



Synthesis of Optically Pure Nitrogenated Ligands and their uses in Asymmetric Catalysis

Bilal El Asaad

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THESIS IN CHEMISTRY

For obtention a PhD degree from

Claude Bernard - Lyon 1 University

and

Lebanese University

Synthesis of Optically Pure Nitrogenated Ligands and their uses in Asymmetric Catalysis

Defended by

Bilal EL ASAAD

07 July 2017

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Bilal EL ASAAD

TO MY FAMILY



*To those innocent laughters that accompanied my path since the
beginnings*

*To those whose destiny didn't give us the chance to stay together
until the end*

To those who left this world but never left my heart

*To those whose memories have always given me the power to
continue what I've started*

To my cousin Mahmoud ELASAAD

To my beloved friend Darine MATAR

To them ...

I dedicate all my achievements

Asking God Success for me and mercy to them

Bilal EL ASAAD

“Never give up on what you really want to do. The person with big dreams is more powerful than one with all the facts.”

A. Einstein

Résumé/Abstract

Synthèses des ligands azotés optiquement purs pour leurs utilisations en catalyse asymétrique

Des nouveaux ligands chiraux diamine N-aromatiques, dérivés de 1,2-diaminocyclohexane et des α et β -cétones cycliques aromatiques, ont été synthétisés par alkylation-déshydrogénation catalysée par le palladium sur charbon (Pd/C). Cette méthode, nous a permis de préparer une série de ligands chiraux de types N,N-di-aryles diamine and N-aryle diamine avec de très bons rendements isolés. Premièrement, les efficacités des ligands synthétisés ont été examinées avec succès dans la réaction de réduction par transfert d'hydrure des cétones aromatiques, catalysée avec des catalyseurs homogènes d'iridium formés *in situ* iridium assistés par l'acide formique et son sel de sodium. Des cétones aromatiques variés ont été réduits, suivant la méthode y développée, en des alcools correspondants avec des complètes et des hautes énantiosélectivités (ee jusqu'au 93%). Ensuite, deux ligands diamine, *N,N'*-dinaphtyle diaminocyclohexane et *N*-naphtyle diaminocyclohexane complexés avec le Cu (II) ont été évalués dans la réaction asymétrique de Henry entre des dérivés de benzaldéhyde et le nitrométhane conduisant aux β -nitro-aryle-alcools avec des bonnes énantiosélectivités (ee jusqu'au 83%) et des bons rendements isolés. On a aussi transformé ces deux ligands, en sels d'imidazolinium précurseurs des carbènes, pour des ultérieures applications en catalyse asymétrique. Le dérivé mono N-aryle diamine a été transformé en ligand mono-thio. Les trois ligands ainsi préparés ont été obtenus avec des très bons rendements isolés.

Mots clés ; *N,N*-Diaryl Diamine Chiraux, Alkylation-deshydrogénation, Transfert d'hydrure asymétrique des cétones aromatiques, Iridium, Réaction de Henry asymétrique, Cuivre (II)

Synthesis of Optically Pure Nitrogenated Ligands and their uses in Asymmetric Catalysis

New chiral *N*-arylated diamine ligands, derived from 1,2-diaminocyclohexane and α and β -cyclic-aromatic ketone, were synthesized by dehydrogenative alkylation catalyzed by palladium on carbon (Pd/C). This method, allowed to prepare a series of chiral *N,N*-diarylated diamine and *N*-aryl diamine ligands with very good isolated yield. First of all, the applicability of the synthesized chiral diamine ligands was successfully examined in asymmetric transfer hydrogenation with homogeneous iridium catalyst associated to formic acid and its sodium salt. Various aromatic ketones were reduced to chiral alcohol with a complete conversion and high enantioselectivity (ee up to 93%). Then, two of the prepared chiral diamine, *N,N'*-dinaphtyl diaminocyclohexane and *N*-naphtyl diaminocyclohexane combined to copper (II), have been evaluated in asymmetric Henry reaction between benzaldehyde derivatives and nitromethane leading to β -nitro-aryl-alcohol with good enantioselectivities (ee up to 83%) and good isolated yields. Furthermore, we transform these two ligands into imidazolinium salts precursor of carbenes, for further application in asymmetric catalysis. The mono *N*-arylated diamine was transformed into mono-thiourea ligand. These three new ligands were obtained with very good isolated yields.

Keywords: Chiral *N,N*-diaryl diamine, Dehydrogenative alkylation, Asymmetric transfer hydrogenation of aromatic ketones, Iridium, Asymmetric Henry Reaction, copper (II)

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List of abbreviations

Pd/C:	Palladium on carbon
<i>ee</i> :	Enantiomeric excess
TON:	Turnover number
TOF:	Turnover frequency
°C:	Degrees Celsius
T:	Temperature
DIOP:	O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP:	Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
DPEN:	Diphenylethylenediamine
TsDPEN:	<i>N</i> -Tosyl-1,2-diphenyl-1,2-diaminoethane
Ts:	<i>para</i> -Toluenesulfonyl/ Transition state
Ti:	Titanium
<i>i</i> PrOH:	Isopropanol
L:	Ligand
Ru:	Ruthenium
<i>n</i> -Bu:	<i>n</i> -Butyl
Me:	Methyl
Et:	Ethyl
Ph:	Phenyl
Ni:	Nickel
Cod:	1,5-Cyclooctadiene
TFA:	Trifluoroacetic acid
OAc:	Acetoxy group
h:	Hours
eq:	Equivalent

GC:	Gas chromatography
HPLC:	High performance liquid chromatography
DCM:	Dichloromethane
Cp*:	Pentamethylcyclopentadien
Ar:	Aryl
δ_C :	^{13}C -NMR chemical shift (ppm)
δ_H :	^1H -NMR chemical shift (ppm)
m/z :	Mass to charge ratio
NMR:	Nuclear magnetic resonance
d:	Doublet
q:	Quartet
s:	Singlet
t:	Triplet m: Multiplet
g:	Gram
ml:	Millilitre
min:	Minutes
rt:	Room temperature
TLC:	Thin layer chromatography
$[\alpha]_D^T$:	Optical rotation
Mp:	Melting point
rpm:	Revolutions per minute
ppm:	Parts per million
R_f :	Retardation factor
M:	Metal
AH:	Asymmetric hydrogenation
ATH:	Asymmetric transfer hydrogenation
Ir:	Iridium
Rh:	Rhodium

TEAF:	Formic acid/triethylamine mixture
d:	Day
<i>o</i> -:	<i>Ortho</i>
<i>m</i> -:	<i>Meta</i>
<i>p</i> -:	<i>Para</i>
Fe:	Iron
Conv.:	Conversion
<i>d.e</i> :	Diastereomeric excess
c:	Concentration
Cu:	Copper
Zn:	Zinc
Co:	Cobalt
Cr:	Chromium
THF:	Tetrahydrofuran
DIPEA:	N,N-Diisopropylethylamine
DMAP:	4-Dimethylaminopyridine
EDG:	Electron donating group
EWG:	Electron withdrawing group
r:	Rate

General Introduction

Molecular enantioselectivity is of crucial importance in both academic and industrial research. It is the basis behind a wide range of applications from pharmaceuticals, agrochemicals, perfumes, cosmetics, and special chemicals^{1,2} to bioactive molecules such as proteins, enzymes, amino acids, carbohydrates, nucleosides and a number of alkaloids and hormones. In 1848, the French chemist and biologist “Louis Pasteur” discovered the first chiral molecule when he tried to separate the two isomers of sodium ammonium tartrate.³ Recently, chirality has become one of the most important topics in different research areas. Particularly, it plays a key role in pharmaceutical developments.

In the pharmaceutical industry 56% of the drugs are chiral, while 88 % of these products are used in a racemic mixture.⁴ Furthermore, the natural bioactive molecules are found in a single enantiomeric form.

Over the last decades, asymmetric catalysis has become the most effective method to obtain enantiomerically enriched molecules in large quantities by using catalytic amount (small percentage) of chiral catalysts. Nevertheless, the development of nitrogen- and phosphorus-based chiral ligands represents a major challenge to researchers due to the detrimental effects of these ligands in this type of catalysis. As a matter of fact, the nature of the ligand has a profound influence on the properties of the catalyst, which could lead to better selectivity and activity depending on reaction to study.

To briefly highlight the importance of asymmetric catalysis at the modern chemistry level, especially in the pharmaceutical industry, the Nobel Prize in Chemistry for 2001 was awarded to William S. Knowles and Ryoji Noyori, for their work on the asymmetric hydrogenation and for Barry Sharpless, for his work on enantioselective epoxidation reaction.

In industrial application, the implication of asymmetric catalysis transformation aims to provide the best conversion toward enantioselective and regioselective target products. The industry basically favors an asymmetric catalysis accomplished with minimum quantity of additives, by-products, and expenses. Additionally, the use of recoverable catalysts, solvent-

¹ P.J. Walsh, H. Li, C. Anaya de Parrodi, *Chem. Rev.* 107 (2007) 2503-2545.

² I. Ojima, *Catalytic Asymmetric Catalysis*, A John Wiley & Sons, New York, (2000).

³ H. D. Flack, *Acta Cryst.* A65 (2009) 371-389.

⁴ K. M. Rentsch, *J. Biochem. Biophys., Methods*, 54 (2002) 1-9.

less reactions and eco-friendly conditions are highly desired factors. Hence, the study of the turnover number (TON) and the turnover frequency (TOF) are crucial especially in an industrial scale process.

$$\text{TON} = \frac{\text{nb of moles of Products}}{\text{nb of moles of Cat.}}$$

$$\text{TOF} = \frac{\text{nb of moles of Products}}{(\text{nb of moles of Cat.}) \text{ time}} = \frac{\text{TON}}{\text{time}}$$

Since more than three decades, our laboratory is involved in the synthesis of new chiral nitrogen-containing ligands derived from 1,2-diamine used in asymmetric catalysis. Currently, our main interest is to develop new ecofriendly N-ligands following easy, versatile, and green methods always with the aim to find new catalysts for asymmetric catalytic reactions, particularly for the hydrogenation reaction of simple ketones and the C-C bond formation reaction *via* Henry reaction.

Synthesis of Enantiopure Ligands Derivatives of *N,N'*-(1*R*,2*R*)-Diamine by Dehydrogenative Alkylation Method

1.1 Bibliographic Introduction

1.1.1 Introduction

1.1.1.1 Necessity of chiral ligands

The development of chiral ligands is extremely important for asymmetric synthesis since chiral ligand is used to induce chirality. Undoubtedly, the presence of a chiral ligand is the core element in any asymmetric catalysis.

Since the discovery of asymmetric catalysis (Kagan and Knowles), a wide library of ligands has been available;⁵ most of them are based on phosphorus, amines or amino alcohol derivatives. These ligands have a significant ability to combine with a variety of metals, to form enantioselective catalysts for the synthesis of optically active compounds such as; chiral amino acids, amines, alcohols, and alkanes in an enantiomerically enriched form.^{6,7}

Asymmetric catalysis has attracted more consideration after the attribution of the Nobel Prize of chemistry in 2001 to three well known discoveries in this domain achieved by Ryoji Noyori, William Knowles and Barry Sharpless.⁸

Early, phosphorus ligands have received a greater attention,⁹ notably the first phosphine ligands such as; DIOP, DIPAMP and BINAP (Figure 1). DIOP was prepared by Kagan¹⁰ in 1972; it demonstrated efficiency in the hydrogenation of α , β -unsaturated carboxylic acids. DIPAMP, developed by Knowles *et al.* at Monsanto in 1975,⁹ was used as an efficient ligand in the industrial process for the synthesis of L-DOPA, the amino acid used for the treatment of Parkinson's diseases¹¹ (first commercial idea introduced by Monsanto).

⁵ W. Sommer, D. Weibel, "Asymmetric Catalysis, Privileged Ligands and Complexes", Chemfiles, Aldrich Chemical Co., Inc. (2015) pp.8.

⁶ Y. Li, H. Zhang, J. Chen, X. Liao, Z. R. Dong, J. X. Gao, *J. Mol. Cat. A: Chem.* 218 (2004) 153–156.

⁷ V. S. Shende, S. K. Shingote, S.H. Deshpande, N. Kuriakose, K. Vanka, A. A. Kelkar, *Royal Society of Chemistry*, 14 (2014), 4635.

⁸ https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001.

⁹ T. Imamoto in *hydrogenation* (Eds.: I. Karamé), InTech, Croatia, (2012) pp.3-24.

¹⁰ H.B Kagan, T. P Dang, *J. Am. Chem. Soc.* 94 (1972) 6429-6433.

¹¹ W. S. Knowles, *Angew. Chem. Int. Ed.* 41 (2002) 1998-2007.

Noyori had developed the BINAP¹² Ligand in 1980, which has known a huge importance in the transition-metal catalyzed asymmetric hydrogenation for a wide range of functionalized olefin and ketones.^{13,14,15} It has been particularly explored for reduction with ruthenium-based catalysts. While the first-generation chiral rhodium catalysts exhibited excellent performance with dehydroamino acids (or esters), the hydrogenation catalysts based on ruthenium/BINAP complexes were also highly enantioselective for other prochiral alkenes. A wide series of rather complex organic molecules has been hydrogenated with high *e.e.*'s. The Ru/BINAP catalysts accomplished enantioselective hydrogenation of acrylic derivatives as *S*-Naproxen, one of the most important analgesic drugs. Its enantiomer, *R*-Naproxen, is a liver toxin. Other di-phosphines such as Duphos, were also reported and used efficiently in asymmetric catalysis.

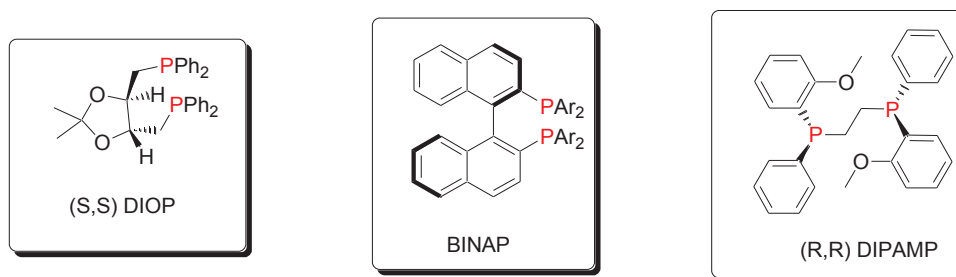


Figure 1: The most famous of phosphine ligands

An important breakthrough in asymmetric catalysis was the Katsuki-Sharpless invention about the asymmetric epoxidation reaction.¹⁶ The reaction uses a chiral Ti(IV) catalyst, t-butylhydroperoxide as the oxidant and it works only for allylic alcohols as the substrate. In the first report, titanium was applied in a stoichiometric amount. The chirality is introduced in the catalyst by reacting titanium tetra-isopropoxide with one molecule of a simple tartarate ester, made from the natural product tartaric acid (Scheme 1).

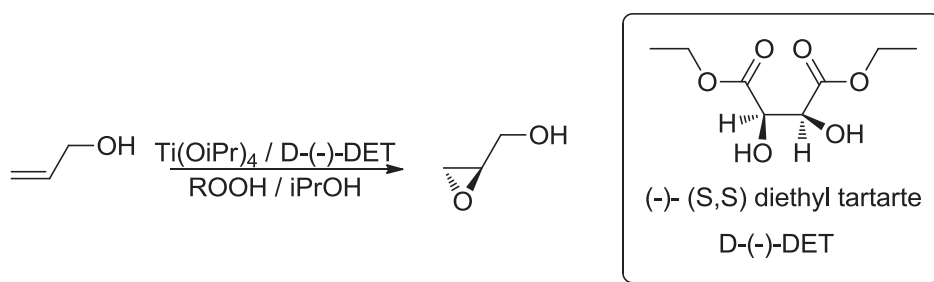
¹² A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi and R. J. Noyori; *Am. Chem. Soc.* 102 (1980) 7932-7934.

¹³ M. Kitamura, T. Ohkuma, S. Inoue, N. Sayot, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takay, R. Noyori, *J. Am. Chem. Soc.* 110 (1988) 629-631.

¹⁴ Q. Jing, X. Zhang, J. Sun, K. Ding, *Adv. Synth. Catal.* 347 (2005) 1193-1197.

¹⁵ R. Noyori and T. Ohkuma, *Angew. Chem. Int. Ed.* 40 (2001) 40-73.

¹⁶ (a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* 102 (1980) 5974-5976. (b) G. J. Hill, K. B. Sharpless, C. M. Exon, R. Regenye *Org. Syn.* 63 (1985) 66. (c) G. J. Hill, K. B. Sharpless, C. M. Exon, R. Regenye *Org. Syn.* 7 (1990) 461.



Scheme 1: Asymmetric epoxidation reaction using a chiral Ti(IV) catalyst by Sharpless

Up till now, extensive efforts have been exerted to design and develop new chiral ligands in order to; 1- develop enantioselective catalysts for almost all organic reactions leading to chiral compounds, 2- improve the catalytic efficiency in terms of activities (turnover number TON, turnover frequency TOF) as well as in terms of enantioselectivities, 3- find cheaper catalysts that are more stable and less sensitive to water and air.

Different research reports demonstrate the interest of nitrogen-containing ligands in asymmetric catalysis, not only because of their efficiency as ligands and as co-ligands with phosphines, but also because of their easier synthesis, their lower costs and toxicities compared to those of phosphine ligands. Moreover, the nitrogen containing ligands are significantly less sensitive to oxidation than the phosphine counterparts.^{17,18}

Many types of nitrogenated ligands have been synthesized and have received greater attention in asymmetric catalysis. They have been largely explored due to their efficiencies, their ecofriendly character, their low cost, and particularly due to their higher stabilities toward oxidation such as bioxazilines, diamines, Salen, thioureas and Carbenes, etc.^{18b}

1.1.1.2 Chiral amine ligands derived from 1,2-diamine

Much progress has been made in the synthesis and development of optically pure 1,2-diamine ligands. The most prevalent initial reagents used in the synthesis of chiral 1,2-diamine are diaminocyclohexane^{19,20} and *N,N'*-diphenylethanediamine (DPEN) developed by Corey *et al.*²¹ in 1988 (Scheme 2).

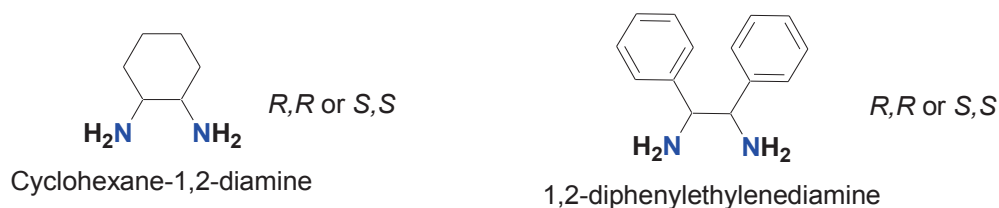
¹⁷ W. Y. Shen, H. Zhang, H. L. Zhang and J. X. Gao, *Tetrahedron: Asymmetry* .18 (2007) 729-733.

¹⁸ (a) J. Canivet, G. Labat, H. S. Evans, and G. S Fink, *Eur. J. Inorg.Chem.* 22 (2005), 4493-4450. (b) V. Caprio & J. M. J. Williams, *Catalysis in Asymmetric Synthesis*, 2nd edition, John Wiley & Sons Ltd, United Kingdom (2009). (c) I. P. Beletskay, A. G. Bessmertnykh, A. D. Averin, F. Denat, R. Guillard, *Eur. J. Org. Chem.* (2005) 261-280. (d) T. W. Funk, J. M. Berlin, R. H. Grubbs, *J. am. Chem. Soc.* 128. (2006) 1840-1846.

¹⁹ H. O. Wieland, O. Schlichting, W. V. Langsdorff, *Hoppe-Seyler's Zeitschrift für physiologische Chemie*, 162 (1926) p. 76.

²⁰ F. Glasbol, P. Steenbol, S. B. Sorenson, *Acta Chem. Scand.* 26 (1980) 3605-3611.

²¹ S. Pikul and E. J. Corey *Org. Synth.* .71 (1993) 22.

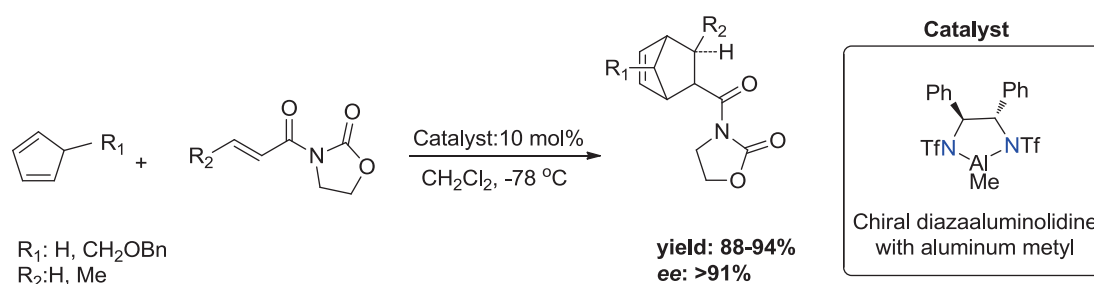


Scheme 2: Chemical structures of the most common initial reagents used in chiral 1,2-diamine ligands

A series of chiral amine ligands derived from 1,2-diamine reagents has been synthesized to find a wide range of applications in realizing metal-based catalysts or organocatalysts to prepare enantiomerically enriched compounds *via* many catalytic reactions such as hydrogenation, epoxidation, Diels-Alder reaction, carbon-carbon bond-formation, Suzuki-Miyaura cross-coupling, and Strecker reaction.

1.1.1.3 Chiral 1,2-diamine Ligands in metallic catalysis

Corey *et al.* have developed the chiral diazaaluminolidine ligands derived from (*R,R*)- or (*S,S*)-1,2-diphenylethylenediamine for the asymmetric Diels-Alder reactions between cyclopentadienes with acrylamide derivatives. The efficient aluminum Lewis acid catalyst had showed excellent yield and enantioselectivities towards the desired cycloaddition products (Scheme 3).²²

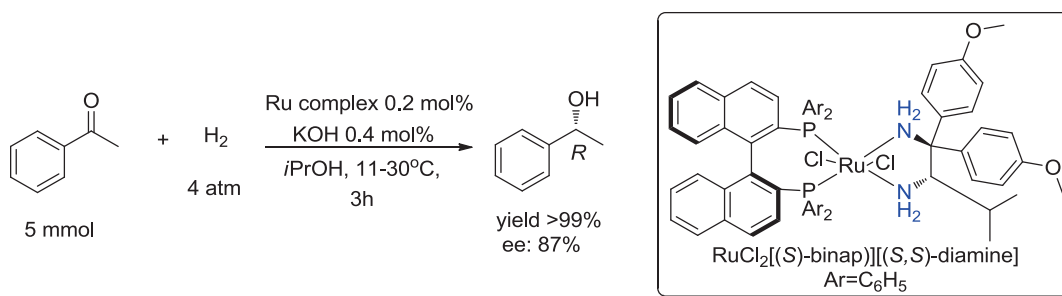


Scheme 3: Asymmetric Diels-Alder reaction catalyzed by chiral 1,2-diamine catalyst

Around 1995, Noyori and his team have developed Diamine BINAP-Ru-chiral 1,2-diamine catalysts prepared from chiral BINAP and chiral diamine. This catalyst shows high activity and enantioselectivity in asymmetric hydrogenation of acetophenone toward alcohol. The addition of a chiral diamine greatly increases the activity (> 99%) and the enantioselectivity (87%) (Scheme 4).²³

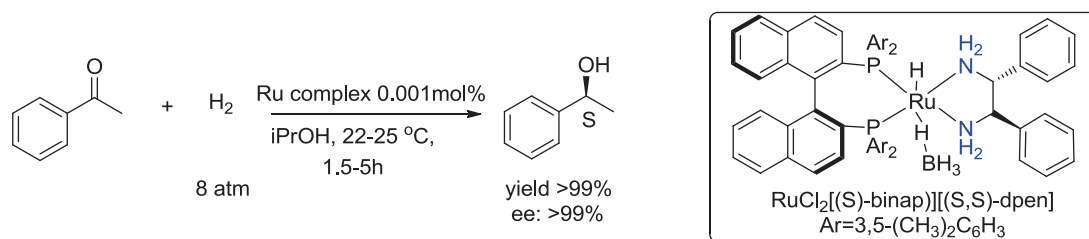
²² E. J. Corey, R. Imwinkelried, S. Pikul and Y.B Xiang; *J. Am. Chem. Soc.* 111 (1989) 5493-5495.

²³ T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* 117 (1995) 2675–2676.



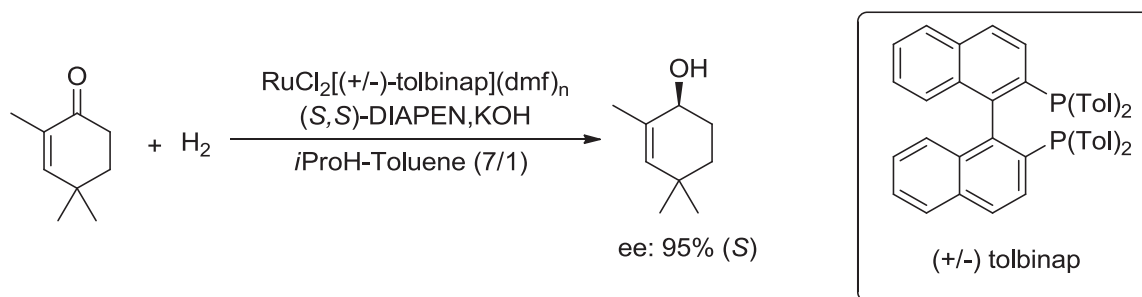
Scheme 4: Asymmetric hydrogenation of acetophenone using BINAP/chiral 1,2-diamine–Ru of Noyori

In 2002, Noyori studied the *trans*-RuH ($\eta^1\text{-BH}_4$) (*S*-xylBINAP) (*1S*, *2S*-DIAPEN) complex in the reduction of acetophenone to (*S*)-1-phenylethanol with 99% enantiomeric excess and conversion (Scheme 5).²⁴



Scheme 5: Asymmetric hydrogenation of acetophenone using BINAP/chiral 1,2-diamine–Ru of Noyori

Furthermore, using the racemic TolBINAP-Ru complex and (*1S*,*2S*) diphenylethylenediamine, the Noyori group carried out the asymmetric hydrogenation of 2,4,4-trimethyl-2-cyclohexanone to the corresponding alcohol with 95% enantiomeric excess. An identical result was obtained with optically pure (*R*)-TolBINAP-Ru (Scheme 6).²⁵ It had been explained that two formed complexes with *R*- and *S*-BINAP and chiral diamine have very different activities, in other words, one is much more active than the other one and thus; reaction is catalyzed by one complex only.



Scheme 6: Asymmetric hydrogenation of 2,4,4-trimethyl-2-cyclohexanone catalyzed by (+/-)-TolBINAP/(*S,S*)-DIAPEN–Ru of Noyori

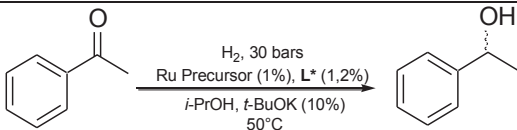
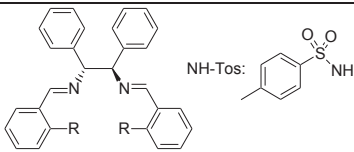
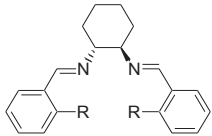
²⁴ T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, *J. Am. Chem. Soc.* 124 (2002) 6508-6509.

²⁵ T. Ohkuma, H. Doucet, H. T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* 120 (1998) 1086-1087.

The complexation of diamine to BINAP-Ru (II) catalysts turns them very efficient in terms of activities and selectivities in the hydrogenation of aromatic ketones (in absence of the diamines BINAP-Ru was practically ineffective for such purpose). The systems BINAP-Ru-chiral NH, N'H-diamine are still the most efficient catalysts for asymmetric hydrogenation of aromatic ketones.⁹ It should be noted that the reduction of the carbonyl group occurs in an outer coordination sphere of 18-electron Ru(H₂)(diphosphine)(diamine), without any direct interaction with the metal center.

In our Laboratory (Lemaire's group), Iyad Karamé *et al.*,²⁶ developed new Schiff bases ligands, Salen's type, investigated in asymmetric hydrogenation of acetophenone following Noyori's conditions (Table 1). These Schiff bases were combined to non-chiral monophosphine (PAr₃) as co-ligands showed a new effective system in terms of enantioselectivity. Although this new system is less efficient than the Noyori's system, it is free of chiral diphosphine.

Table 1: Catalytic system of Karamé *et al.* for asymmetric hydrogenation of acetophenone

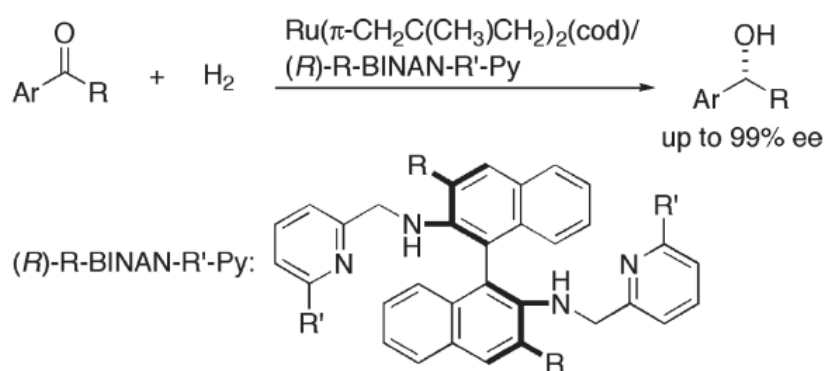
				
L*	R	Ru Precursor	Conv. (%)	ee (%)
	H	Ru(PPh ₃) ₃ Cl ₂	100	0
	NH ₂	Ru(PPh ₃) ₃ Cl ₂	100	54 (S)
	NH-Tos	Ru(PPh ₃) ₃ Cl ₂	100	76 (S)
	H	[Ru(COD)Cl ₂] _x	37	0
	H	Ru(PPh ₃) ₃ Cl ₂	100	56 (S)
	NH ₂	[Ru(COD)Cl ₂] _x	100	37(R)
	NH ₂	Ru(PPh ₃) ₃ Cl ₂	100	55 (S)

The results of this study have showed that in the absence of phosphine, the simple Schiff bases were not enantioselective and less active, whereas, the Schiff base of Salen's type complexed to Ru containing monophosphine led to good enantioselectivities up to 76% *ee*. Authors have demonstrated that without phosphine, their catalysts were formed *in situ* conducting the enantiomeric excess with opposite chirality. That observation has allowed them to propose two different mechanisms: *Diimine-Ru-Monophosphine* catalytic species in the

²⁶ I. Karamé, M. Jahjah, A. Messaoudi, M. L. Tommasino, M. Lemaire, *Tetrahedron: Asymmetry*, 15 (2004) 1569–1581.

presence of phosphine and *Diimine-Ru-Diamine* catalytic species of no chiral monophosphine in the absence of that coligand.

Inspired by the work reported by Karamé and Lemaire, Kitamura's group developed a series of ligands complexed "*in situ*" to Ru conducting enantioselectivities close to those obtained by Noyori's group in the asymmetric hydrogenation of aromatic ketones.²⁷ This group has coupled the characteristics of Noyori's system (binaphtyl skeleton) and Karamé-Lemaire's system (Diimine-Ru-Diamine), whereas the diamine groups, which are the hydrogen transmitter as described by Noyori and confirmed our group, are closer to stereogenic axis (Scheme 7).²⁸



Scheme 7: Kitamura's Ligand for Asymmetric hydrogenation

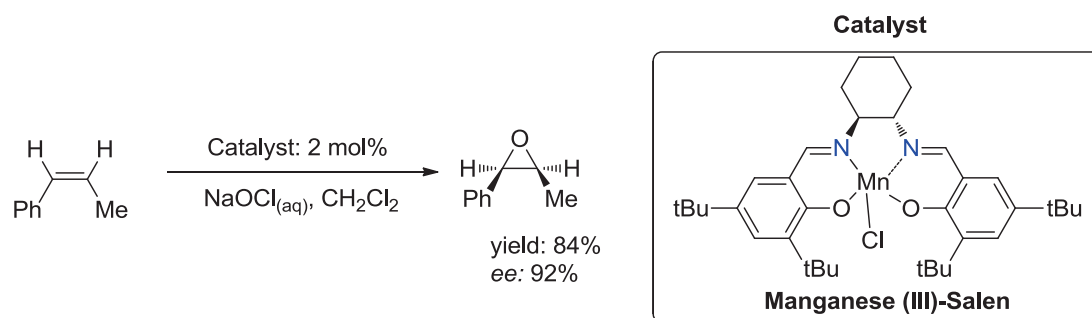
An important breakthrough in asymmetric catalysis was the Jacobsen epoxidation, which have also been studied using chiral Schiff bases ligands (Salen ligands). Jacobsen *et al*, described an effective method for the asymmetric epoxidation of unfunctionalized alkenes using manganese (III)-Salen complex. The desired products were obtained in 84% yield and 92% ee (Scheme 8).^{29,30}

²⁷ H. Huang, T. Okuno, K. Tsuda, M. Yoshimura, M. Kitamura *J. Am. Chem. Soc.*, 128 (2006) 8716-8717.

²⁸ "Syntheses nouvelles bases de schiff chirales et evaluation de leurs complexes pour la catalyse asymetrique" (French Edition) by **Iyad Ezzeddine Karamé**, 120 Pages, Published 2011, by Editions universitaires européennes.

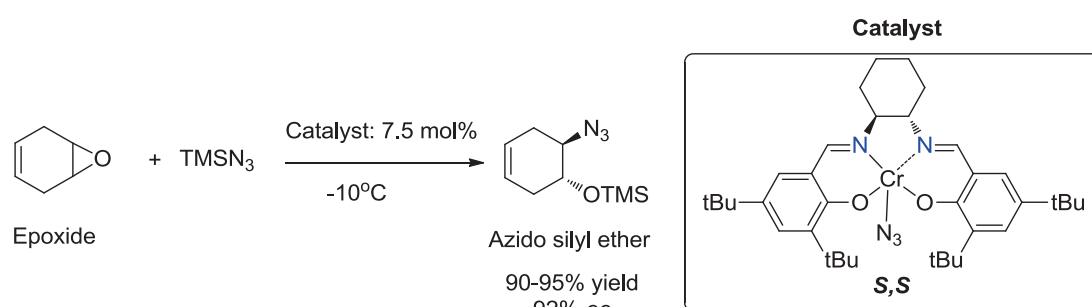
²⁹ E.N Jacobsen, W. Zhang, A.R Muci, J.R. Ecker, L. Deng, *J. Am. Chem. Soc.* 113 (1991) 7063 -7064.

³⁰ Iyad Karame Thesis, p11. (2004).



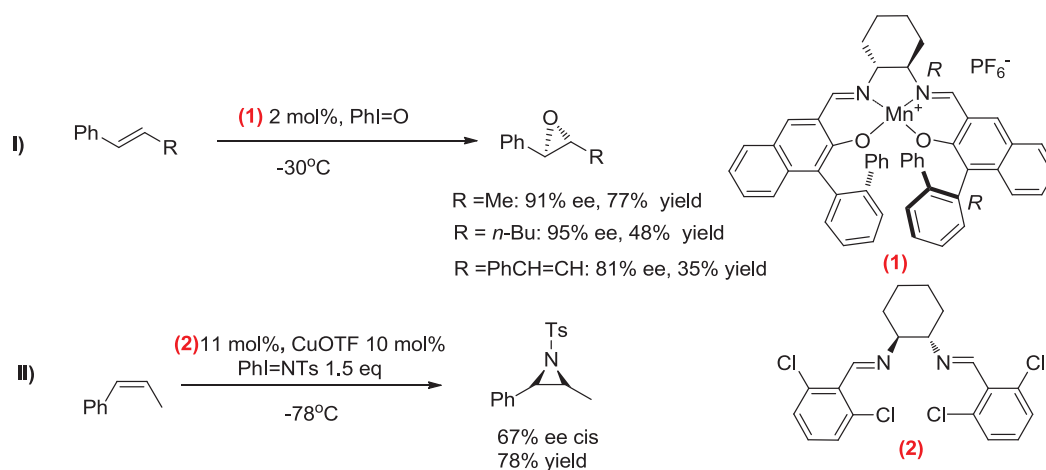
Scheme 8: Jacobsen epoxidation catalyzed by Manganese (III) Salen

Later, Jacobsen's group reported the use of his Schiff base ligand to prepare chromium complexes in asymmetric ring-opening (Scheme 9).³¹



Scheme 9: Asymmetric ring-Opening by Jacobsen's catalyst

Katuski's group and others developed a series of Salen ligands derived from 1,2-diamine (scheme 10), which were explored in asymmetric epoxidation^{32,33} and asymmetric alkene aziridination.³⁴



Scheme 10: I) asymmetric epoxidation II) asymmetric alkene aziridination

³¹ M. H. Wu and E. N. Jacobsen, *Tetrahedron Lett.* 38 (1997) 1693-1696.

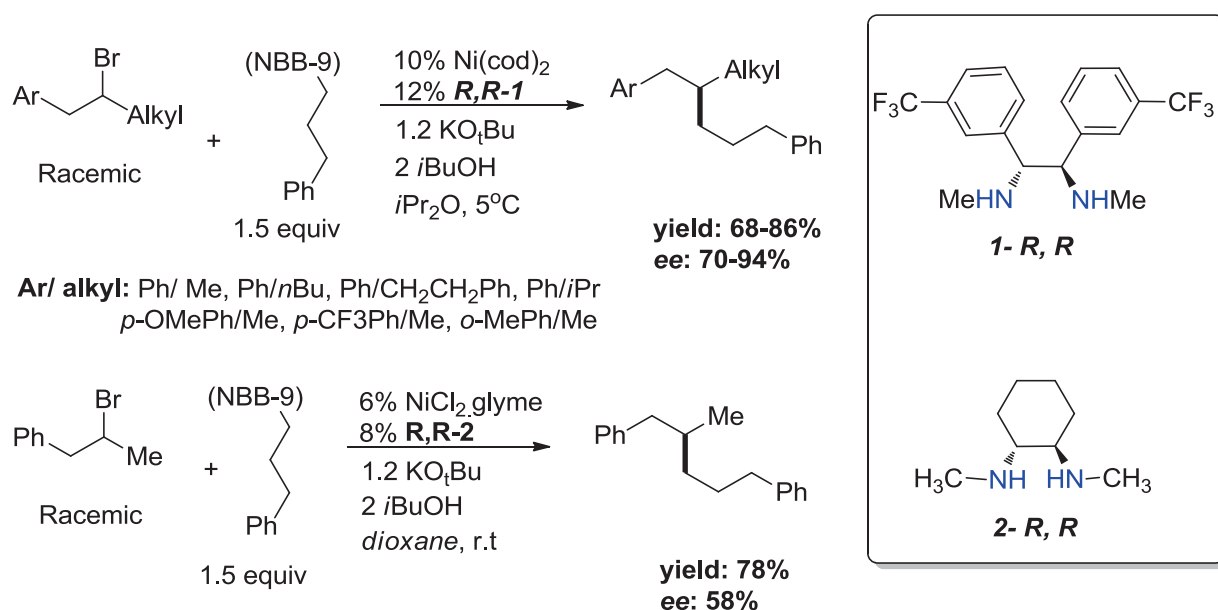
³² H. Nishikori, C. Ohta, T. Katsuki, *Synlett* (2000) 1557-1560.

³³ H. Imanishi and T. Katsuki, *Tetrahedron Lett.* 38 (1997) 251-254.

³⁴ Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.* 115 (1993) 5326-5327.

Numerous chiral 1,2-ligands are developed and used in asymmetric transfer hydrogenation, including ligands from our laboratory. These ligands will be cited in chapter 2.

B. Saito and G. C. Fu studied enantioselective alkyl-alkyl Suzuki cross-couplings of unactivated homobenzylic halides. Usage of (1*R*,2*R*)-*N,N'*-dimethylcyclohexane-1,2-diamine (*R,R*-2) combined to nickel catalyst gave the desired products with 78% isolated yield and 58% ee. Whereas, chiral ligand derived from (*R,R*)- trifluoromethylphenylethane-1,2-diamine combined to nickel showed the best isolated yield and enantiomeric excess for a series of homobenzylic bromide (Scheme 11).³⁵



Scheme 11: Enantioselective alkyl-alkyl Suzuki cross-couplings using 1,2-diamine ligands

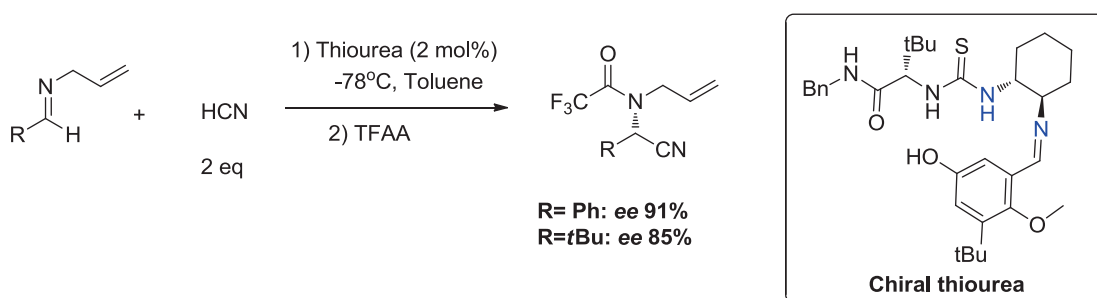
According to the variety of organic asymmetric reactions, metal-catalyzed reactions have become major tools in organic synthesis. However, some drawbacks remain such as the high cost and toxicity of some transition metals employed and specially their residues, mainly in pharmaceutical products. Nevertheless, the metal catalysts will certainly continue to have an important impact in synthetic organic chemistry in the future. Alternatively, organocatalysis has recently attracted larger importance and could be a powerful tool for the preparation of optically enriched organic molecules. Organocatalysis meets green chemistry principles, especially the reduction of toxicity, the biodegradability, and the tenacity in the environment.

³⁵ B.Saito and G.C Fu, *J. Am. Chem. Soc.* 130 (2008) 6694-6695.

1.1.1.4 Chiral 1,2-diamine Ligands as Organocatalysts

Recently, the development of new organocatalysts has become one of the most attractive topics in organic chemistry. It's mostly composed of C, H, N, S and P. Organocatalysts have many advantages as nontoxic organic compounds, stable in air and water, easy to prepare, not expensive, and an alternative to transition metal catalysts.³⁶ A wide variety of novel organocatalysts derived from chiral 1,2-diamines has been synthesized due to their availability in both enantiomeric forms. In particular, chiral thiourea ligands originated from chiral 1,2-diamine also take a great attention as organocatalysis in asymmetric reactions. Some representative reactions are described herein.

In 1998, Jacobsen had described the first 1,2-diamine-containing thiourea as organocatalysis used in asymmetric Strecker reactions. The product obtained with high *ee* up to 91%.³⁷ (Scheme 12)



Scheme 12: Asymmetric Strecker reaction catalyzed by a thiourea ligand

This type of organocatalysts has been used in many asymmetric reactions. Some examples are given in figure 2. Thiourea **A** has been developed by Jacobsen's team and used as an organocatalyst in Pictet-Spengler and acyl-Mannich reactions.³⁸ Whereas, thiourea **B** has been synthesized by Takemoto and tested in a variety of conjugate addition and nitro-Mannich reactions.^{39,40}

³⁶ MacMillan, D. W. C. *Nature*. 455 (2008) 304.

³⁷ M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* 120 (1998) 4901-4902.

³⁸ (a) M. S. Taylor, N. Tokunaga, E. N. Jacobsen. *Angew. Chem. Int. Ed.* 44 (2005) 6700-6704. (b) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* 126 (2004) 10558-10559.

³⁹ (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* 125 (2003) 12672-12677. (b) B. J. Li, L. Jiang, M. Liu, Y. C. Chen, L. S. Ding, Y. Wu, *Synlett*. 4 (2005), 603606.

⁴⁰ (a) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* 6 (2004) 625-627. (b) X. Xu, T. Furukawa, T. Okino, H. Miyabe, Y. Takemoto, *Chem. Eur. J.* 12 (2006) 466-476.

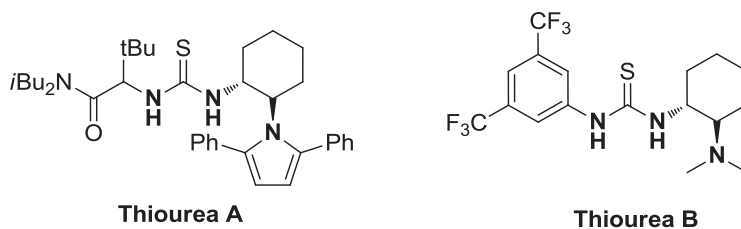
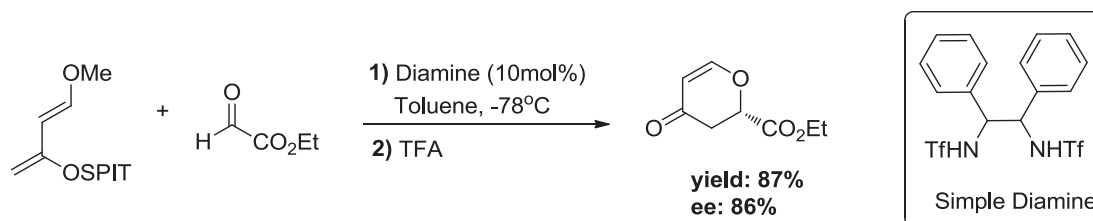


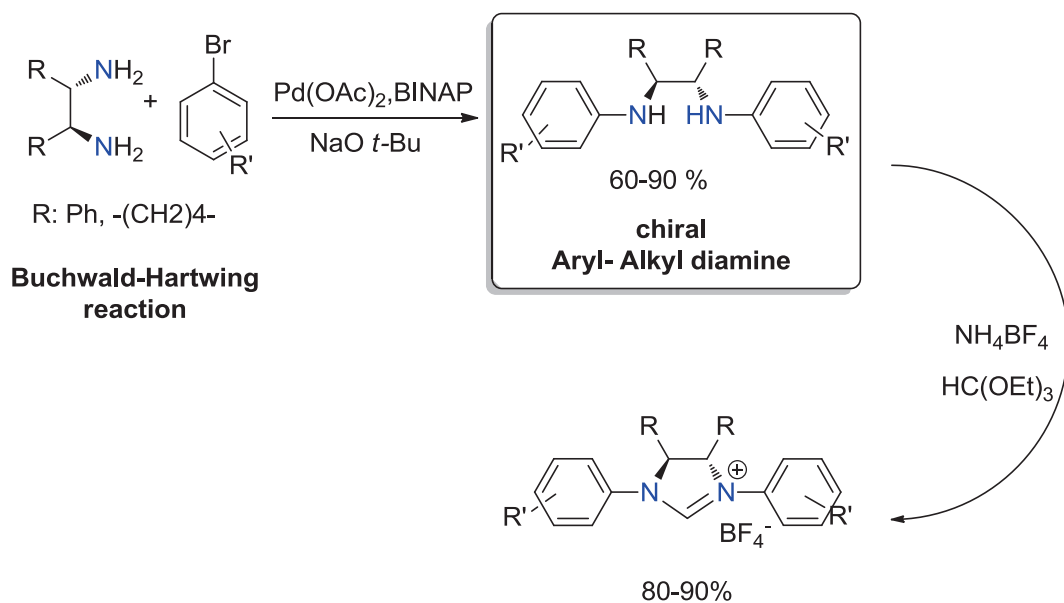
Figure 2: Examples of 1,2-diamine-containing thiourea catalysts

Even a simple diamine has been studied by Mikami's group in hetero-Diels-Alder reactions. It showed high enantioselectivity toward the desired product (Scheme 13).⁴¹



Scheme 13: Hetero-Diels-Alder reactions catalyzed by a simple 1,2-diamine catalyst

Based on the literature, synthesis of chiral *N*-aryl was described by Robert H. Grubbs, as an intermediate of *N*-aryl imidazolinium salts precursor of Grubbs catalyst “2nd generation” for olefin metathesis.^{18d}



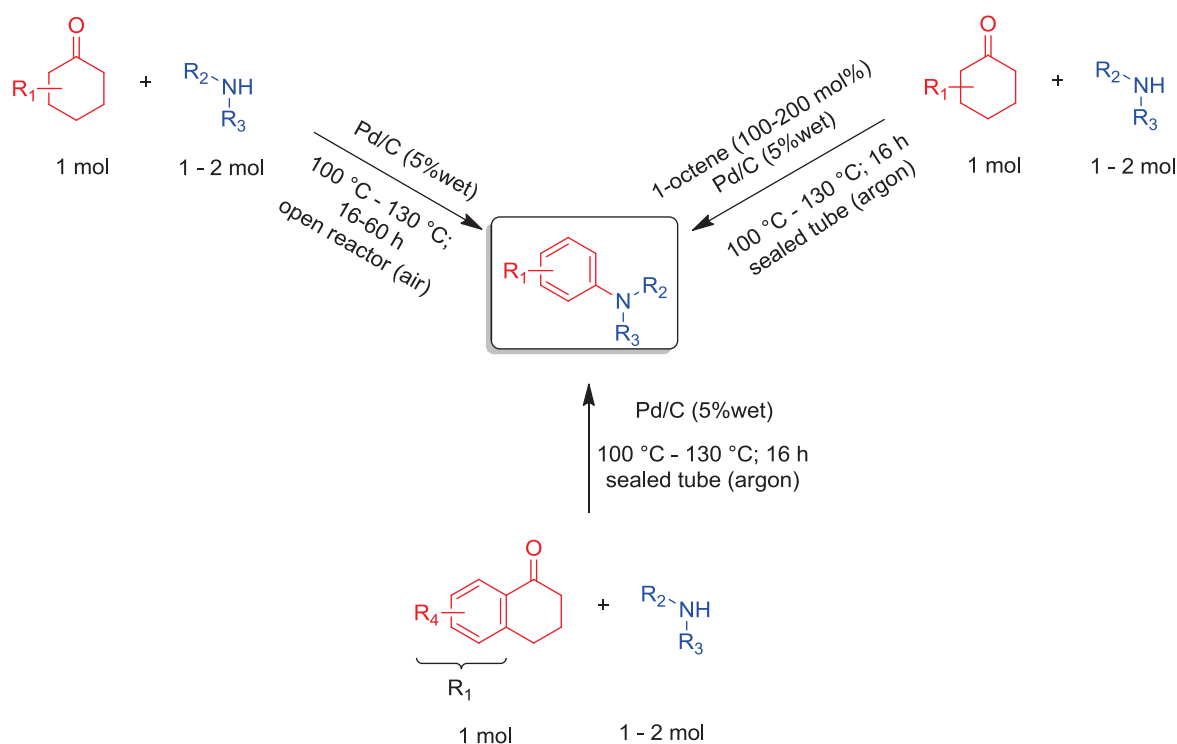
Scheme 14: Synthesis of aryl-alkyl diamine and *N*-aryl imidazolinium using Buchwald–Hartwing N-C coupling

⁴¹ T. Tono, K. Mikami, *Tetrahedron Lett.* 46 (2005) 6355-6358.

Grubbs followed Buchwald–Hartwig *N*-arylation method to synthesize the diamine ligands by Pd(BINAP) catalyzed amination of the appropriate aryl bromides with (1*R*,2*R*)-1,2-diaminocyclohexane or (1*R*,2*R*)-diphenylethylenediamine (Scheme 14).

From this point, we concentrated to develop new, cheap, and easy alternative methods to synthesize a chiral *N,N'*-aryl diamine ligands. Our group (CASYEN), has developed new method of the preparation of aryl-alkyl amine from cyclohexyl ketones and an amine via an dehydrogenative arylation. This method consists on a succession of three reactional steps: 1) imine formation, 2) enamine formation and 3) dehydrogenation.

Solvent free reactions are performed by the catalysis with the Pd/C (palladium on charcoal).⁴² Different conditions have been established for this reaction: 1- in an open reactor under air without additives, 2- in a closed reactor under argon, 3- in the presence of alkene as hydrogen trap. (Scheme 15)

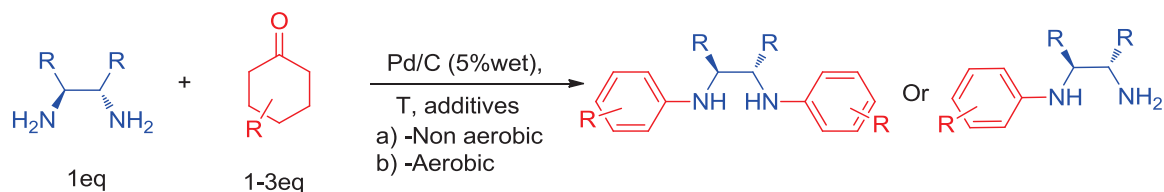


Scheme 15: Lemaire's group strategy for the preparation of *N*-aryl amines; dehydrogenative -alkylation

The extension of dehydrogenative alkylation to synthesize arylamines from non-aromatic substrates catalyzed by Pd/C as a heterogeneous catalyst was successful for the

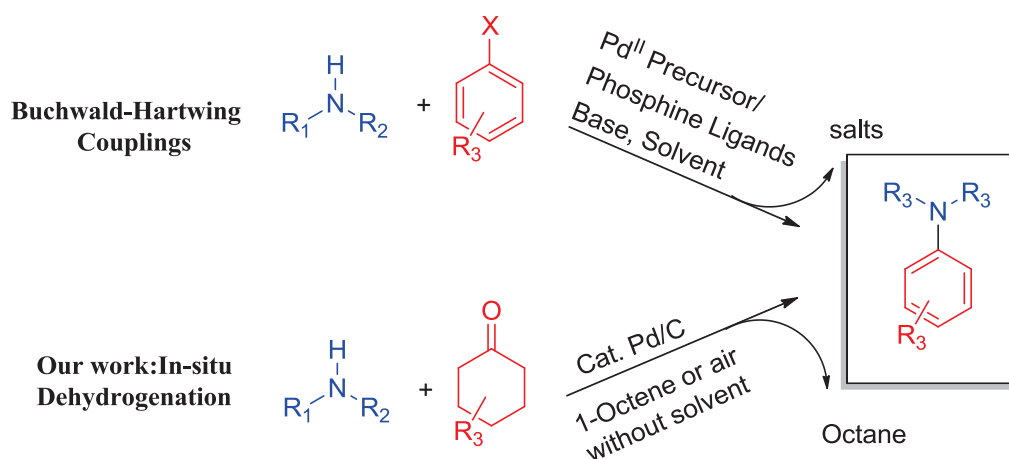
⁴²M. Sutter, N. Sotto, Y. Raoul, E. Métay, M. Lemaire, *Green Chem.* 15 (2013) 347-352.

synthesis of chiral *N,N'*- aryl-alkyl diamine ligand with good to excellent isolated yield (Scheme 16).



Scheme 16: Synthesis of chiral aryl-alkyl amine by dehydrogenative alkylation

Comparing with Buchwald–Hartwing *N*-arylation method, we can conclude that the dehydrogenative alkylation constitutes a green, cheap, and an easy alternative method to the existing ones used to form chiral aryl alkyl-amines. This method avoids the formation of salts or by-products difficult to eliminate and avoids the utilization of costly BINAP ligand (Scheme 17).



Scheme 17: Our work compared to the literature

In this chapter, we describe an efficient preparation of optically pure *N*-aryl-alkyl amines ligands by dehydrogenative alkylation from (1*R*,2*R*)-cyclohexane-1,2-diamine.

1.2 Results and discussions

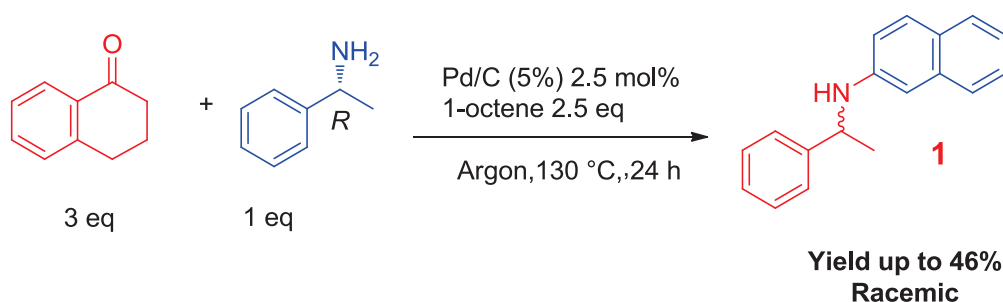
1.2.1 Synthesis of Chiral *N,N'*-diaryl-alkyl amine Ligands

We have adopted a method that was recently developed in Lemaire's laboratory for the preparation of *N*-aryl amine from amine with α and β aromatic-cyclic ketone.⁴³

First, we prepared one *N*-aryl-benzyl amine as monodentate ligand from a chiral amine. Next, we applied the method to prepare *N,N'*-diaryl diamine derived from chiral *N,N'*-diamine using the commercial diamine, (1*R*, 2*R*)-diaminocyclohexane. One trial was made using (1*R*, 2*R*)-*N,N'*-1,2-diphenylethylene-diamine.

1.2.2 Synthesis of *N*-(1-phenylethyl) naphthalene-2-amine

This synthesis was performed using enantiopure (1*R*) α -methylbenzylamine and α -tetralone as starting materials. The reaction was catalyzed by Pd/C at 130 °C (Scheme 18). After 24 h, 46% of the desired product (Ligand **1**) was isolated by flash chromatography, but unfortunately a complete racemization was observed by HPLC analysis.



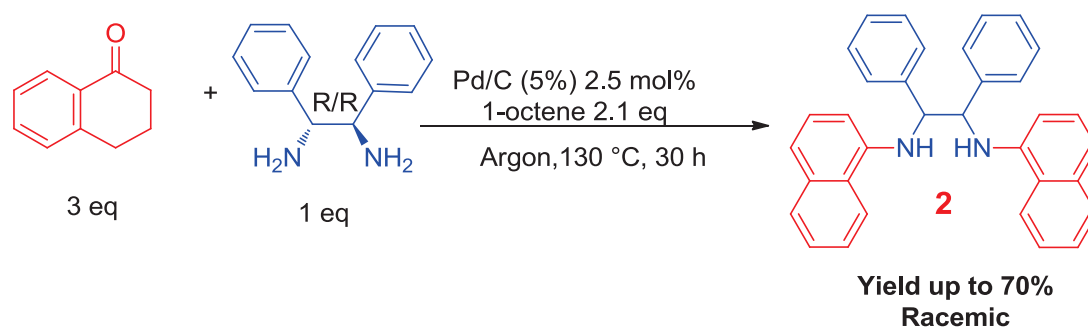
Scheme 18: Synthesis of aromatic amines (**1**) by alkylation and dehydrogenation starting from α -methylbenzylamine

1.2.3 Synthesis of *N,N'*-di(naphthalen-2-yl)-1,2-diphenylethane-1,2-diamine

(1*R*,2*R*)-1,2-Diphenylethylene-diamine as well as its derivatives showed high efficiency in asymmetric catalysis. Thus, this diamine was engaged in the reaction of dehydrogenative alkylation with α -tetralone, to prepare the corresponding *N,N'*-diaryl diamine ligand. Although good isolated yield (70%) in ligand **2** was obtained with this diamine, but a complete racemization has also been observed (Scheme 19).

⁴³ M. Sutter, M. Duclos, B. Guichet, Y. Raoul, E. Méta, M. Lemaire, *ACS Sust. Chem. Eng.* (1) (2013) 1463–1473.

In both cases, the acidity of the benzylic proton could be responsible of the loss of the chirality. The non-rigidity of the structure and the high temperature could also be possible factors. The racemization of meso-diphenylethanediol at 100°C in presence of base in ethanol was already described by André Collet.⁴⁴

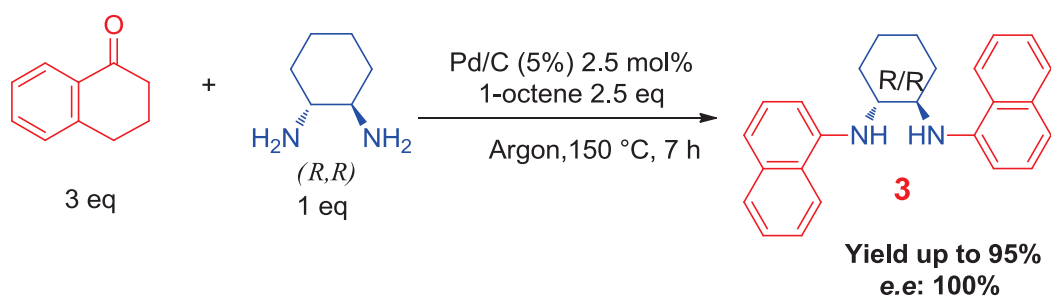


Scheme 19: Synthesis of aromatic amines (ligand 2) by alkylation and dehydrogenation starting from (1*R*, 2*R*)-1,2-Diphenylethane-1,2-diamine

1.2.4 Synthesis of (1*R*,2*R*)-*N*¹,*N*²-di(naphthalen-1-yl)cyclohexane-1,2-diamine ligand

With cyclohexanediamine, the racemization is not easy due to the rigidity of cyclohexane ring. This diamine, which is widely used to prepare chiral ligands for asymmetric synthesis, commercially available and relatively not expensive, was then considered. At the beginning, the dehydrogenative alkylation was performed with α -tetralone and cyclohexanediamine in racemic form, in presence of 2 mol% of Pd/C, 1-octene, and under argon atmosphere at 130°C during 7 h (non-aerobic). The product, ligand **3** was purified by silica flash chromatography; the isolated yield reached 73%. This reaction was then realized with (1*R*,2*R*)-cyclohexanediamine, a similar isolated yield was obtained. Furthermore; increasing temperature to 150 °C with 2.5% Pd/C, improved the isolated yield of ligand **3** to 95% (Scheme 20). The chiral HPLC (Chiralcel OJ–H column, eluent *n*-hexane/ isopropanol) analysis proved the yielding of one enantiomer (one peak only is observed on HPLC chromatogram (Figure 3, Spectrum **B**)).

⁴⁴ Andre Collet, Synthesis 11 (1973) 664-665.



Scheme 20: Synthesis of ligand **3** by alkylation and dehydrogenation starting from α -tetralone

The products of both reactions (with racemic 1,2-cyclohexanediamine and (1*R*,2*R*) cyclohexanediamine) were analyzed by chiral HPLC. For the racemic ligand **3**, this analysis reveals two peaks at 7.24 minutes for *R/R* and 17.11 minutes for *S/S* within 10 min between each (Figure 3, Spectrum **A**). This very large difference of retention time supposes that enantiomers are well differentiated by the cyclodextrines. For the ligand **3** obtained from enantiomerically pure cyclohexanediamine, only one peak at 7.14 minutes was observed related to the *R/R* configuration (Figure 3, Spectrum **B**).

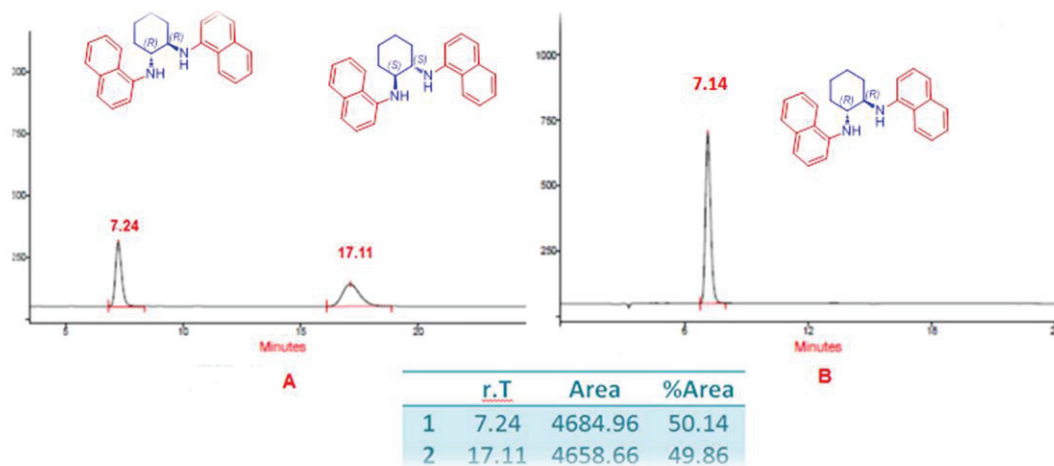
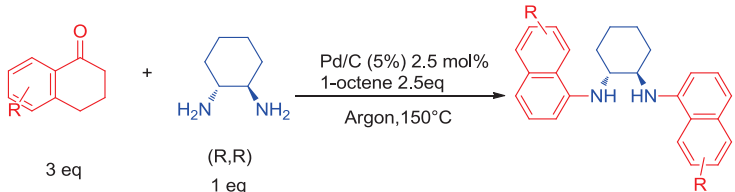
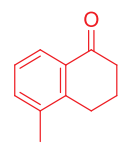
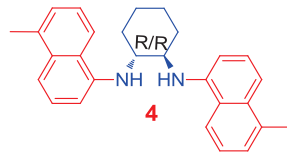
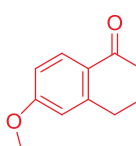
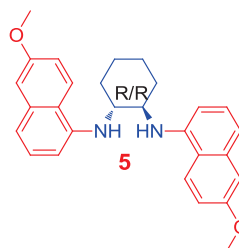
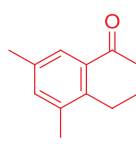
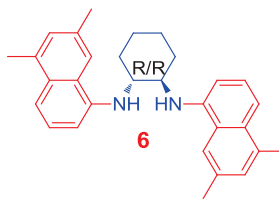


Figure 3: Spectra related to racemic and chiral ligands using chiral HPLC column

1.2.5 Synthesis of series of (1*R*, 2*R*)-*N,N'*-di(naphthalen-1-yl)cyclohexane-1,2-diamine from α -tetralone derivatives

Following the optimized condition, a series of ligands *N,N'*-arylated diamine were synthesized with different α -tetralone derivatives substituted on naphthyl entity. Good to excellent isolated yields were obtained (Table 2).

Table 2: Dehydrogenative alkylation of α -tetralone derivatives with (1*R*,2*R*)-cyclohexane-1, 2-diamine

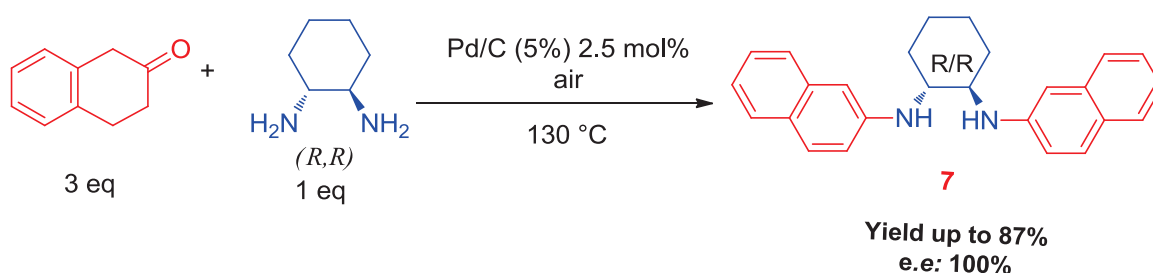
			
Entry	α -Tetralone derivatives	Product (ligand)	Isolated yield (%)
1		 (1 <i>R</i> ,2 <i>R</i>)- <i>N</i> ¹ , <i>N</i> ² -bis(5-methylnaphthalen-1-yl)cyclohexane-1,2-diamine	57
2		 (1 <i>R</i> ,2 <i>R</i>)- <i>N</i> ¹ , <i>N</i> ² -bis(6-methoxynaphthalen-1-yl)cyclohexane-1,2-diamine	73
3		 (1 <i>R</i> ,2 <i>R</i>)- <i>N</i> ¹ , <i>N</i> ² -bis(5,7-dimethylnaphthalen-1-yl)cyclohexane-1,2-diamine	94

Conditions: molar ratio tetralone derivative / (1*R*,2*R*)-cyclohexane-1, 2-diamine 3: 1, 2 mol% Pd / C (5 %) 1-octene (2 eq), 150 °C, 16 h, in non-aerobic condition.. All necessary analysis, such as ¹H NMR, ¹³C NMR, exact mass, Chiral HPLC, Mp and α_D have been carried out for the obtained products.

The reaction between (1*R*,2*R*)-cyclohexanediamine and 5,7-dimethyl-3,4-dihydronaphthalen-1(2H) produced the ligand **4**. A good isolated yield up to 79% was obtained. The 6-methoxyl-3,4-dihydronaphthalen-1(2H)-one was successfully used to prepare the ligand **5** with a moderate isolated yield (up 57%). Furthermore; 5-methyl-3,4-dihydronaphthalen-1(2H)-one was also used under the same conditions to give the enantiomeric ligand **6** with 82% in yield after purification. One peak on chiral HPLC was detected for each product to prove the enantiomeric purity.

1.2.6 Synthesis of (1*R*,2*R*)-*N,N'*-di(naphthalen-2-yl)cyclohexane-1,2-diamine using β -tetralone as a substrate

The conditions were adapted for the dehydrogenative arylation with β -tetralone to obtain the ligand **7**. At the beginning, when the reaction was done under non-aerobic condition (argon) at 130°C, the product was formed with yield not exceeding 66%. When the reaction was carried out in aerobic condition (under air using reflux) without 1-octene, the isolated yield increased up to 87% with less impurity (Scheme 21).

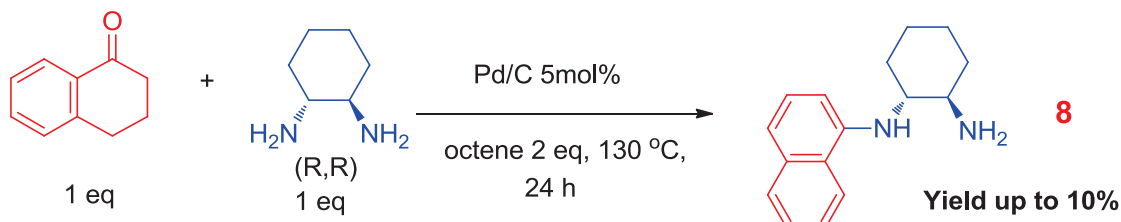


Scheme 21: Synthesis of ligand **7** by alkylation and dehydrogenation starting from β -tetralone

1.2.7 Synthesis of chiral *N*-monoaryl diamine Ligand

1.2.7.1 Synthesis of (1*R*, 2*R*)-*N*-(naphthalen-1-yl) cyclohexane-1,2-diamine

With the successful preparation of the diaryl ligands, we were interested to selectively prepare the monoaryl derivative. First of all, the reaction was done in one pot using 1 mol% of Pd/C under argon in the presence of 1-octene, with one equivalent of α -tetralone and that of (1*R*,2*R*)-cyclohexanediamine. Only 10% isolated yield of the desired ligand **8** was obtained after purification on flash chromatography (Scheme 22). In addition, 2 mol% of Pd/C (5%) was used under the same conditions; this resulted in the same low conversion (10 % yield).

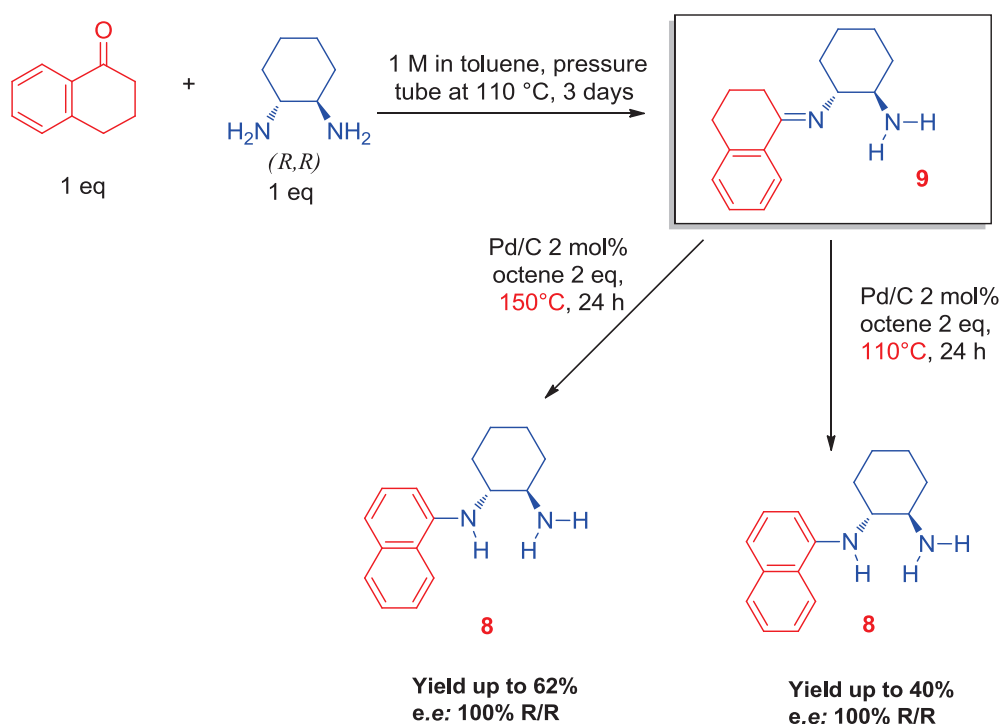


Scheme 22: Synthesis of monoarylated ligand **8** in one pot reaction

Then procedure with two pots was carried out, as shown in Scheme 25. The reaction was realized stepwise; the formation of the imine (ligand **9**) first followed by the

aromatization in the presence of palladium catalyst. This revealed to be the best procedure to obtain the desired monoarylated product with good yield.

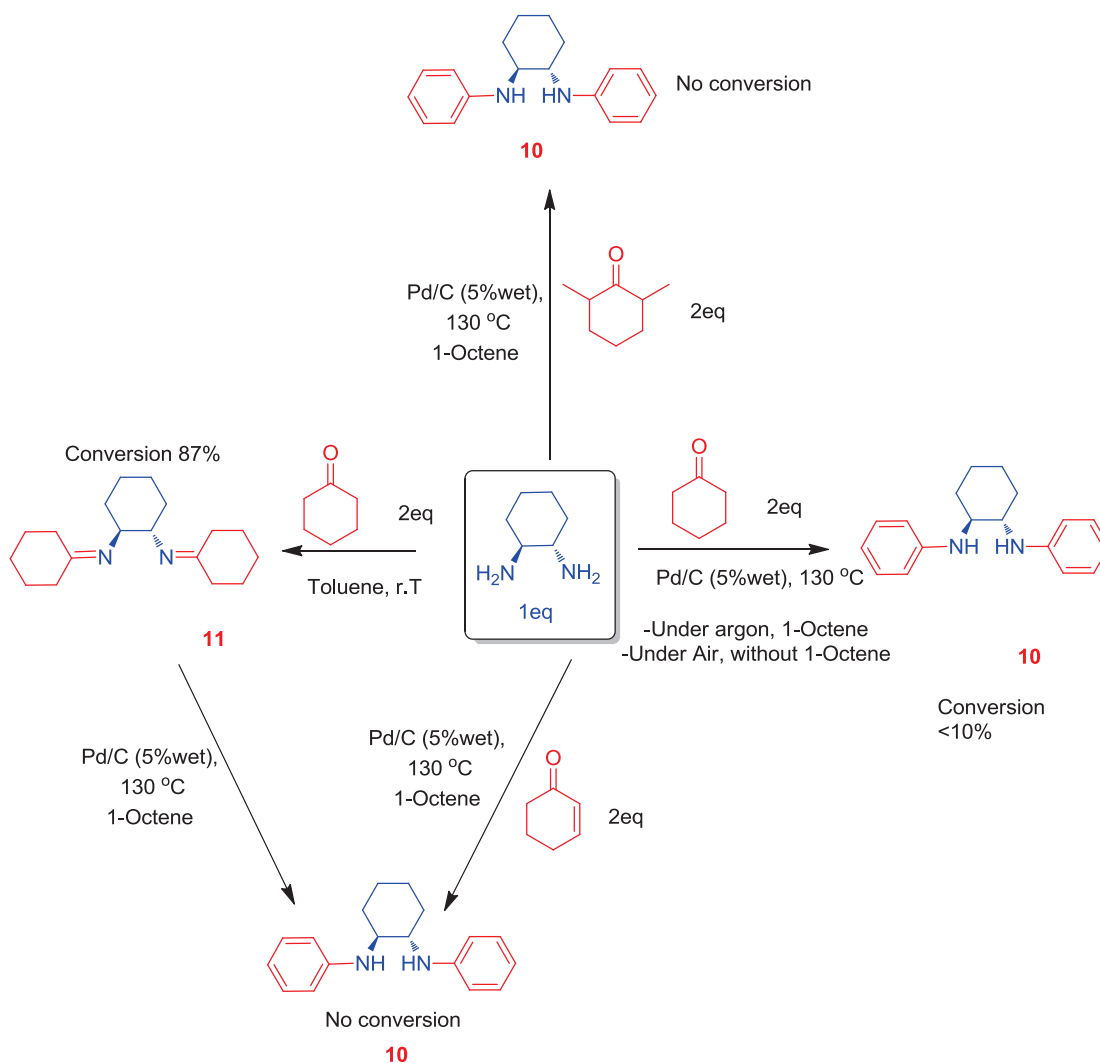
At 110 °C, only 40 % of the monoarylated ligand **8** was isolated with a mixture of incomplete aromatization of α -tetralone. Increasing the temperature to 150 °C, 62% of pure ligand **8** was then achieved (Scheme 23). In both cases, the *N,N'*-diarylated amine was obtained in very low quantity as well as remained quantity of starting materials. No racemization was observed.



Scheme 23: Synthesis of monoarylated ligand **8** by alkylation and dehydrogenation starting from α -tetralone

1.2.8 Synthesis of Chiral *N,N'*-diarylamine Ligands derived from cyclohexanone

In continuation of our work on the preparation of aromatic chiral amine ligands by alkylation dehydrogenation, cyclohexanone was assessed instead of tetralone to synthesize chiral diphenylcyclohexane-1,2-diamine.



Scheme 24: Synthesis of chiral diphenylcyclohexane-1,2-diamine (ligand 10)

The first reaction trial with cyclohexanone was carried out in one pot using 2.5% of Pd/C (5%) at 130 °C with 2 equiv. of 1-Octene and under argon (Scheme 24). Less than 10% of the desired ligand **10** was observed by GC analysis. The product was eluted with some impurities of close polarities even after several purifications using flash chromatography.

Cyclohex-2-en-1-one and 2,6-dimethylcyclohexanone were also used instead of cyclohexanone under the same conditions. No conversion was detected in both cases (Scheme 24).

Furthermore; the reaction was also realized using aerobic condition (under air without 1-Octene), but no reaction was observed (Scheme 24). Different experimental conditions were studied to synthesize *N,N'*-diphenylcyclohexane-1,2-diamine by changing the temperature, solvent, and hydrogen trap, but we didn't achieve the goal unfortunately.

We tried to prepare the desired ligand, *N,N'*-diphenylcyclohexane-1,2-diamine, in two steps: the first one is the preparation of the imine (product **11**) followed by the aromatization in the presence of palladium on charcoal as a catalyst under air (Scheme 24). After 4hrs, the conversion toward product **11** reached 87% with selectivity up to 99% (Figure 4, Spectrum **A**). Then, Pd/C (5%) was added to the mixture at 130 °C, a mixture of products was obtained as shown in the GC data (Figure 4, Spectrum **B**). This mixture has contained only traces of the desired product.

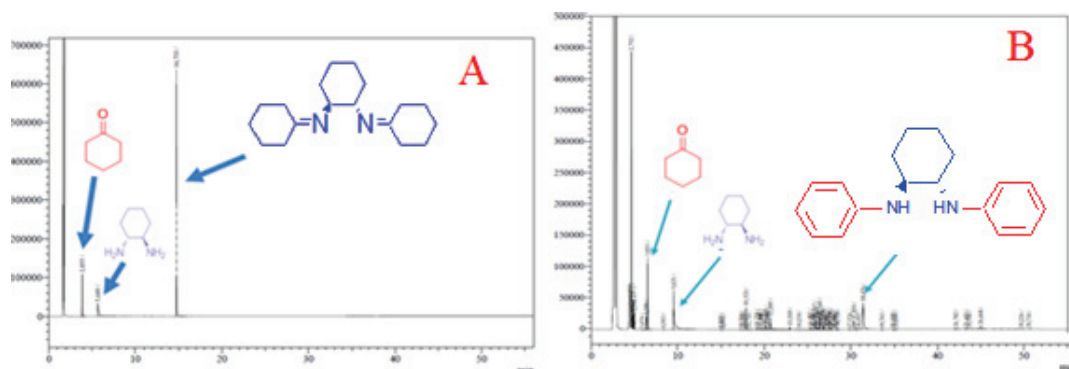
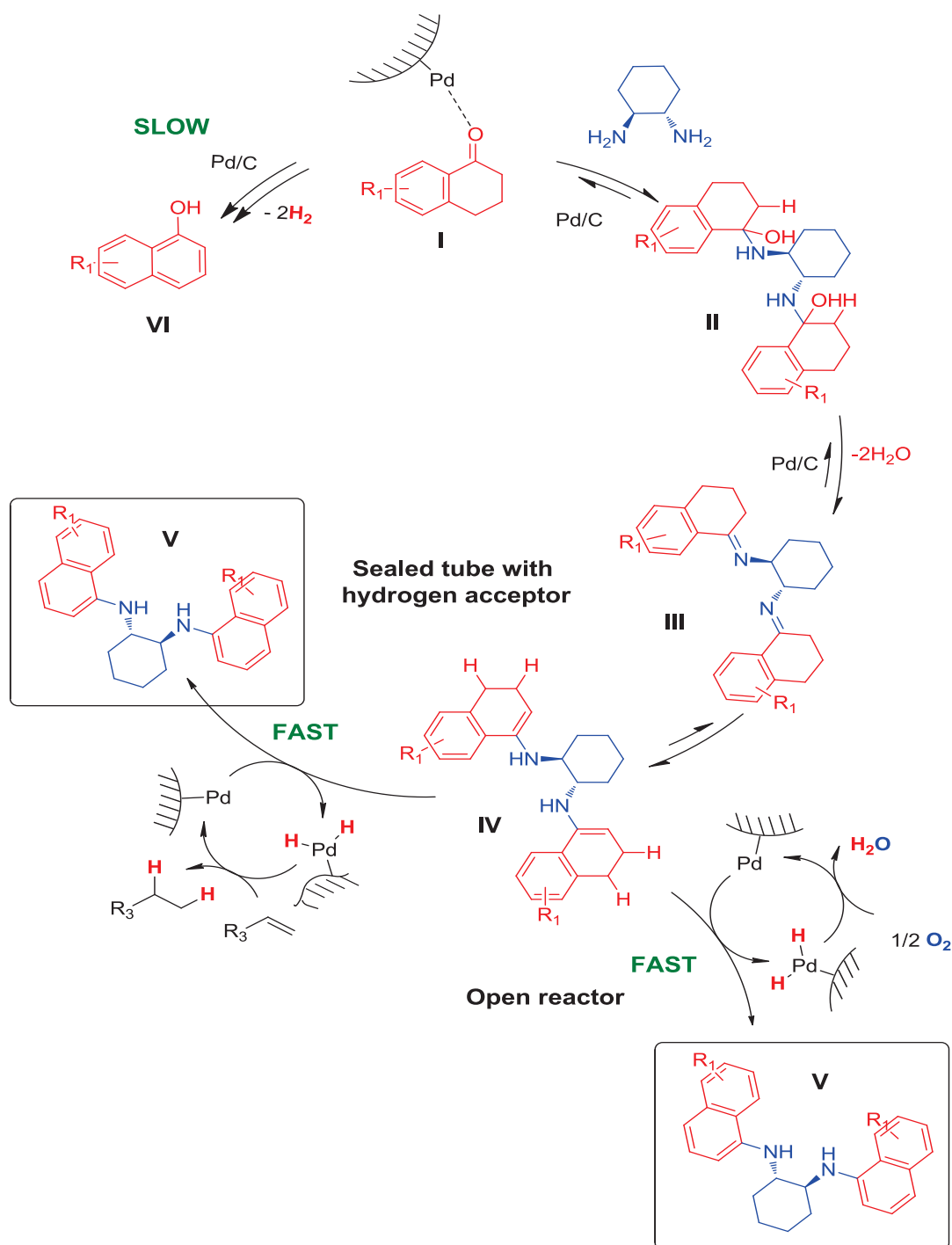


Figure 4: GC data for the synthesis of diphenylcyclohexane-1,2-diamine before and after adding Pd/C for aromatization step.

1.2.9 Mechanism proposal

The proposed mechanism for the synthesis of chiral *N*-arylated diamine ligands followed the same mechanism proposed by Marc Sutter for the synthesized *N*-Aryl-Alkyl Amine using the dehydrogenative alkylation method. Pd/C could accelerate the speed of this reaction by activating the carbonyl. The first step is the condensation of an amine with tetralone derivatives **II**, giving the imine **III** after dehydration. The enamine **IV** is then formed by tautomerization of **III**. The second dehydrogenation or loss (-2H) of Hydrogens adsorbed on the palladium surface to afford the aromatic amine **V**.

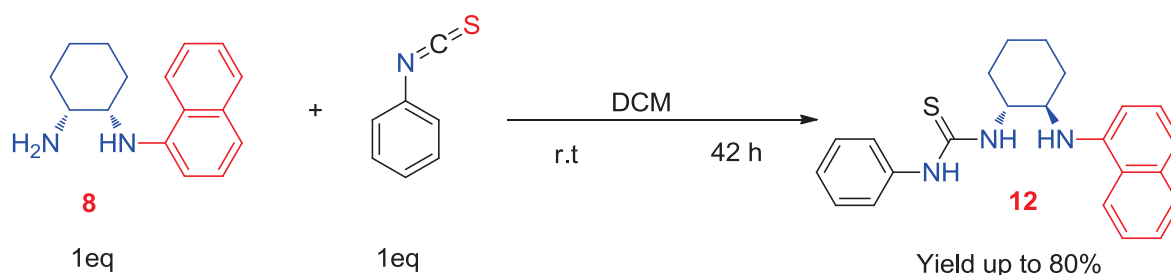
Depending on the process conditions (aerobic or anaerobic), the hydrogen adsorbed on the surface is consumed by the oxygen in the air or the alkene added in the medium. The addition of an alkene as a hydrogen acceptor (lead to the formation of alkane) was required when tetralone derivatives were involved. It was also possible to use open aerobic reactor without additives (lead to the formation of water in the medium) and with recyclable heterogeneous palladium catalyst



Scheme 25: Proposed mechanism for the dehydrogenative alkylation

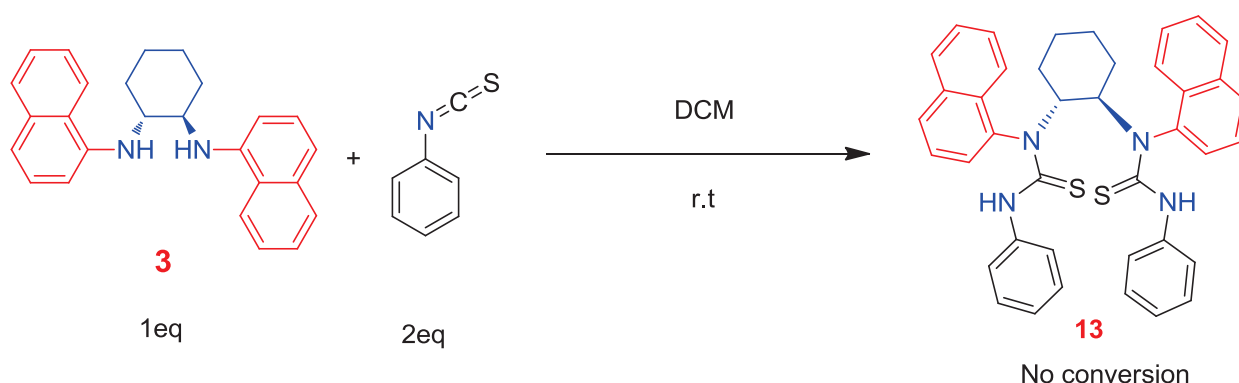
1.2.10 Synthesis of thiourea ligand

The synthesized ligands have been used to synthesize chiral thiourea ligands by mixing 1 eq. of monoarylated ligand **8** with 1 eq. of isothiocyanatobenzene in DCM at room temperature. The ligand **12** was purified by flash column chromatography with 80% of isolated yield (Scheme 26).



Scheme 26: Synthesis of thiourea ligand derived from ligand **8**

Then, another synthesis has been studied by using 1 eq. diarylated amine ligand **3** with 2 eq. of isothiocyanatobenzene. The reaction was performed at room temperature with DCM, no conversion toward ligand **13** was detected even after 42h (Scheme 27).



Scheme 27: Synthesis of thiourea ligand derived from ligand **3**

Increasing temperature to 60°C and then to 80°C also gave no reaction. Boron trifluoride etherate was also used as a catalyst. Regrettably, nothing was detected. We can assume that the reaction didn't work because of the low nucleophilic character of NH due to the aromatic substitution.

1.2.11 Synthesis of Imidazolinium salts

N-heterocyclic Carbenes are the most powerful classes of ligands that have been successfully engaged in organic synthesis. The first stable carbenes was discovered by Bertrand and co-workers in 1988,⁴⁵ and took a great attention after being successfully isolated by Arduengo in 1991.⁴⁶ *N*-heterocyclic carbenes are known for their strong nucleophilic and Lewis base properties. These properties enabled the carbenes to be not only superior ligands in organometallic catalysis but also organocatalysts. A wide range of NHC ligands are now

⁴⁵ A. Igau, H. Grutzmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **110** (1988) 6463-6466.

⁴⁶ A. J. Arduengo, R.L Harlow, M. Kline, *J. Am. Chem. Soc.* **113** (1991) 361-363.

commercially available. They affirmed their activities in important classes of modern organic reactions such as Metathesis,⁴⁷ Hydrosilylation of terminal alkynes,⁴⁸ Suzuki coupling,⁴⁹ C-C coupling reaction,⁵⁰ Nitroso Coupling Reaction,⁵¹ enantioselective alkylation of secondary alcohol,⁵² Homo-benzoin reactions.⁵³ Furthermore, several reactions have been reported using *N*-heterocyclic carbenes as pre-catalysts.⁵⁴

Our synthesized chiral *N*-Aryl Alkyl Amine ligands could be also transformed into chiral carbene-metal complexes. This class of ligands^{55,56} is interesting since *N*-heterocyclic carbenes are electronically (orbital overlap) and sterically stabilized. Different from traditional carbenes, NHCs are electron rich and can be altered by changing the nature of the azole ring: benzimidazole<imidazole<imidazoline (order of electron donating power). NHC ligands form very strong bonds with the majority of metals (stronger than phosphines).

In the laboratory, imidazolinium salts were prepared by the reaction of the diamine ligand with triethyl orthoformate and ammonium tetrafluoroborate. Two ligands were synthesized: starting from ligand **3** to obtain (4*R*,5*R*)-1,3-di(naphthalen-1-yl)-octahydron-1*H*-benzoimidazol-3-ium tetrafluoroborate (ligand **14**) and from ligand **6** to obtain (3*aR*,7*aR*)-1,3-bis(5,7-dimethylnaphthalen-1-yl)-3*a*,4,5,6,7,7*a*-hexahydro-1*H*-benzo[d]imidazol-3-ium tetrafluoroborate (ligand **15**). (Scheme 28) In both reactions, very good isolated yields were obtained (85% & 81%) after purification by flash column chromatography on silica gel using a gradient of DCM/MeOH.

⁴⁷ a) Handbook of Metathesis, ed. R. H. Grubbs, Wiley-VCH, Weinheim, Germany (2003). b) A. Hoveyda, R. Zhugralin, *Nature*. 450 (2007) 243-251. c) R. H Grubbs, J. P. Jordan, *Angew. Chem. Int. Ed.* 46 (2007) 5152-5155.

⁴⁸ F. Silbertri, J. C. Flores, E. de Jesus, *Organometallics*. 31 (2012) 3355-3360.

⁴⁹ E. Peris, P. Maracena, S. Candela, G. Fernando, *Organometallics*. 30 (2011) 684-688.

⁵⁰ L. X. Shao, S. X. Bao, G. T. Ting, L. J. Mei, *Appl. Organomet. Chem.* 25 (2011) 493-497.

⁵¹ L. Yang, B. Tan, F. Wang, G. Zhong, *J. Org. Chem.* 74 (2009) 1744-1746.

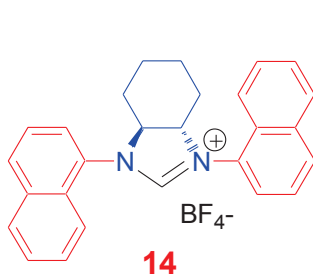
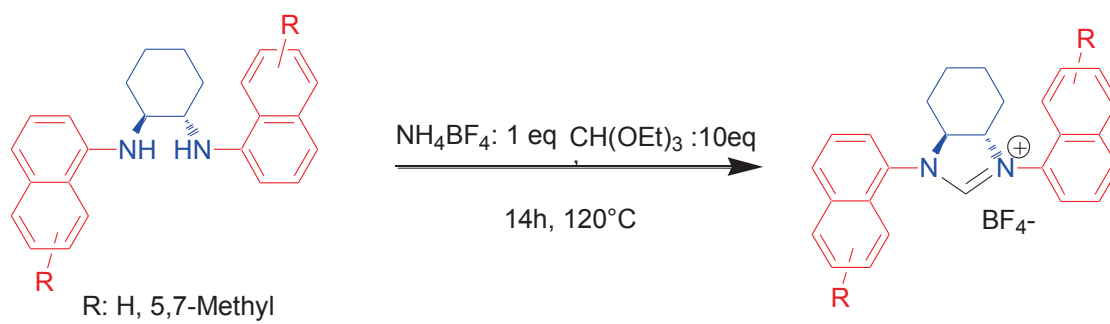
⁵² T. Kano, K. Sasaki, K. Maruoka, *Org. Lett.* 7 (2005) 1347-1349.

⁵³ K. Iwamoto, M. Hamaya, N. Hashimoto, H. Kimura, Y. Suzuki, M. Sato, *Tetrahedron Lett.* 47 (2006) 7175-7177.

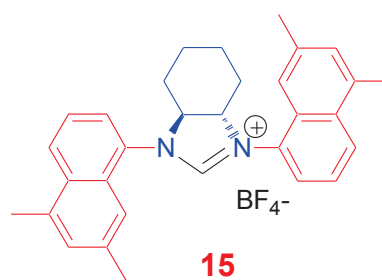
⁵⁴ R. S. Menon, A. T. Biju and V. Nair, *Beilstein J. Org. Chem.* 12 (2016) 444-461.

⁵⁵ S.P. Nolan, *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH; Weinheim, (2006) pp 1-304.

⁵⁶ F. Glorius, *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Topics in Organometallic Chemistry; Springer-Verlag: Berlin Heidelberg, Vol. 21 (2006) pp 1-218.



Yield up to 85%



Yield up to 81%

Scheme 28: Synthesis of Imidazolinium salts.

1.3 Conclusion

In this work, we developed a new method to synthesize chiral *N*-aryl alkyl diamine ligands starting from α or β -aromatic ketones like tetralone derivatives and 1,2-cyclohexanediamine *via* dehydrogenative alkylation. A series of chiral *N,N'*-diaryl diamine ligands and chiral *N*-monoaryl diamine ligands was synthesized with good to excellent isolated yields (57 to 95%) of enantiopure molecules. We have realized the transformation of two selected ligands of the series to two amidazolinium salts with excellent isolated yields (81 and 85%).

Some of the advantages of this *N*-arylation method are: 1- Its simplicity, its high efficiency, and its stereospecificity with rigid diamines, 2- Its ability to be performed in solvent-free condition 3- Its green character. 4- The use of heterogeneous catalyst (Pd/C) simple, cheap, ligands-free and easy to separate

1.4 Experimental Section

1.4.1 Method and materials

All reagents were obtained from commercial sources and used as received. Cyclohexane-1, 2-diamine, cyclohexanone and tetralone derivatives were purchased from Sigma–Aldrich[®]. Pd/C 5 wt% on active carbon, reduced and dry (ES cat TM 1431) was purchased from Strem Chemicals Inc. All reactions were performed under an inert atmosphere (argon) unless otherwise stated. Silica gel (40–63 micron) was used for column chromatography.

Thin layer chromatography (TLC) was performed on pre-coated silica gel 60–F 254 plates. UV light, phosphomolibdic acid and ninhydrin were used as Revelator for analysis of the TLC plates.

All compounds were characterized by spectroscopic analysis. The NMR spectra were recorded with a Bruker ALS or DRX300 (¹H: 300 MHz, ¹³C: 75 MHz), chemical shifts are expressed in ppm, J values are given in Hz; CDCl₃, CD₃OD and dimethyl sulfoxide DMSO-d₆, were used as solvent and internal standard (CDCl₃: 7.26 ppm in ¹H and 77.1 ppm in ¹³C. CD₃OD: 4.87 ppm, 3.31 in ¹H and 49.1 ppm in ¹³C. DMSO: 2.5 ppm in ¹H and 39.5 ppm in ¹³C). The peak patterns are indicated as follows: (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, for broad).

Chiral GC was performed on Shimadzu Gas Chromatograph GC–14A coupled with an integrator ShimadzuC–R6A Chromatopac using a Rt[®] βDEXm capillary column (30.0 m × 0.25 mm × 0.25 μm) purchased from Restek Chromatography Products and an FID (flame ionization detector). N₂ gas was used as a carrier at 1.75 kg/cm².

Chiral HPLC was performed on a Perkin Elmer Series 200 (pump, UV/VIS detector at 254 nm, Vacuum degasser) with a chiral column Chiralcel OJ–H column 0.46 × 25 cm (Daicel Chemical Ind., Ltd.).

Optical rotations were determined at 589 nm (sodium D line) at 20°C by using a PerkinElmer –343 MC digital polarimeter. Optical rotations are reported as follows $[\alpha]_D^T$ (concentration c = g/100 mL of solvent) and solvent. Configurations were determined by comparison of the measured $[\alpha]_D^T$ with the one reported in the literature.

Melting points were recorded on a Heizbank system Kofler Type WME (Wagner & Munz).

1.4.2 General method for preparation of ligands

1.4.2.1 Synthesis of chiral diaryl alkyl amine Ligand

1.4.2.1.1 Procedure A: Dehydrogenative alkylation of functionalized tetralone with (1*R*, 2*R*)-cyclohexane-1, 2-diamine:

To a pressure tube were successively added under inert atmosphere, 1 eq of diamine (2 mmol, 0.23 g), 3 eq of α -tetralone (6 mmol, 0.90 g) and 2.5 mol% of Pd/C (5% wet) (0.05 mmol, 107 mg). Then, the tube was sealed and placed in preheated oil bath ($T = 150\text{ }^{\circ}\text{C}$). After 24 h of stirring at 800 rpm, the crude was cooled down, diluted in a mixture (50/50) of CH_2Cl_2 and CH_3OH , and then filtered off on Millipore filter (Durapore filter $0.01\text{ }\mu\text{m}$). The solvents were removed under vacuum and the crude material was purified by flash column chromatography on silica gel (Eluent: cyclohexane (500 mL), then cyclohexane/ethyl acetate 90:10).

1.4.2.1.2 Procedure B: Dehydrogenative alkylation of functionalized β -tetralone with (1*R*, 2*R*)-cyclohexane-1, 2-diamine:

To a pressure tube were successively added under inert atmosphere, 1 eq of diamine (2 mmol, 0.23 g), 2.5 eq of β -tetralone (5 mmol, 0.75 g) and 2 mol% of Pd/C (5% wet) (0.04 mmol, 85 mg). Then, the tube was sealed and placed in preheated oil bath ($T = 130\text{ }^{\circ}\text{C}$). After 24 h of stirring at 800 rpm, the crude was cooled down, diluted in a mixture of (50/50) of CH_2Cl_2 and CH_3OH , and then filtered off on Millipore filter (Durapore filter $0.01\text{ }\mu\text{m}$). The solvents were removed under vacuum and the crude material was purified by flash column chromatography on silica gel (Eluent: cyclohexane (500 mL) then cyclohexane/ethyl acetate 90:10).

1.4.2.2 Synthesis of chiral monoaryl alkyl amine Ligand

1.4.2.2.1 Procedure C: Dehydrogenative alkylation of functionalized α -tetralone with (1*R*, 2*R*)-cyclohexane-1, 2-diamine:

To a pressure tube were successively added under inert atmosphere, 3 eq of diamine (9 mmol, 1.03 g), 1 eq of α -tetralone (3 mmol, 0.40 g) and 3 mL of toluene as a solvent. The tube

was sealed and placed in a preheated oil bath (110°C) for 64 h. Thereafter; 2 mol% of Pd/C (5%) (0.06 mmol, 127 mg) and 2 eq of octene (6 mmol, 0.67 g) were added to the mixture under inert atmosphere. The tube was sealed again and placed in a preheated oil bath (150°C). After 24 h of stirring at 800 rpm, the crude was cooled down, diluted in a mixture of (50/50) CH₂Cl₂ and CH₃OH, and then filtered off on Millipore filter (Durapore filter 0.01 µm). The solvents were removed under vacuum and the crude material was purified by flash column chromatography on silica gel (Eluent: DCM (500 mL) then DCM/MeOH 95:5).

1.4.2.3 Synthesis of Amidazoline Salt

1.4.2.3.1 Procedure **D**: Synthesis of amidazoline salt form dinaphthaleneyl cyclohexane 1, 2-diamine

In a sealed tube under argon, 1 eq of dinaphthaleneyl cyclohexane 1, 2-diamine (done by using procedure **A**, 10 eq of triethylorthoformate (CHOEt₃), 1eq ammonium tetrafluoro borate (NH₄BF₄), and two drop of formic acid were mixed, warmed to 120°C, and stirred at 800 rpm for 14 h. The resulting mixture was dissolved in CH₂Cl₂ and CH₃OH then filtered off (Durapore filter 0.01µm). The solvents were removed under vacuum and the crude material was purified by flash column chromatography on silica gel (eluent DCM/ ethylacetate (100:0 to 90:10)).

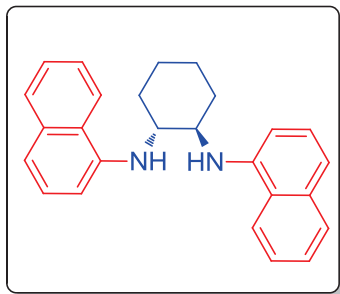
1.4.2.4 Synthesis of thiourea

1.4.2.4.1 Procedure **E**: Synthesis of thiourea from mononaphthalenyl cyclohexane 1, 2-diamino

In a sealed tube, 1 eq of mononaphthaleneyl cyclohexane 1, 2-diamino (product **8** done by using procedure **B**) was mixed with 1 eq of isothiocyanatobenzene in DCM as a solvent at room temperature and stirred at 800 rpm for 14 h. The solvents were removed under vacuum and the crude material was purified by flash column chromatography on silica gel (eluent DCM/ ethylacetate (100:0 to 90:10)).

1.4.3 Characterization data for Chiral Amine Ligand

(1*R*,2*R*)-*N*¹, *N*²-Di(naphthalen-1-yl)cyclohexane-1,2-diamine [640276-57-9]:



The compound was obtained following the typical procedure **A** starting from (1*R*, 2*R*)-cyclohexane-1,2-diamine (0.23 g, 0.24 ml, 1 eq) and α -tetralone (0.90 g, 0.80 ml, 3 eq). The crude material was purified by flash column chromatography on silica gel using a gradient of cyclohexane/ethyl acetate (100:0 to 90:10) to afford 540 mg (74%) of the desired product as a light pink crystal, for TLC (eluent: cyclohexane / ethyl acetate: 80/20), $R_f = 0.8$. If not of satisfying purity, this material can be further recrystallized from diethyl ether and hexane at room temperature to afford brilliant light pink crystal. HREIMS calculated for $C_{26}H_{26}N_2 = 366.2096$ and found $m/z = 366.2081$.

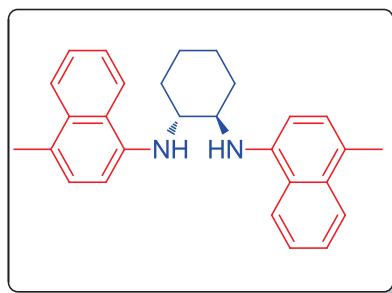
$[\alpha]_D^{20} = -305$ (c 1.02, CH_2Cl_2)

Mp: Around 116 °C

1H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.44 (m, 2H, CH_2), 1.54–1.60 (m, 2H, CH_2), 1.88–1.91 (m, 2H, CH_2), 2.59 (d, $J = 15.0$ Hz, 2H, CH_2), 3.64–3.67 (m, 2H, CH_2), 4.65 (s, 2H, NH), 6.81, (d, $J = 6.0$ Hz, 2H, CH_{arom}), 7.43–7.29 (m, 8H, CH_{arom}), 7.67 (d, $J = 6.0$ Hz, 2H, CH_{arom}), 7.78 (d, $J = 9.0$ Hz, 2H, CH_{arom})

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 ($2CH_2$), 32.1 ($2CH_2$), 57.6 ($2CH$), 105.4 ($2CH_{arom}$), 117.9 ($2CH_{arom}$), 120.2 ($2CH_{arom}$), 124.2 ($2C_{qarom}$), 124.9 ($2CH_{arom}$), 125.9 ($2CH_{arom}$), 126.4 ($2CH_{arom}$), 128.6 ($2CH_{arom}$), 134.5 (C_{qarom}), 142.8 (C_{qarom}).

(1*R*, 2*R*)-*N*₁, *N*₂-bis(5-methylnaphthalen-1-yl)cyclohexane-1,2-diamine



The compound was obtained following the typical procedure A starting from (1*R*, 2*R*)-cyclohexane-1, 2-diamine (0.69 g, 0.72 ml 6 eq) and 4-methyl-1-tetralone (2.9 g, 2.7 ml, 9 eq). The crude material was purified by flash column chromatography on silica gel using a gradient of cyclohexane/ethyl acetate (100:0 to 90:10) to afford 0.70 mg (57%) of the desired product as a white crystal, for TLC (eluent: cyclohexane / ethyl acetate: 80/20), $R_f = 0.85$. If not of satisfying purity, this material can be further recrystallized from diethyl ether and hexane at room temperature to afford brilliant white crystal. HREIMS calculated for $C_{28}H_{30}N_2 = 394.2409$ found $m/z = 394.2392$.

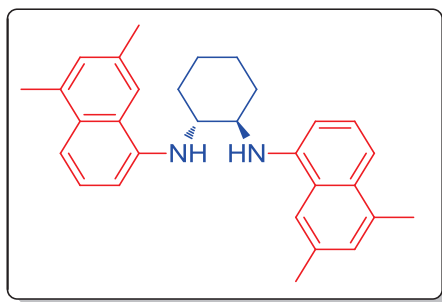
$[\alpha]_D^{20} = -201.98$ (c 1.01, CH_2Cl_2)

Mp: Around 130 °C

1H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.34-1.31 (m, 2H, CH_2), 1.52-1.45 (m, 2H, CH_2), 1.82-1.80 (m, 2H, CH_2), 2.52-2.47 (m, 2H, CH_2), 2.54 (s, 6H, 2 CH_3), 3.56-3.54 (m, 2H, CH_2), 4.3-4.76 (s, 2H, NH), 6.74-6.71 (d, 2H, CH_{arom}), 7.45-7.18 (m, 8H, CH_{arom}), 7.72-7.69 (d, 2H, CH_{arom}), 7.91-7.88 (d, 2Hⁱ, CH_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 18.9 (2 CH_3), 24.8 (2 CH_2), 32.0 (2 CH_2), 57.7(2CH), 106.0 (2 CH_{arom}), 120.8 (2 CH_{arom}), 124.0 (2 CH_{arom}), 124.88 (2 C_q arom), 124.70 (2 CH_{arom}), 124.78 (2 CH_{arom}), 125.7 (2 CH_{arom}), 126.8 (2 CH_{arom}), 133.3 (C_q arom), 141.1 (C_q arom).

(1*R*, 2*R*)-*N*¹, *N*²-bis(5,7-dimethylnaphthalen-1-yl)cyclohexane-1,2-diamine



The compound was obtained following the typical procedure A starting from (1*R*, 2*R*)-cyclohexane-1,2-diamine (0.69 g, 0.72 ml, 6 eq) and 5,7-dimethyl-1-tetralone (3.14 g, 9 eq). The crude material was purified by flash column chromatography on silica gel using a gradient of cyclohexane/ethyl acetate (100:0 to 90:10) to afford 1.79 g (94%) of the desired product as an orange solid, for TLC (eluent: cyclohexane / ethyl acetate: 80/20), *R_f* = **0.8**. If not of satisfying purity, this material can be further recrystallized from diethyl ether and hexane at room temperature to afford brilliant orange crystal. HREIMS calculated for C₃₀H₃₅N₂ = 423.2722 found *m/z* = 423.2786.

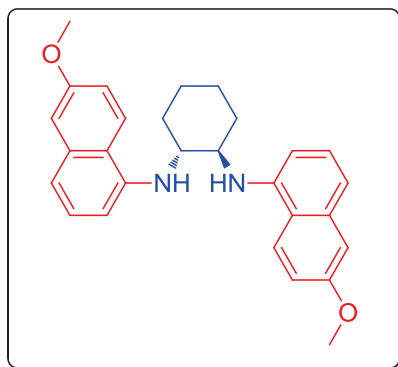
[α]_D²⁰ = -262.94 (*c* 0.976, CH₂Cl₂)

Mp: Around 134 °C

¹H NMR (300 MHz, CDCl₃): δ = 1.39-1.36 (m, 2H, CH₂), 1.58-1.52 (m, 2H, CH₂), 1.89-1.86 (m, 2H, CH₂), 2.32 (s, 6H, 2CH₃), 2.6 (s, 6H, 2CH₃), 3.66-3.63 (m, 2H, CH₂), 4.63 (s, 2H, NH), 6.68-6.81 (m, 2H, CH_{arom}), 7.10 (s, 2H, CH_{arom}), 7.30 (s, 2H, CH_{arom}), 7.38-7.37 (d, 2H, CH_{arom}).

¹³C NMR (75 MHz, CDCl₃): δ = 20.0 (2CH₃), 221.9 (2CH₃), 24.9 (2CH₂), 32.2 (2CH₂), 57.7(2CH), 105.7 (2CH_{arom}), 114.8 (2CH_{arom}), 117.0 (2CH_{arom}), 124.4 (2C_q arom), 125.2 (2CH_{arom}), 129.9 (2CH_{arom}), 131.8 (2C_q arom), 134.11 (2C_q arom), 134.7 (2C_q arom), 142.8 (2C_q arom).

(1*R*,2*R*)-*N*¹,*N*²-Bis(6-methoxynaphthalen-1-yl)cyclohexane-1,2-diamine



The compound was obtained following the typical procedure A starting from (1*R*, 2*R*)-cyclohexane-1, 2-diamine (0.23 g, 0.24 ml, 1 eq) and 6-methoxy-1-tetralone (1.06 g, 3 eq). The crude material was purified by flash column chromatography on silica gel using a gradient of cyclohexane/ethyl acetate (100:0 to 90:10) to afford 0.49g (73%) of the desired product as a pink solid. For TLC (eluent: cyclohexane / ethyl acetate: 80/20), *R_f*= 0.62. If not of satisfying purity, this material can be further recrystallized from diethyl ether and hexane at room temperature. HREIMS calculated for C₂₈H₃₀N₂O₂= 426.2307 found *m/z* = 426.2289

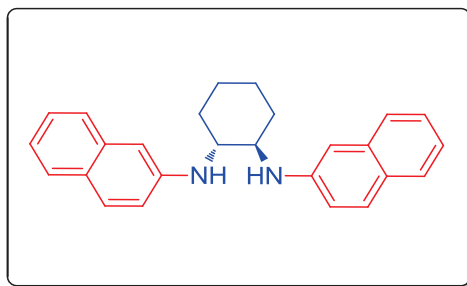
$[\alpha]_D^{20} = -279.5$ (*c* 1.03, CH₂Cl₂)

Mp: decomposed around 72 °C

¹H NMR (300 MHz, CDCl₃): δ= 1.40 (m, 2H, CH₂), 1.53-1.49 (m, 2H, CH₂), 1.86-1.85 (m, 2H, CH₂), 2.56-2.52 (s, H, CH₂), 3.64-3.61 (m, 2H, CH₂), 3.88 (s, 2-O-CH₃), 4.98 (s, 2H, NH), 6.74-6.72 (d, 2H, CH_{arom}), 7.98-7.95 (m, 2H, CH_{arom}), 7.01 (s, 2H, CH_{arom}), 7.30-7.15 (m, 4H, CH_{arom}), 7.62-7.59 (d, 2H, CH_{arom}).

¹³C NMR (75 MHz, CDCl₃): δ= 24.7 (2CH₂), 26.9 (2CH₂), 55.2 (2CH₃), 57.8 (2CH), 106.8 (2CH_f), 117.1 (2CH_{arom}), 119.4 (2C_q), 121.9 (2CH_{arom}), 127.1 (2C_q), 135.9 (2C_q), 157.9 (2C_q arom).

(1*R*, 2*R*)-*N*¹,*N*²-Di(naphthalen-2-yl)cyclohexane-1,2-diamine



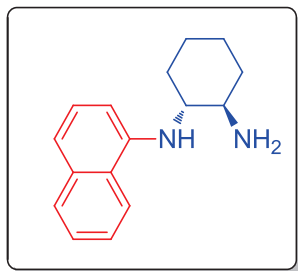
The compound was obtained following the typical procedure B starting from (1*R*, 2*R*)-cyclohexane-1, 2-diamine (0.7 g, 0.72 ml, 3 eq) and 2-tetralone (2.19 g, 1.98 ml, 3 eq). The crude material was purified by flash column chromatography on silica gel using a gradient of cyclohexane/ethyl acetate (100:0 to 90:10) to afford 1.90 g (87%) of the desired product as light brown foam. For TLC (eluent: cyclohexane / ethyl acetate: 80/20), R_f = 0.875. The product reserved in the refrigerator. HREIMS calculated for $C_{26}H_{26}N_2$ = 366,2096 found m/z = 366.2077.

$[\alpha]_D^{20}$ = +348.36 (c 1.018, CH_2Cl_2)

1H NMR (300 MHz, $CDCl_3$): δ = 1.35-1.30 (m, 2H, CH_2), 1.53-1.56 (m, 2H, CH_2), 1.89-1.85 (m, 2H, CH_2), 2.52-2.47 (m, 2H, CH_2), 3.45-3.42 (m, 2H, CH_2), 4.16 (s, 2H, NH), 6.91-6.85 (m, 4H, CH_{arom}), 7.71-7.21 (m, 10H, CH_{arom}),

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6 ($2CH_2$), 32.2 ($2CH_2$), 57.2 ($2CH$), 105.2 ($2CH_{arom}$), 118.6 ($2CH_{arom}$), 122.2 ($2CH_{arom}$), 125.9 ($2CH_{arom}$), 126.4 ($2CH_{arom}$), 129.1 ($2CH_{arom}$), 130.0($2C_{q\ arom}$), 135.1 ($C_{q\ arom}$), 145.1($C_{q\ arom}$).

(1*R*, 2*R*)-*N*¹-(naphthalen-1-yl) cyclohexane-1, 2-diamine [847901-48-8]:



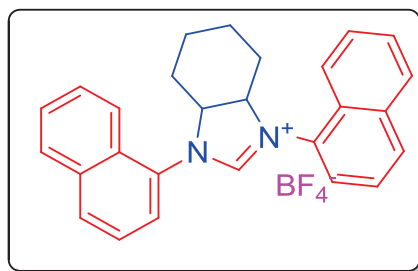
The compound was obtained following the typical procedure C starting from (1*R*, 2*R*)-cyclohexane-1,2-diamine (1.03 g, 1.08 ml, 3 eq) and 2-tetralone (0.44 g, 0.4 ml, 1 eq). The crude material was purified by flash column chromatography on silica gel using a gradient of DCM/MeOH (100:0 to 90:05) to afford 0.45 g (62%) of the desired product as brown solid. For TLC (eluent: DCM / MeOH: 60/40), R_f = 0.3. HREIMS calculated for $C_{16}H_{20}N_2$ = 240.1626 found m/z = 240.1624.

$[\alpha]_D^{20}$ = -126.35 (c 0.2, CH_2Cl_2)

1H NMR (300 MHz, $CDCl_3$): 0.97–1.01 (m, 1H), 1.29 (m, 3H), 1.71 (m, 2H), 1.99 (m, 1H), 2.22–2.27 (m, 1H), 2.54 (m, 1H), 2.77 (br. s, 2H), 3.32 (m, 1H), 4.21 (br. s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 7.22 (m, 4H), 7.78 (d, J = 7.32 Hz, 1H), 7.90–7.92 (d, J = 7.98 Hz, 1H) ppm

^{13}C NMR (75 MHz, $MeOH\ d_4$): 25.8 (CH_2), 26.1 (CH_2), 32.2 (CH_2), 33.9 (CH_2), 55.8 (CH), 59.1 (CH), 106.1 (CH_{arom}), 118.2 (CH_{arom}), 122.14 (CH_{arom}), 125.4 (CH_{arom}), 126.6 (C_{qarom}), 126.6 (CH_{arom}), 127.58 (CH_{arom}), 129.4 (CH_{arom}), 136.1 (C_{qarom}), 144.6 (C_{qarom}).

(4*R*,5*R*)-1,3-Di(naphthalen-1-yl)-octahydron-1*H*-benzoimidazol-3-ium tetrafluoroborate.



The compound was obtained following the typical procedure D starting from (1*R*, 2*R*)-*N*¹,*N*²-di (naphthalen-1-yl) cyclohexane-1,2-diamine (0.73 g, 1 eq), triethyl ortho formate (CHOEt₃) (2.96 g, 10 eq), ammonium tetrafluoroborate (NH₄BF₄) (0.21 g, 1 eq), and two drop of formic acid. The crude material was purified by flash column chromatography on silica gel using a gradient of DCM/MeOH (100:0 to 98:02) to afford 0.6364 g (85%) of the desired product as light brown foam. For TLC (eluent: DCM / MeOH: 95/5), *R_f* = 0.5.

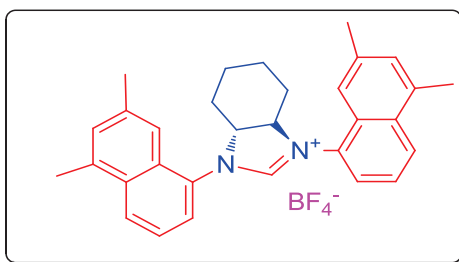
$[\alpha]_D^{20} = -47.238$ (*c* 0.21, CH₂Cl₂)

Mp: decomposed around 142 °C

¹H NMR (300 MHz, 80 °C DMSO-*d*₆): δ= 1.39-1.266(m, 2H, CH₂), 1.8711 (s, 6H, 3CH₂), 4.76 (s, 2H, 2CH-N), 8.34-7.72 (m, 14H, 7CH_{arom}) 9.59 (s, H, N-CH=N);

¹³C NMR (75 MHz, DMSO-*d*₆): δ= 23.7 (CH₂), 27.43 (CH₂), 71.6 (CH), 122.7 (CH), 125.2 (C_q arom), 126.07 (CH), 127.7 (CH_{arom}), 128.3 (CH_{arom}), 128.9 (CH_{arom}), 129.5 (C_q arom), 130.7 (CH_{arom}), 131.4 (C_q arom), 134.54 (C_q arom), 162.5 (N-CH=N).

(3a*R*,7a*R*)-1,3-Bis (5,7-dimethylnaphthalen-1-yl)-3a,4,5, 6, 7, 7a-hexahydro-1*H*-benzo[d]imidazol-3-ium



The compound was obtained following the typical procedure **D** starting from (1*R*, 2*R*)-*N*1,*N*2-bis (5,7-dimethylnaphthalen-1-yl) cyclohexane-1, 2-diamine (0.85 g, 1 eq), triethyl ortho formate (CHOEt₃) (2.96 g, 10 eq), ammonium tetrafluoroborate (NH₄BF₄) (0.21 g, 1 eq), and two drop of formic acid. The crude material was purified by flash column chromatography on silica gel using a gradient of DCM/MeOH (100:0 to 98:02) to afford 0.702 g (81%) of the desired product as yellow foam.

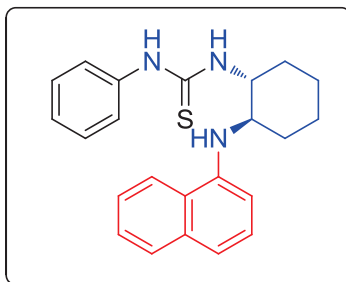
$$[\alpha]_D^{20} = -63.53 (c\ 1.014, \text{CH}_2\text{Cl}_2)$$

Mp: decomposed around 144 °C

¹H NMR (300 MHz, 80 °C ,DMSO-*d*₆): δ= 1.29 (m, 2H, CH₂), 1.75 (s, 6H, 3CH₂), 2.38 (s, 1H, CH), 2.5 (s, 6H, 2CH₃), 2.6 (s, 6H, 2CH₃), 4.64 (s, 2H, 2CH-N), 8.12-7.31 (m, 8H, 8CH_{arom}) 9.45 (s, H, N-CH=N);

¹³C NMR (75 MHz, DMSO-*d*₆): δ= 19.4 (CH₃), 22.0 (CH₃), 23.7 (CH₂), 27.42 (CH₂), 71.48 (CH), 119.5 (CH), 124.5 (CH), 125.06 (CH), 126.80 (CH), 130.12 (C_q arom), 130.62 (CH), 131.26 (C_q arom), 132.11 (CH_q arom), 135.38 (C_q arom), 137.73 (C_q arom), 162.68 (N-CH=N).

(1*R*,2*R*)-2-(Naphthalen-1-ylamino)cyclohexyl)-3-phenylthiourea



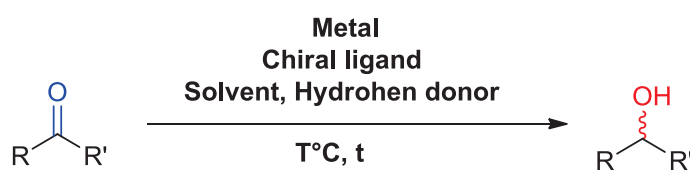
The compound was obtained following the typical procedure E starting from (*1R*, *2R*)-*N*¹-(naphthalen-1-yl) cyclohexane-1, 2-diamine (244 mg, 1 eq), isothiocyanatobenzene (135 mg, 1 eq), and 1 ml of DCM. The crude material was purified by flash column chromatography on silica gel using a gradient of cyclohexane/ethyl acetate (100:0 to 90:10) to afford 298 mg (80%) of the desired product as a yellow solid. for TLC (eluent: cyclohexane / ethyl acetate: 80/20), R_f = 0.54. HREIMS calculated for $C_{23}H_{25}N_3S$ = 375.177 found m/z = 375.1756.

$[\alpha]_D^{20}$ = -180 (c 0.2, CH_2Cl_2)

1H NMR (300 MHz, $CDCl_3$): δ = 0.97-1.02 (m, 4H, CH_2), 1.35-1.55 (m, 2H, CH_2), 1.87-1.92 (d, 2H, CH_2), 2.29-2.33 (m, 1H, CH), 2.52-2.55 (d, 1H, CH), 3.38-3.44 (m, 1H, NH), 4.82-4.85 (d, 2H, NH), 6.09-6.12 (d, 1H, CH_{arom}), 6.53-6.55 (d, 1H, CH_{arom}), 7.02-7.04 (m, 2H, CH_{arom}), 7.26-7.35 (m, 2H, CH_{arom}), 7.48-7.51 (m, 2H, CH_{arom}) 8.08 (s, 1H, CH_{arom}) 8.17-8.20x (m, 2H, CH_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5 (CH_2), 25.1 (CH_2), 31.9 (CH_2), 32.7 (CH_2), 58.4 (CH), 58.9 (CH), 103.1 (CH_{arom}), 116.3 (CH_{arom}), 121.29 (CH_{arom}), 124.7 (C_q arom), 125.09 (2 CH_{arom}), 125.82 (CH_{arom}), 126.4 (CH_{arom}), 127.0 (CH_{arom}), 127.5 (CH_{arom}), 130.0 (2 CH_{arom}), 134.6 (CH_{arom}), 135.8 (C_q arom), 142.8 (C_q arom).

Asymmetric Transfer Hydrogenation of Ketones



2.1 Bibliographic Introduction

Chiral enantiopure alcohols are one of the most important classes in organic molecules due to their high prevalence in natural products, pharmaceuticals, agrochemicals, flavors, and fragrances as well as their applications as chiral building blocks in synthetic chemistry.^{57,58} Different strategies for the preparation of chiral alcohols have been well developed. The most practical and straightforward methods to convert prochiral ketones to chiral alcohols are asymmetric hydrogenation (AH), asymmetric transfer hydrogenation (ATH), and hydrosilylation.

Asymmetric transfer hydrogenation for the reduction of ketone draws a great attention in recent years, mainly due to the avoidance of the using of molecular hydrogen in addition to its efficiency in enantioselective synthesis of optically active alcohols with excellent selectivity. Large series of chiral ligands for asymmetric transfer hydrogenation have been developed with high efficiencies to produce enantiopure products. The most commonly used catalysts for these strategies are ruthenium (Ru), iridium (Ir), and rhodium (Rh) complexes bearing chiral ligands.

2.1.1 Hydrogen donor (Reducing agent)

The most conventional hydrogen sources in ATH are 2-propanol and formic acid. Often a mixture of hydrogen source and base gives high conversions without reversibility and racemization when formic acid/triethylamine mixture (TEAF) is used as the reducing system.⁵⁹ These sources of hydrogen are cheap and “green” reducing agents. Further, they

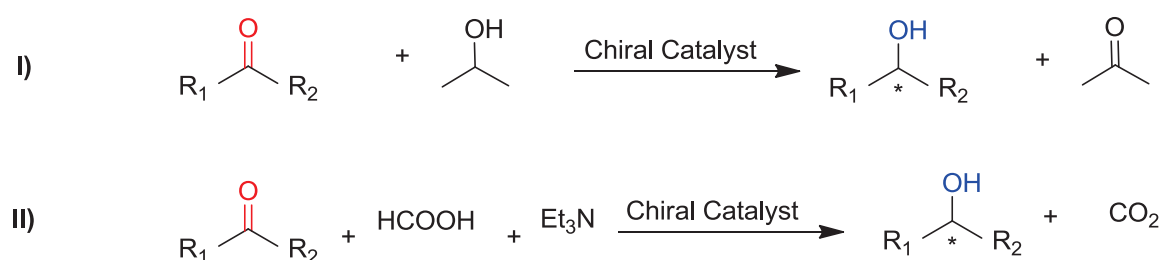
⁵⁷ A. Ferrand, M. Bruno, M. L. Tommasino and M. Lemaire, *Tetrahedron: Asymmetry*, 13 (2002) 1379-1384.

⁵⁸ S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, and R. Noyon, *J. Am. Chem. Soc.* 117 (1995) 7562-7563.

⁵⁹ S. Gladiali, E. Alberico, *Chem. Soc. Rev.* 35 (2006) 226-236.

avoid the problem of hydrogen's flammability or high reactivity of metal hydrides with air and water.

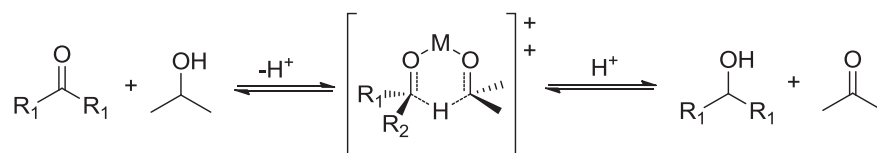
Isopropanol is environmentally friendly, cheap and easy to handle. One of the major drawbacks for using 2-propanol is that the reaction is reversible. In principle, formic acid, formate salt and a mixture of formic acid / triethylamine are more convenient hydrogen donors than 2-propanol due to the irreversible formation of carbon dioxide which shifts the reaction in the direction of the desired product upon hydrogen donation but the use of large amount of amine induce a low atom economy^{60,61}



Scheme 29: I) with 2-propanol; II) with formic acid / triethylamine; the most popular hydrogen donors in transfer hydrogenation reactions

2.1.2 Mechanism overview

Hydride transfer from donor to substrate occurs by two different mechanisms: Metal-mediated direct hydrogen transfer or by metal hydride intermediate (multi-step process). In the case of the metal mediated direct hydrogen transfer, the mechanism is shown in Scheme 30. The substrate and the donor are simultaneously coordinated to the metal center that acts as Lewis acid to form six-membered cyclic transition state which facilitates the activation of substrate toward the nucleophilic attack of the hydride.^{62,63}



Scheme 30: Metal-mediated direct hydrogen transfer (MPV Reduction/Oxidation)

⁶⁰ T. Ikariya and J. A. Blacker, *Acc. Chem. Res.* 40 (2007) 40 1300-1308.

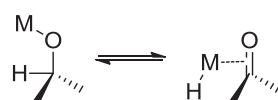
⁶¹ R. Noyori, and S. Hashiguchi, *Acc. Chem. Res.* 30 (1997) 97-102.

⁶² J. S. M. Samec, J-E. Backvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.* 35 (2006) 237-248.

⁶³ M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry.* 10 (1999) 2045-2061.

On the other hand; for the metal hydride intermediate, the catalytic activity depends on the nature of the complexes (mono-hydride or di-hydride complex).

At the mono-hydride mechanism, the hydride metal that is formed from C-H of the reducing agent (hydrogen donor) and the attendant O-H of the donor could be used to reduce the carbonyl compound. This process keeps the identity of the hydride and that of the proton throughout the reaction. Moreover, Mono-hydride mechanism is divided into two types of operations known as inner and outer sphere mechanism. The formation of a transition metal-alkoxide could occur in the inner-sphere mechanism followed by the β -elimination of hydrogen to the metal to form Metal- hydride (scheme 31).⁶²



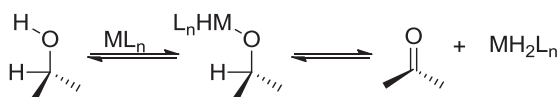
Scheme 31: Mono-hydride inner sphere Mechanism

For the outer sphere mechanism, the substrate and the hydrogen donor don't coordinate to the metal, the formation of six-membered cyclic transition state could occur to transfer hydrogen in a concerted or in step-wise manner as shown in the scheme 32.



Scheme 32: Mono-hydride outer sphere Mechanism

The two hydrides C-H and O-H from the hydrogen donor (2-propanol or formic acid) lose their identity in the di-hydride mechanism. The reason for this is related to the equilibrium that occurs for the two hydrogens when they are bonded to the metal to form metal dihydride.⁶⁴



Scheme 33: Di-hydride mechanism

⁶⁴ S. Y. R. Laxmi, J-E.Backvall, *Chem. Commun.* (2000) 611-612.

2.1.3 Overview of catalysts in ATH of ketones

The design of new suitable classes of chiral ligands remains the main target in the asymmetric catalytic domains due to its performance in this type of catalysis, especially the activity and the stereoselectivity of the designed catalyst. The type of Ligands used for this reaction could be bidentate, tridentate, or tetradentate.

The bidentate ligands show excellent stereoselectivities for asymmetric transfer hydrogenations and asymmetric hydrogenations,⁶⁵ due to their chelation effect, strong conformation stability, which mainly depends on the structural characteristics of the ligands such as their rigidity. Furthermore; the complexation between metal and chiral ligands facilitates and simplifies the mechanistic study as well as the experimental structure reactivity.⁶⁶

The chiral phosphine ligands remain the most efficient ligand in asymmetric hydrogenation reactions, whereas the chiral amine ligands show a great attention in asymmetric transfer hydrogenation reactions.⁶⁷

A family of asymmetric transfer hydrogenations of ketones has been developed based on ruthenium, rhodium, and iridium complexes with chiral ligands.⁶⁸ A library of chiral ligands have been designed and synthesized to be useful as organometallic catalysis with suitable metals in the hydrogenation of prochiral ketones to produce chiral alcohols. Hence, a historical overview has been mentioned below about ATH and the types of metals, ligands, and sources of hydrogen used for this asymmetric reaction.

First of all, ATH was reported for the first time by Doering and Young (in 1950) *via* a partially asymmetric version of the Meerwin-Ponndorf-Verley reduction that proceeds through a six membered transition state as shown in scheme 34. Successful reductions of ketones using chiral alcohol such as (S)-2-butanol or (S)-3-methyl-2-butanol in the presence of Lewis acid aluminum (aluminum alkoxide) were reported but with very low enantiomeric excess that didn't exceed 22%.⁶⁹

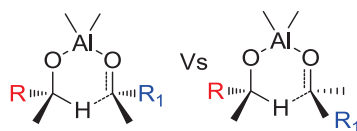
⁶⁵ H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo and K. Itoh, *Organometallics*. 8 (1989) 846-848.

⁶⁶ D. Seebach, A. K. Beck, and A. Heckel, *Angew. Chem. Int. Ed.* 40 (2001) 92-138.

⁶⁷ G. Zassinovich, G. Mestroni and S. Gladiali, *Chem. Rev.* 92 (1992) 1051-1069.

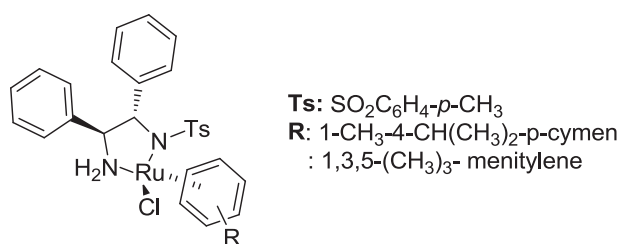
⁶⁸ Z. Xu, Y. Li, J. Liu, N. Wu, K. Li, S. Zhu, R. Zhang, Y. Liu, *Org. Biomol. Chem.* 13 (2015) 7513-7516.

⁶⁹ W. E. Doering and R. W. Young, *J. Am. Chem. Soc.* 72 (1950) 631-637.



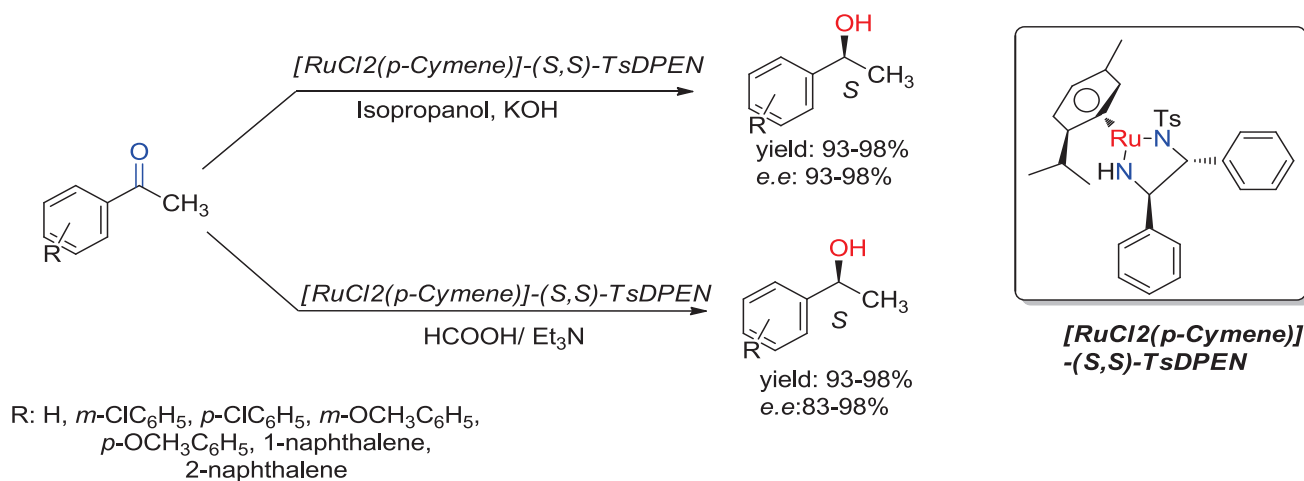
Scheme 34: Asymmetric Meerwein-Ponndorf-Verley Reduction

In 1995, Noyori, Ikariya, and co-workers made ATH as one of the most efficient method for asymmetric reduction of carbonyl compound, after the development of an efficient asymmetric catalyst for ATH using ruthenium complexes with chiral diamine ligands (Scheme 35).⁷⁰



Scheme 35: Noyori's ATH catalysts

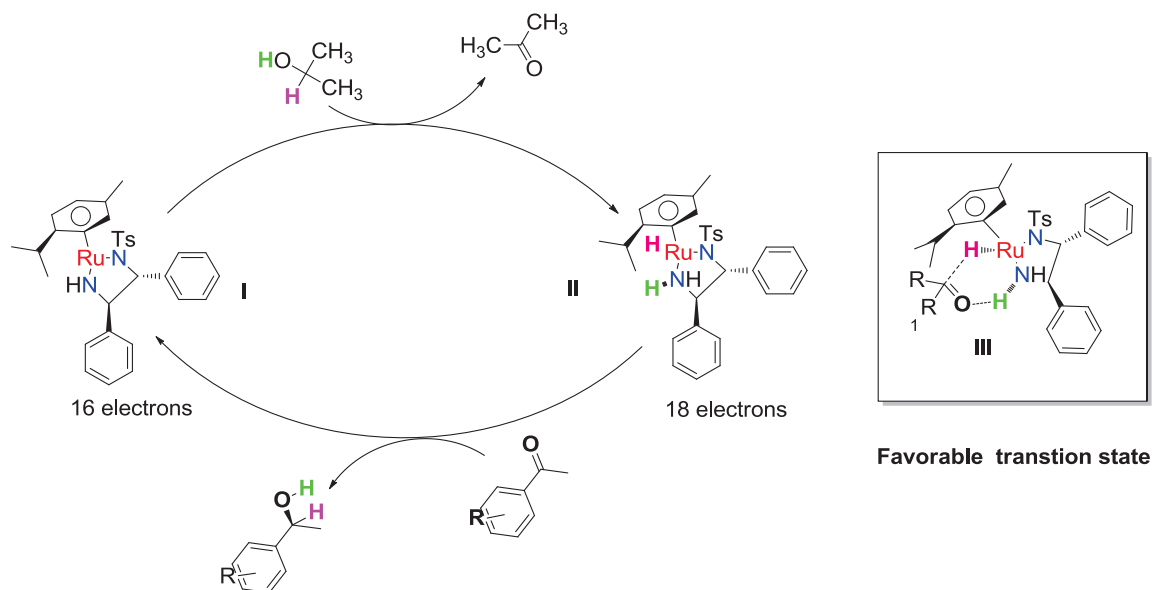
The reduction of ketones into the alcohol was investigated with this type of catalyst even in the presence of isopropanol or formic acid as a hydrogen source and as a solvent. In both cases, a high enantioselectivity of *S* configuration was obtained up to 98% for the desired alcohols and the conversions were excellent (Scheme 36).⁶⁰



Scheme 36: The ATH reactions of aromatic carbonyl compounds to their corresponding chiral alcohols, using isopropanol and formic acid as hydrogen source

⁷⁰ S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori. *J. Am. Chem. Soc.* **117** (1995) 7562-7563.

Furthermore; Noyori *et al.*, proposed a new mechanism for ATH of ketone (Scheme 37) due to the excellent performance of Noyori's catalyst with diamine as a ligand.



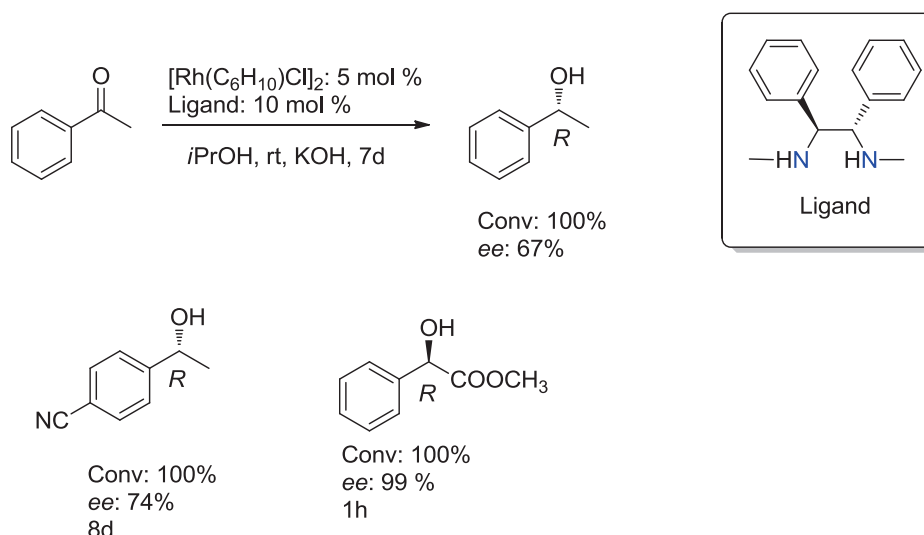
Scheme 37: ATH mechanism with catalyst Noyori's complex

The mechanism is described as a bifunctional metal-ligand mechanism. This mechanism is based on the participation of basic ligands (nitrogen containing ligands) with chiral ruthenium complex and in the presence of hydrogen atom transfer. The active species **II** of 18-electron ruthenium-diamine complex is derived from the species **I** of 16-electron ruthenium-amido complex in the presence of formic acid or isopropanol and base. The activated complex **II** in cooperation with the prochiral ketone formed a favorable six-membered cyclic transition state **III** that facilitate the production of chiral alcohol with high enantiomeric form (Scheme 37).⁷¹

Nitrogen containing ligands have taken great attention in asymmetric transfer hydrogenation in our laboratory. In the early 90's, Gamez *et al.* had studied the influence of diamine ligands in asymmetric transfer. They have shown that using (1*S*,2*S*)-*N,N'*-dimethyl-1,2-diphenylethane-1,2-diamine with [Rh(COD)Cl]₂ would reduce acetophenone to its desired alcohol with complete conversion and *ee* up to 67%. The same catalytic system has also been tested for *p*-acetylbenzonitrile and methyl 2-oxo-2-phenylacetate to give complete conversion toward the desired products with good to excellent *ee* (74% and 99%) (Scheme 38).^{72,73}

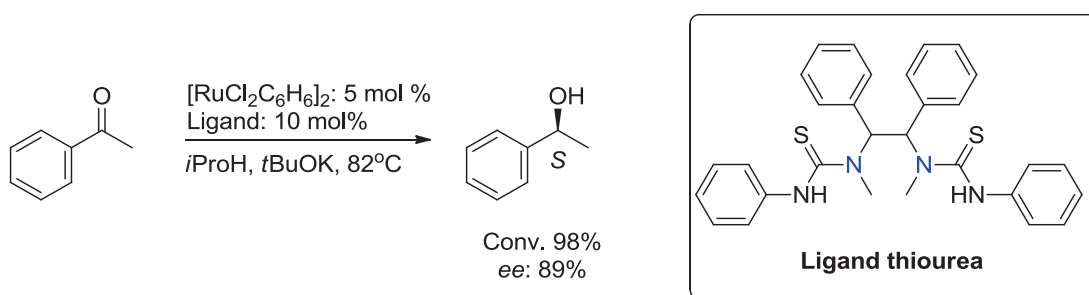
⁷¹ M. Yamakawa, H. Ito and R. Noyori, *J. Am. Chem. Soc.* 122 (2000) 1466-1478.

⁷² P. Gamez F. Fache, P. Mangeney M. Lemaire, *Tetrahedron: letter*, 34, (1993), 6897-6898.



Scheme 38: Asymmetric reduction of various ketones using (1*S*,2*S*)-*N,N'*-dimethyl-1,2-diphenylethane-1,2-diamine

In the late 90's, Touchard *et al.* had developed thiourea ligands derived from chiral diamine for asymmetric transfer hydrogenation. These ligands were combined to rhodium, ruthenium, and iridium. The best thiourea among the series, combined with suitable Ru metal, has shown high conversion (98%) and ee (89%) for acetophenone (Scheme 39). Several ketones have also been reduced to their corresponding desired alcohols with good to excellent ee's.⁷⁴



Scheme 39: Enantioselective reduction of acetophenone using thiourea

Later they have studied series of dialkyldiamines ureas and other thioureas as Rh's ligands for the asymmetric transfer hydrogenation of acetophenone showing good conversions with moderate ee (up to 47%).⁷⁵

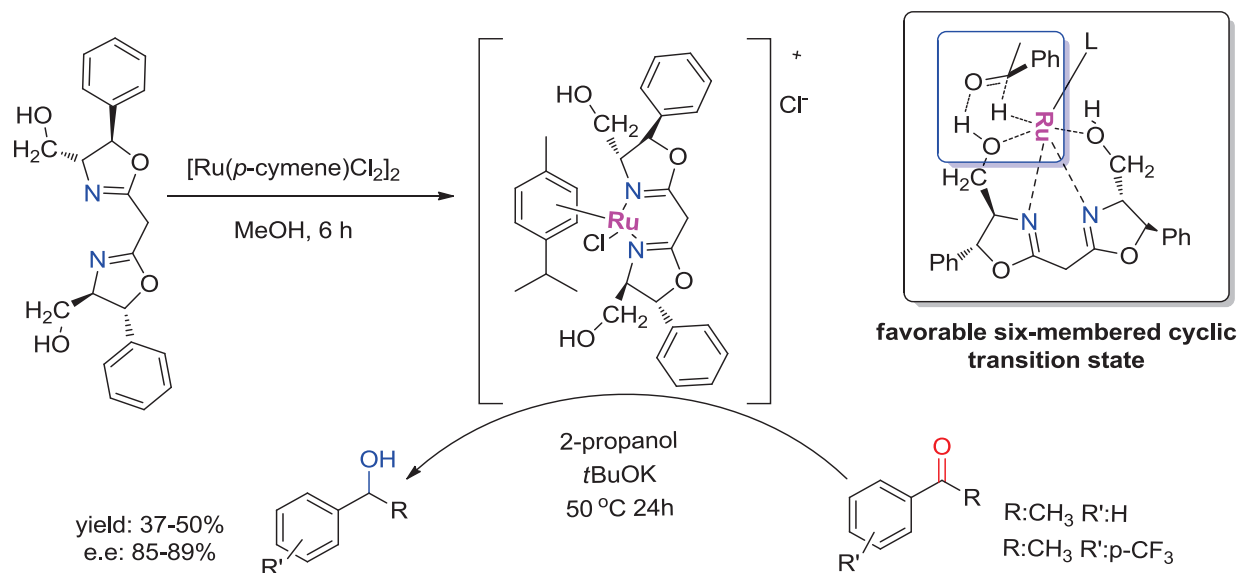
In 2004, Djakovitch *et al.* had developed chiral bis(oxazoline) ligand based on Ru^{II} complex for asymmetric transfer hydrogenation of prochiral ketones. This type of ligands has shown a moderate conversion up to 50% with good selectivity up to 89%. Isopropanol was

⁷³ P. Gamez F. Fache, M. Lemaire, *Tetrahedron: letter*, 6, (1995), 705-718.

⁷⁴ F. Touchard, F. Fache, M. Lemaire, *Tetrahedron:Asymmetry*, 8 (1997) 3319-3326.

⁷⁵ F. Touchard, M. Bernard, F. Fache, M. Lemaire, *J. Mol. Cata. A: Chem*, 140 (1999) 1–11.

used as the source of hydrogen with *t*BuOK as the base. The team supposed that the presence of CH₂OH substituent in the ligand could promote the reaction by forming six-membered cyclic transition state (Scheme 40).⁷⁶

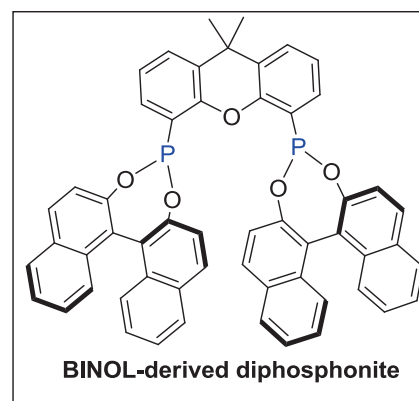
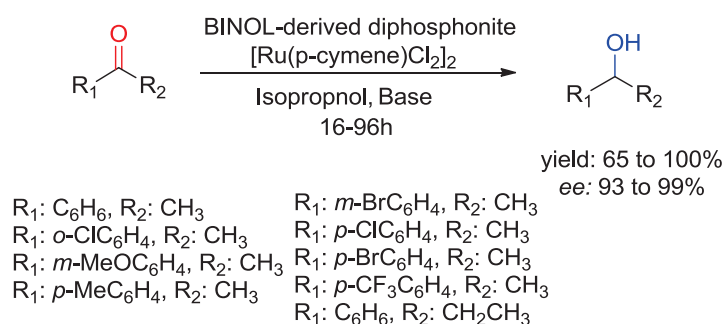


Scheme 40: Chiral bis(oxazoline) Ligand based on Ru II complex for ATH of Ketones

As famed, phosphine ligands especially the bidantate phosphine donor ligands had showed impressive results in asymmetric hydrogenation then in asymmetric transfer hydrogenation of ketone. In 2006, Reetz and Li developed a new type of phosphine ligands "BINOL-derived diphosponite ligand " (scheme 41) which improved the efficiency and the activity of the catalyst in the presence of [Ru(*p*-cymene)Cl₂]₂ for the reduction of ketones to produce chiral alcohol using isopropanol as the source of hydrogen and solvent. Good to excellent conversions with high *ee* up to 99% of *R* configuration were obtained.⁷⁷

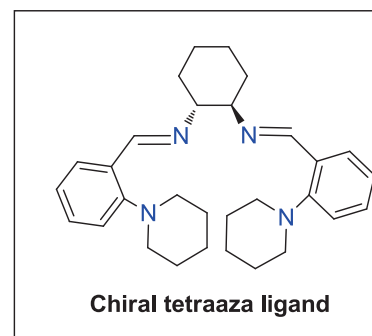
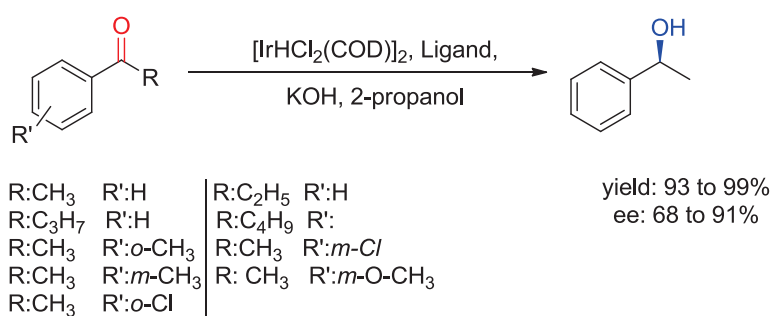
⁷⁶ N. Debono, M. Besson, C. Pinel and L. Djakovitch, *Tetrahedron Letters*.45 (2004) 2235-2238.

⁷⁷ M. T. Reetz, X. Li, X. *J. Am. Chem. Soc.* 128 (2006) 1044-1045.



Scheme 41: Ru-Catalyzed Asymmetric Transfer Hydrogenation of Ketones using BINOL-derived diphosphonite ligand

In 2007, W. Y. Shen *et al.* published achiral tetraaza ligand that was examined for the first time in ATH of prochiral aromatic ketones. $[\text{IrHCl}_2(\text{COD})]_2$ was used as the metal precursor and 2-propanol as the hydrogen source. A variety of aromatic ketones was reduced to the corresponding optically active secondary alcohols in high yields and good ee's (up to 91%) under mild reaction conditions (Scheme 42).⁷⁸

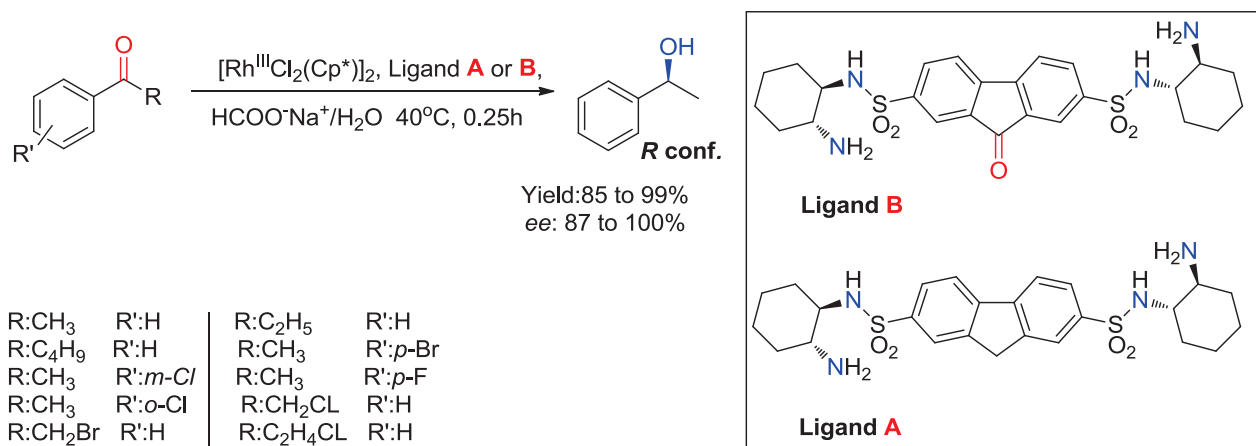


Scheme 42: Chiral tetraaza ligand based on $[\text{IrHCl}_2(\text{COD})]_2$ For ATH of ketones

Three years later, Montalvo-González *et al.* reported two C₂-symmetric bis(sulfonamide) ligands complexed to Rh^{III}(Cp*) precursor to form an efficient organometallic catalyst in the reduction of aromatic ketones to the corresponding chiral secondary alcohols. The reaction occurred under asymmetric transfer hydrogenation (ATH) conditions with an aqueous sodium formate as the hydrogen source (Scheme 43). Excellent isolated yield (85-99%) and ee (87 to 100%) were obtained.⁷⁹

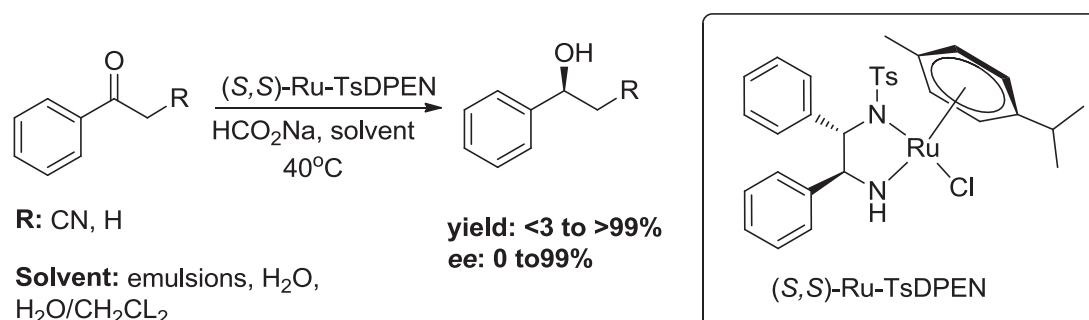
⁷⁸ W-Yi. Shen, H. Zhang, H-L. Zhang and J-X. Gao, *Tetrahedron: Asymmetry*. 18 (2007) 729-737.

⁷⁹ R.M-Gonzalez, D.Chavez, G.Aguirre, M.P-Hake and R. Somanathan, *J. Braz. Chem. Soc.* 3 (2010) 431-435.



Scheme 43: Chiral tetraaza ligand based on $[\text{Rh}^{\text{III}}\text{Cl}_2(\text{Cp}^*)]_2$ For ATH of ketones using HCOO^-Na^+ as reducing agent

In 2010, W. Wang *et al.* reported N-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine ligands (TsDPEN) derived from (R,R) or (S,S) 1,2-diphenyl-ethylenediamine for asymmetric transfer hydrogenation of ketones. The Ru-TsDPEN showed high enantioselectivities up to 99% for the reduction of ketones to alcohols (Scheme 44).⁸⁰

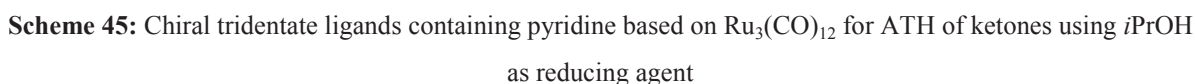


Scheme 44: Asymmetric transfer hydrogenation of ketones

In 2013, M. O. Darwish *et al.* synthesized chiral tridentate ligands starting from (1*R*,2*R*)-TsDPEN, or (1*R*,2*R*)-(-)-*N*-*p*-tosyl-1,2-diamine structure with an additional pyridine groups. These types of ligands were tested in ATH of ketones based on $\text{Ru}_3(\text{CO})_{12}$ as the metal source and *i*PrOH as the reducing agent and solvent. Chiral alcohols were formed with *ee* up to 93% in the best case and isolated yield up to >99% in some cases (Scheme 45).⁸¹

⁸⁰ W. Wang, Z. Li, W. Mu, L. Su, Q. Wang. *Cata. Com.* 11 (2010) 480–483.

⁸¹ M. O. Darwish, A. Wallace, G. J. Clarkson and M. Wills, *Tetrahedron lett.* 54 (2013) 4250–4275.



Reaction scheme showing the asymmetric hydrogenation of ketones catalyzed by $[\text{Et}_3\text{NH}][\text{HFe}_3(\text{CO})_{11}][(\text{S,S})\text{-PNNP}]$ (1 mol%), KOH (6 mol%), *i*PrOH, 7 h, 82 °C.

Reaction 1: Acetophenone to (S)-1-phenylethanol. Conv. 92%, ee. 56%.

Reaction 2: 4-methoxyacetophenone to (S)-1-(4-methoxyphenyl)ethanol. 11h, Conv. 44%, ee. 52%.

Reaction 3: 4-chloroacetophenone to (S)-1-(4-chlorophenyl)ethanol. 11h, Conv. 36%, ee. 49%.

Reaction 4: General reaction of a ketone with substituent R to a chiral alcohol. R: CH_2CH_3 (45°C, 3h, Conv. 87%, ee. 72%), $\text{CH(CH}_3)_2$ (45°C, 3h, Conv. 90%, ee. 78%), $\text{C(CH}_3)_3$ (82°C, 7h, Conv. 19%, ee. 93%).

Structure of the chiral ligand $(\text{S,S})\text{-PNNP}$ is shown in a box.

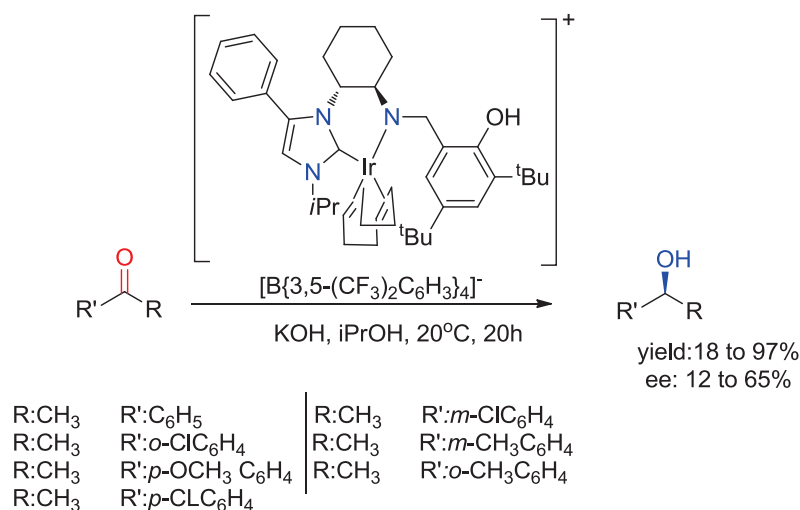
Scheme 46: ATH of various ketones catalyzed by $[\text{Et}_3\text{NH}][\text{HFe}_3(\text{CO})_{11}]/(S,S)\text{-PNNP}$

Since few years, the family of *N*-heterocyclic carbene (NHC) ligands has also been investigated in ATH of ketones as an organometallic catalyst. This is due to the strong

⁸² Y.-Y. Li, S.-L. Yu, W.-Y. Shen J.-X. Gao, *Acc. Chem. Res.* 98 (2015) 2587-2598.

coordination of σ -donors in addition to the conformation of steric and electronic (orbital overlap) stabilization on the metal center. Using NHC as a ligand in ATH has been limited and only few examples have been reported. Most of them have showed moderate to good conversions and acceptable enantioselectivities.^{83,84}

In 2009, Douthwaite *et al.*⁸⁵ have advertised the synthesis of NHC-phenoxyimine Ligand. The catalytic application of the complexes between iridium metals and (NHC) ligands has been investigated in enantioselective ATH of ketones in the presence of *i*PrOH as the hydrogen donor (Scheme 47). The conversions of prochiral ketone derivatives to chiral alcohols have been performed with acceptable *ee*'s in most cases. The authors have reported that the highest *ee* has been obtained with 3-chloroacetophenone (up to of 65%) with 31% of yield.



Scheme 47: NHC-phenoxyimine were investigated with Ir metal as a catalytic application in enantioselective ATH of ketones

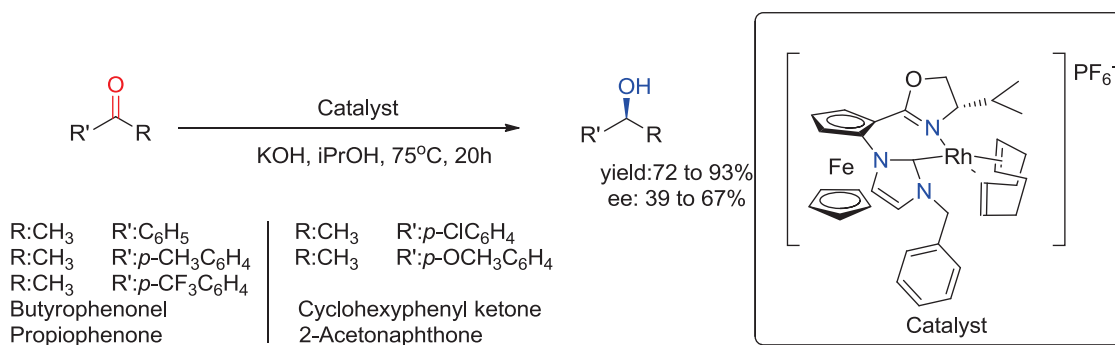
During the same year, Kuang *et al.*⁸⁶ have also reported a chelated ferrocene-based planar chiral NHC-rhodium (Scheme 48) complex to the ATH of ketone derivatives using *i*PrOH as the source of hydrogen. High catalytic activity and moderate enantioselectivity have been observed. Acetophenone and cyclohexylphenyl ketone were reduced to chiral secondary alcohols with 60% *ee* and 67% *ee*, respectively

⁸³ H. Seo, B. Y. Kim, J. H. Lee, H. J. Park, H. U. Son and Y. K. Chung, *Organometallics*. 22 (2003) 4783-4791.

⁸⁴ R. Hodgson and R. E. Douthwaite, *J. Organomet. Chem.* 690 (2005) 5822-5831.

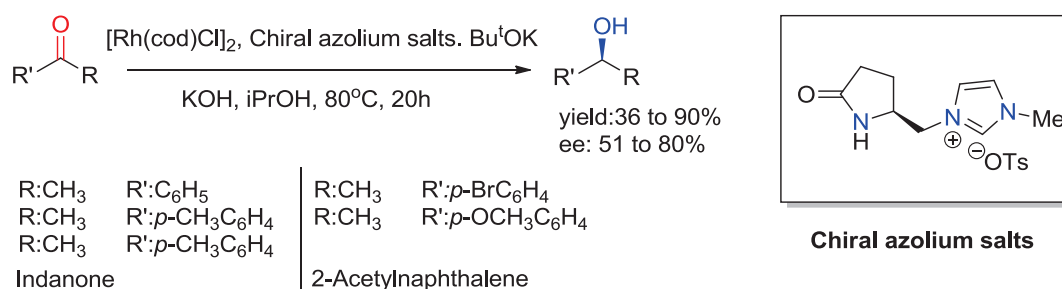
⁸⁵ G. Dyson, J-C. Frison, A. C. Whitwood and R. E. Douthwaite, *Dalton Trans.* (2009) 7141-7151.

⁸⁶ R. Jiang, X. Sun, W. He, H. Chen and Y. Kuang, *Appl. Organometal. Chem.* 23 (2009) 179-182.



Scheme 48: A chelated ferrocene-based planar chiral NHC-rhodium complex IN asymmetric transfer hydrogenation of ketones derivative

Two years later, Giang Vo-Thanh *et al.*⁸⁷ have also reported a chiral azolium salts (NHC) derived from (S)-pyroglutamic acid. The evaluation of rhodium catalysts containing chiral azolium ligand has been studied in the ATH of aromatic ketone with *i*PrOH. Good isolated yield up to 90% and enantioselectivity up to 80% have been obtained for acetophenone (Scheme 49).

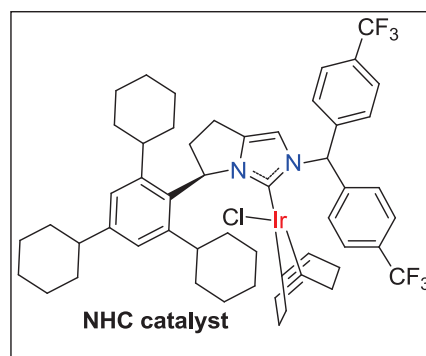
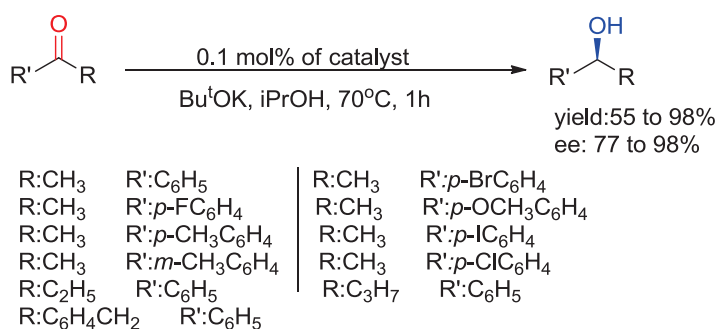


Scheme 49: Chiral Azolium salts (NHC) with of rhodium metal in the ATH of aromatic ketone with *i*PrOH

In 2015, Kazuhiro Yoshida's group⁸⁸ reported an excellent iridium catalyst containing monodentate chiral NHC ligands in the ATH of aromatic ketones (Scheme 50). The reduction of prochiral ketones with NHC/Ir catalyst was conducted fluently gave chiral alcohols with high enantioselectivities (up to 98%) and productivities (TON up to 4,500).

⁸⁷ A. Aupoix, C. Bournaud and G. V-Thanh, *Eur. J. Org. Chem.* (2011) 2772-2776.

⁸⁸ K. Yoshida, T. Kamimura, Kuwabara and A. Yanagisawa, *Chem. Commun.* 51 (2015) 15442-15445.

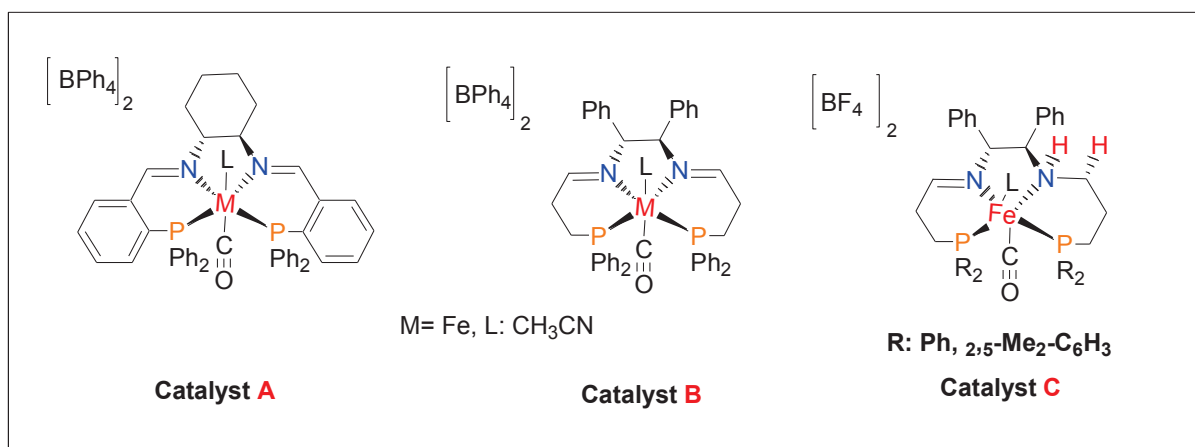


Scheme 50: Iridium catalyst containing monodentate chiral NHC ligands in the ATH of aromatic ketones

Since the last years, the investigation of *N*- heterocyclic carbene ligands takes a wide range in asymmetric reactions and especially in ATH of ketones as mentioned above. Thus, the development of more efficient chiral NHC ligands remains a challenge in chemistry for ATH and many other reactions.

Recently, Iron metal also joined this field as a fascinating candidate and alternative to precious metals (such as Rh, Ir, Ru). Fe is one of the most abundant metals on earth. It is a cheap, greener, and less toxic metal. Nowadays, Iron presents as a revolution in asymmetric hydrogenation catalysis.

In 2008, Robert H. Morris group developed a series of iron-catalyzed asymmetric transfer hydrogenation of ketone (Scheme 51, catalyst **A**, **B** and **C**).

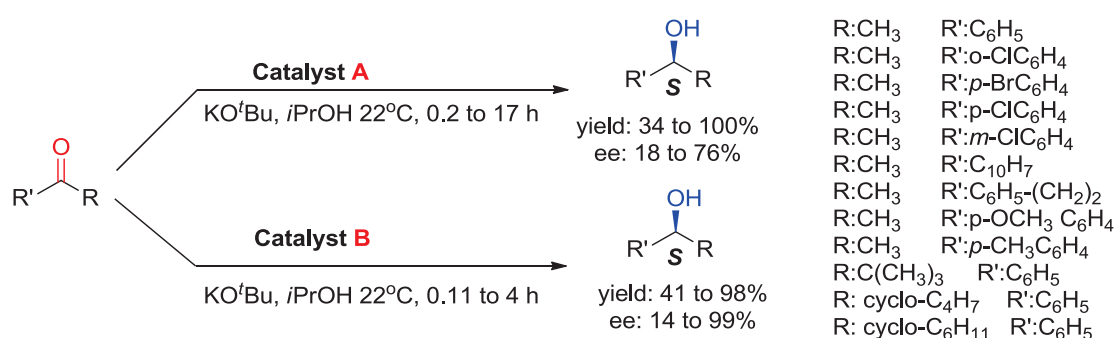


Scheme 51: Active asymmetric transfer hydrogenation catalyst for ketones (R. H. Morris's catalyst) using Fe as a procurer metal with PNP ligands

The first iron-catalyzed ATH of ketone was catalyst **A** comprising a chiral ligand of PNP tetradentate diiminodiphosphine derived from (1*R*,2*R*)-diaminocyclohexane and a commercially available phosphine aldehyde. Catalyst **A** showed a very good activity in the

reduction of ketones once activated with KO^tBu in *i*PrOH. Excellent TOF was obtained (up to 995 h⁻¹) with moderate *ee* in some cases (Scheme 52).⁸⁹

One year later, Morris *et al.* have also mentioned another Fe catalyst (catalyst **B**) using chiral ligand containing PNNP tetradentate ligand derived from (1*R*,2*R*)-diphenylethylenediamine that has been used in asymmetric transfer hydrogenation of ketone (Scheme 52). Catalyst **B** has shown a very high activity and enantioselectivity in ATH of ketones with a scope of substituent groups. Excellent *ee* values and TOF (Up to 4900 h⁻¹) have been obtained (Scheme 52).⁹⁰



Scheme 52: Robert H. Morris's catalyst for ATH of ketones using *i*PrOH as reducing agent

Four years later, Morris *et al.* have also developed new ligands (Scheme 51, Catalyst **C**) to be more effective in ATH of ketones with a scope of substituent groups that improved the enantiomeric excess, the TOF, and the conversion.⁹¹ Those results have showed that Fe metal could be an alternative to those of the Ru, Ir, and Ru metals in this type of reactions.

⁸⁹ C. S-Seng, F. Freutel, A. J. Lough and R. H. Morris, *Angew. Chem.* 120 (2008) 954-957.

⁹⁰ A. Mikhailine, A. J. Lough and R. H. Morris, *J. Am. Chem. Soc.* 131 (2009) 1394-1395.

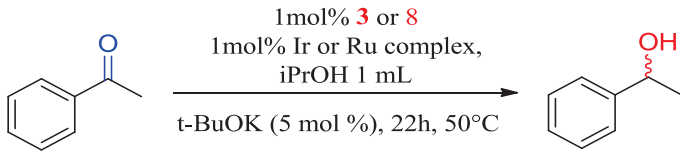
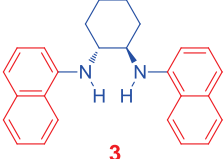
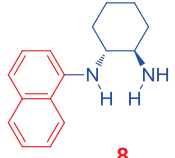
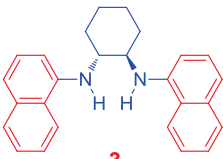
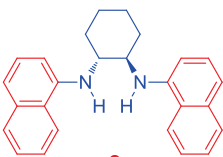
⁹¹ W. Zuo, A. J. Lough, Y. F. Li and R. H. Morris, *Science*. 342 (2013) 1080-183.

2.1 Result and discussions

2.1.1 Screening of metals and chiral asymmetric ligands in the reduction of ketone

Our suitable synthesis of *N,N'*-arylated diamine ligands prompts us to evaluate their interest in asymmetric transfer hydrogenation. Inspired by the literature data, transfer hydrogenation of ketones has been developed essentially with Ru or Ir catalysts associated to isopropanol in the presence of potassium tert-butoxide.^{92,93}

Table 3: Transfer hydrogenation of acetophenones using Ru and Ir metal with ligand 3 and 8.

				
Entry	Metal precursor	Ligand	Conv ^a (%)	e.e ^a (%)
1	[RuCl ₂ (<i>p</i> -cymene)] ₂	 3	90	Rac
2	[RuCl ₂ (<i>p</i> -cymene)] ₂	 8	35	11 (S)
3	[Ir(COD) ₂] BF ₄	 3	0	-
4	[IrCp*Cl ₂] ₂	 3	76	Rac

^a Conversion and ee were determined by chiral GC

⁹² J. A. Fuentes, M.B. France, A.M. Z. Slawina and M. L. Clarke, *New Journal of Chemistry*, **33** (2009) 466–470.

⁹³ D. Maillard, G. Pozzi, S. Quici and D. Sinou, *Tetrahedron*, **58** (2002) 3971–3976.

The reduction of acetophenone was considered first, since this ketone represents the typical substrate in the reduction studies of aromatic ketones. When $[\text{RuCl}_2(p\text{-cymene})]_2$ was used as metal precursor with ligand **3** (Table 3, entry 1). 1-phenyl-ethanol was formed with 90% conversion in a racemic mixture, while with ligand **8** the conversion was much lower (34%) with a poor enantiomeric excess didn't reach 11% (Table 3, entry 2). With $[\text{Ir}(\text{COD})_2]\text{BF}_4$ and ligand **3** no transformation was observed (Table 3, entry 3). While when the $[\text{IrCp}^*\text{Cl}_2]_2$ was used, a good conversion was obtained but unfortunately without enantioselectivity (Table 3, entry 4). This difference of activity, especially with the two iridium precursors could be related to diene ligands, particularly the strong coordination of cyclooctadiene (COD), which is usually eliminated under molecular hydrogen.

In view of these results, the nature of the reductant was modified following Carreira conditions:⁹⁴ the reduction of acetophenone was carried out with $[(\text{COD})_2\text{Ir}]\text{BF}_4$ and ligand **3** in water/methanol (1v:1v) at room temperature under argon atmosphere for one hour, before adding formic acid as a reducing agent.

Table 4: Transfer hydrogenation of acetophenone using $[\text{Ir}(\text{COD})_2]\text{BF}_4$ /ligand **3** system and formic acid

Entry	HCO_2X (equiv.)	t (h)	Conv ^a (%)	TON	TOF ^b (h ⁻¹)	e.e. ^a (%) (S)
1*	HCO_2H , 5 eq	40	30	60	1.5	77
2	HCO_2H , 5 eq	40	65	130	3.25	78
3	HCO_2H , 10 eq	40	24	48	1.2	70
4	HCO_2Na 5 eq	48	49	98	2.45	50
5**	HCO_2H 5 eq	40	26	52	1.3	82
6	HCO_2H 2.5 eq / HCO_2Na 2.5 eq	23	>99	≈200	8.7	85

* ligand/metal= 1; ** Under air, ^a Conversion and ee are determined by chiral GC ^b minimum TOF

⁹⁴ H. Vázquez-Villa; S. Reber; M. Ariger; E. Carreira, *Angew. Chem. Int. Ed.* 50 (2011) 8979–8981.

Initially, for 1:1 ratio metal/ligand **3**, a low conversion was tested, a relatively good enantiomeric excess was obtained (*e.e* 77%), while using 1:2 ratio metal/ligand **3** the conversion reached 65% with 78% *e.e* (Table 4 entry 1 and 2). The configuration of the alcohol was identified as S isomer by comparison with the literature.

An increasing of formic acid load to 10 equiv. (instead of 5) seemed not beneficial for the reduction since the conversion was lower (Table 4, entry 3) that may be due to the dilution effect and to the modification of the pH. Sodium formate was also examined and no improvement was observed for both conversion and enantiomeric excess (Table 3, entry 4). Carrying out the reaction under air conducted to a decreasing of conversion (26%) with almost same *e.e* (82%) (Table 4, entry 5). Then, a mixture of formic acid and sodium formate of ratio 1:1 was used; a complete conversion was achieved with 85% *e.e* after 22 h (entry 6).

The [(COD)₂Ir]BF₄/ligand **3** system using a mixture of formic acid and sodium formate (with pH 3.5 at the beginning of the reaction) as a reductant gave the best results for this reduction (conversion >99%). This pH-dependent reactivity with formic derivatives was previously observed by Ogo.⁹⁵ The other derived ligands were evaluated in the same conditions.

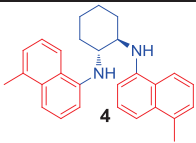
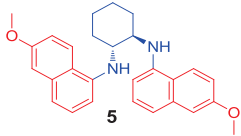
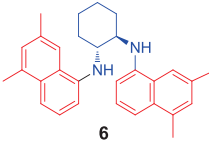

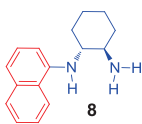
2.1.2 Screening of asymmetric diamine ligands in the reduction of ketone

Following the best conditions that we defined, the complexes of [(COD)₂Ir]BF₄ with chiral diamine ligands **4**, **5**, **6**, **7** and **8** have been also tested for the reduction of acetophenone.

The substituents on the aromatic ring revealed not to have a notable influence on the reaction, complete conversions and almost similar enantiomeric excess were observed with ligands **4**, **5** and **6** derived from α -tetralone derivatives (Table 5, entries 1, 2 and 3). Similar results were also observed with the derivative of β -tetralone **7** (Table 5, entry 4), while a loss of the enantiomeric excess was noticed with the monoarylated diamine ligand **8** (Table 5, entry 5).

⁹⁵ S. Ogo, N. Makihara, Y. Watanabe *Organometallics*. 18 (1999) 5470-5474.

Table 5: Chiral diamine ligands for transfer hydrogenation of acetophenone

Entry	Ligand	Time (h)	Conv (%)	TON	TOF* (h ⁻¹)	e.e (%)
1		24	100	200	8.33	83
2		24	100	200	8.33	83
3		16	100	200	12.5	86
4		16	100	200	12.5	83
5		24	96	192	8	52

* The minimum TOF.

2.1.3 Reduction of ketones derivatives

With the optimized condition in hand, a range of aromatic ketones were reduced to their corresponding alcohols with high to moderate isolated yields and good *e.e* using catalytic system [(COD)₂Ir]BF₄/ligand **3** as shown in table 6.

The substitution of acetophenone in aromatic ring with halogen did not affect the reaction since ketones were efficiently and enantioselectively reduced regardless of the *meta* or *para* position of the halogen (Table 6, entries 2, 3, 4). The reduction of acetophenone bearing a EWG nitro group in *para* position of aromatic ring afforded the corresponding alcohol with a good yield but with a lower enantiomeric excess (Table 6, entry 5), but with EWG like trifluoromethyl in the same position (*para*), the reduction occurred with a similar conversion and enantioselectivity compared to acetophenone (Table 6, entry 6).

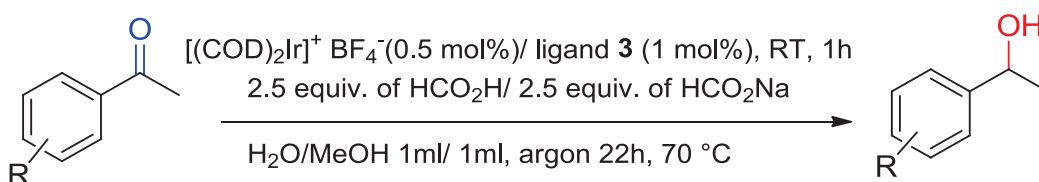
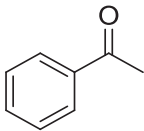
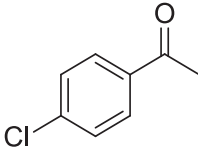
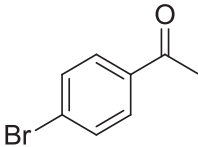
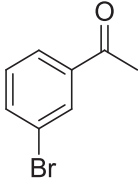
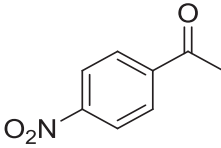
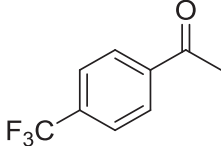
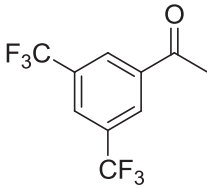
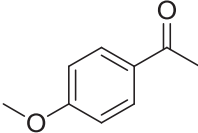
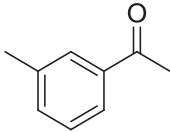
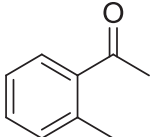


Table 6: Reduction of ketones derivatives:

Entry	Ketone	Yield ^a (%)	TON	TOF ^b (h ⁻¹)	e.e. ^c (%)
1		86	172	7.2	(<i>S</i>)-85
2		70	140	6.37	(<i>S</i>)-85
3		80	160	7.27	(<i>S</i>)-80
4		79	168	7.63	(<i>S</i>)-84
5		87	174	7.91	(<i>S</i>)-52
6		86	172	7.2	(<i>S</i>)-86
7		71	142	6.45	(<i>S</i>)-63
8		31	62	2.82	(<i>R</i>)-25
9		66	132	6	(<i>S</i>)-86
10		81	162	7.36	(<i>S</i>)-93

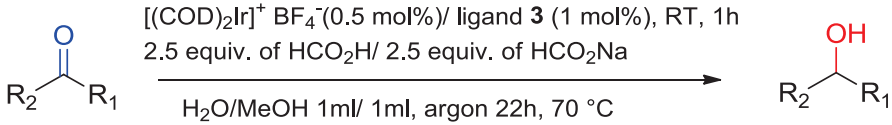
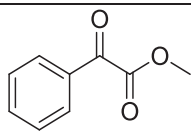
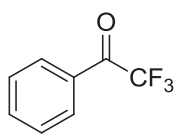
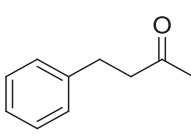
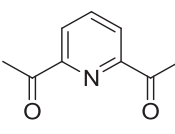
^a Isolated yield, ^b TOF minimum, ^c ee determined by GC chiral column or OD HPLC chiral column

Nevertheless, the substitution with two CF₃ groups in *meta* positions was deleterious for the enantiomeric excess (Table 6, entry 7). The acidity of the benzylic proton in the formed alcohols from the nitro and the di-trifluoromethyl derivatives might be responsible for the decrease of enantiomeric excess, by making possible the reversible reaction followed by racemization. Acetophenone bearing p-methoxy group was reduced with a low yield as well as a low enantioselectivity (Table 6, entry 8).

In this particular case, the configuration of the carbon is inverted compared to other, possibly is due to the coordination or EDG character of methoxy group. Electron donating group as a methyl in *meta* position gave a lower isolated yield of alcohol but with similar ee. And the same group in *ortho* position has a positive effect on the enantiomeric excess (Table 6, entries 9 and 10). In conclusion, many parameters related to substrate can affect the activity and the selectivity of the reaction like electronic, chelation and steric hindrance effects.

The reduction of more functionalized ketones was also investigated. (Table 7)

Table 7: Reduction of functionalized ketones

<div style="text-align: center;">  </div>					
Entry	Ketone	Yield ^a	TON	TOF ^b (h ⁻¹)	e.e. ^c %
1		71	144	6.55	(<i>S</i>)-43
2		86	172	7.82	(<i>R</i>)-59
3		41	82	3.73	(<i>R</i>)-15
4		47	92	4.18	(<i>S,S</i>)> 99 d.e: 67 ^d %*

^a Isolated yield, ^b TOF minimum, ^c ee determined by GC chiral column OD HPLC chiral column. ^d the major diastereoisomer is the optically active (*S,S*) of [α]_D²⁰ = -21.5. * (*S,S*)/meso= 83.5/16.5

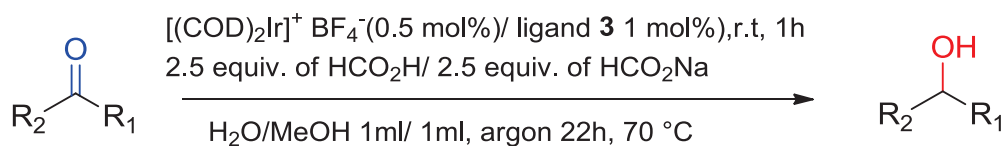
For activated ketone, α -acetophenone ester, the corresponding α -hydroxy ester (Table 7, entry 1) was obtained with a modest induction 43% *e.e* (*S*) and 71% isolated yields. Close results were observed with the α,α,α -trifluoroacetophenone (Table 7, entry 2): a good isolated yield 86% with 59% *e.e* of corresponding alcohol with the opposite configuration (*R*). This change is linked to the CF_3 group, which inverts the priority order of the group as already described. Dialkyl-ketones (Table 7, entry 3), gave low *e.e* 15% of *S* configuration with moderate isolated yield. The reaction of 2,6-diacetylpyridine afforded the corresponding diol (Table 7, entry 4) in 67% d.e and >99% *e.e* of (*S, S*) configuration

2.2 Conclusion:

The interest of our synthesized ligands has been evaluated in asymmetric transfer hydrogenation of prochiral ketone, catalyzed by homogeneous iridium catalysts formed *in situ*. Best results are obtained using a mixture of sodium formate and formic acid as a hydrogen source, improving the efficiency of the catalyst at pH=3.5 at the beginning of the reaction. These achievements demonstrated the interest of this type of ligands.

2.3 Experimental Section

2.3.1 General Procedure for the reduction of ketone with [(COD)₂Ir]BF₄ and chiral amine ligand



In a pressure tube, 0.5 mol% of metal precursor $[(COD)_2Ir]BF_4$ (2.48 mg, 0.005 mol) and 1 mol% of chiral amine ligand (3.66 mg, 0.01 mmol) were dissolved in 2 mL of water and methanol (ratio 1:1) and stirred at room temperature for 1 h under argon atmosphere. Then formic acid (2.5 eq, 0.1 mL), sodium formate (2.5 eq, 170 mg) and 1 eq of ketone substrate (1 mmol) were introduced.

The reaction mixture was stirred at 500 rpm and heated at 70 °C for 22 h. After that, the tube was cooled to room temperature. The organic compound was extracted with either ethyl acetate or CH_2Cl_2 . Then, the solution was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel using cyclohexane/ethyl acetate as the gradient eluent (90:10–7:3). After evaporation, alcohols were obtained as oil or solid. The products were identified by NMR. The conversion and the enantioselectivity were determined by chiral GC or chiral HPLC analysis.

2.3.2 Characterizations data for chiral alcohols

The chiral alcohol products mentioned below are characterized by NMR, furthermore; the spectra are compared with those already reported.

(1) (S)-1-phenylethanol [1445-91-6]:

Oil

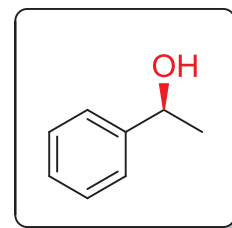
¹H NMR (300 MHz, CDCl₃): δ = 7.14–7.28 (m, 5 H, Ar), 4.79 (q, J = 6.42 Hz 1 H, CH-OH), 1.77 (br. s, 1 H, OH), 1.39 (d, J = 6.5 Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 145.8 (C_q), 128.5 (2 x CH), 127.5 (CH), 125.4 (2 x CH), 70.4 (CH-OH), 25.1 (CH₃) ppm.

GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 70 °C at 1 °C/min, retention time: 21.5 min (minor, *R*), 22.2 min (major, *S*), 85% *ee*.

$[\alpha]_D^{25} = -44$ (c = 1, CHCl₃), 85% *ee* (*S*).

Literature value: $[\alpha]_D^{23} = -43.7$ (c = 0.9, CHCl₃), 69% *ee* (*S*).⁹⁶



(2) (S)-1-(4'-Bromophenyl) ethanol [100760-04-1]:

Oil.

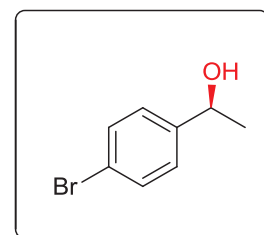
¹H NMR (300 MHz, CDCl₃): δ = 7.48 (d, , 2 H, Ar), 7.24(d, 2 H, Ar), 4.88 (q, J = 6.39 Hz, 1 H, CH-OH), 1.9 (br. s, 1 H, OH), 1.48 (d, J = 6,39 Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 144.7 (C_q), 131.6 (2 x CH), 127.2 (2 x CH), 121.2 (C_q), 69.8 (CH-OH), 25.2 (CH₃) ppm.

GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 100–140 °C at 1 °C/min, retention time: 30.5 min (minor, *R*), 31.3 min (major, *S*), 80% *ee*.

$[\alpha]_D^{25} = -30$ (c = 1.0, CHCl₃), 80% *ee* (*S*).

Literature value: $[\alpha]_D^{20} = -37.6$ (c = 5.0, CHCl₃), 94% *ee* (*S*).⁹⁵

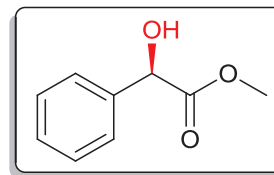


⁹⁶ N. A.Salvi and S.Chattopadhyay, *Tetrahedron*, 57 (2002) 2833-2839.

(3) (R)-(-)- Mandelic acid methyl ester [20698-91-3]:

¹H NMR (300 MHz, CDCl₃): δ = 7.26 -7.44 (m, 5 H, Ar), 5.18 (d, J = 4.95 Hz, 1 H, CH-OH), 3.76 (s, 3 H, COOCH₃), 3.5 (br.d, 1 H, OH) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 174.2 (C_q), 138.2 (C_q), 128.6 (2 x CH), 128.5 (CH), 126.6 (2 x CH), 72.9 (CH-OH), 53.1 (CH₃) ppm.



GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 90 °C, retention time: 62.95 min (major, *R*), 66.07 min (minor, *S*), 52% *ee*.

$[\alpha]_D^{25}$ = -67 (c = 1, CHCl₃), 51% *ee* (*R*).

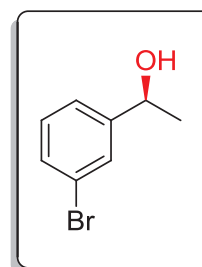
Literature value: $[\alpha]_D^{20}$ = -142 (c = 1, Methanol) 99% *ee* (*S*).⁹⁷

(4) (S)-1-(3-Bromophenyl) ethanol [134615-22-8]:

Oil

¹H NMR (300 MHz, CDCl₃): δ = 7.11-7.5, (m, 4 H, Ar), 4.78 (q, J = 6.42 Hz, 1 H, CH-OH), 1.93 (br. s, 1 H, OH), 1.4 (d, J = 6.42 Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 148 (C_q), 130.5 (CH), 130.1 (CH), 128.6 (CH), 127.9 (CH), 124 (CH), 122.6 (C_q), 69.8 (CH-OH), 25.3 (CH₃) ppm.



GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 100 °C at 1 °C/min, retention time: 23.23 min (minor, *R*), 23.7 min (major, *S*), 84% *ee*.

$[\alpha]_D^{25}$ = -24.4 (c = 1, CHCl₃), 80% *ee* (*S*).

Literature value: $[\alpha]_D^{20}$ = +28.1 (c = 1, CHCl₃) 82% *ee* (*R*).⁹⁸

⁹⁷ S. S. Weng, H. C. Li, T. M. Yang, *R.S.C Advances.*, 3 (2013) 12939–12944.

⁹⁸ C. Guyon, E. Métay, N. Duguet and M. Lemaire, *Eur. J. Org.Chem.*, (2013) 5439-5444.

(5) (S)-1-(4'-chlorophenyl) ethanol [99528-42-4]:

Oil

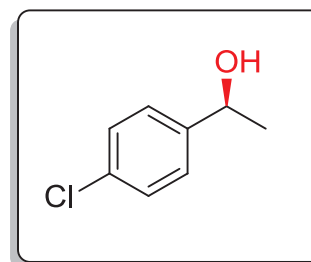
¹H NMR (300 MHz, CDCl₃): δ = 7.31, (s, 4 H, Ar), 4.88 (q, J = 6 Hz, 1H, CH-OH), 1.93 (br. s, 1 H, OH), 1.47 (d, J = 6 Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 144.2 (C_q), 133.1 (2 \times CH), 128.6 (2 \times CH), 126.8 (C_q), 69.8 (CH-OH), 25.3 (CH₃) ppm.

GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 100 °C at 1 °C/min, retention time: 45.8 min (minor, *R*), 47.2 min (major, *S*), 85% *ee*.

$[\alpha]_D^{25}$ = -43 (c = 1, CHCl₃), 85% *ee* (*S*).

Literature value: $[\alpha]_D^{20}$ = -48.4 (c = 7.3, CHCl₃) 91% *ee* (*S*).⁹⁵



(6) (S)-1-(3-Methylphenyl) ethanol:

Oil.

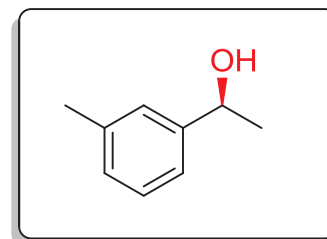
¹H NMR (300 MHz, CDCl₃): δ = 7.52 (d, 2 H, Ar), 7.22-7.12 (m, 2 H, Ar), 5.14 (q, 1 H, CH-OH), 2.35 (s, 3 H, CH₃), 1.75 (br. s, 1 H, OH), 1.47 (d, J = 6.4 Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 143.8 (C_q), 134.2 (C_q), 130.4 (CH), 127.2 (CH), 126.4 (CH), 124.5 (CH), 66.8 (CH-OH), 23.9 (CH₃) ppm, 18.9 (CH₃) ppm.

GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 60–120 °C at 1 °C/min, retention time: 39.2 min (minor, *R*), 41.1 min (major, *S*), 86% *ee*.

$[\alpha]_D^{25}$ = -41.5 (c = 1.0, CHCl₃), 86% *ee* (*S*).

Literature value: $[\alpha]_D^{16}$ = -47.3 (c = 0.84, CHCl₃), 90% *ee* (*S*).⁹⁹



⁹⁹ W. Wang and Q. Wang, *Chem. Commun.*, 46, (2010) 4616-4624.

(7) (S)-1-(2-Methylphenyl)ethanol [51100-05-1]:

Oil.

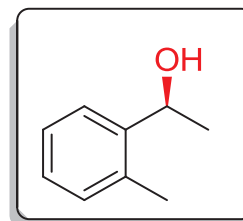
¹H NMR (300 MHz, CDCl₃): δ = 7.28-7.09 (m, 4 H, Ar), 4.88 (q, J = 6 Hz 1 H, CH-OH), 2.38 (s, 3 H, CH₃), 1.91 (br. s, 1 H, OH), 1.50 (d, J = 9 Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 145.8 (C_q), 138.2 (C_q), 128.4 (CH), 128.2 (CH), 126.1 (CH), 122.4 (CH), 70.5 (CH-OH), 25.1 (CH₃) ppm, 21.5 (CH₃) ppm.

GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 60–120 °C at 1 °C/min, retention time: 42.55 min (minor, *R*), 45.4 min (major, *S*), 93% ee.

$[\alpha]_D^{25}$ = -70 (c = 1, CHCl₃), 93% ee (*S*).

Literature value: $[\alpha]_D^{25}$ = -71.9 (c = 1.06, CHCl₃), 99% ee (*S*).⁹⁵



(8) (R)-1-(4'-Methoxyphenyl) ethanol [1572-97-0]:

Oil

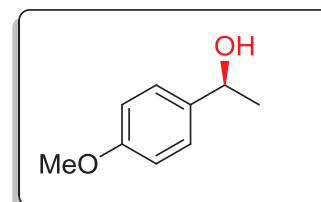
¹H NMR (300 MHz, CDCl₃): δ = 7.20 (d, 2 H, Ar), 6.80 (d, 2 H, Ar), 4.75 (q, J = 6 Hz, 1 H, CH-OH), 3.71 (s, 3 H, OCH₃), 1.99 (br. s, 1 H, OH), 1.38 (d, J = 6 Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 158.9 (C_q), 139.4 (C_q), 126.7 (2 x CH), 113.8 (2 x CH), 69.9 (CH-OH), 55.3 (OCH₃), 25 (CH₃) ppm.

GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 100 °C, retention time: 47.3 min (major, *R*), 48.7 min (minor, *S*), 25% ee.

$[\alpha]_D^{25}$ = -15 (c = 1, CHCl₃), 25% ee (*S*).

Literature value: $[\alpha]_D^{20}$ = -1.1 (c = 4.7, CHCl₃), 10% ee (*S*).⁹⁵

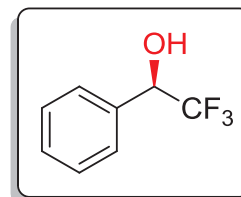


(9) (*R*)-(-)-2,2,2-Trifluoro-1-phenylethanol [10531-50-7]:

Oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.55–7.35 (m, 5 H, Ar), 5.03 (qd, J = 6.5, 4.5 Hz, 1 H, CH-OH), 2.53 (d, J = 4.5 Hz, 1 H, OH) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 134.2 (C_q), 129.6 (CH), 128.7 (CH), 127.6 (CH), 122.6 (q, J_{CF} = 282 Hz, C_q), 72.6 (q, J_{CF} = 32 Hz, CH-OH) ppm.



GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 80 °C, retention time: 31.17 min (minor, *S*), 32.55 min (major, *R*), 59% ee.

$[\alpha]_D^{25}$ = -13.5 (c =1, CHCl₃), 59% ee (*R*).

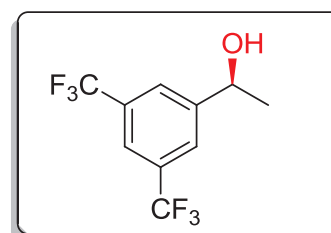
Literature value: $[\alpha]_D^{20}$ -5.60 (c = 1.16, CHCl₃), 22% ee (*R*).⁹⁶

(10) (*S*)-1-[3,5-Bis(trifluoromethyl)phenyl] ethanol [225920-05-8]:

White Crystal

¹H NMR (300 MHz, CDCl₃): δ = 7.84 (s, 2 H, Ar), 7.79 (s, 1 H, Ar), 5.05 (q, J = 6Hz, 1 H, CH-OH), 2.10 (br. s, 1 H, OH), 1.55-1.53 (d, J = 6Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 148.2 (C_q), 131.7 (q, J_{CF} = 33 Hz, 2C_q), 125.4 (2 \times CH), 125.13 (J_{CF} = 30Hz, 2C_q (2xCF₃)) 121.3 (J_{CF} = 3.7 Hz, 2 \times CH), 69.2 (CH-OH), 25.4 (CH₃) ppm.



GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 90 °C, retention time: 20.13 min (major, *S*), 21.4 min (minor, *R*), 63% ee.

$[\alpha]_D^{25}$ = -14.5 (c = 1, CHCl₃), 63% ee (*S*).

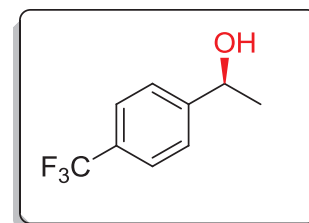
Literature value: $[\alpha]_D^{20}$ = +22.7 (c = 1, CHCl₃), 98% ee (*R*).¹⁰⁰

¹⁰⁰ W. Liu, M.L. Yuan, X.H. Yang, J.H. Xie, Q.L. Zhou, *Chem. Commun.*, 51 (2015) 6123-6128.

(11) (S)-1-(4'-Trifluoromethylphenyl) ethanol [98120-43-4]:

Colorless oil

¹H NMR (300 MHz, CDCl₃): δ = 7.58 (d, J = 8.16 Hz, 2 H, Ar), 7.45 (d, J = 8.16 Hz, 2 H, Ar), 4.90 (q, J = 6.42 Hz, 1 H, CH-OH), 2.49 (br. s, 1 H, OH), 1.47 (d, J = 6.51 Hz, 3 H, CH₃) ppm. **¹³C NMR (75 MHz, CDCl₃):** δ = 149.8 (Cq), 129.7 (q, J_{CF} = 32 Hz, C_q), 125.7 (2 x CH), 125.7 (q, J_{CF} = 3.8 Hz, 2 x CH), 122.5 (q, J_{CF} = 271 Hz, C_q), 69.9 (CH-OH), 25.4 (CH₃) ppm.



GC: Rt[®]- β DEXm capillary column (30.0 m x 0.25 mm x 0.25 μ m), carrier gas: 1.75 kg/cm² N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 80–110 °C at 1 °C/min, retention time: 23.105 min (minor, *R*), 24.554 min (major, *S*), 86% *ee*. $[\alpha]_D^{25}$ = -21.3 (c = 1, CHCl₃), 86% *ee* (*S*).

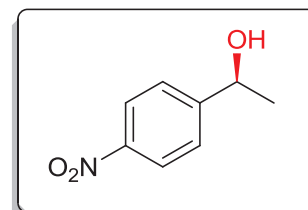
Literature value: $[\alpha]_D^{27}$ = -31.5 (c = 4.7, CHCl₃), 90% *ee* (*S*).⁹⁵

(12) (S)-1-(4'-Nitrophenyl)ethanol [96156-72-8]:

Oil

¹H NMR (300 MHz, CDCl₃): δ = 8.1 (d, J = 7.14 Hz, 2 H, Ar), 7.54 (d, J = 8.07 Hz, 2 H, Ar), 5.02 (q, J = 6.5 Hz, 1 H, CH-OH), 2.3 (br. s, 1 H, OH), 1.5 (d, J = 6.4 Hz, 3 H, CH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 153.1 (Cq), 147.1 (Cq), 126.1 (2 x CH), 123.7 (2 x CH), 69.4 (CH-OH), 25.5 (CH₃) ppm



Chromatography: CHIRALCEL OD, heptane/ 2-propanol (95:5 in 30 min, 0.8 mL/min) Retention time: 32.63 min (major, *S*), 36.05 min (minor, *R*), 58% *ee*.

$[\alpha]_D^{25}$ = -17.1 (c = 1, CHCl₃), 58% *ee* (*S*).

Literature value: $[\alpha]_D^{27}$ = -24.6 (c = 0.5, CHCl₃), 96% *ee* (*S*).¹⁰¹

¹⁰¹ G. A. B. Vieira et al., *J. Braz. Chem. Soc.*, **21** (2010) 1509;

(13) (*R*)-(-)-4-phenylbutan-2-ol [2344-70-9]:

Colorless oil

¹H NMR (300 MHz, CDCl₃): δ = 7.36–7.21 (m, 5 H, Ar), 3.87 (q, J = 6 Hz, 1 H, CH-OH), 2.86–2.66 (m, 2 H, CH₂-CH-OH), 1.83–1.81 (m, 2 H, CH₂), 1.58 (br. s, 1 H, OH), 1.27 (d, J = 6 Hz, 3 H, CH₃) ppm.

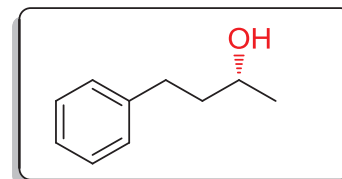
¹³C NMR (75 MHz, CDCl₃): δ = 142.1 (C_q), 128.4 (4 × CH), 125.8 (CH), 67.5 (CH, CH-OH), 40.8 (CH₂), 32.2 (CH₂), 23.6 (CH₃) ppm.

GC: Rt[®]-βDEXm capillary column (30.0 m x 0.25 mm x 0.25 μm), carrier gas: 1.75 kg/cm²

N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 100 °C at 1 °C/min, retention time: 50.2 min (minor, *S*), 50.7 min (major, *R*), 15% *ee*.

$[\alpha]_D^{20}$ = -1 (c = 1, CHCl₃), 15% *ee* (*R*).

Literature value: $[\alpha]_D^{20}$ = -2.9 (c = 0.71, CHCl₃), 9% *ee* (*R*).⁹⁶



(14) (*S,S*)-2,6-Bis(1-hydroxyethyl)pyridine[1195-59-1]:

Oil

¹H NMR (300 MHz, CDCl₃): δ = 7.76-7.71 (t, J = 7.7 Hz, 1 H, Ar), 7.25 (d, J = 7.8 Hz, 2 H, Ar), 4.97-4.90 (q, J = 6.5 Hz, 2 H, 2 x CH-OH), 3.81 (br. s, 2 H, 2 x OH), 1.53 (d, J = 6.5 Hz, 6 H, 2 x CH₃) ppm.

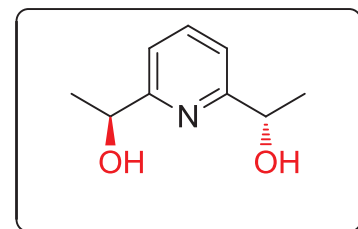
¹³C NMR (75 MHz, CDCl₃): δ = 162.2 (2 x C_q), 137.7 (CH), 118.3 (2 x CH), 69.3 (2 x CH-OH), 24.0 (2 x CH₃) ppm.

GC: Rt[®]-βDEXm capillary column (30.0 m x 0.25 mm x 0.25 μm), carrier gas: 1.75 kg/cm²

N₂, injection temperature: 230 °C, detection temperature: 230 °C, column temperature: 110 °C, retention time: 41.092 min (minor, meso isomer), 39.58 min (major, (*S,S*)), 67% *de*, >99% *ee*.

$[\alpha]_D^{20}$ = -21.5 (c 1, CHCl₃), 67% *de*, >99% *ee*. (*S,S*).

Literature value: $[\alpha]_D^{20}$ = +22.9 (c 0.93, CHCl₃), 66% *de*, 100% *ee*. (*R,R*).⁹⁶

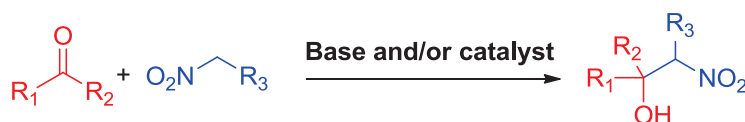


Asymmetric Henry Reaction

3.1 Bibliography

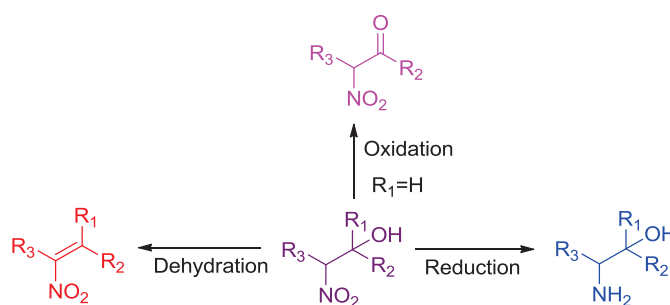
3.1.1 Introduction

Henry Reaction is a C-C bond formation. It is one of the reactions with ideal atom economy in organic synthesis. This reaction was discovered in 1895 by Louis Henry¹⁰² and was reported for the first time as an asymmetric synthesis in 1992 by Shibasaki and co-workers.¹⁰³ This reaction is referred to as nitroaldol condensation between nucleophilic nitro alkanes and aldehydes or ketones resulting in β -nitro alcohols. Consequently, asymmetric Henry reaction leads to chiral β -nitro alcohols, which are important key intermediates of series of biologically active molecules including natural compounds, insecticides, fungicides and antibiotics.¹⁰⁴



Scheme 53: Henry Reaction

Henry Reaction is also one of the most beneficial reactions in the area of organic chemistry due to the simplicity of transforming β -nitroalcohol into nitroalkenes by dehydration, into α -nitro ketones by oxidation, and into β -amino alcohols by reduction (Scheme 54).^{105,106}



Scheme 54: Main transformations reactions of β -nitro alcohols

¹⁰² L. Henry *Compt. Rend. Hebd. Seances Acad. Sci.* 120 (1895) 1265-1267.

¹⁰³ H. Sasai, S. Takeyuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* 114 (1992) 4418-4420.

¹⁰⁴ S. E. Milner, T. S. Moody, A. R. Maguire, *Eur. J. Org. Chem.* (2012) 3059-3067.

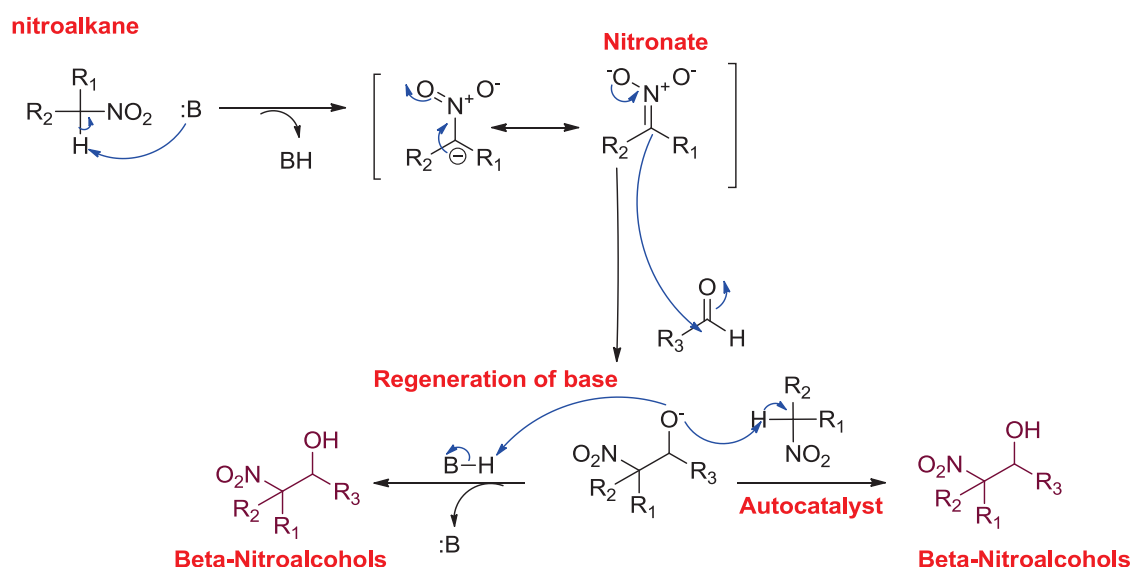
¹⁰⁵ R. S. Varma, R. Dahiya, S. Kumar, *Tetrahedron Lett.* 38 (1997) 5131-5133.

¹⁰⁶ W. E. Noland, *Chem. Rev.* 55 (1955) 137-155.

Several types of catalysts have been used in Henry Reactions included organic and inorganic bases, biocatalysts, organocatalysts and metal complex catalysts.

The classical nitro-aldo reaction has been catalyzed by base at room temperature to form β -Nitro alcohols in a good yield. The most widespread inorganic bases used for this reaction are alkali metal hydroxide, carbonates, bicarbonate and alkoxides in water or ethanol.¹⁰⁷ The effective organic base for this reaction is ammonia and amine. Furthermore the reaction between nitro compound and aldehyde in the presence of amine as a base followed by acidification gives very good to excellent yield. This method is useful for the separation of ammonium salts from the organic reaction phase.

The mechanism of the base catalyzed reaction starts probably by the deprotonating of the carbon at α position of nitroalkane and formation of a resonance stabilized anion. Furthermore alkylation of the nitroalkane with the carbonyl compound takes place (aldehydes or ketones) to form β -nitro alkoxide then β -Nitro alcohols after protonation of the alkoxide by protonated base. (Scheme 55)



Scheme 55: General mechanism for Henry Reaction catalyzed by base

3.1.2 Asymmetric Henry Reaction

Asymmetric Henry reaction was engaged in the synthesis of various pharmaceutical products by using chiral β -nitro alcohols as key intermediates for many drugs such as (-)-

¹⁰⁷ L.W. Herman, J.W. Simon, *Tetrahedron Lett*, 26 (1985) 1423-1425.

Denopamine,¹⁰⁸ which is a cardiogenic drug used in the treatment of angina and congestive heart failure,¹⁰⁹ (-)-Arbutamine,¹⁰⁵ which is a cardiac stimulant that stimulates adrenergic receptors,¹¹⁰ and R-Salmeterol¹¹¹ which is used in the prevention of asthma symptoms and chronic obstructive pulmonary disease (Figure 5).

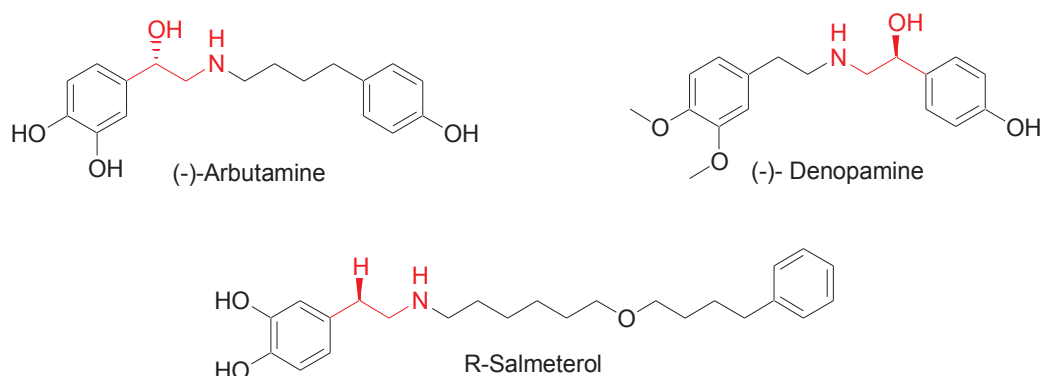


Figure 5: Drugs syntheses used Henry Reaction as a key step

A library of asymmetric metallic catalysts of Cu,¹¹² Zn,¹¹³ Co,¹¹⁴ Cr¹¹⁵ and rare metallic ions¹¹⁶ have been widely used in this reaction with a variety of chiral ligands. Several types of nitrogenated chiral ligands have also attracted great attention in this type of reaction and improved the efficiency of the catalytic system such as: biosoxazolidines,¹¹⁷ bisoxazoline,¹¹⁸ sulfonamides,¹¹⁹ aminopyridines,¹²⁰ imidazolidine-pyridine,¹²¹ Salen, *N,N*-

¹⁰⁸ B. M. Trost, V.S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* 4 (2002) 2621-2623.

¹⁰⁹ T. Ishide, *Chiba Medical* (2013) No. 29, 33.

¹¹⁰ G. A. Mohamed, R. Nagarajan, T. M. Ibrahim, R. W. Caldwell, *Cardiovascular Drugs and Therapy*. 10 (1996) 39-47.

¹¹¹ N. Ananthi, S. Velmathi, *Ind. J. Chem.*, 52 (2013) 52B, 87-108.

¹¹² (a) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C.W. Downey, *J. Am. Chem. Soc.* 125 (2003) 12692-12693. (b) W. Jin, X. Li, B. Wan, *J. Org. Chem.* 76 (2011) 484-491. (c) J. L. Li, L. Liu, Y. N. Pei, H. J. Zhu, *Tetrahedron*. 70 (2014) 9077-9083. (d) S. Selvakumar, D. Sivasankaran, V. K. Singh, *Org. Biomol. Chem.* 7 (2009) 3156-3162.

¹¹³ (a) B. M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* 4 (2002) 2621-2623. (b) M. Luo, B. Yan, *Tetrahedron Letters*. 51 (2010) 5577-5580.

¹¹⁴ (a) J. Dimroth, M. Weck, *RSC. Adv.* 5 (2015) 29108-29113. (b) Y. Kogami, T. Nakajima, T. ashizawa, S. Kezuka, T. Ikeno, T. Yamada, *Chem. Let.* 33 (2004) 614-615. (c) Y. Kogami, T. Nakajima, T. Ikeno, T. Yamada, *Synthesis*. 12 (2004) 1947-1950.

¹¹⁵ (a) R. Kowalczyk, P. Kwiatkowski, J. Skarzewski, J. Jurczak, *J. Org. Chem.* 74 (2009) 753-756. (b) A. Zulauf, M. Mellah, E. Schulz, *J. Org. Chem.* 74 (2009) 2242-2245. (c) R. Kowalczyk, L. Sidorowicz, J. Skarzewski, *Tetrahedron: asymmetry*. 18 (2007) 2581-2586.

¹¹⁶ (a) H. Sasai, T. Toku-naga, S. Watanaba, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* 60 (1995) 7388-7389. (b) F. Tur, M. J. Saa, *Org. Let.* 9 (2007) 5079-5082.

¹¹⁷ a) S. Liu, C. Wolf, *Org. Lett.* 10 (2008) 1831-1834. (b) K. Y. Spangler, C. Wolf, *Org. Lett.* 11 (2009) 4724-4727.

¹¹⁸ (a) K. Lang, J. Park, S. Hong, *J. Org. Chem.* 75 (2010) 6424-6435. (b) E. Wolinska, *tetrahedron: Asymmetry*. 25 (2014) 1478-1487.

¹¹⁹ (a) M. Steurer, C. Bolm, *J. Org. Chem.* 75 (2010) 3301-3310. (b) W. Jin, X. Li, Y. Huang, F. Wu, B. Wen, *Chem. Eur. J.* 16 (2010) 8259-8261.

dioxides¹²² and diamine.¹²³ However, some ligands were used as organocatalysts in free metal medium. Our interest focused on the asymmetric Henry reaction based on the metal complex catalysis using chiral diamine ligands especially with the copper complexes that have gained great attention in this reaction due to its reactivity, availability, and non-toxicity. The reviews below have shown an asymmetric version of the Henry reaction in the presence of the metal complex catalysis and short review for some organocatalysis.

3.1.3 Asymmetric Henry Reaction catalyzed by metals complexes

3.1.3.1 Rare Earth catalysis

In 1992, Shibasaki and co-workers reported the first catalytic system for asymmetric Henry reaction using (*S*)-(2,2')-binaphthol in conjunction with a lanthanum alkoxide and lithium chloride to form a called heterobimetallic catalyst (Figure 6).

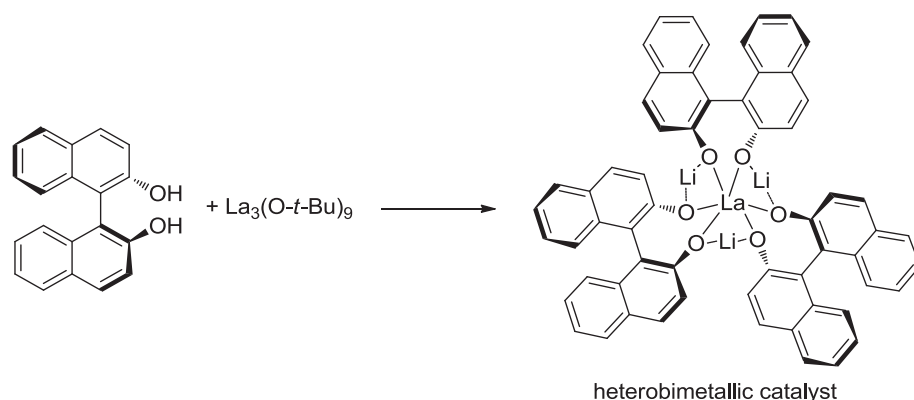


Figure 6: Synthesis of Shibasaki's Catalyst using Lanthanum metal

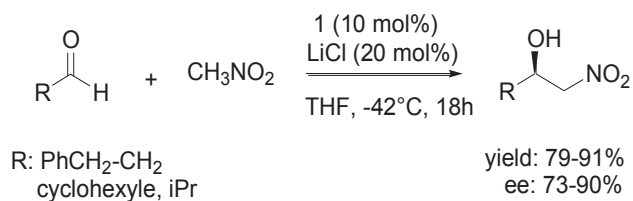
This catalyst allowed producing (*R*)- β -nitro alcohol in 79-91% yield and 73-90% ee from direct reactions between nitromethane and aldehydes. The efficiency of the catalyst is due to the complementary effects of the Lewis acid and Bronsted base offered by the phenoxy-lithium groups, respectively (Scheme 56).¹⁰³

¹²⁰ a) G. Blay, E. Climent, I. Fernandez, V. H-Olmos, J. R. Pedro, *Tetrahedron: asymmetry*. 18 (2007) 1603-1612. (b) G. Blay, V. Hernandez-Olmos, J. R. Pedro, *Tetrahedron: asymmetry*. 21 (2010) 578-581. (c) A. Gualandi, L. Cerisolo, H. S. Evans, D. Savoia, *J. Org. Chem.* 76 (2011) 3399-3408.

¹²¹ T. Arai, K. Suzuki, *Syn. Lett.* (2009) 3167-3170.

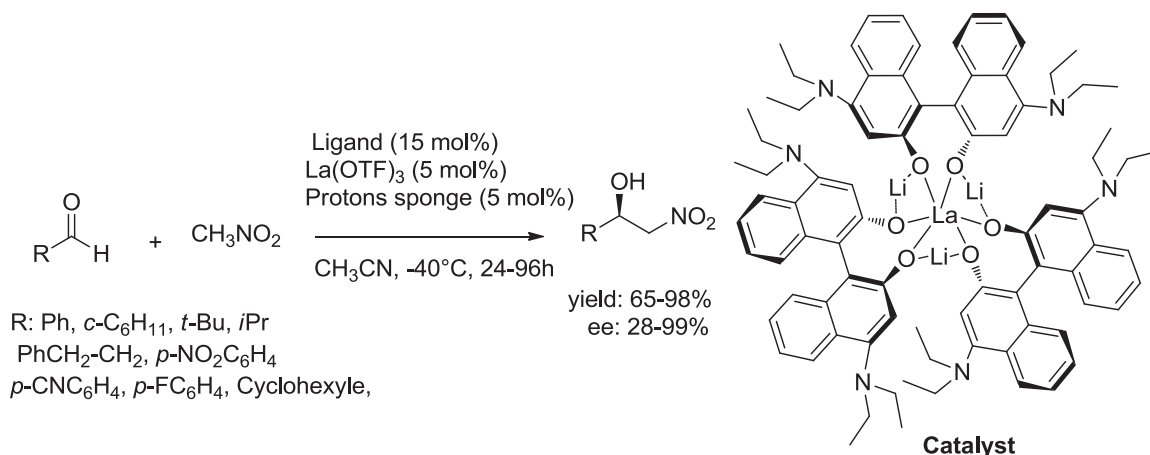
¹²² B. Qin, X. Xiao, X. Liu, J. Huang, Y. Wen, X. Feng *J. Org. Chem.* 72 (2007) 9323-9328.

¹²³ (a) R. Kowalczyk, L. Sidirowicz, J. Skarazewski, *Tetrahedron: Asymmetry*. 19 (2008) 2310-2315. (b) F. Luia, S. Gou, L. Li, *Appl. Organometal. Chem.* 28 (2014) 186-193.



Scheme 56: Henry Reaction catalyzed by Shibasaki's Catalyst

In 2006, Saà et al. reported the bifunctional lanthanide base catalyst similar to the one described above but using binaphthol ligands armed with aminoalkyls at the 3,3'-positions. The presence of array base side on binaphthols increased enantiomeric excesses up to 99%, as well as a very good yield also reached 98% (Scheme 57).¹²⁴ In general, aliphatic aldehydes gave the best yield and *e.e* (around 90%), while aromatic and α,β -unsaturated aldehyde were less efficient. Furthermore, the monometallic complex was more selective and active than heterobimetallic complex Shibasaki's catalyst (Figure 6) in the presence of proton sponge that accelerates the reaction.



Scheme 57: Enantioselective Henry Reaction catalyzed by lanthanide complex

3.1.3.2 Copper-Based Catalysis With ligands bis (oxazoline) and bis(thiazoline)

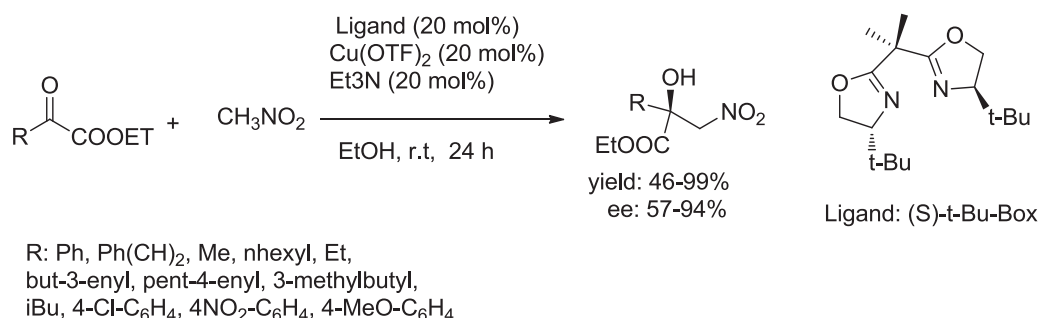
Chiral complexes of copper have found a wide range of application in the catalytic asymmetric transformations. The availability, cheapness, and non-toxicity of copper make it enchanting to the researchers to synthesize a chiral complex. Most of the asymmetric Henry Reactions are catalyzed by copper complexes. Firstly, Christensen *et al.*^{125,126} developed the first chiral copper complex for enantioselective Henry Reaction using (*S*)-*t*-Bu-BOX as a

¹²⁴ J. M. Saa, F. Tur, J. Gonzalez, M. Vega, *Tetrahedron: Asymmetry*. 17 (2006) 99-106.

¹²⁵ C. Christensen, K. Juhl, R. G. Hazell, K. A. Jorgensen, *Chem Commun.* (2001) 2222-2223.

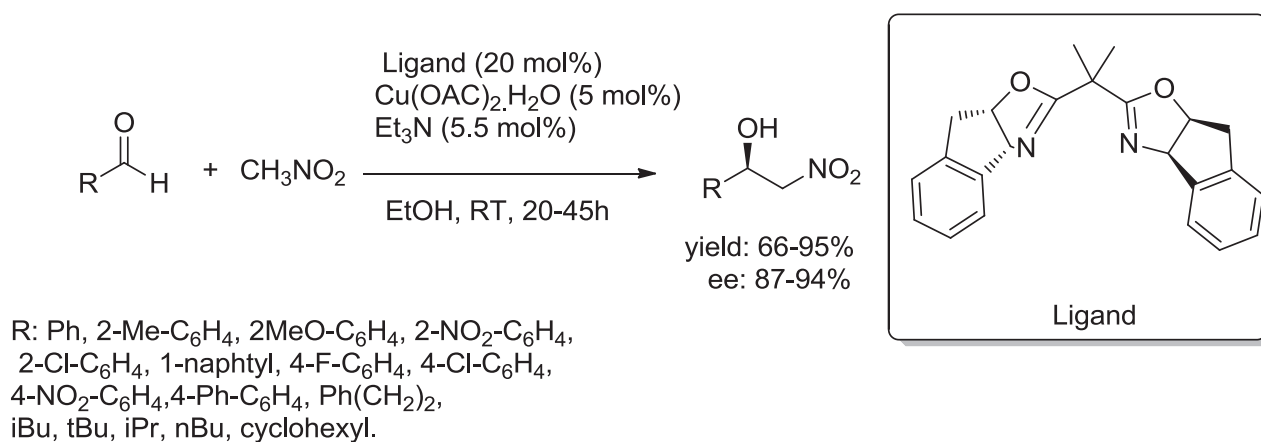
¹²⁶ C. Christensen, K. Juhl, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* 76 (2002) 4875-4881.

ligand with Cu(OTF)₂ as Lewis acid in the presence of trimethylamine that gave very good results with high *e.e* and conversions. (Scheme 58)



Scheme 58: Enantioselective Henry Reaction reported by Christensen et al

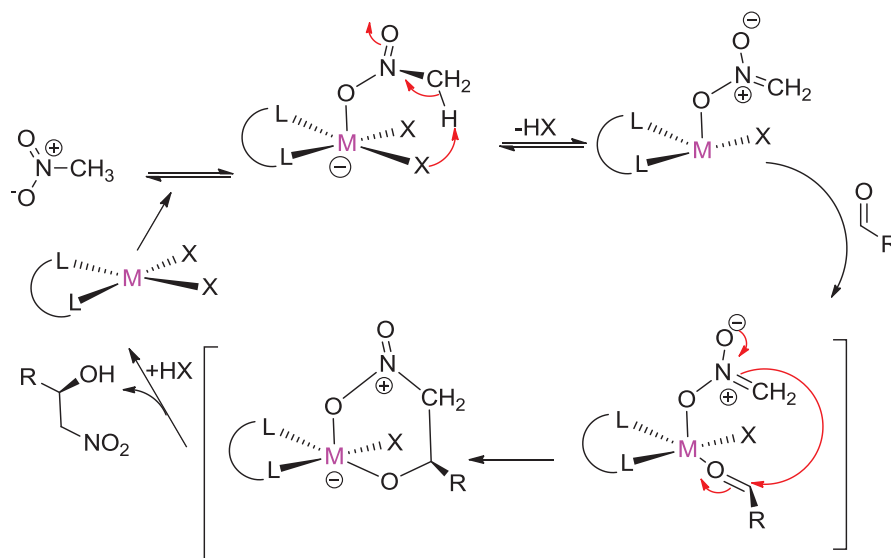
In 2003, *Evans et al.*^{112a} reported the use of a chiral copper catalyst derived from copper acetate and bis(oxiazoline), that was evaluated for its catalytic capacity for asymmetric Henry Reaction using various pro-chiral aldehydes including aliphatic and substituted aromatic aldehyde; the chiral products were obtained in good to excellent yields and *e.e*. (Scheme 59)



Scheme 59: Enantioselective Henry Reaction reported by Evans et al

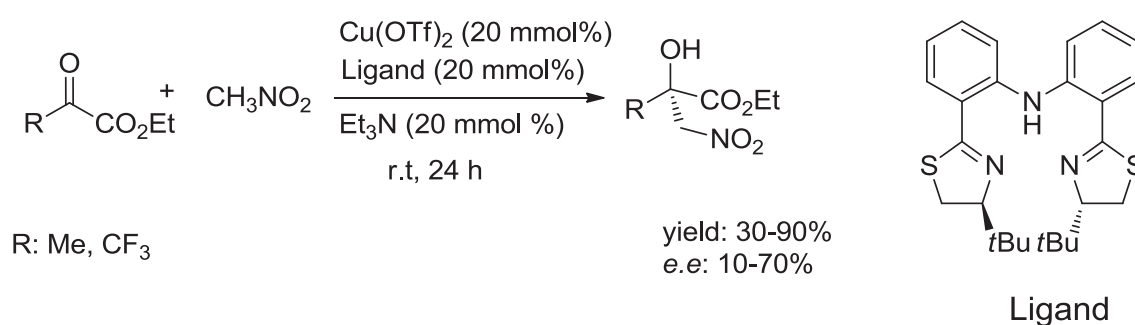
The authors have proposed the mechanism as shown below in the Scheme 60. First, the presence of a weakly acidic metal complex with a moderately basic charged ligand (X⁻ = AcO⁻) facilitates deprotonating of nitromethane to form complex with still at 18 electrons. Then nitronate occurs by elimination of acetic acid. Furthermore, the aldehyde approaches to metal and the nucleophilic addition takes place simultaneously, directly giving a complex (at

18 electrons). Then, the chiral product is produced by protonolysis of copper alkoxide, in the presence of acetic acid.



Scheme 60: Mechanism proposed by Evans et al. for Enantioselective Henry Reaction

Later, tridentate chiral bis(thiozoline) ligands with combination copper triflate have been used by Jiaxi Xu et al. to perform asymmetric Henry reaction, in the presence of trimethylamine that helps the deprotonation of nitromethane. Nitroalcohols have been obtained where the maximum enantioselectivity has not exceeded 70% *e.e* (Scheme 61).¹²⁷

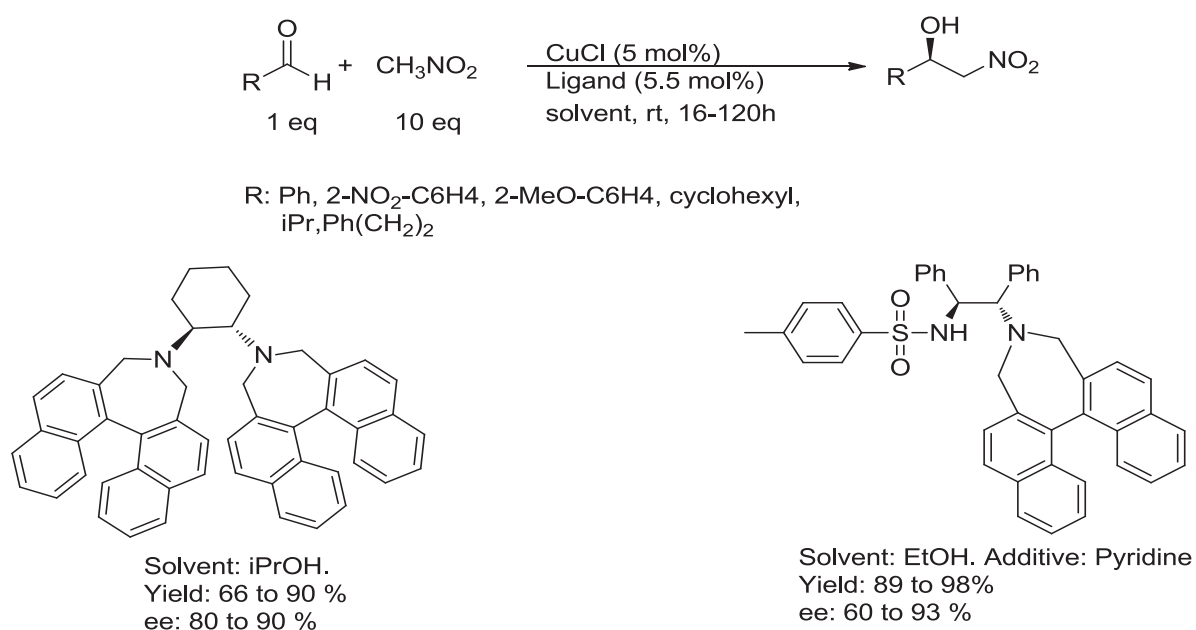


Scheme 61: Tridentate bis(thiozoline) ligands for Cu(II) catalyzed Henry Reaction of α -keto esters

¹²⁷ S.-F. Lu, D.-M. Du, S.-W. Zhang, J. Xu, *Tetrahedron: Asymmetry*. 15 (2004) 3433-3441.

3.1.3.3 Copper-Based Catalysis With diamine ligands and its derivative

In 2006, Arai *et al.* demonstrated the importance of the chiral asymmetric diamine ligands with copper chloride as a metal precursor in Henry Reaction. Good to excellent isolated yields with high enantiomeric excess (80 to 90%)¹²⁸ were obtained. Later (in 2008), the same group has reported the use of other diamine N-substituted ligands, in the presence of pyridine as auxiliary base in similar conditions. The enantiomeric excess has proven to be also good with gradually improved yields (Scheme 62).¹²⁹



Scheme 62: Example of using chiral asymmetric N-substituted diamine ligands in combination with CuCl

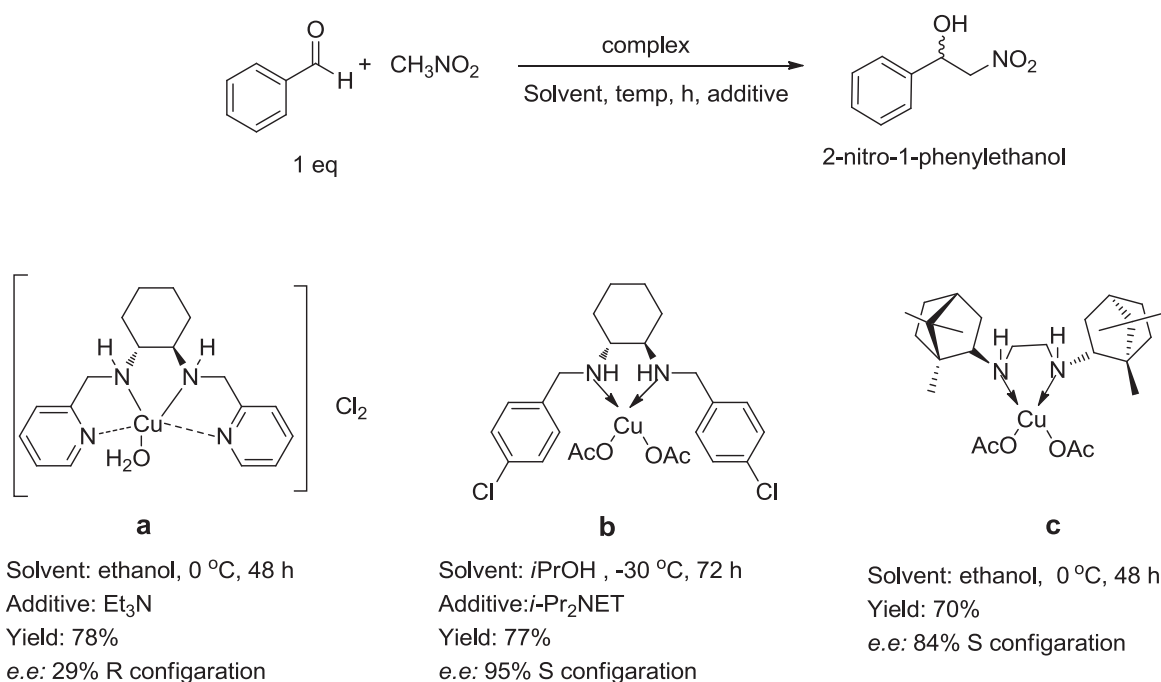
In 2008, Zhang *et al.* used an *in situ* formed copper complex of (1*S*,2*S*)-*N,N*-bis(pyridin-2-ylmethyl)cyclohexane-1,2-diamine (Scheme 63, **a**), used as a catalyst in asymmetric Henry Reaction in the presence of trimethylamine to synthesize 2-nitro-1-phenylethanol in *R* configuration with 78% yield and 29% *e.e.*¹³⁰ In 2009, also Kowalczyk *et al.* have also reported copper complex of (1*S*,2*S*)-*N,N*-bis(4-chlorobenzyl)cyclohexane-1,2-diamine. The complex showed to be effective in asymmetric Henry Reaction using *N,N*-diisopropylethylamine (Scheme 63, **b**), generating 2-nitro-1-phenylethanol of *S* configuration

¹²⁸ T. Arai, M. Watanabe, A. Fujiwara, N. Yokoyama, A. Yanagisawa, *Angew. Chem. Int. Ed.* 45 (2006) 5978-5981.

¹²⁹ T. Arai, R. Takashita, Y. Endo, M. Watanabe, A. Yanagisawa, *J. Org. Chem.* 73 (2008) 4903-4906.

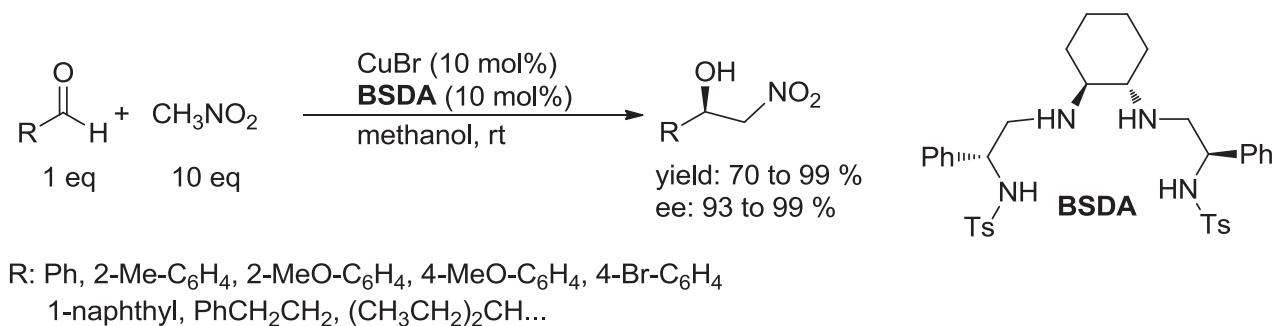
¹³⁰ Y. Zang, L. Xiang, Q. Wang, Z. X. Duan, G. Zi, *Inorg chim Acta.* 361 (2008) 1246-1254.

with 77% yield and 95% *e.e.*¹³¹ Furthermore in 2009, Sanjeevakumar *et al.* in 2009 have designed a new copper complex of chiral ligands (1*S*,2*S*)-*N,N*- bis(isobronyl)ethylene diamine, (Scheme 63, **c**). This complex led to 2-nitro-1-phenylethanol of *S* configuration with isolated yield 70% and *e.e* up to 84%. This last complex was also used for the Henry Rreaction with various aldehydes to prepare β-hydroxy nitro alkanes with a yield of 95% and high *e.e* (90%).¹³²



Scheme 63: Some examples of copper metals combined with asymmetric diamine ligands

In 2010, Wei Jin *et al.* have developed a chiral bis(sulfonamide)-diamine (BSDA) ligand complexed to copper (CuBr) conducting very good results for enantioselective Henry Reaction.^{112b} High yields and excellent enantioselectivities were achieved with the addition of nitromethane to a range of aldehydes. (Scheme 64)

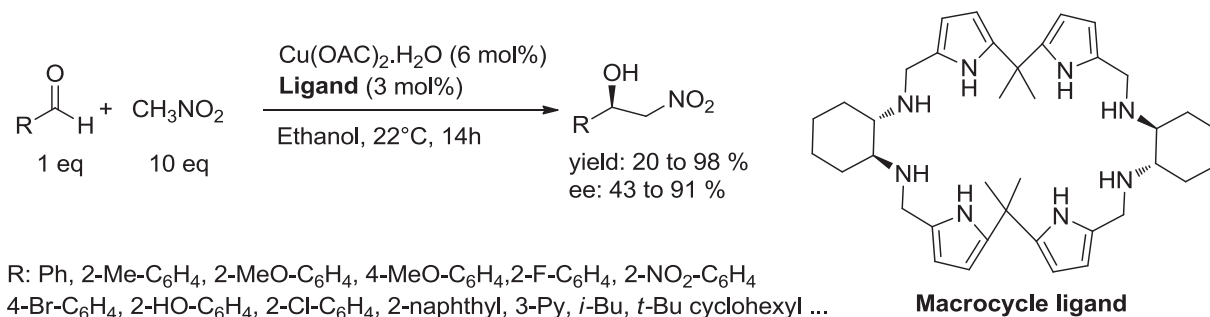


Scheme 64: Cu enantioselective catalytic Henry Reaction using BSDA Ligand

¹³¹ R. Kowalczyk, J. Skarzewski, *Tetrahedron: Asymmetry*. 20 (2009) 2467-2473.

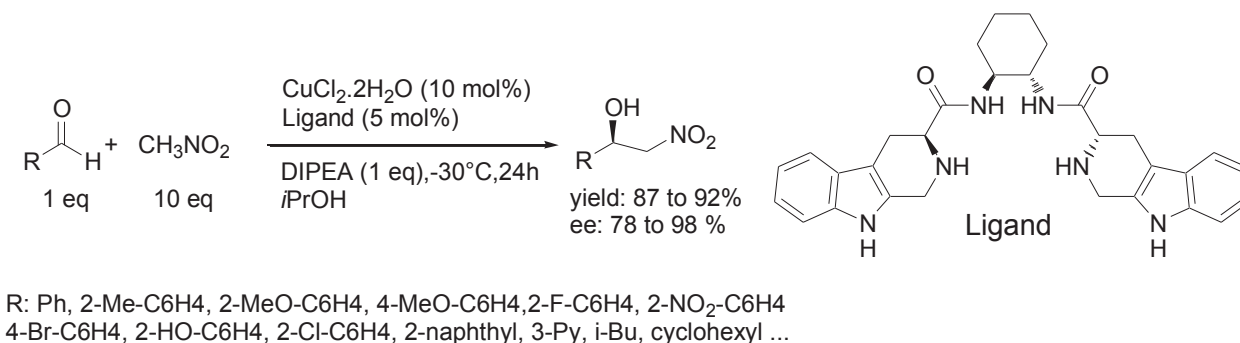
¹³² N. Sanjeevakumar, M. Periasamy, *Tetrahedron: Asymmetry*. 20 (2009) 1842-1847.

In 2011, A. Gualandi et al. have reported the synthesis of chiral macrocyclic molecule containing pyrrole rings and its application as a ligand of copper in asymmetric Henry reaction. The coordination complex between Cu metal and macrocycle ligand has allowed producing β -nitroalcohol in 20-98% yield with 43-91% ee.¹³³ (Scheme 65)



Scheme 65: Cu enantioselective catalytic Henry Reaction using macrocycle Ligand

In 2014, J. L Liu et al. have studied enantioselective Henry reaction using C₂-symmetric diamides chiral ligands combined with Cu (II) metal. High yield (87% to 92%) and high enantioselectivity (75% to 98%) were achieved in this type of chiral diamides ligand.^{112c} (Scheme 66)

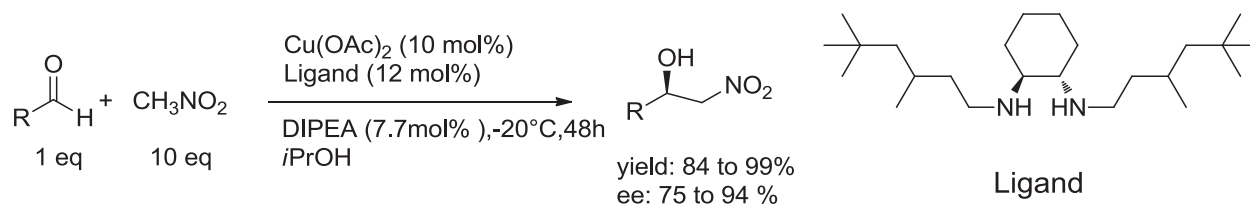


Scheme 66: Cu enantioselective catalytic Henry Reaction using asymmetric chiral diamide Ligand

In 2014, Shaohua Goa et al. have designed a series of *N,N*-dialkyl-1,2-cyclohexanediamine derivatives. These ligands have been used to develop efficient complex catalysts with copper acetate precursor for asymmetric Henry Reaction. The ligand leading to the best results in this reaction is represented in Scheme 67 with excellent isolated yields (84 to 99%) where the enantiomeric excess was improved up to 94%. The optimized catalyst was efficient to prepare β -nitro alcohol from aliphatic and aromatic aldehydes with excellent *e.e* and high isolated yields.¹³⁴

¹³³ A. Gualandi, L. Cerisoli, H. S. Evans, D. Savoia, *J. Org. Chem.* 76 (2011) 3399-3408.

¹³⁴ Z. Chunhong, F. Liu, S. Gou, *Tetrahedron: Asymmetry* 25 (2014) 278-283.

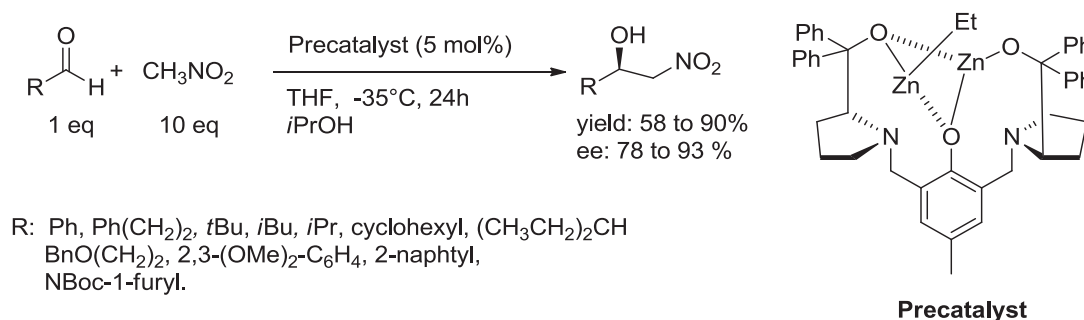


R: CH_3CH_2 , $\text{CH}_3\text{CH}_2\text{CH}_2$, $(\text{CH}_3)_2\text{CH}$, $(\text{CH}_3)_3\text{C}$, Ph, 4-Me- C_6H_4 ,
 2-MeO- C_6H_4 , 3-MeO- C_6H_4 , 2-F- C_6H_4 , 2- NO_2 - C_6H_4 , 3- NO_2 - C_6H_4 ,
 4- NO_2 - C_6H_4 , 4-Br- C_6H_4 , 2-HO- C_6H_4 , 2-Cl- C_6H_4 , 3-Cl- C_6H_4 , 4-Cl- C_6H_4 ,
 2-naphthyl, 1-naphthyl, 2-furyl, cyclohexyl, PhCH=CH

Scheme 67: Asymmetric Henry Reaction using (1*R*,2*R*)-*N*1,*N*2-bis(3,5,5-trimethylhexyl)cyclohexane

3.1.3.4 Zinc-Based Catalysis With diamine ligands and its derivative

In 2002, Trost *et al*, reported for the first time the development of Zn metal in the catalysis of asymmetric Henry reaction, using so called semi-azacrown as a ligand. The catalyst was used in enantioselective Henry Reaction of nitromethane with several aldehydes. Good enantioselectivities (78–93 % *ee*) and yields (58–90 %) were obtained (Scheme 68).¹³⁵



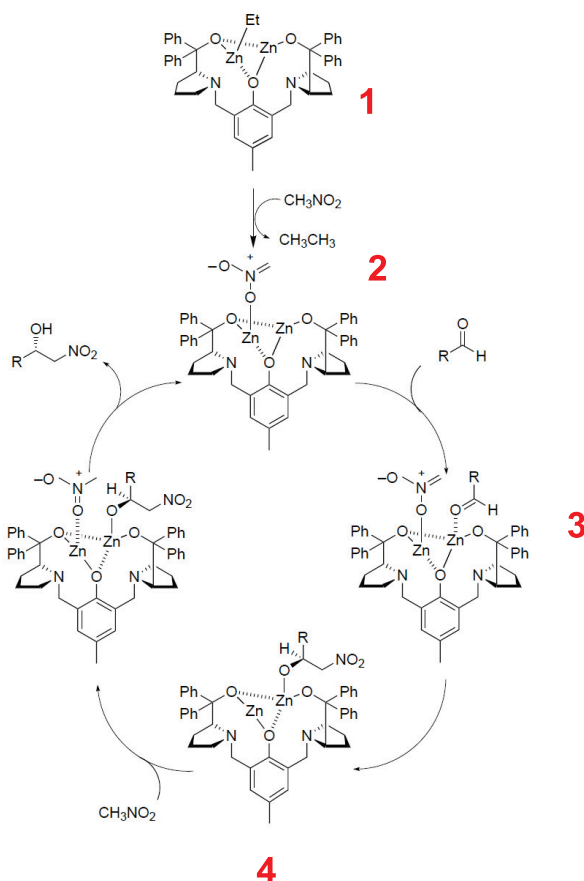
R: Ph, $\text{Ph}(\text{CH}_2)_2$, *t*Bu, *i*Bu, *i*Pr, cyclohexyl, $(\text{CH}_3\text{CH}_2)_2\text{CH}$
 $\text{BnO}(\text{CH}_2)_2$, 2,3-(OMe) $_2$ - C_6H_4 , 2-naphthyl,
 NBoc-1-furyl.

Scheme 68: Asymmetric Henry Reaction using Trost's Zinc complex

Trost proposed a mechanism for Henry Reaction with the planned zinc complex, as shown in the illustrated example, (Scheme 69).

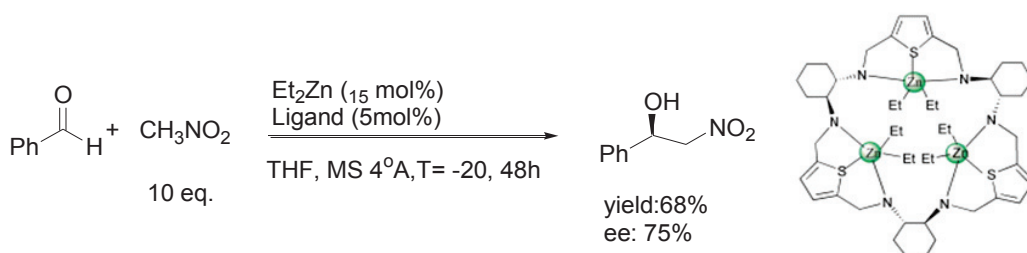
First; nitromethane was coordinated as nitronate anion at one of the zinc metal, (2) followed by approaching the aldehyde to the other zinc metal. (3) A nucleophilic attack took place to form C-C bonding with nitromethane (4) a nitroaldolisation product was produced, while another nitromethane was deprotonated (5) to release the product with good to excellent *e.e*, this step fully regained the bimetallic catalyst activity. (2)

¹³⁵ B.M. Trost, V.S. C. Yeh, *Angew. Chem. Int. Ed.* 41 (2002) 861-863.



Scheme 69: The proposed mechanism for Henry Reaction in the presence of Zinc metal

In 2003, the chiral macrocyclic diamine ligand has been synthesized by Martell et al. and was applied in enantioselective Henry Reaction to be efficient with diethylzinc. Using benzaldehyde as a substrate; 75% of enantiomeric excess was obtained with a 68% yield.¹³⁶ (Scheme 70)

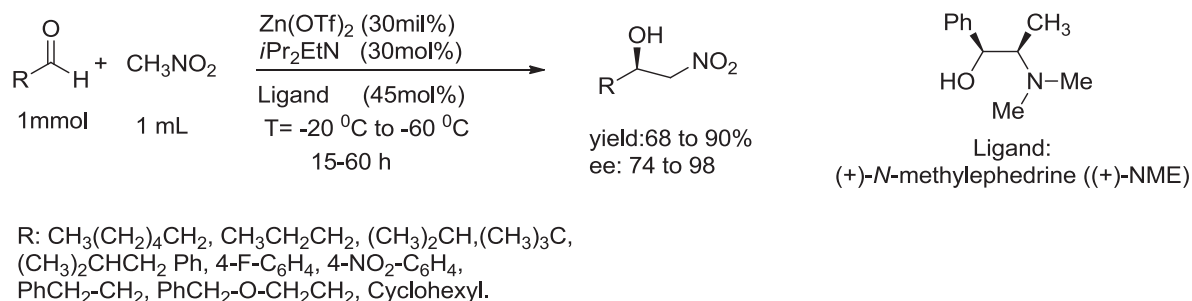


Scheme 70: Henry Reaction in the presence of cyclic diamine ligand with diethyl zinc

In 2005, Claudio Palomo et al. studied Henry Reaction that was carried out using chiral amino alcohol ((+)-N-methylephedrine) with Zinc trifluoromethanesulfonate $\text{Zn}(\text{OTf})_2$

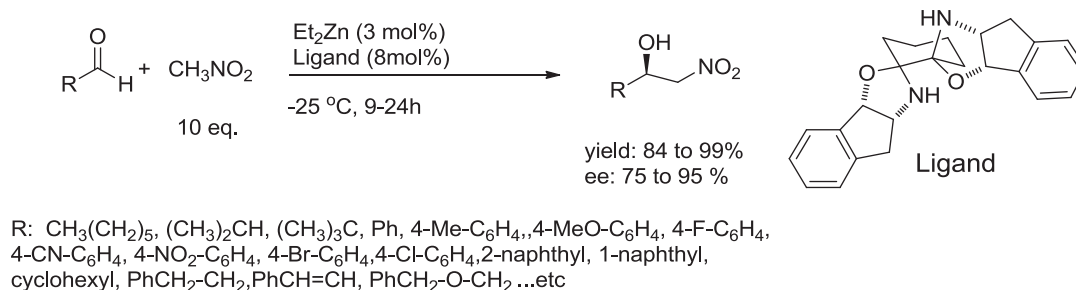
¹³⁶ J. Gao, A. E. Martell, *Org Biomol Chem.* 1 (2003) 2801-2806.

in the presence of diisopropylethylamine as a base.¹³⁷ The reaction was done at -20 °C and in some cases at lower temperature (-40°C or even -60°C) to enhance the enantiomeric excess. In this example, the enantiomeric excesses reached 98% of target products with yields up to 90%. (Scheme 71)



Scheme 71: Henry Reaction in the presence of Zinc metal and chiral amino alcohol

In 2008, Wolf *et al.* synthesized C2-symmetric bis oxazolidine in one pot by condensation of enantiopure cis-1-amino-2-indanol and 1,2-cyclohexanedione.^{117a} This Ligand was efficient for Henry Reaction with diethyl zinc as a metal precursor and produced β-hydroxy nitromethane with good to excellent yield (84 to 99%) and enantiomeric excess (up to 95%). (Scheme 72)



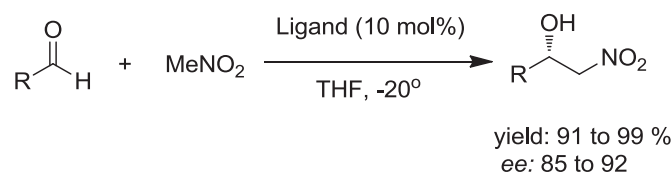
Scheme 72: Henry Reaction using bis(oxazolidine) ligand with diethylzinc

3.1.3.5 Organocatalysts

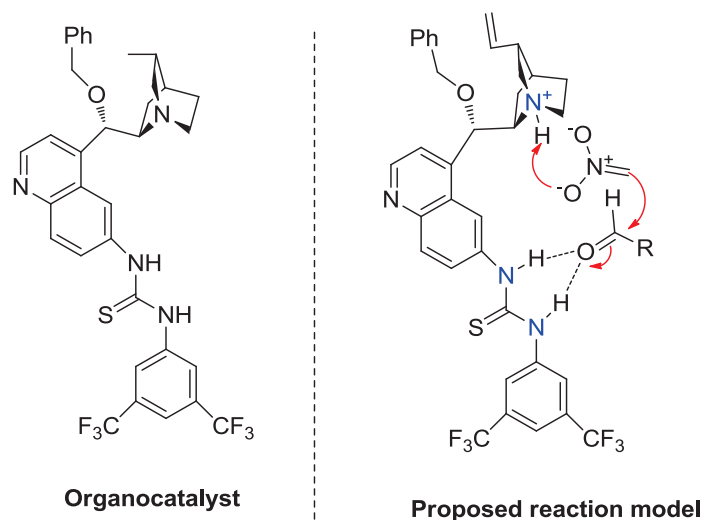
Catalytic studies without metal for the Henry reaction have also been reported. In 2006, Hiemstra's team¹³⁸ reported an amino-thiourea ligand (Scheme 73) as an efficient organocatalysis for enantioselective Henry Reaction and its performance to transform aldehydes to β-nitro alcohols using various nitroalkanes. Very good yields and *e.e* values (85 up to 95%) were obtained.

¹³⁷ C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem. Int. Ed.* 44 (2005) 3881-3884.

¹³⁸ T. Marcelli, R. N. S. Haas, J. H. Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* 45 (2006) 929-931.



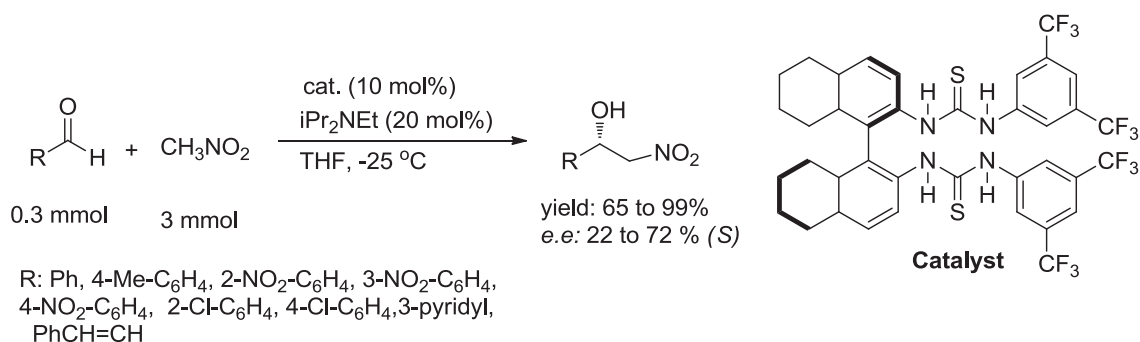
R: Ph, 1-Me-C₆H₄, 4-MeO-C₆H₄, 4-F-C₆H₄,
4-NO₂-C₆H₄, 1-naphthyl, pyridine, NBoc-1-furyl



Scheme 73: Chiral amine-thiourea Organocatalyst and its performance in Henry Reaction

Furthermore; Hiemstra's team supposed a model of action for the Organocatalyst to explain the reaction outcome based on hydrogen bonding catalysis. They mentioned that the acceptor carbonyl group is activated by thiourea moiety *via* the two hydrogen bonds, while nitromethane is activated by the protonated quinuclidine nitrogen atom. (Scheme 73)

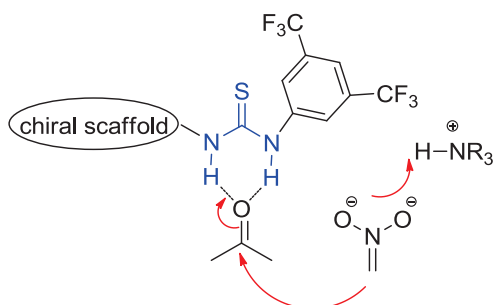
Another thiourea ligand was prepared by Xu-Guang Liu et al.¹³⁹ known as axially chiral bis (arylthiourea)-based organocatalyst (Scheme 74). The catalyst was identified also as an effective organocatalyst for the enantioselective Henry Reaction of arylaldehydes with nitromethane. Moderate enantioselectivities and good yields were observed.



Scheme 74: Axially chiral bis (arylthiourea)-based organocatalyst in enantioselective Henry Reaction

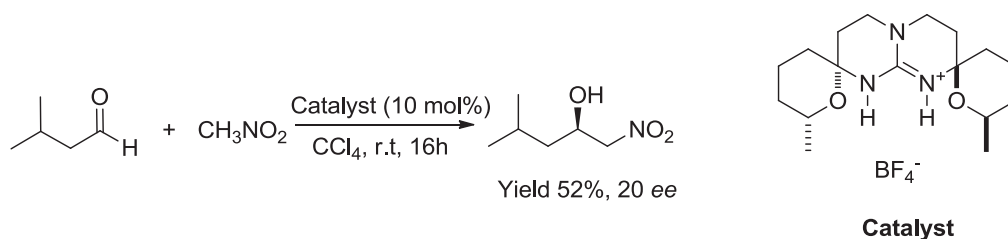
¹³⁹ G. L. Xu, J. J. Jia, S. Min, *Tetrahedron: Asymmetry*. 18 (2007) 2764-2773.

Furthermore; the team proposed a model for this reaction similar to that of Hiemstra's team, in order to understand the stereochemical outcome. The aldehyde is activated also by a thiourea moiety through double hydrogen-bonding, but the nitromethane is activated by the additive basic nitrogen atom (Scheme 75).



Scheme 75: Mode of activation

In 2003; Matthew T. Allingham¹⁴⁰ have synthesized a guanidine tetrafluoroborate salt and reported its application for Henry Reaction between nitromethane and isovaleraldehyde with low enantioselectivity and moderate yield (Scheme 76).

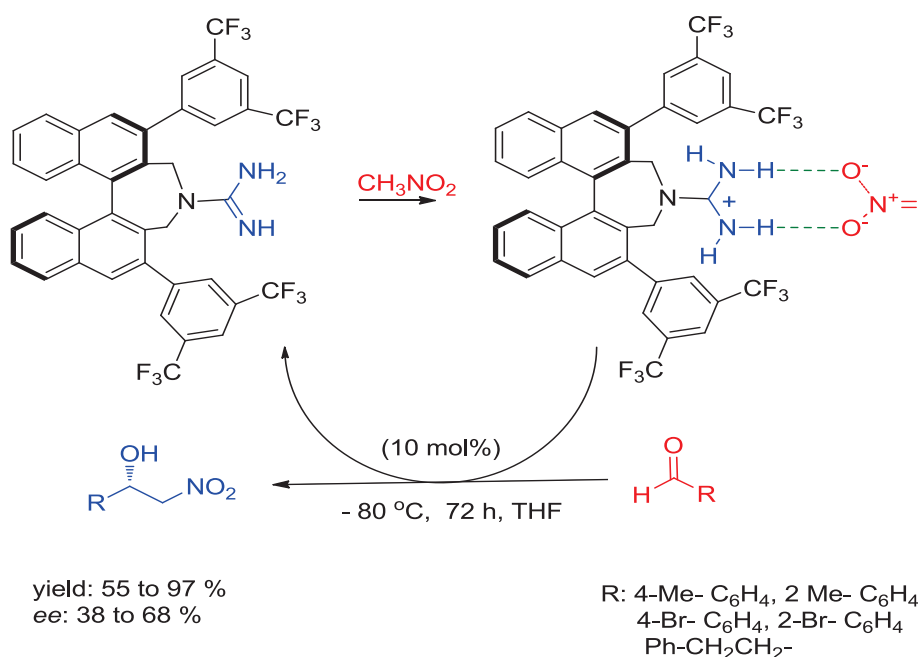


Scheme 76: Chiral guanidinium tetrafluoroborate salt in enantioselective Henry Reaction

In 2009; Terada team studied the enantioselective Henry reaction of nitromethane with aldehydes using axially chiral guanidine as a catalyst.¹⁴¹ Moreover; they described the complexation between chiral guanidinium and nitronate through two hydrogen bonds as a model for the reaction. A satisfactory yield and fairly good *ee* were obtained (Scheme 77).

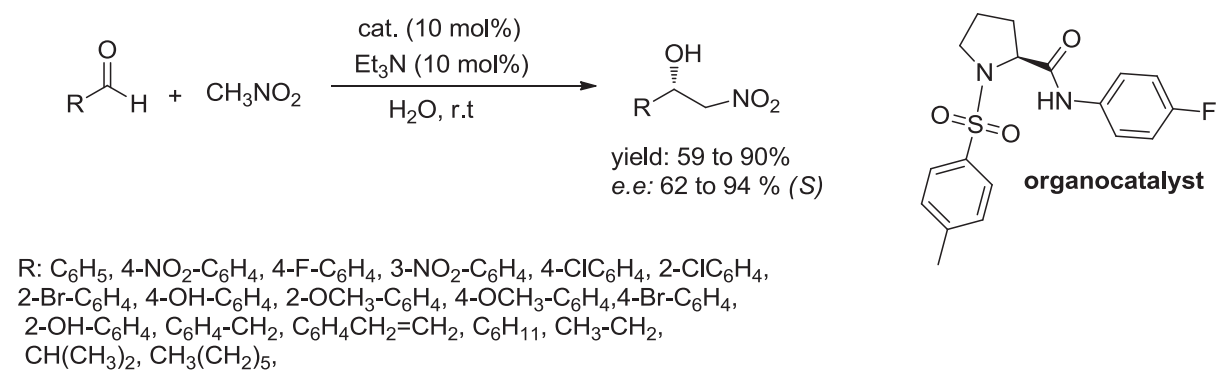
¹⁴⁰ M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas, P. W. R. Caulkett, *Tetrahedron Lett.* 44 (2003) 8677-8680.

¹⁴¹ H. Ube, M. Terada, *Bioorg. Med. Chem. Lett.* 19 (2009) 3895-3898.



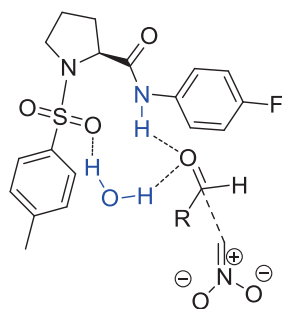
Scheme 77: Organometallic chiral guanidine in enantioselective Henry Reaction

In 2013; Prashant et al.¹⁴² developing a new method for enantioselective Henry Reaction using the organocatalyst (*S*)-*N*-(4-fluorophenyl)-1-tosylpyrrolidine-2-carboxamide (Scheme 78) and eco-friendly solvent as water. Prashant's team mentioned that water has a big effect on stereoselectivity. Moreover; it is a support for the organocatalyst in providing strong hydrogen bond (Scheme 79).



Scheme 78: Organometallic chiral guanidine in enantioselective Henry Reaction

¹⁴² B. T. Prashant, V. G. Santosh, N. J. Wamanrao, R. B. Sudhakar, *Aust. J. Chem.* **66** (2013) 661-666.



Scheme 79: The proposed model for enantioselective Henry Reaction in the presence of water

Furthermore; the organocatalyst proved its effectiveness and efficiency for aliphatic, aromatic and non-aromatic aldehydes to prepare β -nitro alcohol with good to excellent *ee* and good to moderate yield.

The development of new asymmetric metallic catalysts holding chiral ligands will certainly continue due to its important impact in the efficiency of asymmetric catalysis. Thus, designing new effective and active ligands will remain a great topic for researchers. Several metal precursors have been widely used with a variety of chiral ligands. Amongst them, copper metal has attracted a great attention in the asymmetric Henry Reaction. However, some ligands were used as organocatalysts in free metal medium.

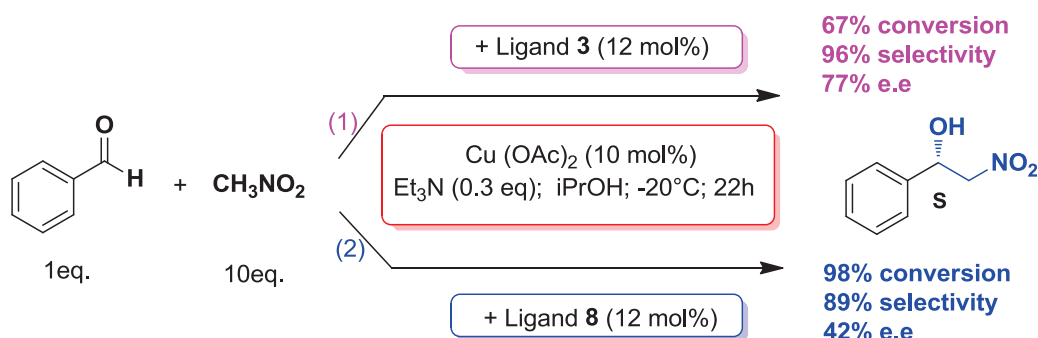
In previous chapters, we described a series of new *N,N*-diaryl-*trans*-1,2-diaminocyclohexane ligands derived from α -tetralone and (1*R*,2*R*)-1,2-Diaminocyclohexane, synthesized by a simple and efficient method. These ligands used in asymmetric transfer hydrogenation of ketone with iridium, showed significant activities and enantioselectivities. Encouraged by these interesting results, we have explored their use in asymmetric Henry Reaction. Herein we describe the utilization of bis-*N,N*-diaryl-diamine (**3**) and *N*-aryl-diamine (**8**) (Scheme 80) as chiral inductors in this reaction. Copper reveals to be the adequate metal to form the enantioselective copper-diamine catalyst.



Scheme 80: *N,N*-dinaphthalene-*trans*-1,2-diaminocyclohexane **3** and *N*-naphthalene-*trans*-1,2-diaminocyclohexane **8**

3.2 Results and discussion

The diamine ligands **3** and **8** have been tested in Henry reaction as chiral inductors complexed with copper. We adopted a procedure already reported by Z. Chunhong group.¹³⁴ Reaction was performed with 0.5 mol.L⁻¹ of benzaldehyde, 10 eq. of nitromethane (5 mol.L⁻¹) using 10 mol% of the following catalytic system Cu(OAc)₂/Ligand (1/1.2), in the presence of 0.3 eq of triethylamine in 1 mL of *i*PrOH at -20°C during 22h.



Scheme 81: Asymmetric Henry reaction using ligand **3** or ligand **8** with copper acetate

Firstly, ligand **3** with copper acetate has been used in this reaction (scheme 81), the *in-situ* formed catalyst leads to a conversion of 67% with a selectivity towards the desired product 2-nitro-1-phenylethanol of 96% and an enantioselectivity in *S* form configuration of 77%. To evaluate and optimize the reaction conditions such as temperature, solvent, and base effect, various tests were carried out with Cu(OAc)₂ in the presence of ligand **3** using benzaldehyde and nitromethane as reactants.

The reaction was performed in several solvents such as; ethanol, butanol, *tert*-amyl alcohol, ethyl acetate, THF, *i*PrOH/THF, acetonitrile and toluene in an objective to homogenize the reaction mixture, because the catalyst seems not to be well soluble in isopropanol. Surprisingly, the best conversion as well as the best selectivity and enantioselectivity were observed when the reaction was achieved in *i*PrOH.

The reaction was also tested in the presence of several bases, organic and inorganic; DIPEA, DMAP, K₂CO₃ others than triethylamine in isopropanol as solvent. The realized tests showed that triethylamine was the best base used. DIPEA conducted similar results to those obtained with Et₃N but less effective (conv. = 67%, selectivity of 87% in **I** and ee= 69%). Then, the effect of temperature has been examined; the results are summarized in table 7. At 0

°C and 5 °C without base, no conversion was observed, while at 10 °C in the absence of base, only 12% of conversion was obtained after 22h.

Table 8: Effect of temperatures in asymmetric Henry reaction.

Entry	T °C	Et ₃ N (eq)	t (h)	Conv. (%)	Selectivity (%)		e.e (%) in <i>S</i>
					I	II	
1	-20	0.3	22	67	96	4	77
2	0	-	22	-	-	-	-
3	5	0.3	22	68	81	10	60
			46	86	81	5	
4	10	-	22	12	92	8	-
5	r. t.	-	22	76	93	7	70
6	r. t.	0.3	22	72	90	8	36

Conversion and selectivity were determined by GC, ee was determined by chiral HPLC, r. T. is between 20-25°C.

However, at 5°C in the presence of base, we obtained the target nitro-alcohol **I**, after 22h, with good enantioselectivity (60% in *S*), moderate conversion (68%) and selectivity (81%), the reaction was allowed to progress with time. Consequently, the conversion was increased to 86% after 46h, while the selectivities were kept unchanged. Furthermore, the reaction was carried out at room temperature with and without base (table 8 entry 5 and 6) in both cases good conversions (76 and 72%) with high selectivity close to 90% were obtained, whereas the enantiomeric excess was found to be 36% in the presence of base and was increased to get 70% in its absence.

When the reaction was done using ligand **8** (monoarylated amino ligand) instead of ligand **3**, in the same conditions, a complete reaction was achieved with a very good

selectivity (89%) toward 2-nitro-1-phenylethanol **I**, but a lower *ee* (42% in *S*) at -20°C (entry 1, table 9).

Table 9: Asymmetric Henry reaction with benzaldehyde and nitromethane using Ligand **8**

Entry	T °C	t (h)	Conv. (%)	Selectivity (%)		<i>ee</i> (%) in <i>S</i>
				I	II	
1 ^a	-20	22	100	89	3	42
2	0	22	60	97	3	59
3	r.t.	46	87	76	7	50

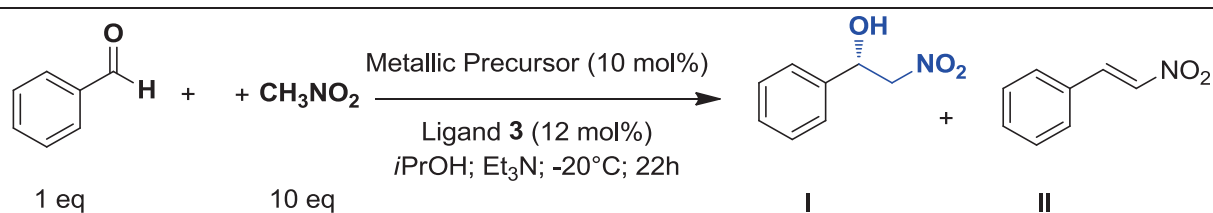
Conversion and selectivity were determined by GC, *ee* was determined by chiral HPLC. ^a in presence of Et₃N

The reaction with ligand **8** was done without triethylamine as base. At 0°C, after 22h, a conversion of 60% was reached with a high selectivity toward **I** (97%) and a better *ee* (59%) (Table 9, entry 2). At room temperature, the conversion was 82% after 46 h, with selectivity toward **I** of 76% and *ee* of 50% (table 9, entry 3).

We notice that ligand **8** is a monoarylated ligand containing NH₂ functionality, which is effectively more basic than aryated function NH-Ar, which could explain the good conversion observed with ligand **8** in the absence of a base. This was not the case with the ligand **3**. However, the *ee* induced with ligand **3** without base was better than **3**. Although, the presence of base revealed to be important to increase the conversion, it seems not suitable for the enantioselectivity at room temperature ($\approx 25^\circ\text{C}$). As expected, lower temperature was better for enantioselectivity.

On the objective to attain a better *ee*, we keep the best conditions previously defined; -20°C, Et₃N with ligand **3**, to test several metallic precursors.

Primarily, a test was carried out without metal, in the presence of ligand **3** only, an organocatalysis was already known for the studied reaction. In this case, a conversion of 41% was obtained without enantioselective excess (table 10, entry 1), which indicates primordial role of metal (Cu) for a good activity as well as for enantioselectivity.

Table 10: Screening of different copper precursor metals with ligand **3** in asymmetric Henry reaction.

Entry	Metallic Precursor	Conv. (%)	Selectivity (%)		ee (%) in <i>S</i>
			I	II	
1	-	41	90	10	Rac
2	Cu(OAc) ₂ ·H ₂ O	61	96	4	77
3	(CF ₃ SO ₃) ₂ Cu	61	94	5	46%
4	CuSCN	4	100	0	-
5	CuBr ₂	56	28	16	46%

Conversion and selectivity were determined by GC, ee was determined by chiral HPLC

The complexation of diamine ligand with the metallic center allows robust rigidity important for enantioselectivity and turns amine functions less basic, which is important for possible hydrogen bonds with substrate. With no symmetric ligand **8**, a mono coordination of ligand is strongly expected keeping the NH₂ free to play the role of intramolecular base. Furthermore, Cu(OTf)₂ was tested (entry 3) instead of Cu(OAc)₂. Close conversion (61%), higher selectivity toward **I** (94%), and lower *ee* (46%) were obtained. When Cu(SCN) (table 3, entry 4) was used, very low conversions (< 20%) and racemic mixture of compound **I** were obtained. CuBr₂ conducted to a medium enantioselectivity (*ee*=46%) with only 28% of conversion in nitroalcohol **I** (table 10, entry 5). It might seem that the use of other copper precursors bearing an anion like TfO⁻ and Br⁻ permits the formation of traces of strong acids, which neutralize the added base.

Furthermore, we investigated the catalytic system Cu(OAc)₂/diamide **3** which gave the best catalytic performance (table 10, entry 2) with benzaldehyde, keeping in use the optimized conditions, to carry out asymmetric Henry reaction with a series of derivatives of benzaldehyde bearing different substituents such as OCH₃, Br, NO₂, NC and CF₃. Moderate to

high isolated yields with good enantiomeric excess were gained. The derivative of benzaldehyde bearing strong EDG at para position as the methoxy (table 11, entry 2) led to moderate conversion (55%) with fair *ee* up to 59%.

Table 11: Screening of different substrate in asymmetric Henry reaction.

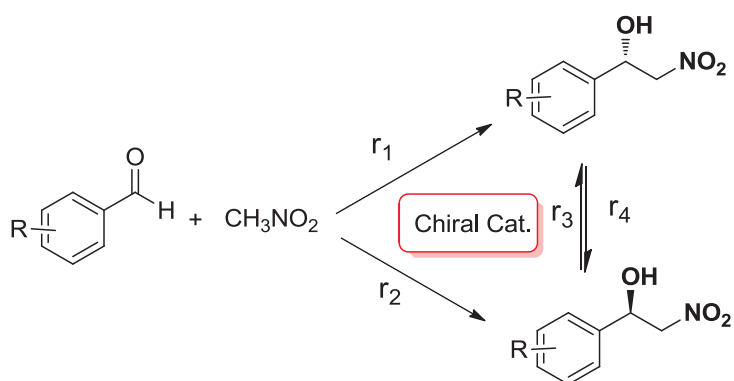
$ \begin{array}{c} \text{R}-\text{C}_6\text{H}_4-\text{CHO} + \text{CH}_3\text{NO}_2 \xrightarrow[\text{r.t. } t(\text{h})]{\text{Cu(OAc)}_2\cdot\text{H}_2\text{O} (10 \text{ mol\%}), \text{Ligand } \mathbf{3} (12 \text{ mol\%}), i\text{PrOH} (1\text{mL})} \text{R}-\text{C}_6\text{H}_4-\text{CH(OH)CH}_2\text{NO}_2 \\ \text{1eq} \qquad \qquad \qquad \text{10eq} \end{array} $					
Entry	Product	t (h)	Conv. (%)	Isolated Yield (%)	ee (%)
1		22	76	66	70
2		22	55	44	59
3		26	67	78	83
		42	>99		70
4		26	85	77	81
		42	>99		71
5		22	67	67	70
		26	>99		68
		42	>99		37
6		22	94	88	71
7		22	82	72	66

Conversion was determined by HNMR, ee was determined by chiral HPLC

Benzaldehyde derivative bearing EWG such as NO₂ at meta position gave 67% of conversion, with *ee* up to 81, whereas the one containing NO₂ at para position led to 85% of conversion with *ee* up to 83% after 26 h. After 42 h, a complete conversion (isolated yield up to 78%) took place, but *ee* was found to decrease to 70%. Substituted benzaldehyde with Br at para position also showed a complete conversion (isolated yield of 67%) after 26 h, with 68% of *ee*. A stronger EWG like CN at para position awarded conversion around 94% (isolated yield of 88%) after 22 h with 71% *ee*. Nevertheless, a conversion of 82% (isolated yield of 72%) with 73% *ee* was obtained when the EWG group was CF₃ at para position. As results, the EDG and the EWG also demonstrated their influences on the conversion as well as on the enantioselectivity.

In order to understand the loss of *ee* in some cases (table 11, entries 3, 4 and 5), several experiments have been performed: firstly (1), the reaction using meta substituted benzaldehyde with NO₂ (entry 3, table 11) was kept after completion of the reaction for 42 h under argon, same result was obtained as before; complete conversion with 70% *ee*. Same procedure was made with para substituted benzaldehyde of Br, also the same result was observed. Secondly (2), the obtained product was purified and subjected to precipitation at 0°C in isopropanol (solvent of the reaction), same enantiomeric excess was obtained for both the supernatant liquid and the precipitate solid.

Based on these observations, we can assume that the loss of *ee* isn't due to the effect of loss of enantiomer during precipitation. The loss of *ee* could be caused by a partial catalyst deterioration or by a possible racemization of the product of the reaction. The chirality of purified product seems to be stable after a couple of weeks. It is also known that racemization can take place under specified circumstances, and in our case the racemization might be catalyzed by the same catalyst.

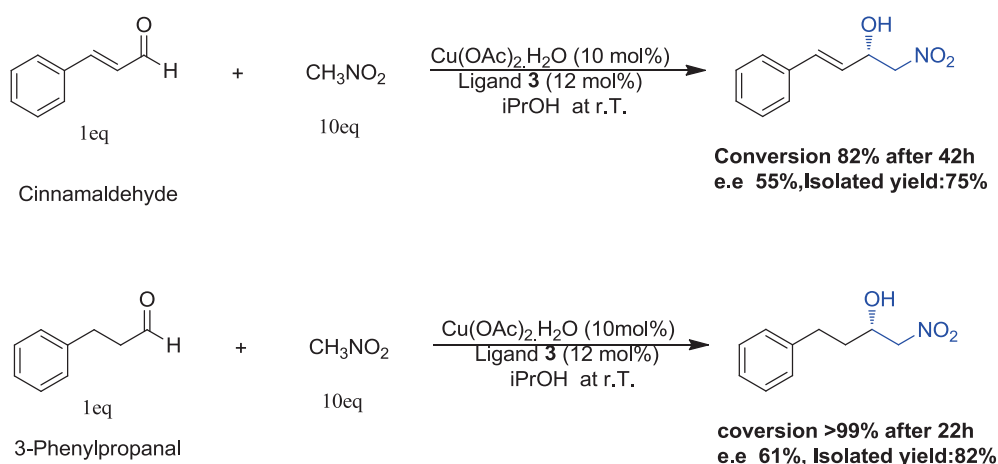


Scheme 82: Possible competitive reactions between

Three possible competitive reactions may occur, two parallel conducting to *R* or *S* and one reversible reaction of global rate = $|r_3 - r_4|$ (Scheme 82).

Thus, stopping the reaction at a convenient time, followed by purification and elimination of catalyst could be a solution to obtain the enantiomeric enriched corresponding products. This observation highlights also the influence of the EDG and the EWG not only on the activity, but also on the enantioselectivity.

Finally, two aliphatic aldehydes have also been used to evaluate our catalytic system $\text{Cu}(\text{OAc})_2/\text{Lig } \mathbf{3}$ in the previously optimized conditions (Scheme 83). Reaction with cinnamaldehyde as an aldehyde substrate, gave conversion of 82% and an *ee* of 55% in *S* configuration with an isolated yield of 75% after 42h. Whereas using 3-phenylpropanal, a complete conversion after 22h was gained with 61% *ee* in *S* configuration and 82% isolated yield.



Scheme 83: Asymmetric Henry reaction with aliphatic aldehyde

3.3 Conclusion

N,N-Dinaphthalene-*trans*-1,2-diaminocyclohexane **3** and *N*-naphthalene-*trans*-1,2-diaminocyclohexane **8**, with $\text{Cu}(\text{OAc})_2$ have been used in the asymmetric Henry reaction of various aliphatic and aromatic aldehydes with nitromethane conducting to enantioselectivities up to 83%. The substitution of benzaldehyde with EDG and EWG confirmed its influence in the conversion as well as in the enantioselectivity. Besides, the presence of NH_2 in the ligand allowed the reaction without the addition of triethylamine, this was observed with the monoarylated ligand **8**. With this ligand, better conversions were obtained but lower *ee* with di-arylated ligand **3**. Moreover, competitive reaction took place with our catalyst system derived from $\text{Cu}(\text{OAc})_2/\text{Lig. } \mathbf{3}$ involved loss of *ee* in some cases.

Further work is in progress to modify the ligand in order to evaluate the potential of this type of ligands as organocatalysts and to find more applications for other enantioselective catalytic process.

3.4 Experimental Section

3.4.1 Procedures for Henry reaction

In a sealed tube, the metal precursor $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (10 mg, 0.05 mmol, 10 mol%) and the chiral amine ligand (22 mg, 0.06 mmol, 12 mol%) were dissolved in 1 mL of *i*PrOH and stirred at room temperature for 1h under argon atmosphere. Then nitromethane (5 mmol, 10 equiv, 0.27 ml), and aldehyde substrate (0.5 mmol, 1 equiv.) were introduced. The reaction mixture was stirred using a magnetic stirrer hotplate at room temperature with a rotation speed of 700 rpm. After that the organic compound was extracted with either EtOAc or CH_2Cl_2 , then dried over Na_2SO_4 , filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel using cyclohexane/ethyl acetate (9:1 to 7:3). After evaporation, nitroaldol were obtained as oil or solid. The products were characterized by NMR. The conversion was determined by GC and ^1H NMR and the enantioselectivity were determined by the HPLC Chiralcel OD-H column. The same procedures were used at low temperatures, and Cryo-Star machine used to stabilize the temperature.

3.4.2 Nitroaldol Product Purification and Characterization

1- (S)-2-Nitro-1-phenylethanol

Oil

The product was purified via column chromatography using cyclohexane/Ethyl acetate (80/20) as eluents, 88% of isolated yield was obtained.

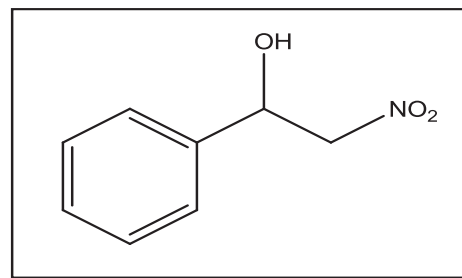
¹H NMR (300 MHz, CDCl₃) δ = 3.22 (s, 1H), 4.49 (dd, J = 3.0 Hz, 6 Hz, 1H), 4.59 (dd, J = 9 Hz, 9 Hz, 1H), 5.41-5.45 (m, 1H), 7.20-7.40 (m, 5H).

¹³C NMR (75MHz, CDCl₃) δ = 71.0, 81.2, 125.9, 128.9, 129.0, 138.2.

70% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (90:10) as the mobile phase, Flow rate: 1 ml/ min and UV: 220, t_1 (minor, *R*) = 11.96 min, t_2 (major, *S*) = 14.49 min.

$[\alpha]_D^{20}$ = +29.5 (*c* 1, CHCl₃), 70% ee (*S*).

Lit: $[\alpha]_D^{25}$ = +33.7 (*c* 1.05, CHCl₃), 72% ee (*S*).^{120a}



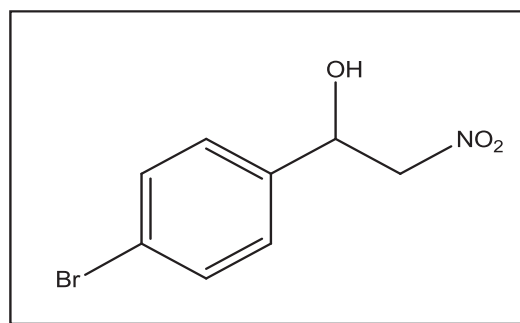
2- (S)-2-Nitro-1-(p-bromophenyl)ethanol

Oil

The product was purified via column chromatography using cyclohexane/Ethyl acetate (80/20) as eluents, 67% of isolated yield was obtained.

¹H NMR (300 MHz, CDCl₃) δ = 3.05(s, 1H), 4.48 (dd, J = 3 Hz, 12 Hz, 1H), 4.57 (dd, J = 9 Hz, 6 Hz, 1H), 5.44 (d, J = 6 Hz, 9.3 Hz, 1H), 7.29 (d, J = 9 Hz, 1H), 7.54 (d, J = 9Hz, 2H).

¹³C NMR (75 MHz, CDCl₃) δ = 70.3, 80.9, 122.9, 127.6, 132.1, 137.1.



68% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (90:10) as the mobile phase, Flow rate: 1 ml/ min and UV: 220, t_1 (minor, *R*) = 16.39 min, t_2 (major, *S*) = 21.44 min.

$[\alpha]_D^{20} = +18.9$ (*c* 0.4, CHCl_3), 68% ee (*S*).

Lit: $[\alpha]_D^{25} = -35.3$ (*c* 5.3, CH_2Cl_2), 97% ee (*R*).^{112a}

3- (*S*)-2-Nitro-1-(*p*-methoxyphenyl)ethanol

Oil

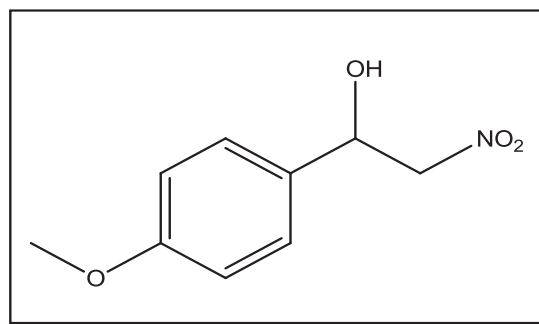
The product was purified with silica gel using cyclohexane/Ethyl acetate (80/20) as eluents, 80% of isolated yield was obtained.

^1H NMR (300 MHz, CDCl_3) δ = 2.94 (s, 1H), 3.78 (s, 3H), 4.43 (dd, J = 3 Hz, 12 Hz, 1H), 4.56 (dd, J = 9 Hz, 6 Hz, 1H), 5.37 (d, J = 9 Hz, 1H), 6.88 (d, J = 6 Hz, 2H), 7.27 (d, J = 3 Hz, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ = 55.37, 70.67, 81.26, 114.39, 127.31, 130.27

59% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (90:10) as the mobile phase, Flow rate: 1 ml/ min and UV: 220, t_1 (minor) = 20.15 min, t_2 (major) = 25.26 min, $[\alpha]_D^{20} = +17.26$ (*c* 0.5 CHCl_3), 59% ee (*S*).

Lit: $[\alpha]_D^{25} = +43.5$ (*c* 0.95, CHCl_3), 98% ee (*S*).¹⁴³



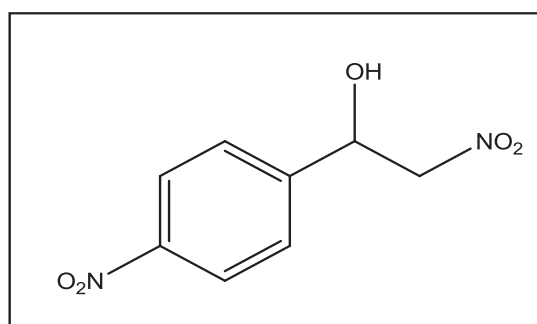
4- (*S*)-2-Nitro-1-(*p*-nitrophenyl)ethanol

Oil

The product was purified with silica gel using cyclohexane/Ethyl acetate (80/20) as eluents, 77% of isolated yield was obtained.

^1H NMR (300 MHz, CDCl_3) δ = 3.17 (s, 1H), 4.52 (m, 2H), 5.54 (ddd, J = 3 Hz, 6 Hz, 6 Hz, 1H), 7.56 (d, J = 6 Hz, 2H), 8.20 (d, J = 9 Hz, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ = 69.9, 80.6, 124.2, 126.9, 144.9, 148.1.



¹⁴³ G. Blay, L. R. Domingo, V. Hernández-Olmo, J. R. Pedro, *Chem. Eur. J.* 14 (2008) 4725-4730.

81% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (90:10) as the mobile phase, Flow rate: 1 ml/ min and UV: 220, t_1 (minor) = 30.02 min, t_2 (major) = 38.48 min.

$[\alpha]_D^{20} = +23.15$ (c 0.73, CHCl_3), 81% ee (*S*).

Lit: $[\alpha]_D^{25} = +33.7$ (c 0.95, CH_2Cl_2), 95% ee (*S*).¹⁴⁴

5- (*S*)-2-Nitro-1-(*m*-nitrophenyl)ethanol

Oil

The product was purified with silica gel using cyclohexane/Ethyl acetate (80/20) as eluents, 78% of isolated yield was obtained.

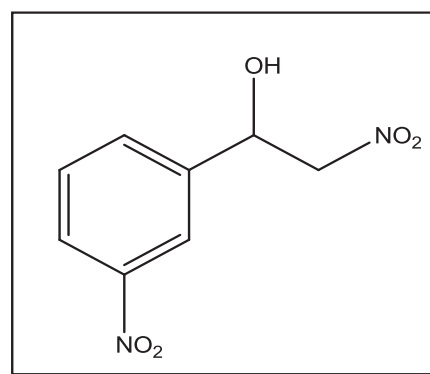
^1H NMR (300 MHz, CDCl_3) δ = 3.52 (s, 1H), 4.61 (m, 2H), 5.6 (m, J = 6 Hz, 3 Hz, 3 Hz), 7.59 (t, J = 6 Hz, 9 Hz, 1H), 7.77 (d, J = 6 Hz, 1H), 8.18 (m, 1H), 8.29 (m, 1H),

^{13}C NMR (75 MHz, CDCl_3) δ = 69.9, 80.6, 124.2, 126.9, 144.9, 148.1

83% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (90:10) as the mobile phase, Flow rate: 1 ml/ min and UV: 220, t_1 (minor) = 27.54 min, t_2 (major) = 31.74 min.

$[\alpha]_D^{20} = +18.65$ (c 0.2, CHCl_3), 83% ee (*S*).

Lit: $[\alpha]_D^{25} = -32$ (c 0.5, CH_2Cl_2), 91% ee (*R*).¹⁴⁵



¹⁴⁴ G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha, Z. Wang, *Chem. Eur. J.* 17 (2011) 1114-1117.

¹⁴⁵ E. C. Constable, G. Zhang, C. E. Housecroft, M. Neuburger, S. Schaffner, W-D. Woggon and J. A. Zampese, *New. J. Chem.* 33 (2009) 2166-2173.

6- (S)-2-Nitro-1-(p-cyanophenyl)ethanol

Brown crystal

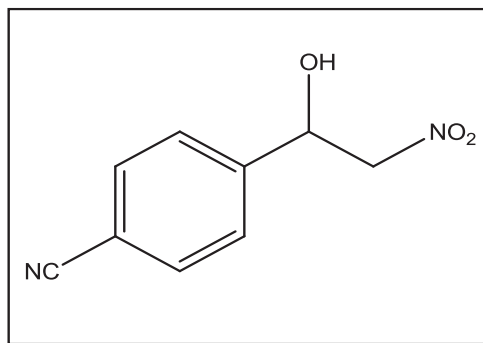
The product was purified with silica gel using cyclohexane/Ethyl acetate (80/20) as eluents, 88% of isolated yield was obtained.

¹H NMR (300 MHz, CDCl₃) δ = 3.21 (s, 1H), 4.55 (m, 2H), 5.54 (dd, J = 3Hz, 6 Hz, 1H), 7.56 (d, J = 9 Hz, 1H), 7.70 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 70.1, 80.7, 112.8, 118.3, 126.7, 132.8, 143.2.

71% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (90:10) as the mobile phase, Flow rate: 1 ml/ min and UV: 215, t_1 (minor) = 14.53 min, t_2 (major) = 18.73 min. $[\alpha]_D^{20}$ = +18.13 (c 0.5, CHCl₃), 71% ee (*S*).

Lit: $[\alpha]_D^{25}$ = -32.8 (c 0.5, CH₂Cl₂), 90% ee (*R*).¹⁴⁵



7- (S)-2-Nitro-1-(p-trifluoromethylphenyl)ethanol

Oil

The product was purified with silica gel using cyclohexane/Ethyl acetate (80/20) as eluents, 83% of isolated yield was obtained.

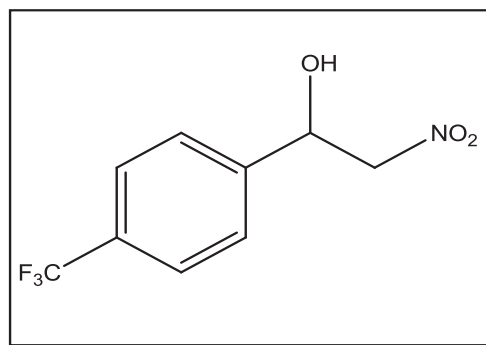
¹H NMR (300 MHz, CDCl₃) δ = 3.29 (s, 1H), 4.56 (m, 2H), 5.53 (dd, J = 3Hz, 6 Hz, 1H), 7.54 (d, J = 9 Hz, 1H), 7.67 (d, J = 9 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 70.3, 80.9, 122.1, 125.6, 125.9, 125.96, 126.01, 126.06, 126.4, 130.9, 131.34, 141.9

73% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (95:5) as the mobile phase, Flow rate: 1 ml/ min and UV: 215, t_1 (minor) = 24.29 min, t_2 (major) = 32.10 min,

$[\alpha]_D^{20}$ = +21.3 (c 0.6, CHCl₃), 73% ee (*S*).

Lit: $[\alpha]_D^{25}$ = +33.7 (c 1, CHCl₃), 90% ee (*S*).^{112d}



8- (S)-1-Nitro-4-phenyl-but-3-en-2-ol

Pink crystal

The product was purified with silica gel using cyclohexane/Ethyl acetate (80/20) as eluents, 75% of isolated yield was obtained.

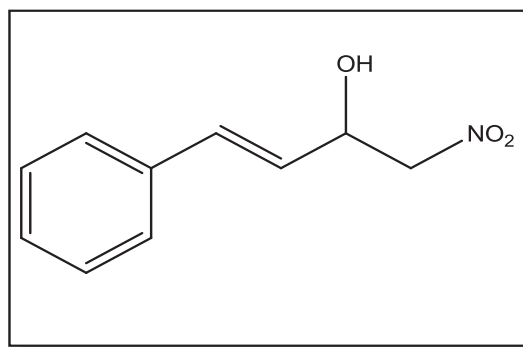
¹H NMR (300 MHz, CDCl₃) δ = 2.87 (s, 1H), 4.51 (d, J = 6 Hz, 2H), 5.04 (m, 1H), 6.14 (dd, J = 6 Hz, 9 Hz, 1H), 6.78 (d, J = 15 Hz, 1H), 7.27-7.40 (m, 5H).

¹³C NMR (75 MHz, CDCl₃) δ = 69.6, 79.9, 125.0, 126.7, 128.5, 128.7, 133.6, 135.5.

55% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (85:15) as the mobile phase, Flow rate: 1 ml/ min and UV: 220, t_1 (major) = 22.56 min, t_2 (minor) = 29.79 min.

$[\alpha]_D^{20}$ = +3.8 (c 0.9, CHCl₃), 55% ee (*S*).

Lit: $[\alpha]_D^{25}$ = -7.4 (c 0.25, CH₂Cl₂), 95% ee (*R*).¹⁴⁵



9- (S)-1-nitro-4-phenylbutan-2-ol

Oil

The product was purified with silica gel using cyclohexane/Ethyl acetate (80/20) as eluents, 82% of isolated yield was obtained.

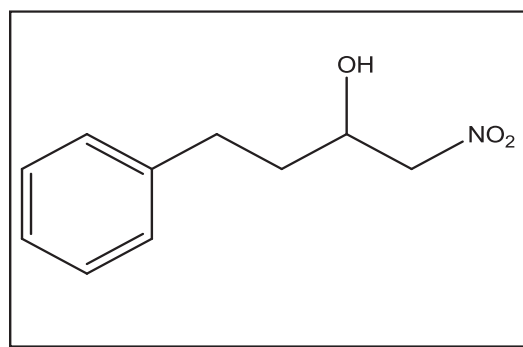
¹H NMR (300 MHz, CDCl₃) δ = 1.78-1.89 (m, 2H), 2.70-2.87 (m, 2H), 4.28-4.41 (m, 3H), 7.19-7.34 (m, 5H).

¹³C NMR (75 MHz, CDCl₃) δ = 31.3, 35.1, 67.8, 80.5, 126.3, 128.4, 128.7, 140.6.

61% of ee was determined by HPLC on Chiralcel OD using n-hexanes: Isopropanol (70:30) as the mobile phase, Flow rate: 1 ml/ min and UV: 215, t_1 (minor) = 8.50 min, t_2 (major) = 7.79 min.

$[\alpha]_D^{20}$ = -8.57 (c 0.8, CHCl₃), 55% ee (*S*)

Lit: $[\alpha]_D^{25}$ = -14.4 (c 1, CHCl₃), 87% ee (*S*)^{112d}



4 General Conclusion and perspective

We have described in this PhD thesis work, the syntheses of new *N*-arylated ligands following a simple coupling of C-N, by dehydrogenative alkylation method. This method recently has described in our CASYEN (our French Laboratory) for the synthesis of *N*-aryl Alkyl compounds and extended by us to synthesize chiral ligands derived from (1*R*, 2*R*)-diaminocyclohexane and α or β aromatic-cyclic ketone. A series of ligands were prepared with good yields. We have successfully transformed two of *N,N'*-diarylated diamine ligand to imidazolium salt and one mono *N*-arylated diamine to mono-thiourea ligand with good yields.

The investigation of synthesized *N,N'*-diarylated diamine in association with cationic iridium precursor $[\text{Ir}(\text{COD})_2]^+\text{BF}_4^-$ in asymmetric transfer hydrogenation of aromatic ketones allow the obtaining of interesting results. Best conditions are obtained using a mixture of sodium formate and formic acid as a hydrogen source which improves the efficiency of the catalyst. This study evidences the presence of pH effect; ultimate pH value found is around 3.5. The efficiency of this catalyst, following the same conditions we defined was confirmed by reducing other aromatic ketones to corresponding chiral alcohol with complete conversions and high enantioselectivities (*ee* up to 93%). While, Mono *N*-aryl diamine complexed to iridium used in asymmetric reduction of acetophenone conducted to a moderate *ee*, showing thus the powerful of *N,N'*-diarylation of diamine.

Two of the prepared chiral diamine, *N,N'*-dinaphtyl diaminocyclohexane and *N*-naphtyl diaminocyclohexane combined to copper (II), have been studied in Henry Reaction between aliphatic and aromatic aldehydes with nitromethane. The desired products β -nitro-aryl-alcohols were obtained with good isolated yield and enantioselectivities up to 83%. The substitution of benzaldehyde with EDG and EWG confirmed its influence in the conversion as well as in the enantioselectivity. Furthermore, the usage of *N*-naphtyl containing the functional group NH_2 which is more basic than NH from *N,N'*-dinaphtyl diaminocyclohexane allowed the reaction without addition of base (free base) with better conversion. Unfortunately, a loss of *ee* has been observed using some aldehyde substrates in asymmetric Henry Reaction using $\text{Cu}(\text{OAc})_2/$ *N,N'*-dinaphtyl diaminocyclohexane catalyst, that is due probably to racemization catalyzed by the catalyst.

This work of synthesis allowed us to show the usefully of these synthesized compounds not only synthesis as intermediate but also in asymmetric catalysis.

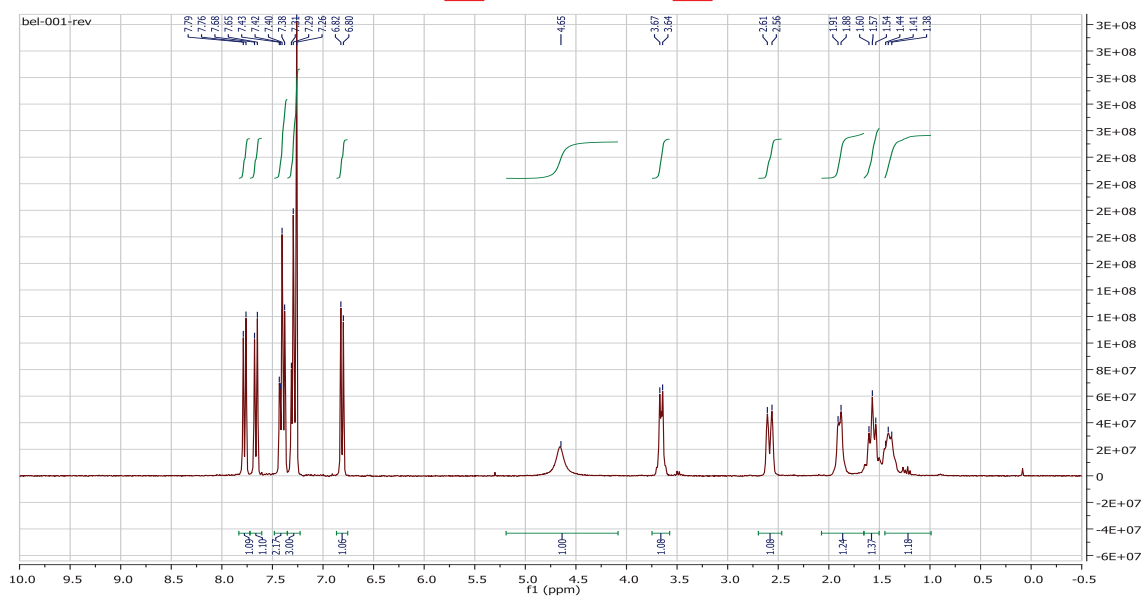
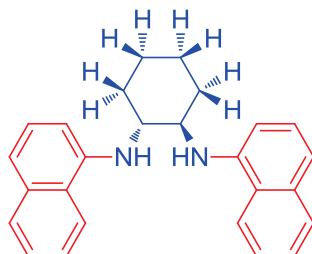
The promote results in asymmetric transfer hydrogenation and in symmetric Henry reaction boost us:

- 1- To explore other applications of the prepared ligands in other reactions in asymmetric catalysis, with or without metals.
- 2- To extend the method of synthesis to prepare other ligand using other amines,
- 3- Modify the prepared ligands or use them to prepare other ligands.

5 Supplementary materials:

^1H and ^{13}C NMR spectra for N,N' -(1R,2R)-diamine

(1R,2R)- N^1, N^2 -di(naphthalen-1-yl)cyclohexane-1,2-diamine



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134.6897
128.6897
126.5118
125.8286
124.5379
124.5372
120.8212
117.8820

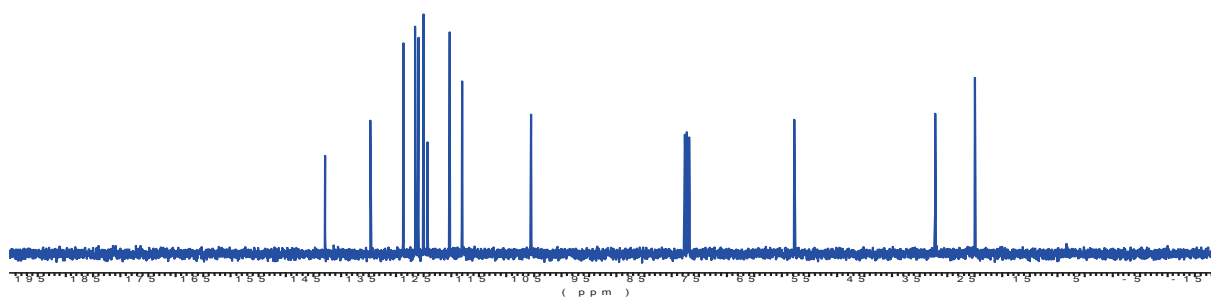
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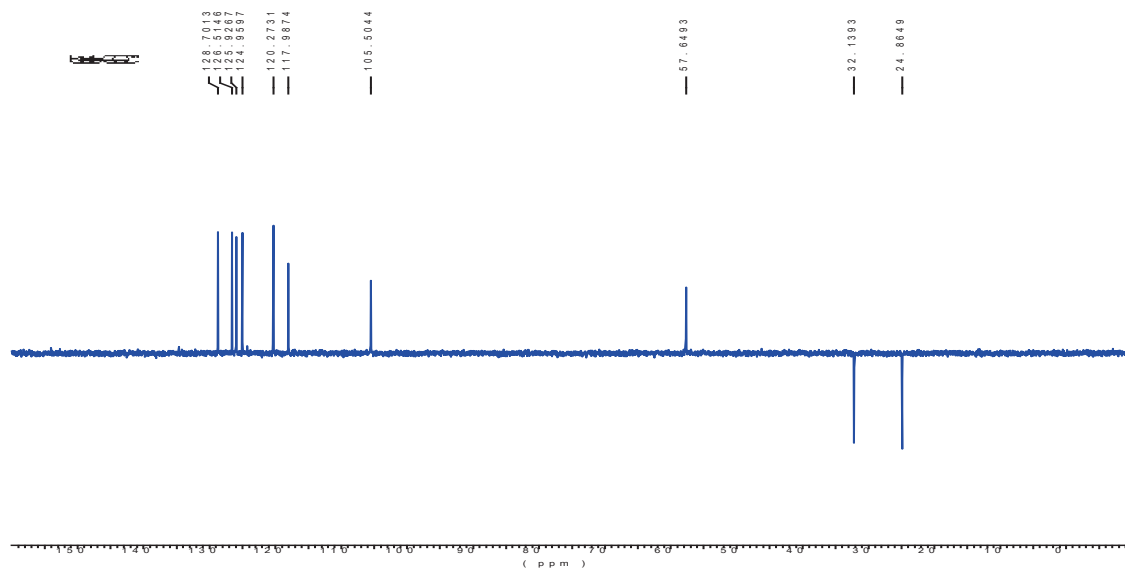
77.6000
77.1771
76.7543

57.6459

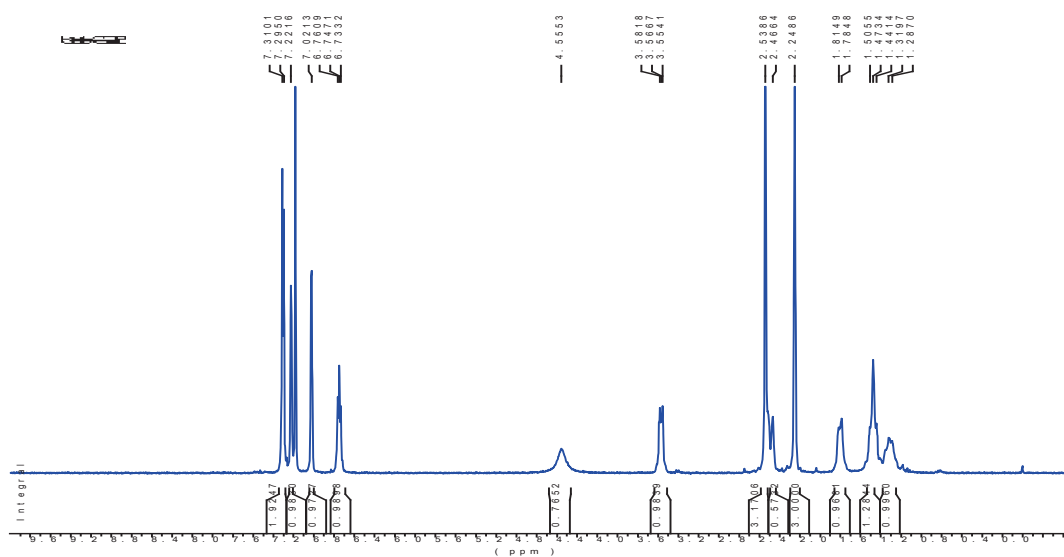
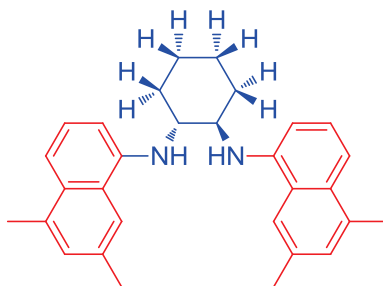
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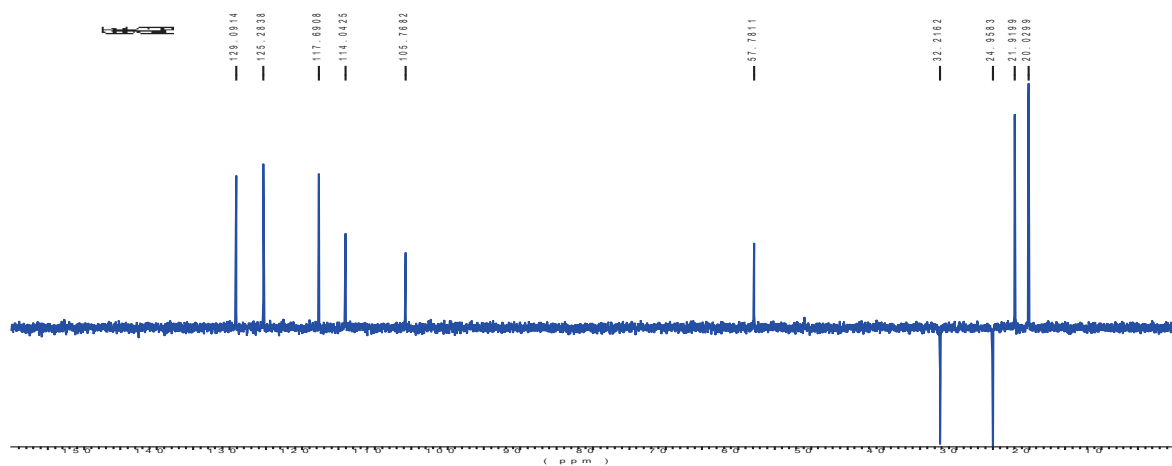
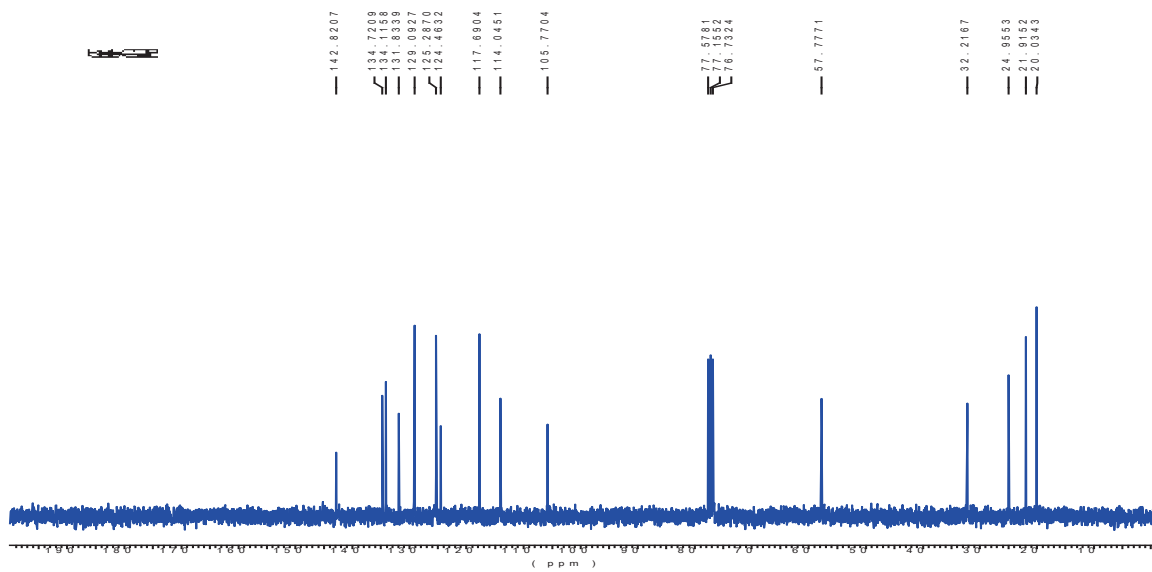
24.8679



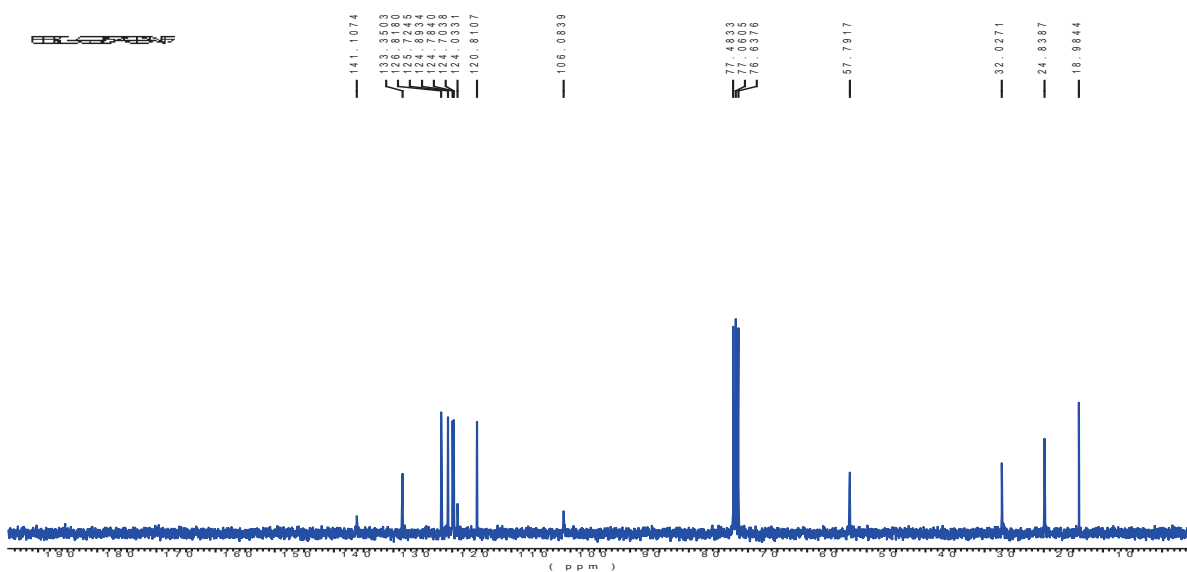
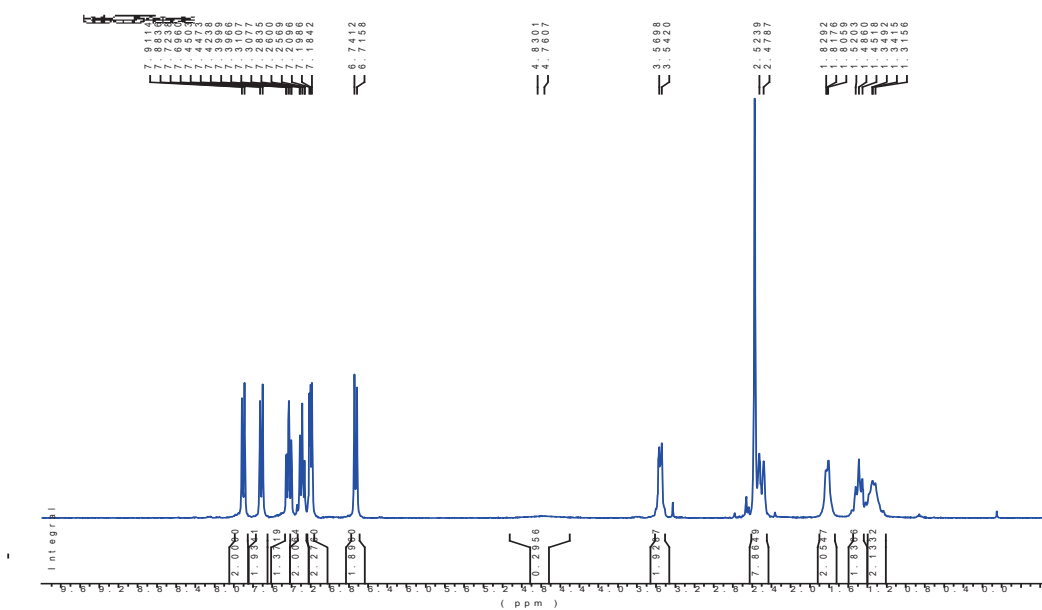
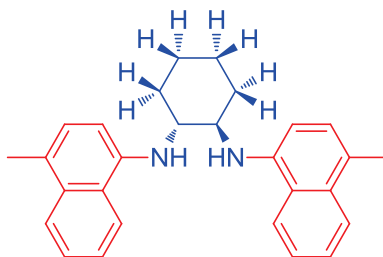


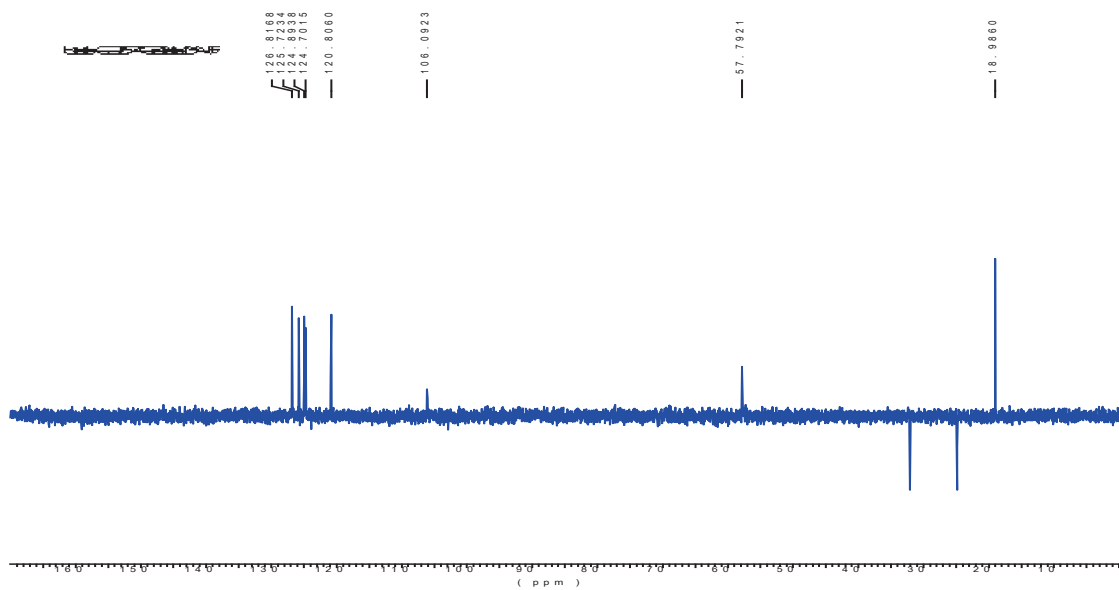
(1R, 2R)- N^1, N^2 -bis(5,7-dimethylnaphthalen-1-yl)cyclohexane-1,2-diamine



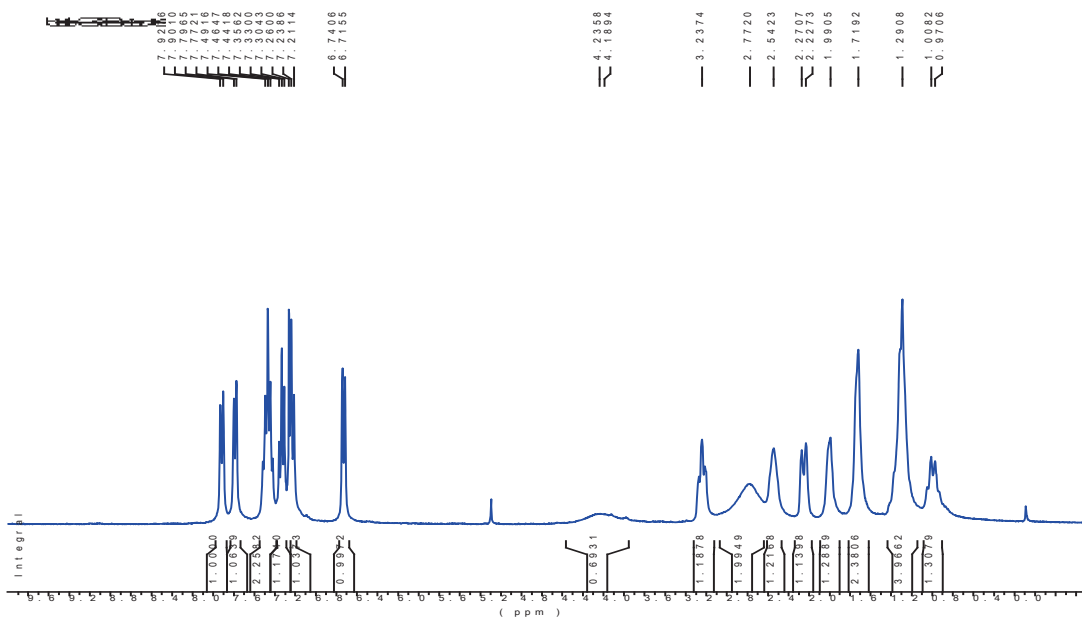
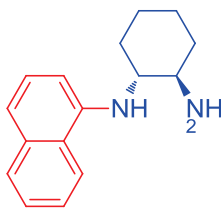


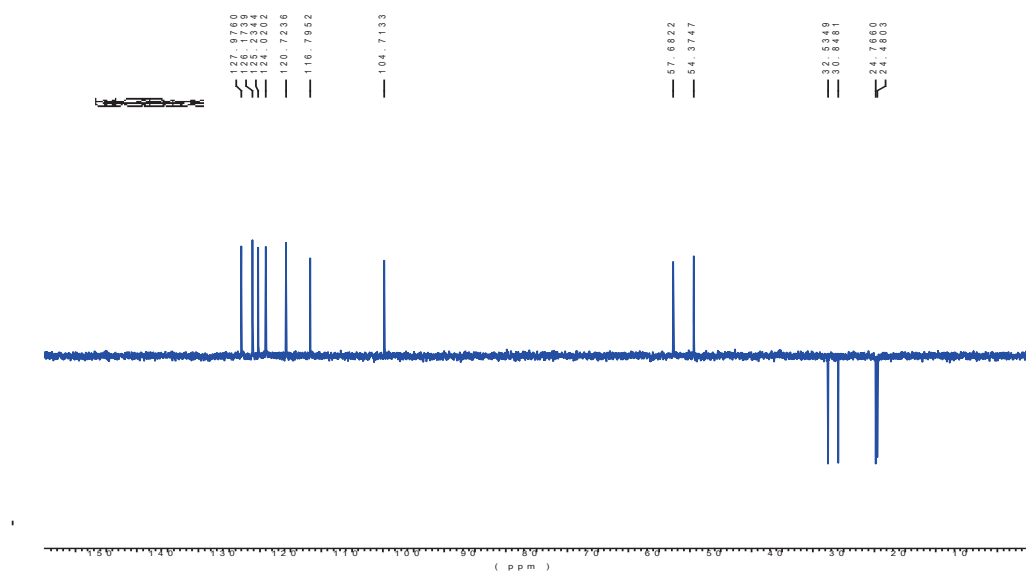
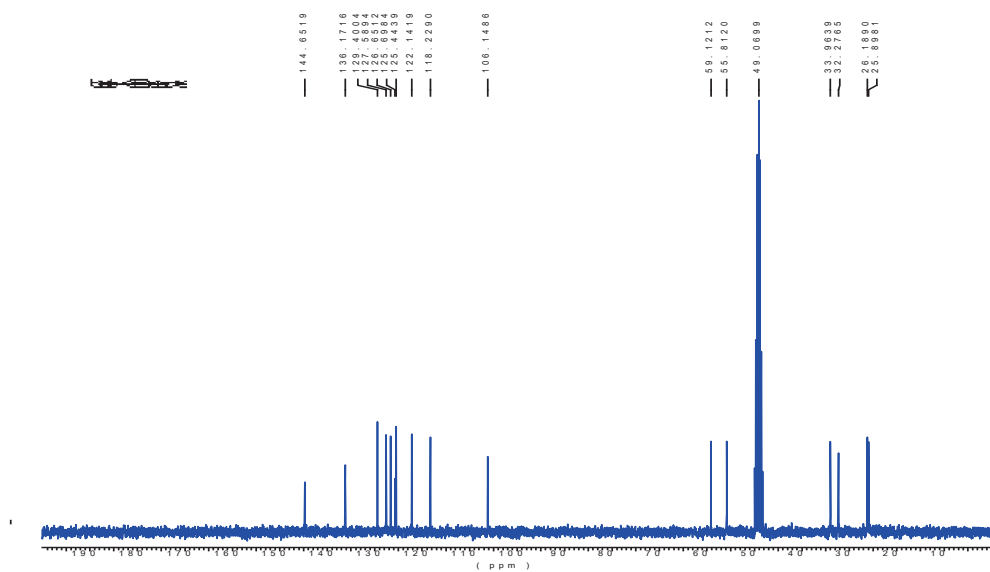
(1*R*, 2*R*)-*N*₁, *N*₂-bis(5-methylnaphthalen-1-yl)cyclohexane-1,2-diamine



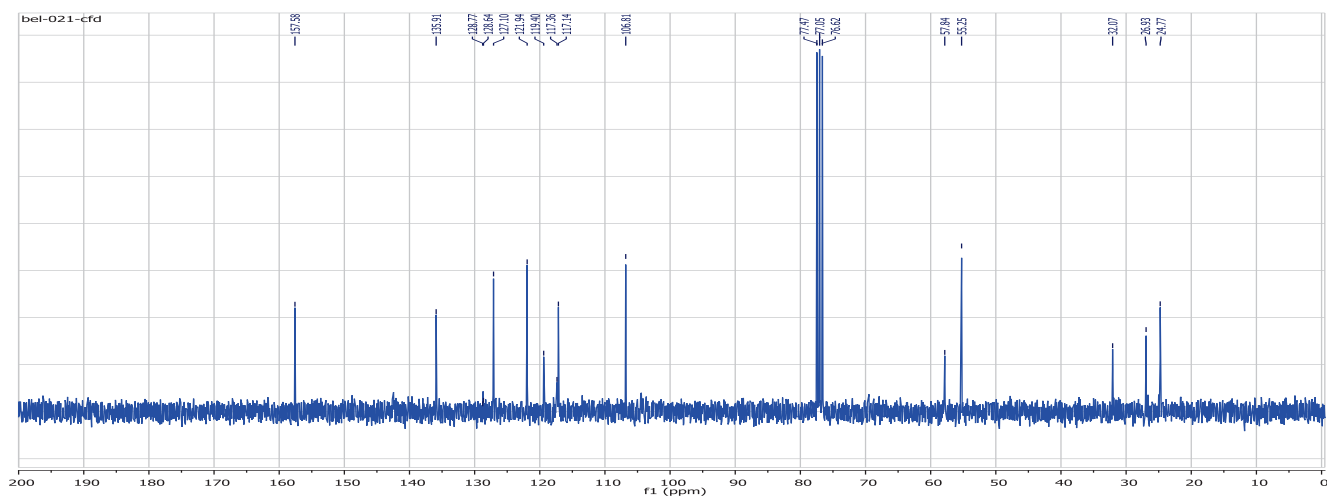
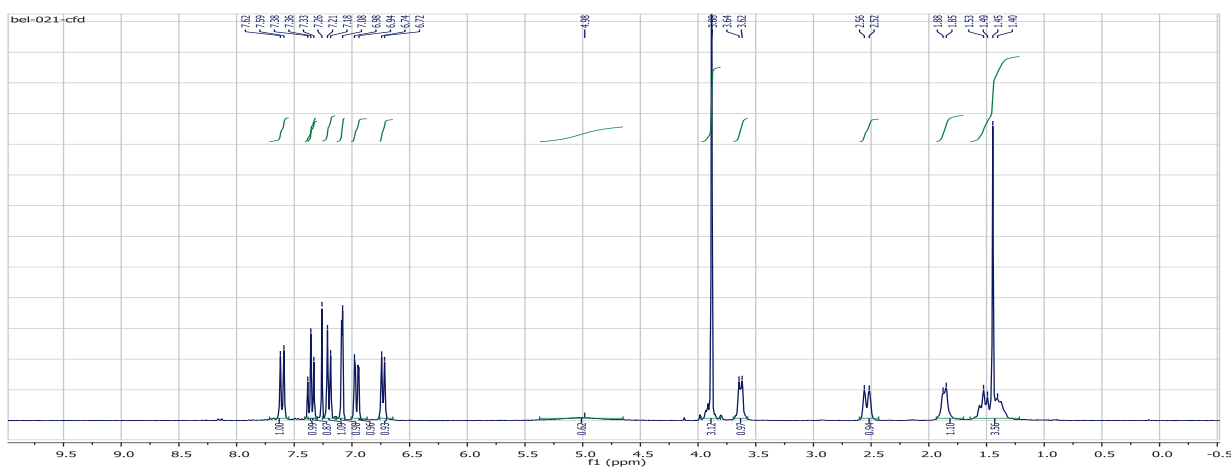
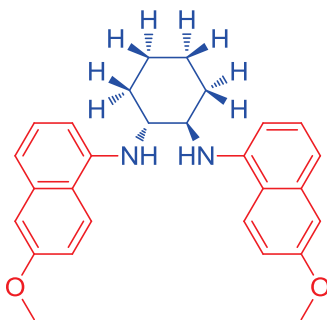


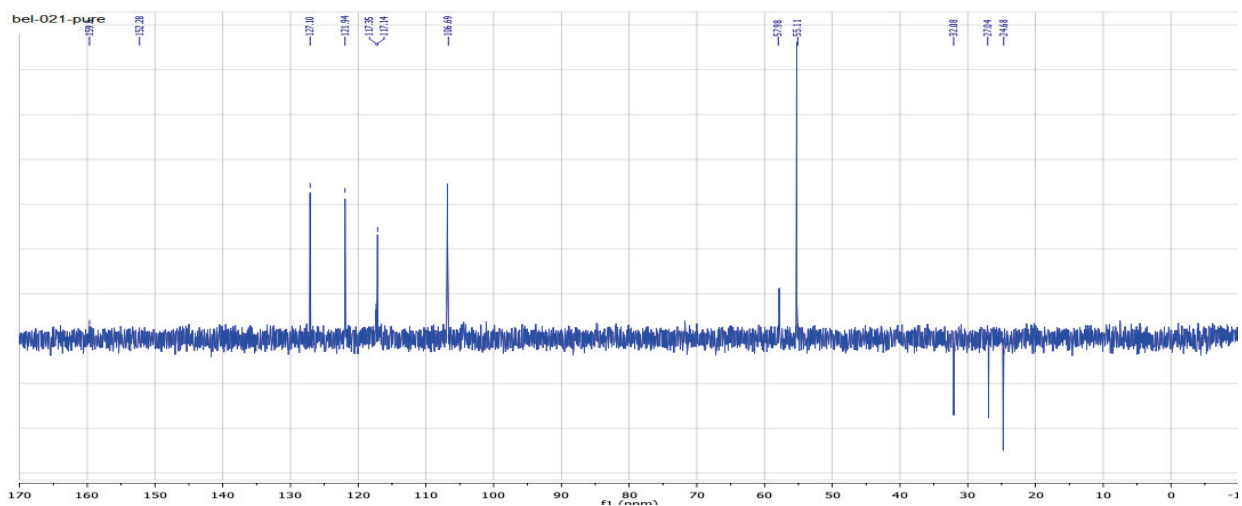
(1R, 2R)-N¹-(naphthalen-1-yl) cyclohexane-1, 2-diamine [847901-48-8]:



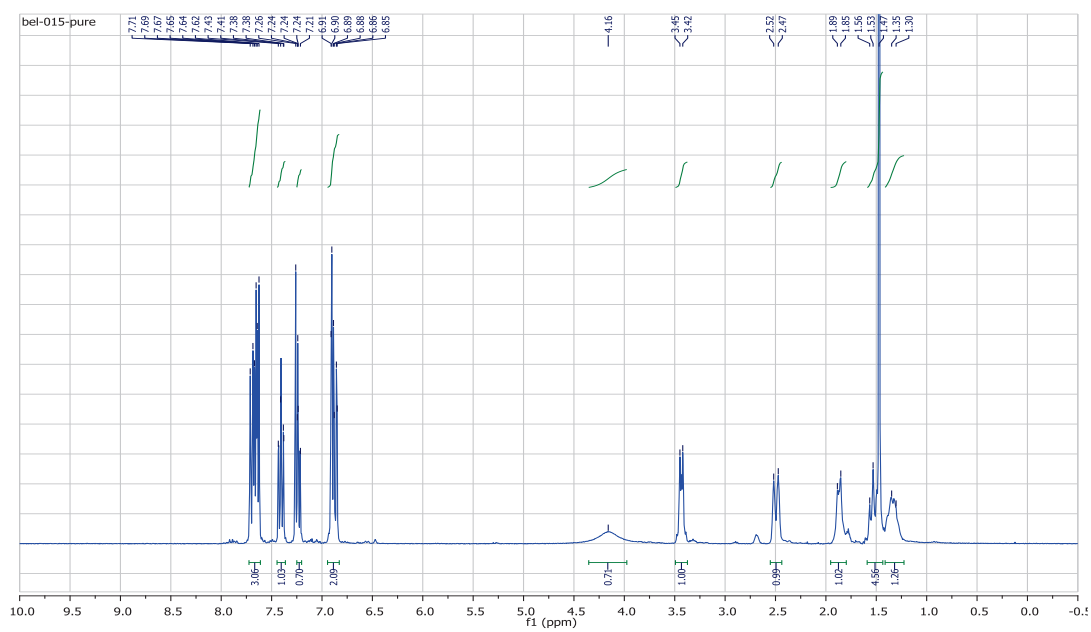
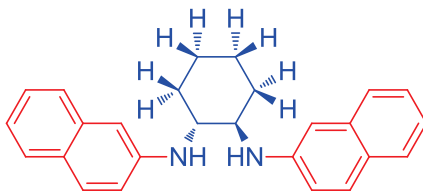


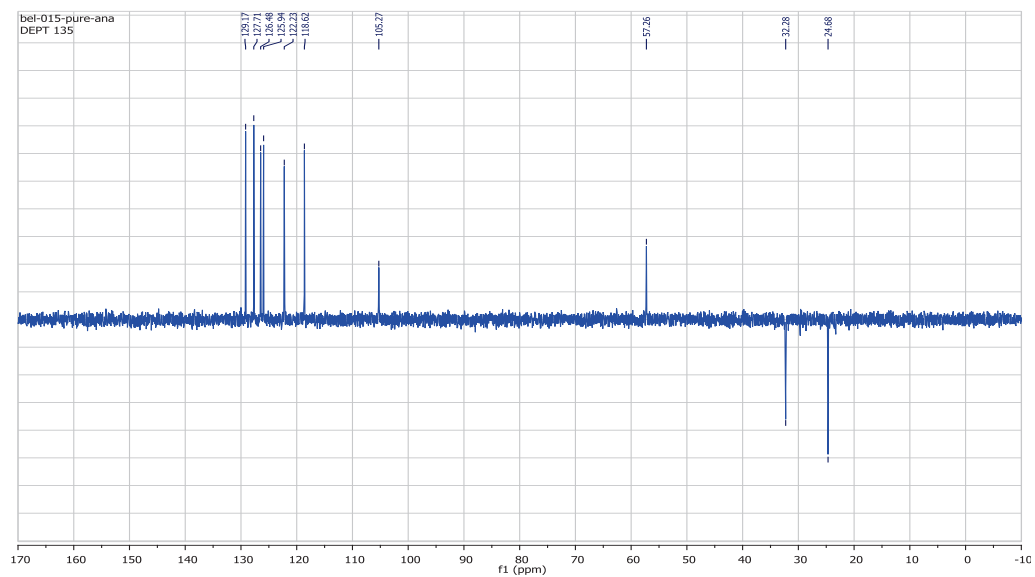
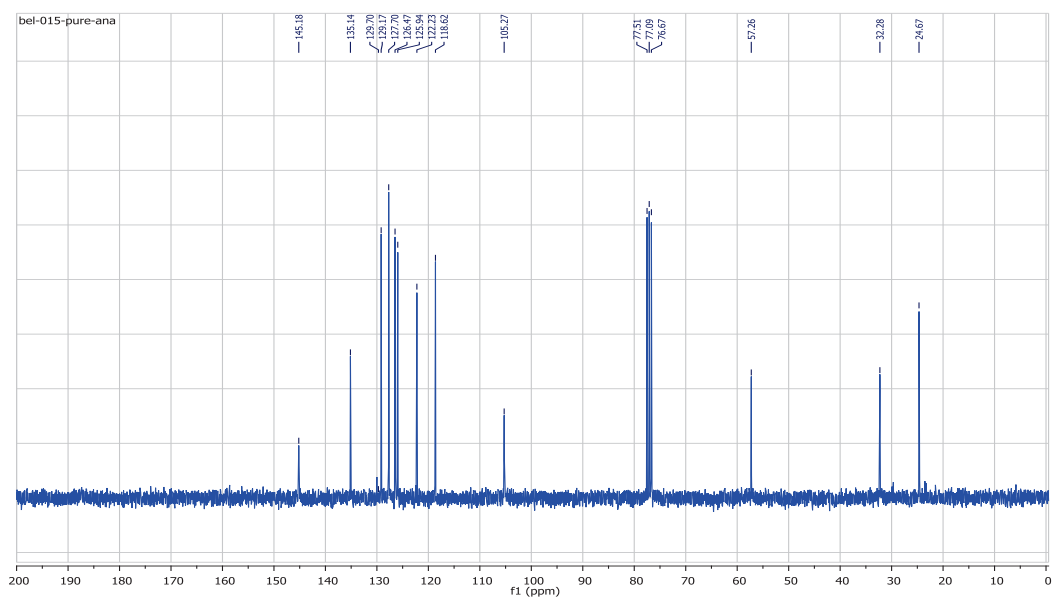
(1*R*,2*R*)-*N*¹,*N*²-bis(6-methoxynaphthalen-1-yl)cyclohexane-1,2-diamine



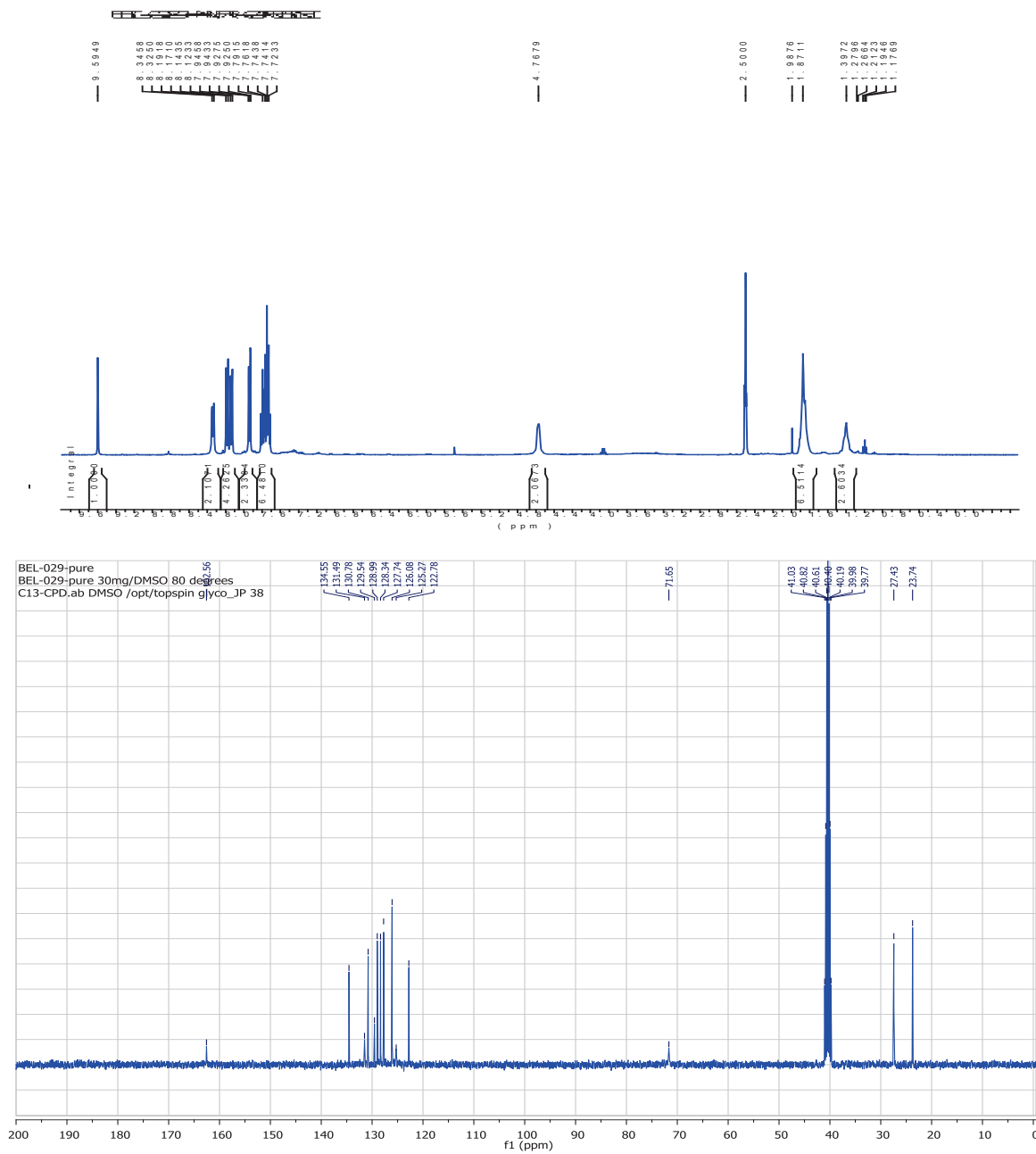
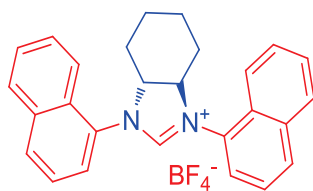


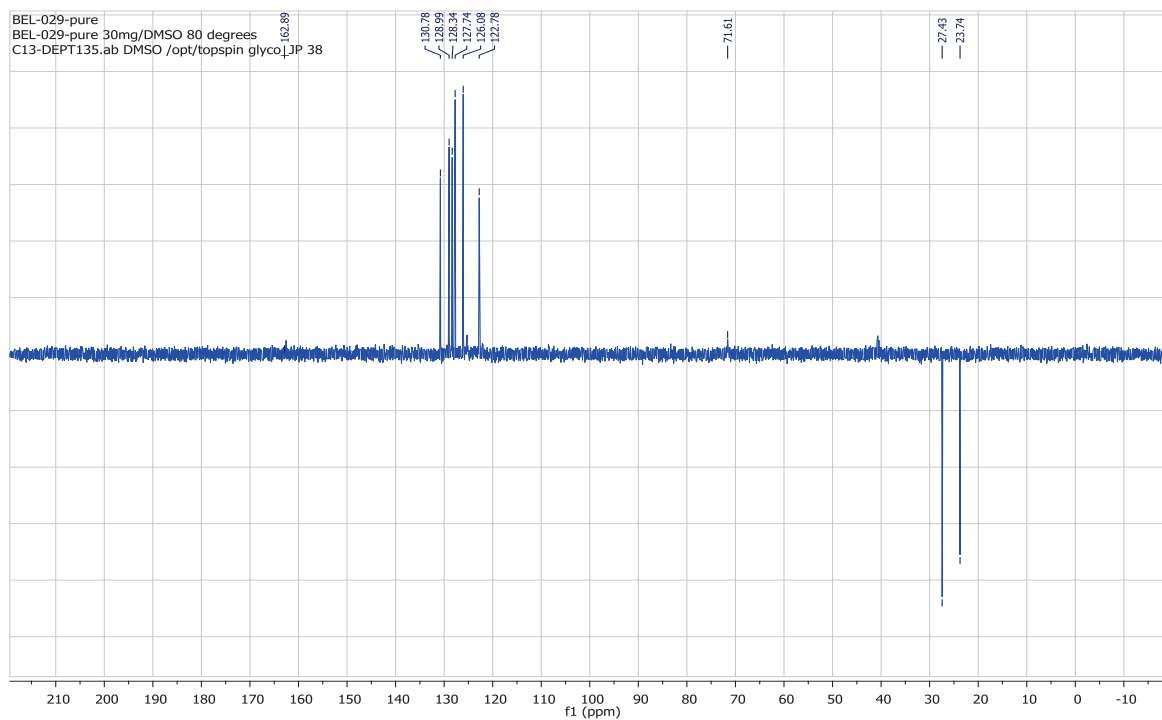
(1*R*, 2*R*)-*N*¹,*N*²-di(naphthalen-2-yl)cyclohexane-1,2-diamine



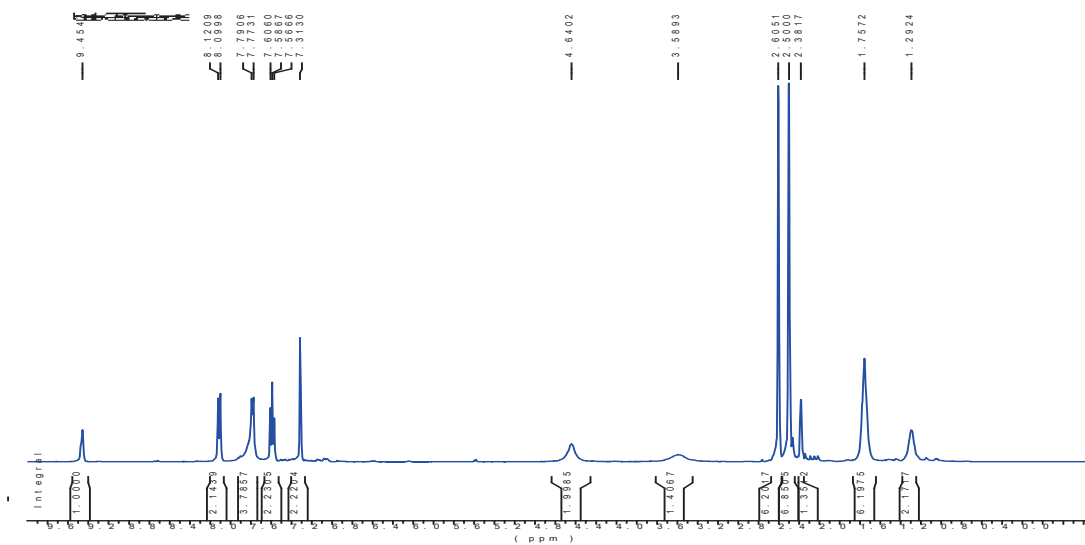
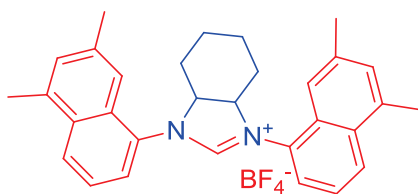


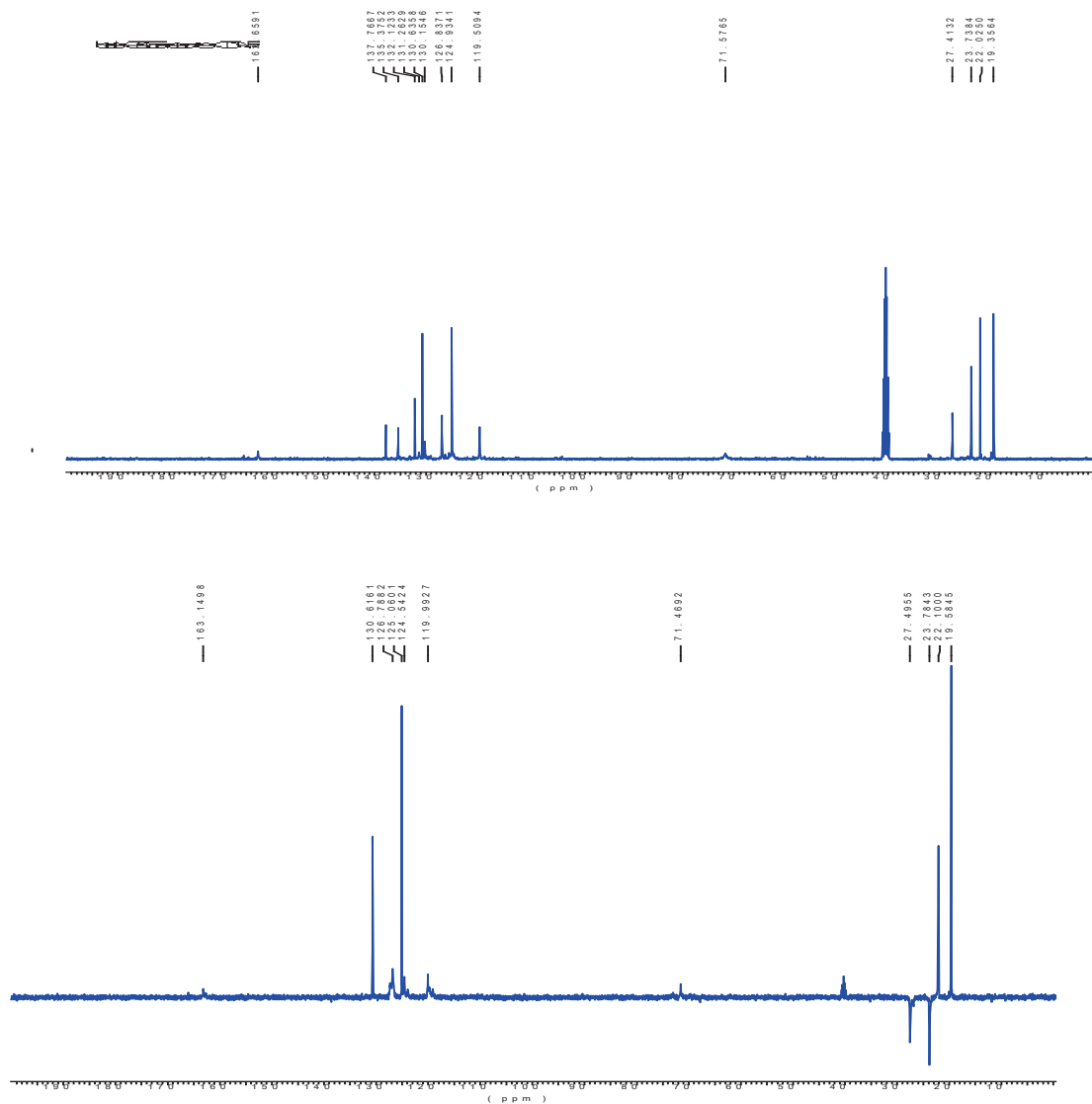
**(4R,5R)-1,3-di(naphthalen-1-yl)-octahydron-1H-benzoimidazol-3-ium
tetrafluoroborate.**





(3aR, 7aR)-1, 3-bis (5, 7-dimethylnaphthalen-1-yl)-3a, 4, 5, 6, 7, 7a-hexahydro-1H-benzo[d]imidazol-3-ium





(1*R*,2*R*)-2-(naphthalen-1-ylamino)cyclohexyl)-3-phenylthiourea

