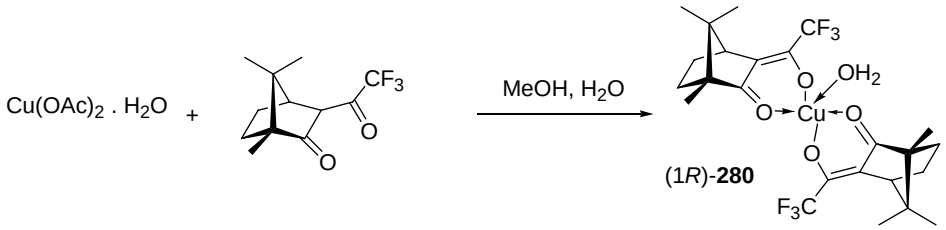
$[\alpha]_D^{30}$ =-1653 (*c*0.1, $CHCl_3$)

**IR** (Nujol mull, $cm^{-1}$) : 1616 (C=N); 1589 ($C_{ar}$-$C_{ar}$); 1541; 1401; 1346; 1236 ($CH_3$); 1213 ($CH_3$); 1140; 1083; 956; 935; 852; 755

**Mass** (APCI) : 502.2 (49.0%); 501.2 (25.1%); 500.2 ($[M+1]^{\cdot+}$, 100%); 314.9 (12.0%); 313.0 (28.7%); 300.9 (37.7%); 298.9 ($[M-L+H_20]^{\cdot+}$, 95.7%); 283.2

(3.5%); 281.2 ([M-L]$^{\cdot+}$, 2.8%); 237.2 (10.2%), 220.3 ([L+1]$^{+}$, 28.3%); 219.3 ([L]$^{\cdot+}$, 2.8%)

## 17.3.2. Synthesis of copper(II) *bis*[3-trifluoroacetyl-(+)-camphor] 280



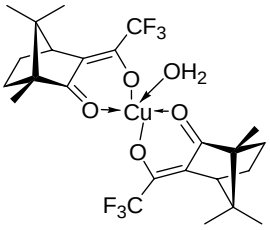

**Ref.** : Vague operating procedures[410,416]

**Operating Procedure** : In a 25 ml one-necked flask, copper(II) acetate monohydrate (197m g, 0.987 mmol, 1 eq.) is dissolved in 4 ml of water and 0.5 ml of methanol. This mixture is slightly heated with a heat gun to dissolve the entire solid.

A solution of 3-trifuoroacetyl)-(+)-camphor (500 mg, 0.42 ml, 1.973 mmol, 2 eq.) in 1 ml of methanol is added to the copper solution. The mixture color changes from blue to green instantly and a precipitate appears. The mixture is then cooled with an ice-bath during three hours before being filtered. The solid is washed with water and dried under vacuum.

The solid is dissolved in ethyl acetate (twice) and evaporated under reduced pressure. The solid is dissolved in toluene (3 times) and then evaporated under reduced pressure. The solid is dried by heating at *ca.* 90°C under reduced pressure with a horizontal distillation apparatus. A khaki solid is obtained, but it turns to bright green upon exposure to the atmosphere over the course of a few hours.

**Name** : (1*R*)-bis[1,7,7-trimethyl-3-(trifluoroacetyl)bicyclo[2.2.1]heptan-2-onato-O,O']copper monohydrate




**CAS-RN** : 85647-73-0 (anhydrous compound)

**M.F.** : $C_{24}H_{28}CuF_6O_4.H_2O$ **M.W.** : 576.03

**Yield** : 0.457 g (80.4%)

**Physical Property** : bright green solid

$[\alpha]_D^{30}$ =-7.0 (*c*0.1, $CHCl_3$)

**Melting point** : 164-165°C (lit. : 162-163°C for anhydrous complex)

**IR** (solid deposit on NaCl, cm$^{-1}$) : 3557, 3477 ($H_2O$); 1650, 1544 (C=O & C=C); 1331; 1296; 1271; 1229; 1182; 1135; 1108; 1082; 812

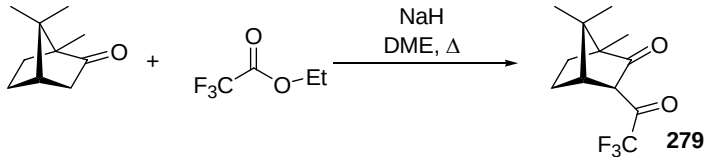
**Mass** (APCI in MeOH) : 874.9 (2.7%); 874.0 (3.7%); 873.0 (6.4%); 872.0 (11.8%); 870.9 (20.8%); 870.2 (4.3%); 869.5 (100%); 868.1 (14.9%); 867.3 ([$Cu_2L_3$]$^{+}$, 24.6%), 590.1 (2.1%); 589.2 ([M+MeOH]$^{+}$, 2.9%); 577.4 (2.3%);

575.6 (2.3%); 574.9 ([M+$H_2O$]$^+$, 3.0%); 560.1 (6.4%); 559.1 (3.5%); 558.2 ([M+1]$^{\cdot+}$, 11.5%); 376.1 (3.8%); 375.2 (3.4%); 374.1 ([M-L+2MeOH]$^{\cdot+}$, 9.1%), 344.1 (3.0%); 343.0 (2.9%); 342.1 ([M-L+MeOH]$^{\cdot+}$, 4.4%)

**Elemental Analysis** : Calculated: C 50.04% H 5.25%
Found: C 50.12% H 5.15%

## 17.3.3. Synthesis of copper(II) *bis*[3-trifluoroacetyl-(-)-camphor] 280

***Synthesis of trifluoroacetyl-(-)-camphor***




**279**

**Ref.** : Operating procedure and analytical data[408]

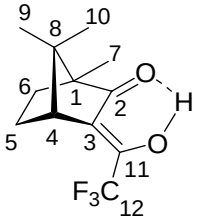
**Operating Procedure** : A 60% dispersion of sodium hydride in mineral oil (2.30 g, 57.5 mmol, 2.18 eq.) is washed twice with pentane beforehand and put to the pump for a brief time. The resulting powder is suspended in 39.5 ml of 1,2-dimethoxyethane and (-)-camphor (4.00 g, 26.3 mmol, 1 eq.) is then added. The mixture is refluxed for 1 hour under an inert atmosphere. At reflux temperature, a solution of ethyl-1,1,1-trifluoroacetate (3.45 ml, 4.12 g, 1.1 eq.) in 13 ml of 1,2-dimethoxyethane is added dropwise with the help of syringe over 90 minutes. The solution is refluxed overnight.

The solution is cooled and then quenched with EtOH (10 ml). Water is added and the media is acidified with HCl to pH 1. The reaction media is extracted with pentane (3 X 50ml). The organic phase is washed with an aqueous solution saturated with $NaHCO_3$ and water before being dried over $MgSO_4$, filtered and concentrated under vacuum.

**Purification** : The solid is purified by flash chromatography (first cyclohexane and then cyclohexane:$Et_2O$, Rf=0.25). A red oil is recovered.

The oil is distilled by bulb-to-bulb distillation. A colorless liquid is recovered.

**Name** : (1*S*)-3-trifluoroacetyl-(-)-camphor
(1*S*,4*S*) 3-(trifluoroacetyl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one




**CAS-RN** : 207742-84-5

**M.F.** : $C_{12}H_{15}F_3O_2$ **M.W.** : 248.24

**Yield** : 2.00 g (31%)

**Physical Property** : colorless liquid

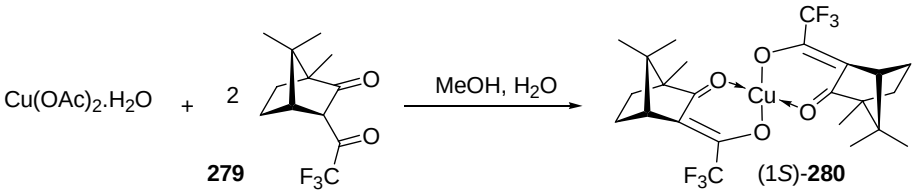
$[\alpha]_D^{30}$ =-82.2 (*c*2.4, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 11.4 (very bs, O*H*); 2.89 (mult, 1H, $H^4$);, 1.3-2.4 (m, 4H, $H^{5,6}$); 1.01 , 0.97 (s, 2x3H, $H^{7,9 \text{ or } 10}$), 0.84 (s, 3H, $H^{7,9 \text{ or } 10}$)

**$^{19}$F NMR** ( $CDCl_3$, 282.2MHz) : -70.97 (s)

**Mass** (CI, $CH_4$-$N_2O$) : 277.1 (8.8%); 250.3 (5.01); 249.0 ($[M+1]^+$, 100%); 247.9 ($[M]^{\cdot+}$, 26.6%), 221.0 ($[M\text{-}CO+1]^+$, 12.4%); 204.9 (17.0%); 179.0 ($[M\text{-}CF_3]^+$, 28.4%)

***Synthesis of copper(II) bis[3-trifluoroacetyl-(-)-camphor] 280***



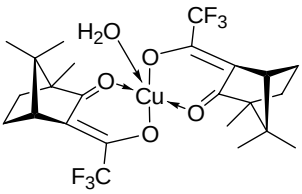

**Ref.** : Vague operating procedures[410,416]

**Operating Procedure** : In a 25 ml one-necked flask, copper(II) acetate monohydrate (197 mg, 0.987 mmol, 1 eq.) is dissolved in 4 ml of water and 0.5 ml of methanol. This mixture is slightly heated with a heat gun to dissolve the entire solid.

A solution of 3-trifluoroacetyl-(-)-camphor (500m g, 0.42 ml, 1.973 mmol, 2 eq.) in 1 ml of methanol is added to the copper solution. The mixture color changes from blue to green instantly and a precipitate appears. The mixture is then cooled with an ice-bath during three hours before being filtered. The solid is washed with water and dried under vacuum.

The green solid is dissolved in ethyl acetate (twice) and evaporated under reduced pressure. The solid is dissolved in toluene (three times) and then evaporated under reduced pressure. The solid is dried by heating at *ca.* 90°C under reduced pressure with a horizontal distillation apparatus. A khaki solid is obtained, but it turns to bright green upon exposure to the atmosphere over the course of a few hours.

**Name** : (1*S*)-*bis*[1,7,7-trimethyl-3-(trifluoroacetyl)bicyclo[2.2.1]heptan-2-onato-*O,O'*]copper monohydrate




**CAS-RN** : 85647-12-7 (anhydrous compound)

**M.F.** : $C_{24}H_{28}CuF_6O_4.H_2O$ **M.W.** : 576.03

**Yield** :0.53 g (93%)

**Physical Property** : bright green solid

$[\alpha]_D^{30}$ =+7.0 (*c*0.1, $CHCl_3$)

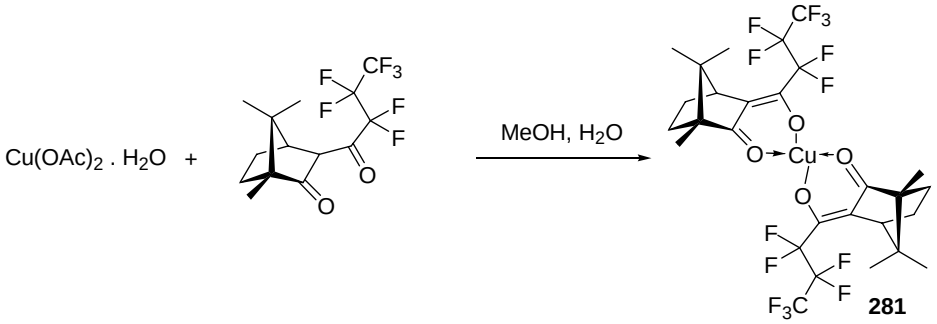
**Melting point** : 160°C (litt: 162-163°C for anhydrous complex)

**IR** (solid deposit on NaCl, $cm^{-1}$) : 3473 ($H_2O$); 1648, 1553 (C=O & C=C); 1331; 1298; 1270; 1226; 1134; 1107; 1081; 1061; 812

**Mass** (APCI in MeOH) : 591.5 (4.3%); 589.5 ([M+MeOH]$^+$, 7.8%); 561.1 (5.4%); 560.0 (29.7%); 559.1 (12.0%); 558.1 ([M+1]$^{\cdot+}$, 63.6%); 364.3 (7.1%); 363.2 (42.4%); 362.2 (14.1%); 361.2 ([M-L+$H_2O$+MeOH+1]$^+$, 100%), 359.8 ([M-L+$H_2O$+MeOH]$^{\cdot+}$, 4.7%), 343.9 (4.6%); 343.0 (5.3%); 341.9 ([M-L+MeOH]$^{\cdot+}$, 12.1%); 327.9 (4.3%); 327.0 (11.0%)

**Elemental Analysis** : Calculated: C 50.04% H 5.25%
Found: C 50.04% H 5.25%

## 17.3.4. Synthesis of copper(II) *bis*[3-heptafluorobutyryl-(+)-camphor] 281



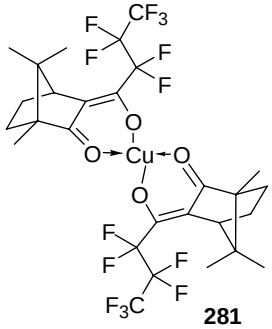

**Ref.** : Analytical data[412]

**Operating Procedure** : In a 25 ml one-necked flask, copper(II) acetate monohydrate (197 mg, 0.987 mmol, 1 eq.) is dissolved in 4 ml of water and 0.5 ml of methanol. This mixture is slightly heated with a heat gun to dissolve the entire solid.

A solution of 3-heptafluorobutyryl-(+)-camphor (687 mg, 0.565 ml, 1.973 mmol, 2 eq.) in 2 ml of methanol is added to the copper solution. The mixture color changes from blue to green instantly and a precipitate appears. The mixture is then cooled with an ice-bath during three hours before being filtered. The solid is washed with water and dried under vacuum.

The solid is dissolved in ethyl acetate (three times) and evaporated under reduced pressure. The solid is dissolved in toluene (twice) and then evaporated under reduced pressure. The solid is dried by heating for one hour at *ca.* 100°C under reduced pressure with a horizontal distillation apparatus.

**Name**:(1*R*)-*bis*[3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutyl)-1,7,7-trimethylbicyclo [2.2.1]heptan-2-onato-O,O']copper




**CAS-RN** : 121376-46-3

**M.F.** : $C_{28}H_{28}CuF_{14}O_4$ **M.W.** : 758.04

**Yield** :0.686 g (91.7%)

**Physical Property** : khaki solid

**[α]** $^{30}_{D}$ =-57.5 (*c*0.04, $CHCl_3$)

**Melting point** : 132-133°C (litt: 134°C)

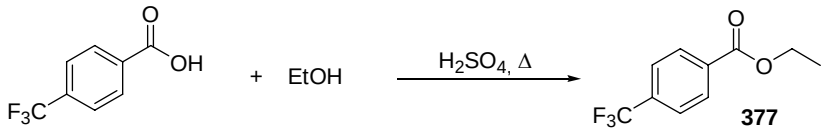
**IR** (Nujol, $cm^{-1}$) : 1632, 1522 (C=O, C=C); 1345; 1261; 1231; 1179; 1110; 1082; 1046; 955; 786; 749

**Mass** (APCI in $CH_2Cl_2$ / MeOH) : 788.8 ($[M+MeOH]^+$, 4.8%); 776.8 (3.4%); 775.9 (2.1%); 774.8 ($[M+H_2O]$, 6.8%); 760.0 (5.3%); 759.0 (3.6%); 758.0 ($[M+1]^{\cdot+}$,12.5%); 475.7 (11.3%); 474.8 (4.8%); 473.8 ($[M-L+MeOH]^{\cdot+}$, 28.7%); 472.6 (2.3%); 292.2 (13.7%); 291.2 (100%)

**Elemental Analysis** : Calculated: C 44.36% H 3.72%
Found: C 44.45% H 3.68%

## 17.3.5. Synthesis of copper(II) bis[3-(4-trifluoromethyl benzoyl)-(+)-camphor] 278

***Synthesis of ethyl-4-trifluoromethylbenzoate***

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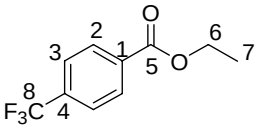
**Operating Procedure** : In a 100 ml one-necked round-bottomed flask, 4-trifluoro methylbenzoic acid (5.00 g, 26.3 mmol, 1 eq.) and ethanol (7 ml, 5.50 g, 119.2 mmol, 4.53 eq.) are dissolved in dichloromethane (45ml). Concentrated sulfuric acid (1.7 ml, 3.06 g, 31.2 mmol, 1.2 eq.) is added and the mixture is heated up at reflux overnight. Some solid remains in the flask. 7 ml of EtOH are added and the mixture is heated up for one additional hour.

The cooled mixture is washed with an aqueous solution saturated with $Na_2CO_3$ (three times), $H_2O$ (twice). The organic phase is dried over $MgSO_4$ and concentrated under vacuum.

**Purification** : used as such

**Name** : ethyl-4-trifluoromethylbenzoate




**CAS-RN** : 583-02-8

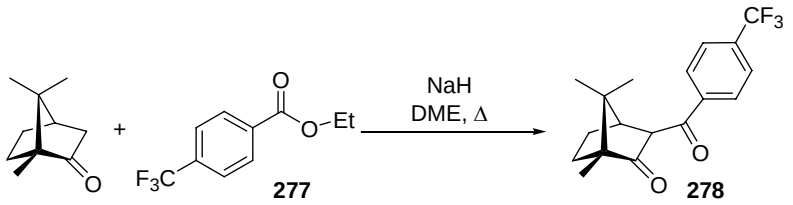
**M.F.** : $C_{10}H_9F_3O_2$ **M.W.** : 218.17

**Yield** : 4.62 g (80.5%)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 8.17 (d, 2H, $^3J_{2,3}$=8.1, $H^2$), 7.70 (d, 2H, $^3J_{2,3}$=8.1, $H^3$), 4.42 (q, 2H, $^3J_{6,7}$=7.2, $H^6$), 1.42 (t, 3H, $^3J_{6,7}$=7.2, $H^7$)

**$^{19}$F NMR** ($CDCl_3$, 282.2 MHz) : -63,98 (s)

***Synthesis of 4-(trifluoromethylbenzoyl)-(+)-camphor***




**Ref.** : Operating procedure and analytical data[413]

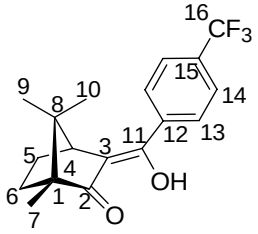
**Operating Procedure** : A 60% dispersion of sodium hydride in mineral oil (0.822 g, 20.6 mmol, 2.35 eq.) is washed twice with pentane beforehand and put to the pump for a brief time. The resulting powder is suspended in 13 ml of 1,2-dimethoxyethane then (+)-camphor (1.33 g, 8.75 mmol, 1 eq.) is added. The mixture is refluxed for 5 hours under an inert atmosphere. At reflux temperature, a solution of ethyl-4-trifluoromethylbenzoate (2.29 g, 10.5mmol, 1.2 eq.) in 5 ml of 1,2-dimethoxyethane is added dropwise with the help of syringe over 30 minutes. The solution is refluxed overnight.

The solution is cooled then quenched with EtOH (10 ml). Water is added and the media is acidified with HCl to pH 1. The reaction media is extracted with pentane. The organic phase is washed successively with an aqueous solution saturated with $NaHCO_3$ and water before being dried over $MgSO_4$, filtered and concentrated under vacuum.

**Purification** : The residue of evaporation is purified by a short flash chromatography on silica gel followed by a flash chromatography on silica gel (cyclohexane:AcOEt, Rf=0.25).

0.983 g of a pinkish-white solid is obtained.

**Name** : (1*R*)- 4-(trifluoromethylbenzoyl)-(+)-camphor




**CAS-RN** : 130552-77-1

**M.F.** : $C_{18}H_{19}F_3O_2$ **M.W.** : 324,34

**Yield** : 0.98 g (34.6%)

**Physical Property** : pinkish-white solid

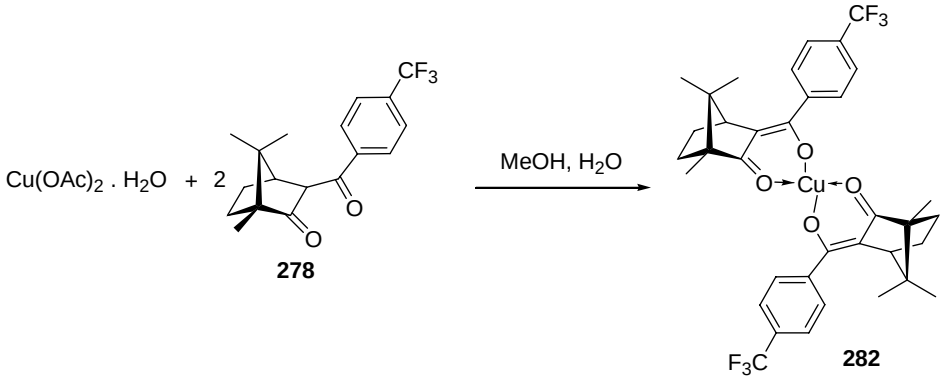
$[\alpha]_D^{30}$ =+286 (*c*1, $CHCl_3$)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 12.3 (bs, 1H, O*H*); 7.76 (d, 2H, $^3J_{13,14}$=8.1, $H^{13\text{ or }14}$); 7.70 (d, 2H, $^3J_{13,14}$=8.7, $H^{13\text{ or }14}$); 2.81 (d, $^3J_{4,5}$=3.6, 1H, $H^4$); 2.07-2.26 (m, 1H, $H^{5\text{ or }6}$); 1.46-1.90 (m, 3H, $H^{5\text{ or }6}$); 1.04 (s, 3H, $H^{7,9\text{ or }10}$); 0.96 (s, 3H, $H^{7,9\text{ or }10}$); 0.83 (s, 3H, $H^{7,9\text{ or }10}$)

**$^{19}$F NMR** ($CDCl_3$, 282.2 MHz) : -64.73 (s)

**Mass** (CI, $CH_4$-$N_2O$) : 325.2 (56.6%); 324.7 ($[M+1]^+$, 100%); 324.2 ($[M]^{\cdot+}$, 38.3%); 305.3 (67.7%); 296.3 (21.7%); 280.5 (12.5%); 179.0 ($[M-(C_7H_4F_3)]^+$, 10.7%); 172.9 ($[M-(C_8H_4OF_3)]$, 23.2%)

***Synthesis of copper(II) bis[3-(4-trifluoromethylbenzoyl)-(+)-camphor] 282***

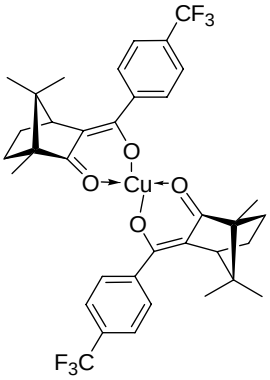



**Operating Procedure** : In a 25ml one-necked flask, copper(II) acetate monohydrate (153 mg, 0.765 mmol, 1 eq.) is dissolved in 3.5 ml of water and 0.5 ml of methanol. This mixture is slightly heated with a heat gun to dissolve the entire solid.

A solution of 4-trifluoromethylbenzoyl-(+)-camphor (506 mg, 1.529 mmol, 2 eq.) in 1.5 ml of methanol is added to the copper solution. The mixture color changes from blue to green instantly and a precipitate appears. The mixture is then cooled with an ice-bath during 30 minutes before being filtered. The solid is washed with water and dried under vacuum.

The green solid is dissolved in ethyl acetate (twice) and evaporated under reduced pressure. The solid is dissolved in toluene (twice) and then evaporated under reduced pressure. The solid is dried by heating at *ca.* 100°C under reduced pressure with a horizontal distillation apparatus.

**Name** : (1*R*)-*bis*[3-(4'-(trifluoromethyloxobenzyl))-1,7,7-trimethylbicyclo[2.2.1] heptan-2-onato-O,O']copper




**M.F.** : $C_{36}H_{36}CuF_6O_4$ **M.W.** : 710,21

**Yield** :0.463 g (85%)

**Physical Property** : khaki solid

**Melting point** : over 245°C

**[α]** $^{30}_{D}$ =-68.0 (*c*0.1, $CHCl_3$)

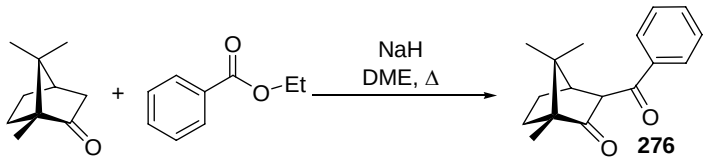
**IR** (Nujol $cm^{-1}$) : 1602, 1519 (C=O and C=C); 1485; 1323; 1170; 1127; 1108; 1068; 858; 813

**Mass** (APCI in MeOH) : 713.9 (2.7%); 713.0 (13.8%); 712.0 (47.5%); 711.1 (34.5%); 710.0 ($[M+1]^{\cdot+}$, 100%); 709.2 (1.0%); 708.0 (1.4%); 437.9 (1.1%); 436.9 (0.7%); 435.8 ($[M\text{-}L+MeOH+H_2O]^{\cdot+}$, 3.0%); 325.1 ($[L+1]^+$, 5.3%)

**Elemental Analysis** : Calculated: C 60.88% H 5.11%
Found: C 60.82% H 5.14%

## 17.3.6. Synthesis of copper(II) bis[3-benzoyl-(+)-camphor] 283

***Synthesis of 4-(trifluoromethylbenzoyl)-(+)-camphor***



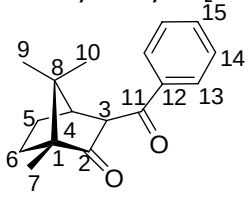

**Ref.** : Operating procedure and analytical data[413]

**Operating Procedure** : A 60% dispersion of sodium hydride in mineral oil (0.822 g, 20.6 mmol, 2.35 eq.) is washed twice with pentane beforehand and put to the pump for a brief time. The resulting powder is suspended in 13 ml of 1,2-dimethoxyethane and then (+)-camphor (1.33 g, 8.75mmol, 1 eq.) is added. The mixture is refluxed for 5 hours under an inert atmosphere. At reflux temperature, a solution of ethyl benzoate (2.29 g, 10.5 mmol, 1.2 eq.) in 5 ml of 1,2-dimethoxyethane is added dropwise with the help of syringe over 30 minutes. The solution is refluxed overnight.

The solution is cooled then quenched with EtOH (5ml). Water is added and the media is acidified with HCl to pH 1. The reaction media is extracted with pentane (3 x 50ml). The organic phase is washed successively with an aqueous solution saturated with $NaHCO_3$ and water before being dried over $MgSO_4$, filtered and concentrated under vacuum.

**Purification** : The oil is dissolved in pentane and left to crystallize at 4°C overnight. A yellow solid is recovered by filtration. The mother liquors are concentrated under reduced pressure and three other crops of solid are recovered. A total of 0.645 g of yellow solid is obtained.

**Name** : (1*R*)-3-benzoyl-(+)-camphor
(1*R*)-3-benzoyl-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one




**CAS-RN** : 125875-27-6

**M.F.** : $C_{17}H_{20}O_2$ **M.W.** : 256.34

**Yield** : 0.65 g (28.8%)

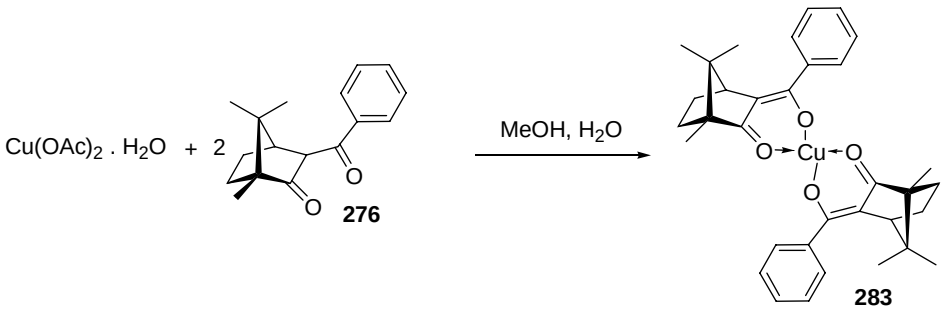
**Physical Property** : yellow-brown solid

**$^1$H NMR** ($CDCl_3$, 300 MHz) : 7.93 (d, 2H, $^3J_{13,14}$=7.2, $H^{13}$); 7.57 (t, 1H, $^3J_{14,15}$=7.2, $H^{15}$); 7.48 (t, 2H, $^3J_{13,14}$=$^3J_{14,15}$=7.5, $H^{14}$); 4.24 (bd, 1H, $^3J_{3,4}$=5.4, $H^3$); 2.52 (bt,

1H, $^{3}J_{3,4}=^{3}J_{4,5}$=4.8, $H^{4}$); 1.65-1.85 (m, 3H, $H^{5 \text{ and } 6}$); 1.25-1.45 (m,1H, $H^{5 \text{ or } 6}$); 1.04, 1.02 (2s, 9H, $H^{7,9 \text{ or } 10}$), 0.981 (s, 9H, $H^{7,9 \text{ or } 10}$)

**Mass** (CI, $CH_4$-$N_2O$) : 258.2 (14.0%); 257.1 ($[M+1]^+$, 100%); 256.0 (18.1%); 229.0 ($[M-CO+1]^+$, 1.7%); 178.9 ($[M-C_6H_5]^+$, 6.1%); 153.7 ($[M-PhCO+1]^{\cdot+}$, 10.5%); 104.9 ($[PhCO]^+$, 4.3%)

***Synthesis of copper(II) bis[3-benzoyl-(+)-camphor] 283***



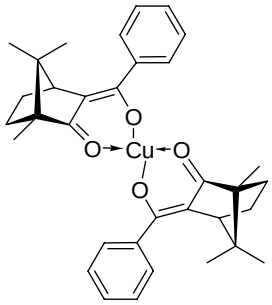

**Ref.** : Description[448]

**Operating Procedure** : In a 25 ml one-necked flask, copper(II) acetate monohydrate (153 mg, 0.765 mmol, 1 eq.) is dissolved in 3.5 ml of water and 0.5 ml of methanol. This mixture is slightly heated with a heat gun to dissolve the entire solid.

A solution of 3-benzoyl-(+)-camphor (400m g, 1.529 mmol, 2 eq.) in 1.5 ml of methanol is added to the copper solution. The mixture color changes from blue to brown-green instantly and a precipitate appears. The mixture is then cooled with an ice-bath during 3 hours before being filtered. The solid is washed with water and dried under vacuum.

The green solid is dissolved in ethyl acetate (three times) and evaporated under reduced pressure. The solid is dissolved in toluene (twice) and then evaporated under reduced pressure. The solid is dried by heating at *ca.* 100°C under reduced pressure with a horizontal distillation apparatus.

**Name** : (1*R*)-*bis*(3-benzoyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-onato-*O,O'*)-copper




**CAS-RN**: 38397-94-3
**M.F.** : $C_{34}H_{38}CuO_4$ **M.W.** : 574.21

**Yield** :0.375 g (85%)

**Physical Property** : yellow-brown solid

**Melting point** : 221-222°C

$[\alpha]_D^{30}$ =-55.0 (*c*0.1, $CHCl_3$)

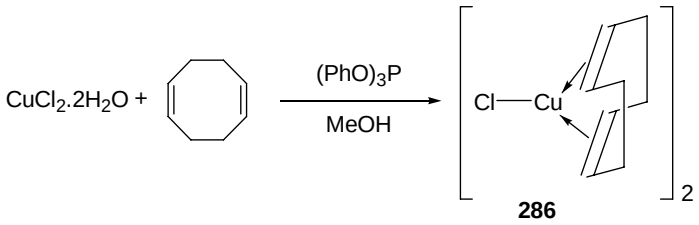
**IR** (solid deposit on NaCl, $cm^{-1}$) : 1592, 1571 (C=O & C=C); 1501; 1469; 1331; 1182; 1161; 1109; 803

**Mass** (APCI in MeOH) : 579.5 (4.2%); 578.3 (7.3%); 577.5 (7.1%); 577.0 (22.2%); 575.0 (67.7%); 574.1 ($[M+1]^{\cdot+}$, 100%); 573.1 ($[M]^{+}$, 1.5%); 546 ($[M-CO]^{\cdot+}$, 2.6%); 369.8 (1.2%); 367.8 ($[M-L+MeOH+H_2O]^{\cdot+}$, 1.4%); 259.2 (2.2%); 258.2 (7.8%); 257.1 ($[L+2]^{+}$, 41.5%)

**Elemental Analysis** : Calculated: C 71.12% H 6.77%
Found: C 71.17% H 6.87%

## 17.3.7. Synthesis of copper(I) 287

***Synthesis of bis[1,5-cyclooctadiene copper(I) chloride] 286***

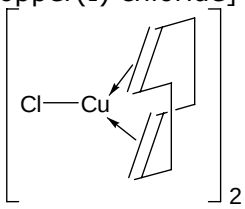



**286**

**Ref.** : Operating procedure[421]

**Operating Procedure** : In a one-necked flask, copper(II) chloride dihydride (3.895 g, 22.85 mmol, 1 eq.) is dissolved in methanol (45 ml). Triphenyl phosphite (6 ml, 7.104 g, 22.89 mmol, 1 eq.) and *cis,cis*-1,5-cyclooctadiene (4.6 ml, 4.057 g, 37.5mmol, 1.64 eq.) are added in sequence. After stirring for one hour, the solid is filtered and washed with 20 ml of MeOH. The product is dried under vacuum and used as such.

**Name** : bis[1,5-cyclooctadiene copper(I) chloride]

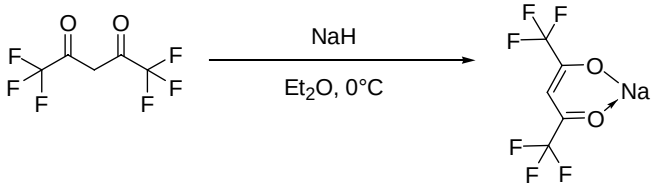



**M.F.** : $C_{16}H_{24}Cl_2Cu_2$ **M.W.** : 414.36

**Yield** : 3.04 g (64.3%)

**Physical Property** : white solid

***Synthesis of sodium hexafluoroacetylacetonate***




**Ref.** : Operating procedure[449]

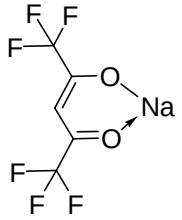
**Operating Procedure** : In a 50 ml one-necked flask, a 60% dispersion of sodium hydride in mineral oil (0.215 g, 5.38 mmol, 1.0 eq.) is washed three times with

pentane beforehand and put to the pump for a brief time. The sodium hydride is suspended in dry ether (4 ml) and cooled to 0°C.

The flask is fitted with an addition funnel and an argon inlet. The addition funnel is loaded with 1,1,1,5,5,5-hexafluoro-2,4-pentadione (1.200 g, 5.65 mmol, 1.05 g) dissolved in dry ether (4ml). The diketone is added slowly drop-by-drop. After the addition, the media is brought back to room temperature and agitated for 2 hours. The media is then concentrated under vacuum.

**Purification** : The white solid is suspended in pentane and filtered.

**Name** : sodium hexafluoroacetylacetonate



**CAS-RN** : 22466-49-5

**M.F.** : $C_5HF_6NaO_2$ **M.W.** : 230.04

**Yield** : 0.980 g (79%)

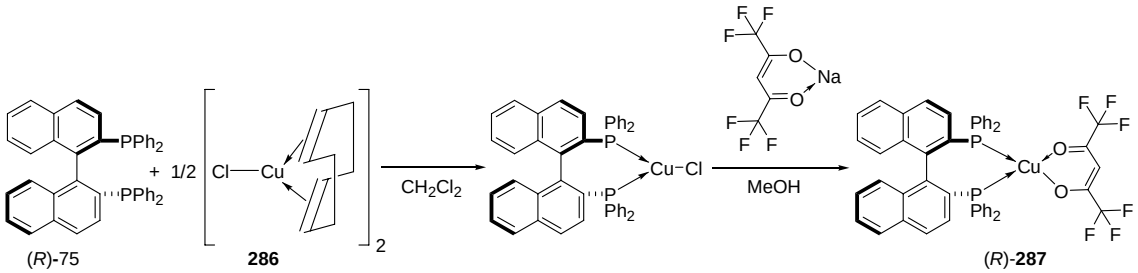
**Physical Property** : white solid

**$^1$H NMR** ($CD_3OD$, 300 MHz) : 5.59 (s)

**$^{19}$F NMR** ($CD_3OD$, 282.2 MHz) : -78.0 (s)

**IR** (Nujol, $cm^{-1}$) : 1674, 1556 (C-O, C=C); 1533; 1491; 1259; 1204; 1139; 802; 664; 580

***Synthesis of (R)-287***



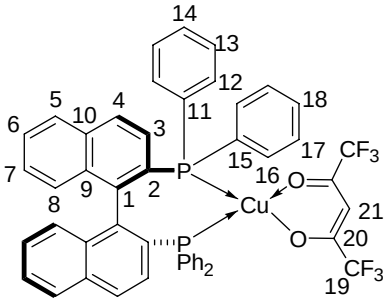

(*R*)-75 **286** (*R*)-**287**

**Ref** : Racemic vaguely described[424]

**Operating Procedure** : In a 25 ml one-necked flask, *bis*[1,5-cyclooctadiene copper(I) chloride] **286** (45.7 mg, 0.110 mmol, 0.55 eq.] is suspended in dichloromethane (12.5 ml). (*R*)-2,2'-*bis*(diphenylphosphino)-1,1'-binaphtyl (125 mg, 0.201 mmol, 1 eq.) is added at once and the reaction media turns yellow and no trace of solid remains. The mixture is stirred for 30 minutes, prior to being filtered on a hydrophilic PTFE membrane. The solution is then concentrated under reduced pressure.

The yellow solid recovered is suspended in methanol (12.5ml) and sodium hexafluoroacetylacetonate (50.8 mg, 0.221 mmol, 1.1 eq.) is added. The mixture is stirred for a week then concentrated under reduced pressure. The orange solid is dissolved in dichloromethane. The organic phase is washed twice with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid is recrystallized by layering a minimum of dichloromethane and pentane.

**Name** : [(R)-[1,1'-binaphtalene]-2,2'-diylbis[diphenylphosphine-κP]](1,1,1,5,5,5-hexafluoro-2,4-pentanedionato-κO,κO')-copper




**CAS-RN** : 679427-31-7

**M.F.** : $C_{49}H_{33}CuF_6O_2P_2$ **M.W.** : 893,27

**Yield** : 0.136 g (75.8%)

**Physical Property** : orange solid

**[α]** $^{30}_{D}$ =230 (*c*0.05, $CHCl_3$)

**Melting point** : 221-223°C

**$^1$H NMR** ($CD_2Cl_2$, 500 MHz) : 7.80 (mult.,4H, $H^{16}$); 7.42-7.52 (m, 10H, $H^{4,5,17,18}$); 7.29 (t, 2H, $^3J_{5,6}$=$^3J_{6,7}$=7.0, $H^6$); 7.23 (2d, 4H, $H^{12}$); 7.16 (2H, $H^3$); 7.05 (t, $^3J_{6,7}$=7.0, 2H, $H^7$); 6.77 (d, 2H, $^3J_{7,8}$=8.4, $H^8$); 6.68 (t, 2H, $^3J_{13,14}$=7.3, $H^{14}$); 6.54 (t, 4H, $^3J_{12,13}$= $^3J_{13,14}$=7.3, $H^{13}$), 5.87 (s, 1H, $H^{21}$)

**$^{13}$C NMR** ($CD_2Cl_2$, 125.7 MHz) : 177.2 (q, $^3J_{C\text{-}F}$=32.6, $C^{20}$); 138.9 (t, $^3J_{C\text{-}P}$=8.5, $C^1$); 135.7 (t, $^3J_{C\text{-}P}$=10.2, $C^{16}$); 134.0 (t, $^3J_{C\text{-}P}$=9.3, $C^{12}$); 133.9 (s, $C^9$); 133.4 (s, $C^{10}$); 133.3 (t, $^1J_{C\text{-}P}$=12.7, $C^2$); 132.9 (t, $^1J_{C\text{-}P}$=17.4, $C^{15}$); 131.0 (s, $C^{18}$); 129.6-129.5 ($C^{11}$, $C^{14}$, $C^{17}$); 129.0 (s, $C^4$); 128.4 (s, $C^5$); 127.9-127.6 (m, $C^8$, $C^{13}$, $C^3$); 126.8 (s, $C^6$); 126.5 (s, $C^7$); 118.6 (q, $^1J_{C\text{-}F}$=287.8, $C^{19}$); 88.1 (s, $C^{21}$)

**$^{19}$F NMR** ($CDCl_3$, 282.2 MHz) : -77.6 (s)

**$^{31}$P NMR** ($CD_2Cl_2$, 202.4 MHz) : -2.96 (bs)

**Elemental Analysis** : Calculated: C 65.88 % H 3.72 % P 6.93%
Found: C 65.83% H 3.70% P 6.50%

**X-Ray Diffraction**: Crystals suitable for X-ray diffraction analysis were obtained by slow diffusion of *n*-pentane in a solution of the complex in a minimum of dichloromethane at 4°C for a week.

## 17.4. Asymmetric Alkylation of Several Aldehydes Catalyzed by Copper(II) *bis*[(1*R*)-trifluoro acetylcamphor] monohydrate 280 and (*R*)-BINAP 75

### 17.4.1. General Procedure Q

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** (0.01 eq.) and (*R*)-BINAP **75** (0.01 eq.) are introduced in an oven-dried Radley's carroussel test tube equipped with a magnetic stirring bar which is then subjected to three vacuum-argon cycles. Dry toluene is added. The obtained solution immediately turns green-yellow.

The aldehyde (1 eq.) is added to the catalyst's precursors. The mixture is stirred for 30 minutes at room temperature before being cooled to -30°C in an isopropanol bath cooled by a cryostat. Neat diethylzinc (1.5 eq.) is added in one fraction by pouring along the flask's wall.

The reaction is monitored by GC to estimate the reaction time. Samples (± 0.1ml) are taken with the help of a syringe and are directly quenched by *ca*. 1ml of methanol (analytical grade) in a capped glass-vial. The salts in the sample are left to settle prior to the injection on the gas chromatography column.

At the end of the reaction, 4ml of methanol are added to the cool reaction media and the white suspension is stirred vigorously.

## 17.4.2. Addition to benzaldehyde (2mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: 2 hours.

**Quantities Engaged** :

Benzaldehyde: 0.63 ml, 0.659 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 70 mg, 12.4 x $10^{-2}$ mmol, 0.02 eq.

(*R*)-BINAP **75**: 78 m g, 12.4 x $10^{-2}$ mmol, 0.02 eq.

Diethylzinc: 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

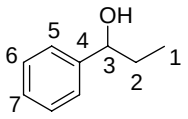
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with 3 portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.705 g of a colorless oil is obtained.

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Yield** : 0.705 g (83%)

**Physical Property** : colorless oil

**Chiral GC** (105/5/4/130/9) : $t_R$= 17.07 min (*R*)

$t_R$= 17.37 min (*S*, major)

**Enantiomeric Excess** : 94.3% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.3. Addition to benzaldehyde (1mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: 4 hours.

**Quantities Engaged** :

Benzaldehyde: 0.63 ml, 0.66 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 35 mg, 6.2 x $10^{-2}$ mmol, 0.01 eq.

(*R*)-BINAP **75** : 39 mg, 6.2 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc : 0.975 ml, 1.15 g, 9.3 mmol, 1.5 eq.

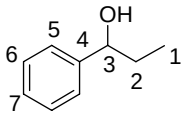
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.742 g of a colorless oil is obtained.

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Yield** : 0.742 g (88%)

**Physical Property** : colorless oil

**Chiral GC** (105/5/4/130/9) : $t_R$= 17.82 min (*R*)

$t_R$= 18.02 min (*S*, major)

**Enantiomeric Excess** : 94.8% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.4. Addition to benzaldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: 12 hours.

**Quantities Engaged** :

Benzaldehyde: 0.63 ml, 0.659 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75** : 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc: 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

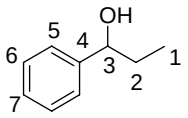
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash chromatography on silica gel (cyclohexane/AcOEt, 85/15, $KMnO_4$). 0.769 g of a colorless oil is obtained.

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Yield** : 0.769 g (88%)

**Physical Property** : colorless oil

**Chiral GC** (105/5/4/130/9) : $t_R$= 17.77 min (*R*)

$t_R$= 17.94 min (*S*, major)

**Enantiomeric Excess** : 93.4% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.5. Addition to benzaldehyde (0.1mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: 48 hours.

**Quantities Engaged** :

Benzaldehyde: 0.63 ml, 0.659 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 3.5 mg, 0.62 x $10^{-2}$ mmol, 0.001 eq.

(*R*)-BINAP **75**: 3.9 mg, 0.62 x $10^{-2}$ mmol, 0.001 eq.

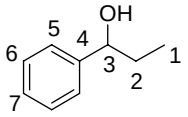
Diethylzinc: 1.3 ml, 1.534 g, 12.4 mmol, 2.0 eq.

Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, 0.836 g of a colorless oil is obtained. No further purification is needed.

**Name** : 1-phenyl-1-propanol




**CAS-RN** : 613-87-6 (*S* enantiomer)

**M.F.** : $C_9H_{12}O$ **M.W.** : 136.19

**Yield** : 0.836 g (99%)

**Physical Property** : colorless oil

**Chiral GC** (105/5/4/130/9) : $t_R$= 17.78 min (*R*)

$t_R$= 18.05 min (*S*, major)

**Enantiomeric Excess** : 90.0% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.6. Addition to *p*-chlorobenzaldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: 19 hours (almost over after 2 hours then real sluggish)

**Quantities Engaged** :

*p*-Chlorobenzaldehyde: 0.873 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75** : 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc : 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

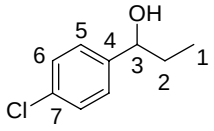
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is distilled by bulb-to-bulb distillation by heating under controlled vacuum. 0.925 g of a colorless oil is obtained.

**Name** : 1-(4'-chorophenyl)-1-propanol




**CAS-RN** : 73890-73-0 (*S* enantiomer)

**M.F.** : $C_9H_{11}ClO$ **M.W.** : 170.63

**Yield** : 0.925 g (87%)

**Physical Property** : colorless oil

**Chiral GC** (105/5/4/190/15) : $t_R$= 23.35 min (*R*, minor)
$t_R$= 23.67 min (*S*, major)

**Enantiomeric Excess** : 94.8% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.7. Addition to *p*-anisaldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: stopped after 24 hours

**Quantities Engaged** :

*p*-Anisaldehyde: 0.754 ml, 0.846 g, 6.2 mmol, 1 eq.

Copper(II)*bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75**: 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc: 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

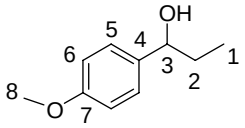
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash chromatography on silica gel ($CH_2Cl_2$/ $Et_3N$, 97/3, $R_f$=0.15). 0.704 g of a colorless oil is obtained.

**Name** : 1-(4'-methoxyphenyl)-1-propanol




**CAS-RN** : 5349-60-0 (*S* enantiomer)

**M.F.** : $C_{10}H_{14}O_2$ **M.W.** : 166,22

**Yield** : 0.704 g (68%)

**Physical Property** : colorless oil

**Chiral GC** (105/5/4/190/15) : $t_R$= 22.20 min (*R*, minor)

$t_R$= 22.39 min (*S*, major)

**Enantiomeric Excess** : 95.4% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.8. Addition to *o*-anisaldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: stopped after 24 hours

**Quantities Engaged** :

*o*-Anisaldehyde: 0.754 ml, 0.846 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75**: 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc: 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

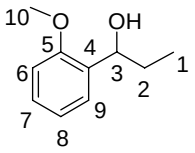
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash chromatography on silica gel ($CH_2Cl_2$/ $Et_3N$, 97/3, $R_f$=0.31). 0.834 g of a colorless oil is obtained.

**Name** : 1-(2-Methoxy-phenyl)-propan-1-ol




**CAS-RN** : 114389-71-8 (*S* enantiomer)

**M.F.** : $C_{10}H_{14}O_2$ **M.W.** : 166,22

**Yield** : 0.834 g (81%)

**Physical Property** : colorless oil

**Chiral GC** (105/5/4/190/15) : $t_R$= 21.55 min (*R*, major)

$t_R$= 22.46 min (*S*, minor)

**Enantiomeric Excess** : 93.1% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.9. Addition to 1-naphtaldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: stopped after 24 hours

**Quantities Engaged** :

1-Naphtaldehyde: 0.843 ml, 0.970 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75**: 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc: 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

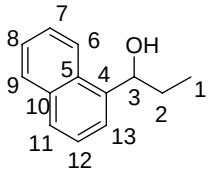
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash chromatography on silica gel (cyclohexane/AcOEt, gradient 90/10 to 80/20, $R_f$=0.35 at 80/20). 0.872 g of a colorless oil is obtained.

**Name** : 1-Naphtalen-1-yl-propan-1-ol




**CAS-RN** : 135818-31-4 (*S* enantiomer)

**M.F.** : $C_{13}H_{14}O$ **M.W.** : 186,25

**Yield** : 0.872 g (75.4%)

**Physical Property** : colorless oil

**GC** (110/5/10/290) : $t_R$= 15.10 min for 1-naphtaldehyde

$t_R$= 17.59 min for 1-Naphtalen-1-yl-propan-1-ol

**HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 90/10, 1ml/min., 25°C, 220 nm)

$t_R$= 8.07 min (major, *S*)

$t_R$= 14.11 min (minor, *R*)

**Enantiomeric Excess** : 87.2% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.10. Addition to 2-furfuraldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: stopped after 24 hours

**Quantities Engaged** :

2-Furfuraldehyde: 0.686 ml, 0.796 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75**: 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc: 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

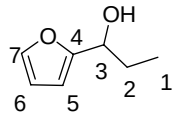
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash-chromatography on silica gel. (cyclohexane/AcOEt, 75/25 $R_f$= 0.25, $KMnO_4$). 0.507 g of a colorless oil is obtained.

**Name** : 1-furan-2-yl-propan-1-ol




**CAS-RN** : 127418-31-9 (*S* enantiomer)

**M.F.** : $C_7H_{10}O_2$ **M.W.** : 126,15

**Yield** : 0.507 g (49%)

**Physical Property** : colorless oil

**HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 98/2, 1.2ml/min., 25°C, 220 nm)

$t_R$= 10.18 min (*R*,minor)

$t_R$= 11.13 min (*S*, major)

**Enantiomeric Excess** : 73.0% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.11. Addition to 4-pyridinecarboxaldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: stopped after 24 hours

**Quantities Engaged** :

4-Pyridinecarboxaldehyde: 0.593 ml, 0.665 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75**: 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc: 1.30 ml, 1.534 g, 12.4 mmol, 2 eq.

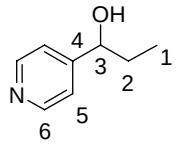
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : A saturated aqueous solution of $NH_4Cl$ is added. The mixture is extracted with three portions of $CH_2Cl_2$. The aqueous phase is basified with $Na_2CO_3$ and extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash-chromatography on silica gel. (AcOEt/$CH_2Cl_2$/$Et_3N$, 65/30/5 $R_f$= 0.26, $KMnO_4$). 0.370 g of a colorless oil is obtained.

**Name** : 1-Pyridin-4-yl-propan-1-ol




**CAS-RN** : 157371-07-8 (*S* enantiomer)

**M.F.** : $C_8H_{11}NO$ **M.W.** : 137,18

**Yield** : 0.370 g (43%)

**Physical Property** : yellow-brown oil

**HPLC** : (Chiracel AS, *n*-hexane/ isopropanol, 90/10, 1ml/min., 25°C, 260 nm)

$t_R$= 12.30min (*R*, minor )

$t_R$= 16.42min. (*S*, major)

**Enantiomeric Excess** : 77% ee (*S*)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.12. Addition to 3-phenylpropionaldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: stopped after 48 hours

**Quantities Engaged** :

3-Phenylpropionaldehyde: 0.821 ml, 0.833 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75**: 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc: 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

Toluene : 15 ml

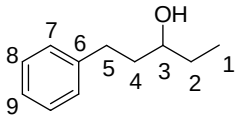
**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed

successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash-chromatography on silica gel. (cyclohexane/AcOEt, 80/20 $R_f$= 0.23). 0.701 g of a colorless oil is obtained.

**Name** : 1-Phenyl-pentan-3-ol




**CAS-RN** : 1992-50-3 (racemic)

**M.F.** : $C_{11}H_{16}O$ **M.W.** : 164,24

**Yield** : 0.701 g (68.7%)

**Physical Property** : colorless oil

**GC** (110/5/10/290) : $t_R$= 8.77 min for 3-phenylpropionaldehyde

$t_R$= 12.51 min for 1-phenyl-pentan-3-ol

**HPLC** : (Chiracel OD-H, *n*-hexane/isopropanol, 95/5, 1ml/min., 25°C, 220 nm)

$t_R$= 8.59 min (minor)

$t_R$= 11.92 min (major)

**Enantiomeric Excess** : 23.7% ee

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.4.13. Addition to cyclohexylcarboxaldehyde (0.5mol% loading)

**Operating Procedure** : see General Procedure O

**Reaction time**: stopped after 48 hours

**Quantities Engaged** :

Cyclohexylcarboxaldehyde: 0.752 ml, 0.697 g, 6.2 mmol, 1 eq.

Copper(II) *bis*[(1*R*)-trifluoroacetylcamphor] monohydrate **280** : 17.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

(*R*)-BINAP **75**: 19.5 mg, 3.1 x $10^{-2}$ mmol, 0.005 eq.

Diethylzinc: 0.975 ml, 1.151 g, 9.3 mmol, 1.5 eq.

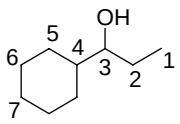
Toluene : 15 ml

**Substrate Concentration** : *ca.* 0.39M

**Purification** : An aqueous solution of HCl (1 M) is added. The mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NaHCO_3$ and water then dried on $MgSO_4$. After concentration by rotatory evaporation, a yellow oil is obtained.

The oil is purified by flash-chromatography on silica gel. (cyclohexane/AcOEt, gradient 90/10 to 75/25 $R_f$= 0.38 at 75/25). 0.389 g of a colorless oil is obtained.

**Name** : 1-Cyclohexyl-propan-1-ol




**CAS-RN** : 17264-02-7 (racemic)

**M.F.** : $C_9H_{18}O$ **M.W.** : 142,24

**Yield** : 0.389 g (44%)

**Physical Property** : colorless oil

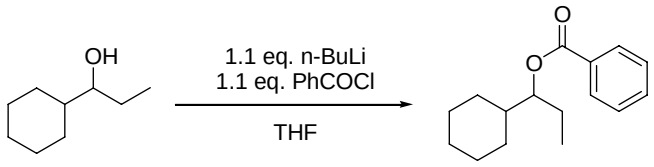
**GC** (110/5/10/290) : $t_R$= 4.56 min for cyclohexylcarboxaldehyde

$t_R$= 8.17 min for 1-cyclohexyl-propan-1-ol

**Enantiomeric Excess** : 11.9% ee (after benzoylation, see page 277)

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

***Benzoylation of 1-cyclohexyl-propan-1-ol***

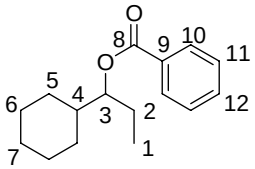



**Operating Procedure** : In a 10 ml round-bottom flask, 1-cyclohexyl-propan-1-ol (95m g, 0.69 mmol, 1 eq.) is solubilizied in 2 ml of THF and cooled to 0°C. 0.5 ml of *n*-BuLi (0.74 mmol, 1.1 eq., 2.5M in hexane) is added to the substrate solution at 0°C then stirred at room temperature for 30 minutes. Benzoyl chloride (8.5 x $10^{-2}$ ml, 0.103 g, 0.74 mmol, 1.1 eq.) in solution in 1 ml of THF is added slowly. The mixture is heated for one hour at reflux.

After cooling, 2 ml of water are added carefully (!!!). After one night, the mixture is extracted with three portions of $CH_2Cl_2$. The combined organic extracts are washed successively with a saturated aqueous solution of $NH_4Cl$ and water prior to being dried on $MgSO_4$. After concentration by rotatory evaporation, a brown oil is obtained.

**Purification** : The oil is purified by preparative TLC on silica-gel with a gradient of eluents (*n*-hexane/diethylether 99/1 ($R_f$=0.18). 10 mg of a colorless oil are recovered.

**Name** : Benzoic acid 1-cyclohexyl-propyl ester




**CAS-RN** : 166031-54-5 (*R* enantiomer)

**M.F.** : $C_{16}H_{22}O_2$ **M.W.** : 246,34

**Yield** : 0.010 g (6%)

**Physical Property** : colorless oil

**HPLC** : (Chiracel AS, *n*-hexane, 0.5ml/min., 20°C, 254 nm)

$t_R$= 11.19 min (major)

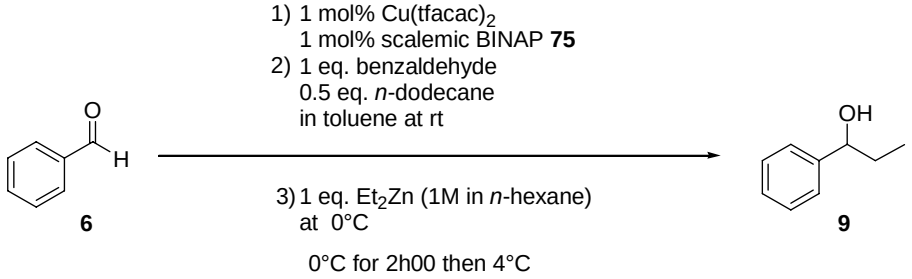
$t_R$= 12.28 min (minor)

**Enantiomeric Excess** : 11.9% ee

**$^1$H NMR** ($CDCl_3$, 300 MHz) : identical to previous sample

## 17.5. Nonlinear effects

The influence of the optical purity of BINAP **75** on the enantioselectivity of the addition of diethylzinc to benzaldehyde catalyzed by copper(II) *bis*(trifluoro acetylacetonate) was tested under reaction conditions of General Procedure P. The catalyst loading was of 1mol% in copper(II) *bis*(trifluoroacetylacetonate) and BINAP. Mixture of enantiopure *(R)*-BINAP and racemic BINAP afforded BINAP ligand samples of various optical purities.




**Operating Procedure :** see General Procedure P

**Reaction time:** reaction followed over 24 hours

**Quantities Engaged** :

Benzaldehyde : 0.204 ml, 0.213 g, 2.0 mmol, 1.0 eq.

Copper(II)*bis*(trifluoroacetylacetonate) : 7.6 mg, 2.0 x $10^{-2}$ mmol, 0.01 eq.

Scalemic BINAP **75** : 12.4 mg, 2.0 x $10^{-2}$ mmol, 0.01 eq.

Diethylzinc (1M in *n*-hexane) : 2.0 ml, 2.0 mmol, 1.0 eq.

*n*-Dodecane : 0.228 ml, 0.171 g, 1.0 mmol, 0.5 eq.

Toluene : 4.0 ml

**BINAP Mixtures :**

| ee% BINAP | 25% ee | 50% ee | 75% ee | 100% ee |
|---|---|---|---|---|
| **(*rac*)-BINAP (mg)** | 9.3 | 6.2 | 3.1 | 0.0 |
| **(*R*)-BINAP (mg)** | 3.1 | 6.2 | 9.3 | 12.4 |

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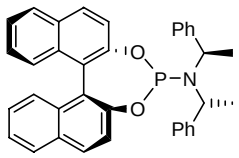
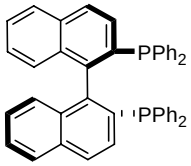
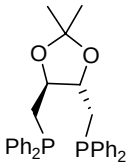
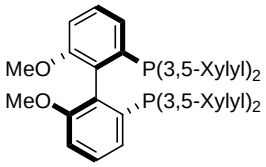
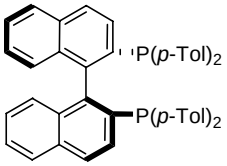
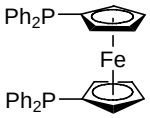
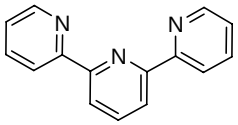
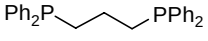
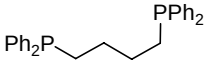
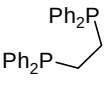
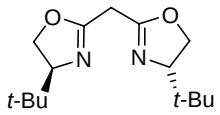
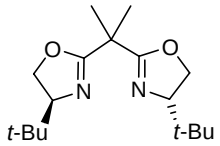
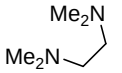
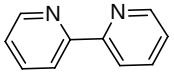
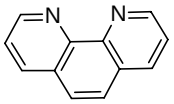
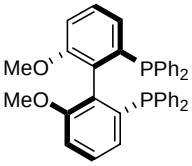
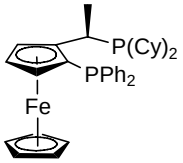
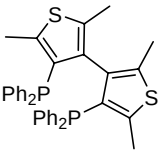
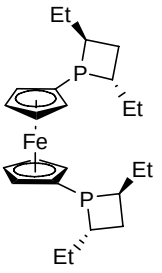
# Acronyms

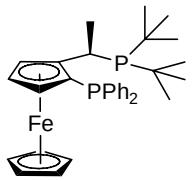
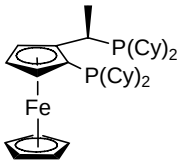
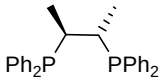
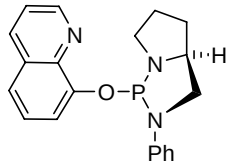
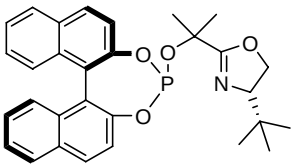
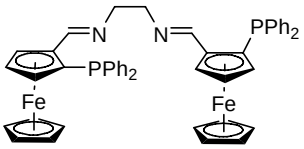
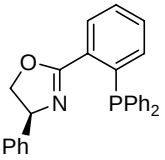
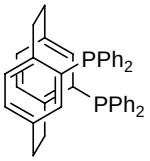
| Acronym | Number | Name | Formula |
|---|---|---|---|
| acac | | acetylacetonate | |
| AcOEt | | Ethyl acetate | |
| DME | | dimethoxyethane | $MeOCH_2CH_2OMe$ |
| DMF | | *N,N*-dimethylformamide | $Me_2NC(O)H$ |
| EWG | | electron-withdrawing group | |
| hfacac | | hexafluoroacetylacetonate | |
| HOMO | | highest occupied molecular orbital | |
| LUMO | | lowest unoccupied molecular orbital | |
| OMes | | mesylate | $MeSO_3^-$ |
| MS | | molecular sieves | |
| NLE | | nonlinear effect | |
| OTf | | triflate | $CF_3SO_3^-$ |
| rds | | rate determining step | |
| TBAF | 120 | tetrabutylammonium fluoride | $n$-$Bu_4N^+F^-$ |

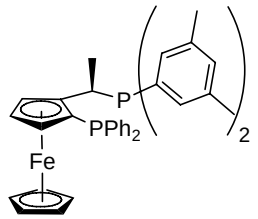
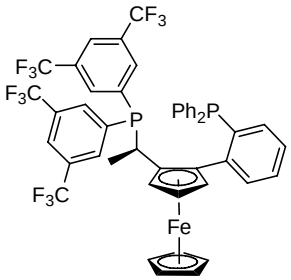
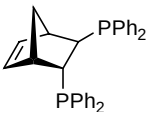
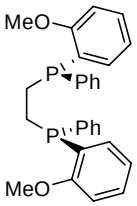
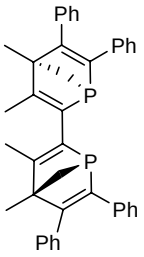
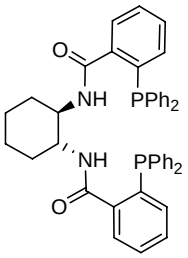
| | | | |
|---|---|---|---|
| TBAT | 130 | tetrabutylammonium triphenyldifluorosilicate | *n*-$Bu_4N^+Ph_3SiF_2^-$ |
| tfacac | | trifluoroacetylacetonate | |
| THF | | tetrahydrofuran | |
| TLC | | Thin Layer Chromatography | |
| EPR | | Electron Paramagnetic Resonance | |

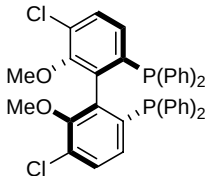
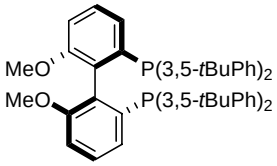
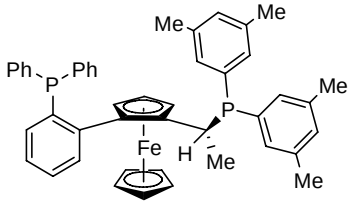
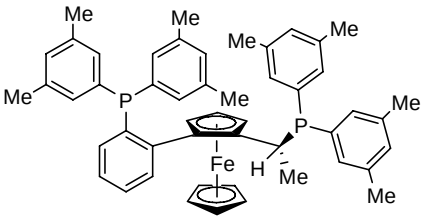
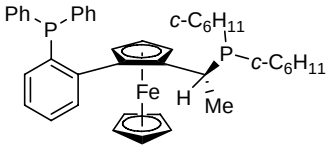
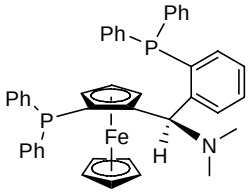
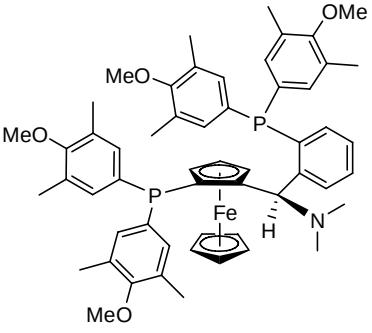
# Tested Ligands

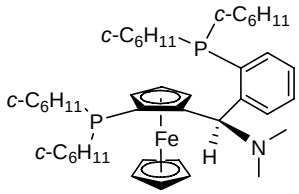
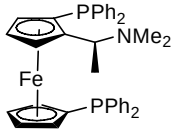
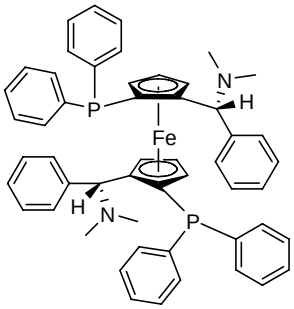
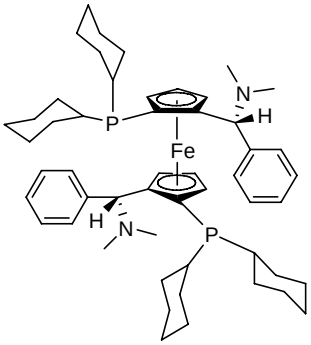
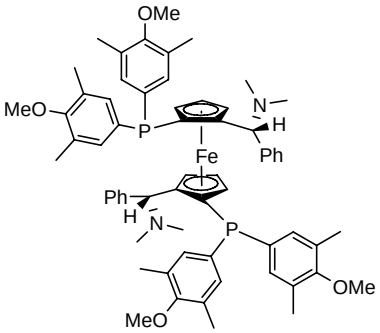
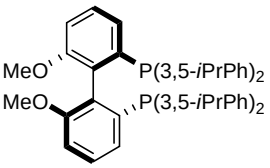
| Ligand Number | Acronym | Formula | Source |
|---|---|---|---|
| **60** | (*S*)-(*R,R*)-PAMID |  | Synthesized |
| **75** | (*R*)-BINAP |  | Strem |
| **79** | (4*S*,5*S*)-DIOP |  | Strem |
| **162** | (*R*)-3,5-xyl-MeO-BIPHEP |  | |
| **166** | (*S*)-*p*-TolylBINAP |  | Strem |
| **171** | dppf |  | |
| **179** | |  | |
| **197** | dppp |  | |
| **198** | dppb |  | |
| **199** | dppe |  | |

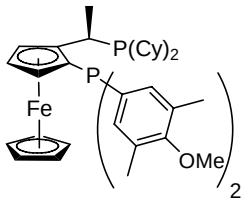
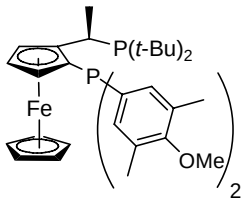
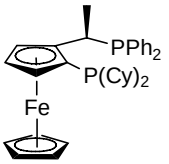
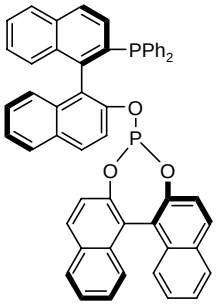
| Ligand Number | Acronym | Formula | Source |
|---|---|---|---|
| **200** | |  | |
| **201** | |  | Strem |
| **202** | TMEDA |  | |
| **203** | bipy |  | |
| **204** | DABCO |  | |
| **205** | |  | |
| **206** | (*R*)-MeOBIPHEP |  | Strem |
| **207** | (*R*)-(*S*)-PPF-P(cy)$_2$ |  | Strem |
| **208** | (+)-TetraMeBITIOP |  | |
| **209** | (*S,S*)-Et-FerroTANE |  | Strem |

| Ligand Number | Acronym | Formula | Source |
|---|---|---|---|
| **210** | (*R*)-(*S*)-PPF-P(*t*-Bu)$_2$ |  | Generous gift from Solvias AG |
| **211** | (*R*)-(*S*)-cy$_2$PF-P(Cy)$_2$ |  | Generous gift from Solvias AG |
| **212** | (*S,S*)-ChiraPhos |  | |
| **213** | (*S*)-QUIPHOS |  | |
| **214** | |  | Generous gift from Prof. A. Pfaltz |
| **215** | |  | |
| **216** | |  | Strem |
| **217** | (*R*)-[2.2]-PhanePHOS |  | Generous gift from |

| Ligand Number | Acronym | Formula | Source |
|---|---|---|---|
| **218** | (*R*)-(*S*)-PPF-P(xyl)$_2$ |  | Generous gift from Solvias AG |
| **219** | (*R*)-(*R*)**-**Walphos Family |  | Generous gift from Solvias AG |
| **222** | (*R,R*)-NORPHOS |  | |
| **223** | (*S,S*)-DIPAMP |  | |
| **224** | (*S,S,S,S*)-BIPNOR |  | |
| **225** | (1*R*,2*R*)-(+)-1,2-Diaminocyclohexane-*N,N'*-*bis*(2'diphenylphosphinobenzoyl)<br><br>or Trost's ligand |  | Strem |

| Ligand Number | Acronym | Formula | Source |
|---|---|---|---|
| **226** | |  | Strem |
| **227** | |  | Generous gift from Roche |
| **228** | Walphos family |  | Generous gift from Solvias |
| **229** | Walphos family |  | Generous gift from Solvias |
| **230** | Walphos family |  | Generous gift from Solvias |
| **231** | Taniaphos family |  | Generous gift from Solvias |
| **232** | Taniaphos family |  | Generous gift from Solvias |

| Ligand Number | Acronym | Formula | Source |
|---|---|---|---|
| **233** | Taniaphos family |  | Generous gift from Solvias |
| **234** | (*S*)-(*R*)-bppfa<br><br>Hayashi's ligand |  | Aldrich |
| **235** | (*R*)-(*S*)-$NMe_2$-$PPh_2$-Mandyphos |  | Solvias |
| **236** | (*R*)-(*S*)-$NMe_2$-$Pcy_2$-Mandyphos |  | Solvias |
| **237** | (*R*)-(*S*)-$NMe_2$-P3,5Me-4-MeOPh)$_2$-Mandyphos |  | Solvias |
| **238** | |  | Generous gift from Roche |

| Ligand Number | Acronym | Formula | Source |
|---|---|---|---|
| **239** | (*R*)-(*S*)-(4-MeO-3,5-MePh)$_2$PF-P(Cy)$_2$ |  | Generous gift from Solvias |
| **240** | (*R*)-(*S*)-(4-MeO-3,5-MePh)$_2$PF-P(*t*-Bu)$_2$ |  | Generous gift from Solvias |
| **241** | (*R*)-(*S*)-cy$_2$PF-PPh$_2$ |  | Strem |
| **242** | (*R*,*S*)-BINAPHOS |  | Generous gift from Prof. K. Nozaki |